Drug Delivery Technology®

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Ground-Breaking TRNA Therapy

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

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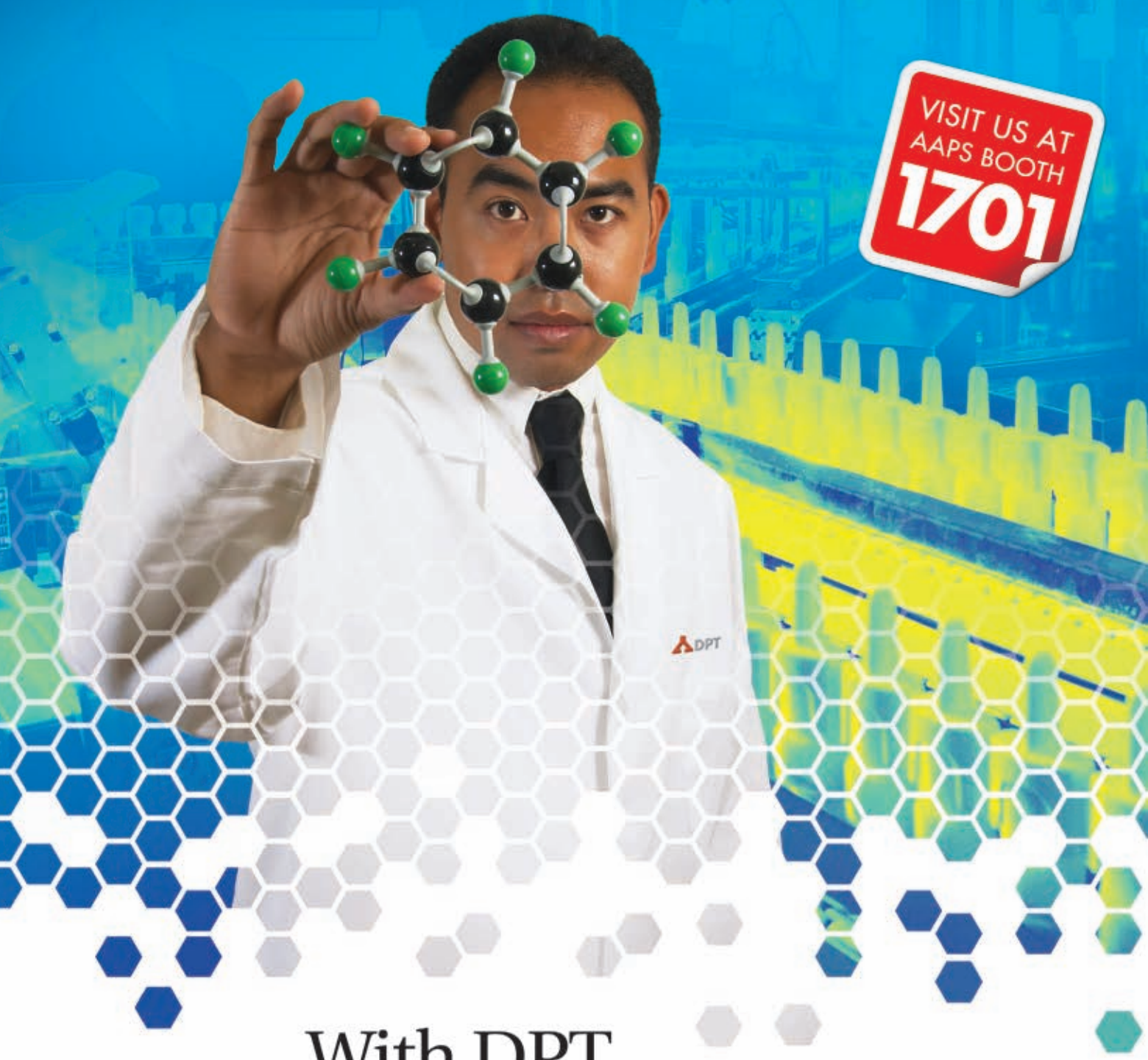

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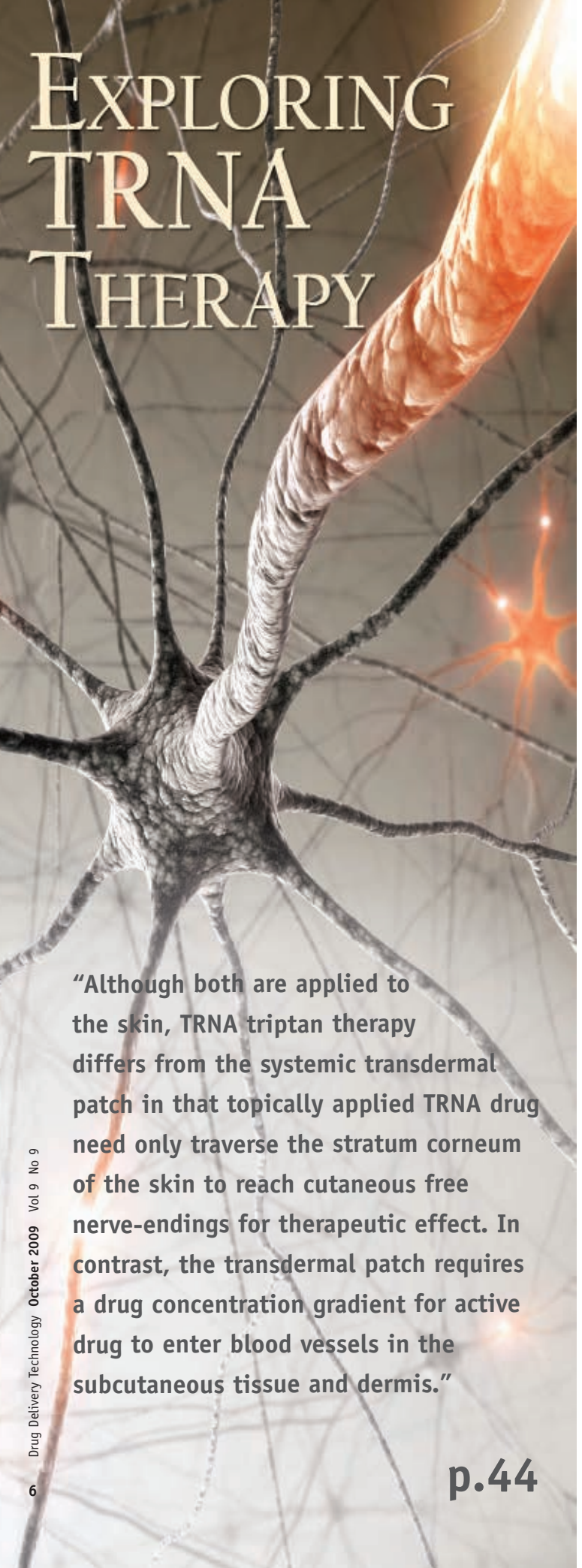

Exploring TRNA Therapy

"Although both are applied to the skin, TRNA triptan therapy differs from the systemic transdermal patch in that topically applied TRNA drug need only traverse the stratum corneum of the skin to reach cutaneous free nerve-endings for therapeutic effect. In contrast, the transdermal patch requires a drug concentration gradient for active drug to enter blood vessels in the subcutaneous tissue and dermis."

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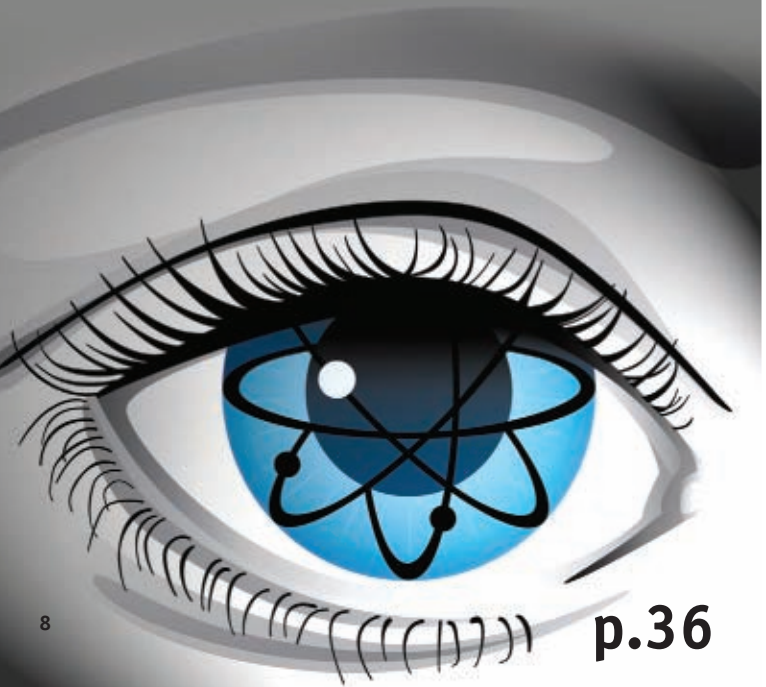

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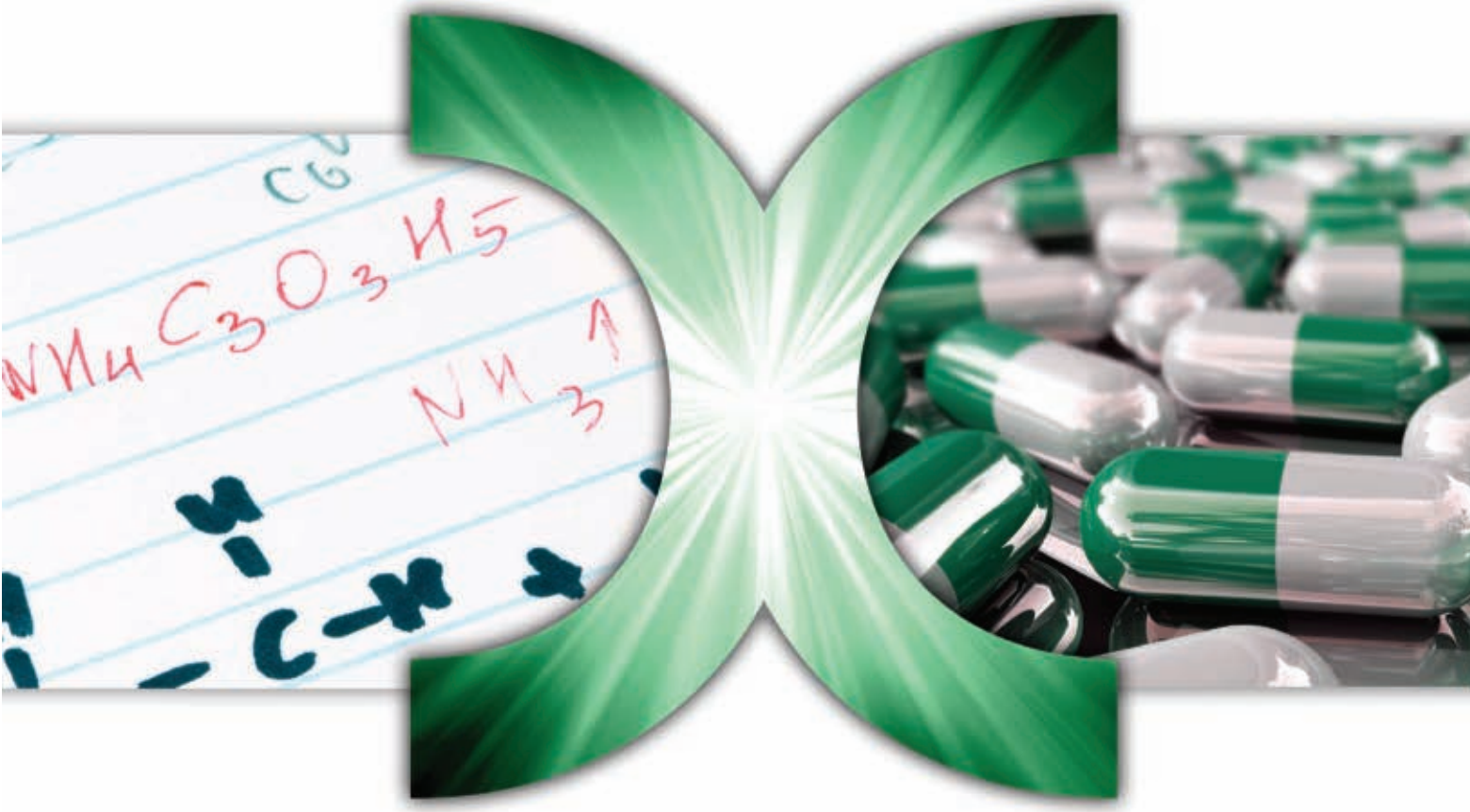

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Market News and Trends

Altair Therapeutics Reports Successful Phase I Study of Inhaled AIR645

Altair Therapeutics, Inc., a privately held biopharmaceutical company developing novel therapeutics for respiratory diseases, recently announced positive results from a Phase I multiple-dose safety and pharmacokinetic study of its lead product, once-weekly inhaled AIR645 in healthy adults and mild asthmatics. The results were presented by Dr. Michael Hodges, MD, Chief Medical Officer for Altair Therapeutics at the European Respiratory Society Annual Congress in Vienna.

AIR645 is a non-steroidal dual inhibitor of cellular responses to interleukin (IL)-4 and IL-13. These pro-inflammatory cytokines orchestrate the adaptive immune response to inhaled allergens and viruses and the development of chronic inflammation in asthma, rhinitis, and other respiratory disorders. The randomized, placebo-controlled trial evaluated the safety, tolerability, bioavailability, and pharmacodynamic activity of nebulized AIR645 at multiple dose levels in 32 healthy adult subjects (0.3, 3, 10, and 20 mg/dose) and 8 mild asthma subjects (20 mg/dose). Subjects were sequentially randomized (6 active: 2 placebo) and received 6 doses on study days 1, 3, 5, 8, 15, and 22.

AIR645 was safe and well tolerated. No dose-limiting toxicities or safety signals were detected in this clinical study. Adverse effects were mostly mild, and none were considered severe, significant, or serious, and no subjects were discontinued due to adverse events. AIR645 exposure in sputum was found to be dose-dependent, and no accumulation of drug was evident. AIR645 half-life in sputum was calculated to be approximately 5 days. AIR645 concentration was > 1000-fold higher in sputum than in plasma, indicating very low systemic bioavailability of the drug.

Following repeated inhalation of AIR645, evidence of anti-inflammatory biomarker activity was seen in subjects with mild asthma (those that had baseline elevations of biomarkers), including reductions in serum total IgE, sputum eosinophils, or level of 15-HETE in sputum.

"The AIR645 pharmacokinetics and distribution profile demonstrated in this study are consistent with preclinical findings and support effective once-weekly or once-daily administration of this 2'-O-methoxyethyl modified oligonucleotide in humans," commented Susan Gregory, PhD, Chief Scientific Officer for Altair Therapeutics. "We believe that IL-4Ralpha inhibition can prevent and retard asthma pathogenesis and will prove to be a valuable therapeutic approach to asthma, chronic obstructive pulmonary disease, and other respiratory disorders."

"The safety and PK data from this study underscore the potential of AIR645 as a new, safe, and effective non-steroidal anti-inflammatory control medication for asthma," added Dr. Hodges. "The dosing flexibility afforded by the projected long-tissue half-life of this drug opens the door to improved patient compliance using a once-daily inhaler or using once-weekly nebulized formulations."

"AIR645 is based upon a proprietary anti-sense molecular design, termed MOE gapmer, that greatly improves potency, stability, safety, and tolerability in vivo," said Joel F. Martin, PhD, President and CEO of Altair Therapeutics. "AIR645 is the first such MOE gapmer oligonucleotide to be administered by inhalation in man and has now demonstrated favorable safety and pharmacokinetic profiles. The results are particularly remarkable because AIR645, a low cost-of-goods drug, inhibits a target that, to date, has been approachable only by expensive biologics."

AIR645 is a dual inhibitor of IL-4 and IL-13, pro-inflammatory cytokines, which are implicated in the pathogenesis of asthma, allergic rhinitis, and other inflammatory disorders. AIR645 is a 2'-O-methoxyethyl second-generation antisense drug targeting the mRNA that encodes the alpha subunit of the human IL-4 receptor (IL-4Ralpha). IL-4Ralpha is the signaling chain that is shared by the IL-4 and IL-13 receptors and is required for cellular responses to IL-4 and IL-13. AIR645 has the potential for less frequent administration with improved local and systemic safety. AIR645 was discovered by Isis Pharmaceuticals, Inc. and licensed to Altair Therapeutics.

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Market News and Trends

to-BBB Technologies BV Will Be Used By MedImmune to Evaluate Brain Drug Delivery Mechanism

to-BBB, the Dutch brain drug delivery company, and MedImmune are starting a research program to evaluate to-BBB's proprietary G-Technology to safely deliver drugs to the brain.

Many brain diseases cannot be treated with today's disease-modifying biologics due to the presence of the neuroprotective blood-brain barrier (BBB). to-BBB's promising G-Technology is designed for safe brain delivery of different classes of drugs by formulating these drugs into proprietary glutathione-coated liposomes. The G-Technology has shown proof-of-concept in different disease models for pain, viral encephalitis, and brain tumors, based on which MedImmune will now evaluate the technology in its own pharmacodynamic models.

MedImmune, the worldwide biologics business for AstraZeneca PLC, has approximately 3,100 employees worldwide and is headquartered in Gaithersburg, MD. With an advancing pipeline of promising candidates, MedImmune aims to be the next revolutionary force in biotechnology by delivering life-changing products, industry-leading performance, and a tireless commitment to improving patient health.

"We are looking forward to working with MedImmune," said Pieter Gaillard, CSO of to-BBB "The project will be of great value to further validate our brain delivery platform and work toward therapies for devastating brain diseases."

to-BBB is a Dutch biotechnology company in the field of enhanced drug delivery across the blood-brain barrier. The company is developing novel treatments for devastating brain disorders by combining existing drugs with its proprietary brain delivery platform. The company's vision is that the treatment of currently unserved, devastating brain diseases will be best achieved by safely enhancing blood-to-brain delivery of drugs.

to-BBB is headquartered in The Netherlands at the Leiden Bio Science Park and established a fully owned subsidiary, to-BBB Taiwan Ltd., in Taipei, Taiwan.

Pancreatic & Colorectal Cancer Novel Antibody Developed From a Vaccine to Begin Phase I Trial

Neogenix Oncology, Inc. recently announced that NPC-1C, the company's first IND was granted permission by the US FDA for the company to begin a Phase I trial. NPC-1C is derived from a colorectal cancer vaccine that had previously demonstrated safety and clinical activity in prior human studies. It is a novel, monoclonal antibody intended for the treatment of advanced pancreatic and colorectal cancer.

This first human trial will evaluate the safety of NPC-1C in patients with late-stage pancreatic or colorectal cancer. Anti-tumor activity has been demonstrated in both in vitro ADCC assays and in multiple animal studies.

"The approval of our first IND for the initiation of our Phase I trial represents an important milestone toward the development of what could prove to be a breakthrough in cancer diagnostics and therapeutics," said Neogenix President and Chief Medical Officer, Philip M. Arlen, MD. "This Phase I trial will evaluate NPC-1C in 12 to 24 patients with pancreatic or colorectal cancer and should provide important additional data regarding the safety and activity of our antibody. We expect the trial to complete enrollment in approximately 6 to 8 months."

Neogenix Oncology is a cancer therapeutics and diagnostic company focused on developing innovative new products for a broad range of cancers. The company's portfolio includes monoclonal antibodies that have been shown to recognize tumor-specific immunogenic proteins derived from specific tumor subtypes. Neogenix Oncology monoclonal antibodies are unique in that they define the immunogenic tumor protein as both a diagnostic marker and as a therapeutic target for tumor destruction. This revolutionary approach could offer patients a new range of therapeutic alternatives in the future.

Founded in 2004 and headquartered in Great Neck, NY, Neogenix Oncology, Inc., is a research-driven biopharmaceutical company that develops and commercializes innovative therapeutics and diagnostics for the management of solid tumors. Neogenix Oncology's pipeline is derived in part from the Hollinshead library of clinically tested vaccines, with the potential to develop products for a wide range of cancers, including pancreas, colorectal, prostate, lung, ovarian, squamous, and others. The company conducts its research and development work in its laboratories in Rockville, MD.

Ambrx & Wyeth Form Multi-Target Alliance to Leverage Recent Ambrx Biologics Platform Advances

Wyeth Pharmaceuticals, a division of Wyeth, and Ambrx Inc. recently announced the formation of a worldwide alliance to discover, develop, and commercialize protein drug candidates for three undisclosed targets in multiple therapeutic areas. The alliance will capitalize on Ambrx's recent breakthroughs in applying its protein medicinal chemistry platform to proteins produced in mammalian cells, such as antibodies and antibody-toxin conjugates.

Ambrx anticipates earning near-term payments from an up-front commitment, target loading fees, and research funding. In addition, Ambrx will be eligible to receive escalating preclinical, clinical, regulatory, and commercial milestone payments as well as tiered royalties on sales of products resulting from the collaboration.

"This collaboration with Ambrx reinforces Wyeth's commitment to sustaining and growing our already robust capabilities in the field of biologics drug discovery through partnerships with biotech innovators," said Mikael Dolsten, MD, PhD, President, Wyeth Research. "We are enthusiastic about working with Ambrx, a company with the ability to create and advance precisely engineered biologic drug candidates into clinical trials using its proprietary platform."

"Wyeth is a long-standing leader in protein therapeutics with a strong record of successfully developing innovative products," added Stephen Kaldor, PhD, President and CEO of Ambrx. "We are pleased that Wyeth recognizes the power of the Ambrx EuCODE platform and look forward to collaborating with Wyeth's talented personnel to produce the next generation of biologic drugs."

Ambrx Inc. is a clinical-stage biopharmaceutical company with a broad biologics platform that allows it to create best-in-class therapeutics, including improved versions of native proteins and therapeutic antibodies. Its most advanced product candidate, ARX201, is a long-acting growth hormone partnered with Merck Serono that has successfully completed initial clinical trials. The company has further validated its biologics platform through additional partnerships with Merck Serono, Eli Lilly, and Company and Merck & Co. Ambrx is advancing a robust portfolio of product opportunities spanning multiple therapeutic areas that are high optimized for efficacy, safety, and ease of use.

TransPharma Announces Successful Completion of Phase II Trial

TransPharma Medical Ltd., a specialty pharmaceutical company focused on the development and commercialization of drug products utilizing a proprietary active transdermal drug delivery technology, recently announced the successful completion of the Phase IIA trial of ViaDerm-hPTH(1-34), which is being developed for the treatment of severe osteoporosis.

In June 2008, Eli Lilly and Company and TransPharma entered a licensing and development agreement relating to TransPharma's ViaDerm-hPTH(1-34) product for the treatment of severe osteoporosis. As part of this project, TransPharma has completed a 3-month Phase IIA trial for transdermal PTH(1-34). The primary and secondary endpoints for efficacy and safety were met. The safety endpoints included a skin safety endpoint for repeated dosing with the ViaDerm system. More details of the Phase IIA study results are expected to be shared during 2010 in one of the leading osteoporosis conferences. Initiation of a dose-ranging Phase IIB study to be jointly conducted by Eli Lilly and TransPharma is planned for later this year.

"We are very pleased with the results of this trial, which demonstrate remarkable progress in the use of the ViaDerm system in clinical trials," said Dr. Daphna Heffetz, CEO of TransPharma Medical. "We have met the primary and secondary endpoints of the Phase IIA trial. We are looking forward to the Phase IIB trial, and hope that in the future, we will be able to improve therapy for people suffering from osteoporosis by offering an alternative to daily injection of PTH."

TransPharma's ViaDerm drug delivery system incorporates a hand-held electronic device, 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. The company aims to develop multiple drug products through strategic partnerships with leading pharmaceutical companies and through independent product development.

Nektar Therapeutics Signs $1.5-Billion Licensing Deal With AstraZeneca PLC

Nektar Therapeutics and AstraZeneca recently announced they have entered into an exclusive worldwide license agreement for two drug development programs: NKTR-118, a late-stage investigational product being evaluated for the treatment of opioid-induced constipation, and the NKTR-119 program, an early stage program intended to deliver products for the treatment of pain without constipation side effects. Both programs were developed by Nektar, utilizing their proprietary small molecule advanced polymer conjugate technology platform.

Under the terms of the agreement, AstraZeneca will assume the responsibility for the continued development of both the NKTR-118 and NKTR-119 programs, including the initiation of late-stage clinical studies for NKTR-118. AstraZeneca expects completion of the design of the Phase III program in the near-term and anticipates filing the drug with regulators in 2013. AstraZeneca will also be responsible for global manufacturing and marketing for both programs. Under the agreement, Nektar will receive an up-front payment of $125 million for both NKTR-118 and NKTR-119.

NKTR-118 has completed a Phase II clinical trial and is being developed to treat constipation caused by the use of opioid pain products. Under the agreement, for NKTR-118, Nektar is eligible to receive up to $235 million in aggregate payments upon the achievement of certain regulatory milestones, as well as additional tiered sales milestone payments of up to $375 million if the product achieves considerable levels of commercial success. Nektar will also be eligible to receive significant double-digit royalty payments on net sales of NKTR-118 worldwide.

NKTR-119 is an early stage drug development program intended to combine oral NKTR-118 with selected opioids, with the goal of treating pain without the side effect of constipation traditionally associated with opioid therapy. AstraZeneca will continue the development of this program, including determining the appropriate opioid combinations with NKTR-118. For NKTR-119, Nektar would receive development milestone payments as well as tiered sales milestone payments. Nektar will also receive significant double-digit royalty payments on NKTR-119 net sales worldwide.

"NKTR-118 is an important late-stage program that has the potential to address a real need for patients," said David Brennan, Chief Executive Officer of AstraZeneca. "We are excited about this agreement with Nektar, as it provides us the opportunity to apply our deep knowledge and expertise in neuroscience, oncology, and gastrointestinal areas of medicine to create real value for patients. This is a good example of using externalization to enrich the company's late-stage pipeline."

"We are extremely pleased to enter into this exclusive global license agreement with AstraZeneca," added Howard W. Robin, President and Chief Executive Officer of Nektar Therapeutics. "AstraZeneca has a strong history of creating and establishing market-leading brands, which makes them the ideal development and commercial partner for our NKTR-118 and NKTR-119 programs. In addition to the promise that these potential products provide to patients, this partnership validates Nektar's successful strategy to create novel oral small molecule drug candidates with our advanced polymer conjugate technology platform."

NKTR-118 is an investigational drug candidate that combines Nektar's advanced small molecule polymer conjugate technology platform with naloxol, a derivative of the opioid-antagonist drug, naloxone. Results from NKTR-118's Phase II clinical trial will be presented at an oral plenary session of the American College of Gastroenterology 2009 Annual Scientific Meeting in October.

PPD Opens Global Central Lab Facility in Singapore

PPD, Inc. recently announced it has opened its global central lab facility in Singapore, strengthening its ability to provide biopharmaceutical clients an extensive range of customized laboratory services in Southeast Asia, a high-growth region for clinical research.

"Expanding our global central lab services into Singapore demonstrates our commitment to deliver high-quality specimens and laboratory results for our clients in a growing biopharmaceutical market," said Steve Lobel, Vice President, Global Laboratory Operations, PPD. "We can expedite delivery of lab data through reduced transportation and shipping time at better logistics costs for our clients."

PPD also has an office in Singapore, where for more than 10 years, it has provided a range of clinical development services, including clinical trial management and monitoring, patient recruitment, site identification, and regulatory affairs.

The laboratory instrumentation and standards in Singapore are identical to platforms located at PPD's global central labs in Brussels, Belgium; Highland Heights, KY; and Beijing, China. Assays are extensively cross validated among all PPD locations to produce combinable data.

The Singapore lab interfaces directly with ConneXion, the company's proprietary single global database, to ensure consistent management and real-time reporting. Clients can view and analyze laboratory results from all lab locations using PPD Clicks, a secure web site launched last year.

PPD is a leading global CRO providing discovery, development, and post-approval services as well as compound partnering programs. Its clients and partners include pharmaceutical, biotechnology, medical device, academic, and government organizations. With offices in 38 countries and more than 10,000 professionals worldwide, PPD applies innovative technologies, therapeutic expertise, and a commitment to quality to help its clients and partners maximize returns on their R&D investments and accelerate the delivery of safe and effective therapeutics to patients.

Biogen Idec Offers to Buy Facet Biotech for $356 Million

Biogen Idec Inc. recently announced it has submitted a proposal to the Board of Directors of Facet Biotech Corporation to acquire all of the outstanding shares of Facet for $14.50 per share in cash. The all-cash offer represents a premium of approximately 64% over the closing price of Facet's common stock on September 3, 2009.

In a letter to Facet's Board of Directors, Biogen Idec's President and Chief Executive Officer James C. Mullen stated that Biogen Idec believes the transaction makes compelling business sense for both companies and is in the best interests of their respective shareholders. The letter underscored that the $14.50 per share, all-cash offer represents an extremely attractive opportunity for Facet's shareholders to realize today the future value of their company. Mr. Mullen also stated that Biogen Idec believes the transaction would enable the important multiple sclerosis and solid tumor clinical programs that the companies have been working on in collaboration for nearly 4 years to have the best chance of reaching the market and improving patients' lives.

Biogen Idec and Facet have been working together since 2005 under a collaboration agreement pursuant to which they have been jointly developing daclizumab for the treatment of relapsing multiple sclerosis and volociximab (M200) for the treatment of solid tumors.

Biogen Idec's proposal is not subject to any financing contingency or approval by Biogen Idec shareholders. Biogen Idec has asked to meet with the Facet Board and its advisors and stated that it is prepared to commit all necessary resources to complete a transaction expeditiously. Biogen Idec has engaged Leerink Swann LLC as financial advisor and Wachtell, Lipton, Rosen & Katz as legal counsel in connection with the proposed transaction.

Biogen Idec's interest in acquiring Facet was first conveyed on August 17, 2009, by Mr. Mullen to Faheem Hasnain, President and Chief Executive Officer of Facet. That interest was confirmed in a letter sent to Mr. Hasnain and the Board of Directors of Facet on August 21 proposing a purchase price of $15.00 per share. The August 21 letter stated that it was very important to Biogen Idec that Facet not undertake any material commercial or strategic transactions prior to the consummation of a transaction with Biogen Idec. On August 28, Facet announced a collaboration with Trubion Pharmaceuticals, which Biogen Idec believes reduces the value of Facet, as apparently do Facet's investors, as evidenced by the 22% reduction in Facet's stock price since announcing the Trubion collaboration. As a result, a revised proposal to acquire Facet for $14.50 per share was conveyed to Mr. Hasnain in a letter sent to Facet's Board of Directors on September 4, 2009.

Biogen Idec creates new standards of care in therapeutic areas with high unmet medical needs. Biogen Idec is a global leader in the discovery, development, manufacturing, and commercialization of innovative therapies. Patients in more than 90 countries benefit from Biogen Idec's significant products that address diseases such as lymphoma, multiple sclerosis, and rheumatoid arthritis.

AVI BioPharma Presents Leading Phosphorodiamidate Morpholino Oligomer Delivery Technology

AVI BioPharma, Inc., a developer of RNA-based drugs, recently announced that Hong Moulton, PhD, Director of Discovery Research, gave oral presentations highlighting improved analogues of AVI's phosphorodiamidate morpholino oligomer (PMO) chemistry at two scientific meetings.

At the Third Intracellular Delivery of Therapeutic Molecules: From Bench to Bedside, taking place in Montpellier, France, Dr. Moulton gave a presentation, titled Targeted Gene Expression In Vivo: Cell Penetrating Peptides Make Antisense Work, as part of the session on applications of delivery systems on September 2. This conference, designed to bring together leading scientists in the field of cell-penetrating peptides and non-viral delivery systems, is celebrating the 15-year anniversary of the discovery of cell-penetrating peptides.

At the Targeted Drug Delivery Conference in Lausanne, Switzerland, Dr. Mouton will presented on Cell Penetrating Peptidomorpholino Conjugates on September 3, as part of the peptide-bases delivery session.

Both presentations focus on AVI's next-generation chemistry, peptide-conjugated PMO (PPMO), which improves delivery to nuclei of muscle cells and so is particularly applicable to drugs that work by exon skipping. With appropriate dosing, PPMO compounds restored dystrophin to nearly normal levels in skeletal and cardiac muscles in a mouse model of Duchenne muscular dystrophy without inducing toxicity or an immune response against the new dystrophin expressed. As a result, force generation and function of both skeletal and cardiac muscles were improved.

AVI BioPharma is focused on the discovery and development of RNA-based drugs utilizing proprietary derivatives of its antisense chemistry, (morpholino phosphorodiamidate oligomers or PMOs) that can be applied to a wide range of diseases and genetic disorders through several distinct mechanisms of action. Unlike other RNA-based therapeutic approaches, AVI's antisense technology has been used to directly target both messenger RNA (mRNA) and its precursor (pre-mRNA), allowing for both up- and down-regulation of targeted genes and proteins. AVI's RNA-based drug programs are being evaluated for the treatment of Duchenne muscular dystrophy as well as for the treatment of cardiovascular restenosis through its partner Global Therapeutics, a Cook Group Company. AVI's antiviral programs have demonstrated promising outcomes in Ebola Zaire and Marburg Musoke virus infections and may prove applicable to other viral targets such as HCV or Dengue viruses.

EXCIPIENT UPDATE

Ultra-Pure Chitosan: Insight on New Non-Animal Sources for Use in Advanced Drug Delivery & Cell Therapy

By: Sandrine Gautier, PhD

INTRODUCTION

Ultra-pure chitosan, a bioresorbable cationic biopolymer made of D-glucosamine and N-acetyl-D-glucosamine, is becoming increasingly used in pharmaceutical formulations, wound and hemostats, regenerative medicine, and medical devices for biosurgery (Table 1). Eatmon and Loxley recently highlighted the unique features brought by chitosan in pharmaceutical formulations, especially in drug delivery systems like tablets, micro- and nanoparticulates, and hydrogels for mucosal and vaccine delivery.[1] Chitosan is particularly well suited for the formulation of biopharma candidates like peptides, proteins, RNA, and DNA, offering unique functionalities such as mucoadhesiveness, enhanced bioavailabilty, enhanced crossing of biological barriers, bioresorbability, targeting power, and easy and robust processing into various forms.

Today, ultra-pure chitosan benefits from an extensive body of research and development in various fields, a large background in formulation and processing, a good safety profile, a large number of commercial biomedical products on the market (particularly for trauma hemostasis and wound care), and an increasing amount of clinical studies underway using various therapeutics strategies and routes of administration.

Ultra-pure chitosan is the endotoxin-free chitosan manufactured in accordance with cGMP, suitable for injectable formulations and implantable devices. It is defined by a monograph in the European Pharmacopea (for chlorhydate chitosan), and a current monograph is now in revision and will eventually be published by the USP.[2] For a supply of ultra-pure chitosan to fulfill the requirements and challenges of todays's pharmaceutical market, it should be manufactured in accordance with cGMP, in particular in accordance with the Joint IPEC-PQG GMP *Guide for Pharmaceutical Excipients*, which are intended for use in parenteral formulations published in 2006.

The traceability, reliability, and reproducibility of the source of the biopolymer are of great importance as well. Until recently, the most frequent commercial sources of ultra-pure chitosan were the exoskeleton of shellfish (shrimps, crabs) and squid. There has been extensive research in manufacturing ultra-pure chitosan from non-animal sources. Microalgae and mushroom sources have recently become commercially available, both providing outstanding quality and consistency, thus overcoming some of the drawbacks of shellfish-derived ultra-pure chitosan.[3-5]

The following highlights the features and advantages of ultra-pure chitosan of mushroom origin, and shows how it is a benefit to pharmaceutical scientists looking for innovative solutions for advanced drug delivery.

MANUFACTURING ULTRA-PURE CHITOSAN OF FUNGAL ORIGIN

KitoZyme has been granted a patent in Europe and the US, which discloses the process of manufacturing chitosan from fungal biomasses.[5] The rationale is that microscopic fungi and mushrooms contain substantial amounts of chitin as the main component of their cell walls. The process was developed starting from different fungal biomasses, in particular Agaricus bisporus, the white edible mushroom available from industrial mushroom growers that gives access to chitosan with excellent purity and tunable molecular weight in the range of 10 K to 200 K in a competitive manner.

The company has now established a fully validated GMP process for the manufacturing of ultra-pure chitosan from Agaricus bisporus that conforms with the requirements for use in injectables and implantables in an ISO7/ISO8 manufacturing facility.

A key aspect of this technology is the control of the complete production process from the mushrooms to final packaging. The selected mushrooms are grown in batches by a large European producer in controlled chambers, enabling a traceable and reproducible source of supply. Controlled growing conditions allow for tight regulation of starting culture, growth substrate, light, temperature, and humidity. All of this ensures a high consistency in the chitin and chitosan output. Another key aspect of the technology is the high purity and tight control of the molecular characteristics of chitosan, achieved using a step-by-step process with strict in-process controls.

The performance of chitosan is generally ruled by its molecular characteristics (molecular weight and proportion of remaining N-acetyl-glucosamine groups), of which the mushroom technology has proven to achieve high control. This enables pharmaceutical scientists to screen variable molecular characteristics for optimum and consistent performances, a requirement becoming increasingly important for excipients, and provides opportunities for customized specification and greater differentiation of the final formulations.

The microbiological quality is also excellent. An accelerated 6-month stability study shows that endotoxin level remains < 0.025 EU/g versus specification of < 10;

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TABLE 1

	Wound & Hemostats[4]	Biosurgery	Scaffolds & Cell Therapy[8,20-22]	Vaccine Delivery[16-19]	Drug Delivery[6,7,9-15]	Ophtalmology[9]
Application Segments	surgical wounds, traumatic wounds, burns, chronic wounds	cardiovascular, neurology, maxillo-facial, general surgery, digestive, orthopedic, urological	scaffold for cell culture, cell delivery, cell encapsulation, tissue engineering	parenteral, transdermal, oral: sublingual, nasal, pulmonary	buccal, sublingual, nasal, pulmonary, oral, ocular, vaginal	topical, intravitreal, sub-conjunctival, artificial tears
Systems	wound dressing, hydrophilic, occlusive, hydrogels, interactive wound dressings, burn dressings, sponges, films, foams	films, sponges, sealants, glues, fibres, tubes	porous scaffolds, porous films, thermosetting gels, tubes	adjuvants, hydrogels, solutions, microparticles, nanoparticules, preservation	microparticles, nanoparticles, hydrogels, films, dressings, tablets…	viscoelastic solutions, nanoparticles, inserts

yeast and molds remain < 10 cfu/g versus specification of < 100; and viable aerobic count remains < 10 cfu/g versus specification of > 100.

The safety and equivalence of fungal origin ultra-pure chitosan compared with shellfish ultra-pure chitosan was proven in different formulations and therapeutic strategies, for instance for the manufacturing of nanoparticles[6-7] and the manufacturing of tubes and fibres.[7,8]

SUMMARY

The availability of ultra-pure GMP chitosan of fungal origin will trigger new developments of chitosan-based pharmaceutical and biomedical applications beyond topical use. Not only is it substantially equivalent to animal-derived chitosan, it also meets or exceeds pharmacopeial monograph specifications. Its 100% animal-free process and outstanding consistent characteristics makes it easier to bring a product to the market. With all the advantages of this new ultra-pure chitosan in hand, innovative drug delivery, cell therapy, and pharmaceutical companies should be keener to take a closer look at the performances of chitosan-based systems.

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BIOGRAPHY

Dr. Sandrine Gautier, through her varied and international professional experience, has gained a multidisciplinary expertise in the field of polymers and polymeric biomaterials, particularly in controlled-release systems, ophthalmology, and tissue engineering. Her interest in biopolymers and the development of renewable resources led to her joining KitoZyme in June 2002 as Product Development Manager. Since April 2008, she has been managing the Business Development team, valorizing the know-how, intellectual property, and technological platform of KitoZyme into partnerships and business ventures on the four target markets of KitoZyme: nutraceuticals, cosmetics, beverage treatment, and biomedicals (drug delivery and medical devices). Dr. Gautier earned her BS in Chemical Engineering specializing Polymer Science (National Institute of Applied Sciences, Rouen, France) and her PhD in Polymer Science (Research Center on Artificial Biopolymers, University of Montpellier 1, France).

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The New World: Life After the Great Recession

Part V of a Six-Part Series

By: Derek G. Hennecke, MBA

At 4:30 AM on January 17, 1994, the young lady awoke to a 20-second earthquake that measured an unprecedented 6.7 on the Richter scale. Half-asleep and without thinking, she did what apparently every southern California elementary school child knows to do, which is to move to the doorway and stay put until the world stops shaking.

Large chunks of ceiling tumbled down on either side of the doorway, but the moment passed. Later, residents of the building would learn the structure had sagged grossly to the left and jumped its foundation. The porch was now 4 feet higher and 5 feet to the right of the front door. But then, in the dark, she fumbled to her door only to realize the building had shifted and the door wouldn't open. She would have to improvise.

In bare feet and pajamas, she navigated through a toppled kitchen to a smashed bathroom, removed the broken glass slats from the old-fashioned window, and climbed through to safety.

There is an acute and chronic phase to every crisis. In the acute phase, it's the simple rules that get you through. You hope you can recall past lessons, you hunker down, and you try to survive. You emerge to find the world has changed. You couldn't have prepared - the rules are different. This is the chronic phase. You adapt.

The earthquake is the analogy my Marketing Director used from her personal experience. For us at Xcelience, the acute phase of this recession hit in October. Like much of the corporate world, my management team and I sat, white-knuckled at the helm, while the economy shuddered and shook.

In hindsight, it's dead clear what happened. The investment firm Fairmont Partners wrote in its June assessment that in the past few quarters, the economy caught a cold, the drug development industry got a bad flu, and as for the CRO industry, "…well," the June Outlook laments, "let's not pursue the analogy any further."

The credit crisis froze out much of the biotech industry, existing clients began canceling orders or delaying indefinitely. Our sales force wrote quote after quote, but few clients had a project they were ready to move on.

We spent hours fine-tooth combing our every decision. Had we done something wrong? Was it just the economy? Was it us? Surely an earthquake of this magnitude couldn't just be a recession. In time though, we learned the entire industry had been hit. Our own strategy was not misguided. The CRO industry is a derivative one. Our revenue flow comes completely from the demand coming from drug development. That means we can do a lot of things like adding service offerings and improving sales, but we can't create demand like, for example, Apple can.

Some of my more silver-haired colleagues reassured me that recessions dip and turn, and so too would this one. But knowing so in your head isn't comforting when the latest plunge in the market still has your stomach tied up in knots.

We worked harder. We tried to work smarter. We cut costs - from the minutiae of buying BJ's coffee instead of the coffee service, to a 10% cut in management pay - a step we took to avoid lay-offs, which we were determined to avoid doing. But no amount of cost cutting will help when the demand isn't there. Almost all of our costs are fixed salaries, which don't fluctuate with demand.

Somehow we hunkered down through the worst of it, without dipping into our reserves and without big lay-offs. Several long-term clients stuck with their projects throughout. When we were singled out as a finalist for the local Chamber of Commerce Business of the Year award, I was reminded of something I had read, "Flat is the new up."

As spring came, we began to see a slight resurgence in our client

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market. A few weeks later, the broader market statistics bore it out. Our orders and our spirits fell and rose approximately 2 to 4 weeks ahead of the Dow Jones Industrial Average throughout the recession. June was the strongest month in sales we've experienced in the past year, and July was firm and confident. August has the potential to be another record month.

I'm declaring the recession over. Like many of my CEO colleagues, I'm nervous and a little scared by this roller coaster of an economy, but I'm also confident the worst is well behind us, and the future is bright. Our plant is running near capacity, and we are using overtime. We have begun hiring modestly. Whether it will be a U-shaped recovery or a V remains to be seen, but history does offer some insights as to who will be the quickest to recover within the industry.

The last major downturn for CROs came in 1999. In that recession, large pharma brought work in house when they saw the large turnover of staff at CROs. Amongst the CROs themselves, the large diversified CROs did not fare as well as smaller, focused pure-play companies.

This makes sense. In the larger companies, managers are made to live or die by quarterly results. This is the nature of reporting to a large body of shareholders. They are forced to execute lay-offs to raise the bottom line for the quarter, but when business comes back, they face the lag time of having to scout, hire, and train again. Smaller companies are more often private and tend to have more tightly-woven personal relations among much smaller shareholder groups - they are more able to overlook a bad quarter or two for longer-term benefit.

I don't want to paint with too wide a brush - there are some notable exceptions to this observation about large versus small. Quintiles and Covance are examples of two large CROs who are known for using long-term growth strategies, and both companies have weathered the storm better than others. So, as we dust ourselves off from the Great Recession and pick up the pieces of our sanity - will we find that the world has changed forever as so many claim?

I believe not. I don't see any radical change yet. I see sound business practices as always separating the winners from the losers in the face of market adversity. But within that context, there are still new trends developing, as always, and the following are some of the trends I am watching most closely today.

The Structural Increase In US Large-Scale Commerical Manufacturing Capacity: In the next few years, as large pharma works through its recent mergers, they will be freeing up considerable capacity for commercial manufacturing. The drive to reduce costs throughout the past few quarters is further freeing capacity. We are also very likely to see new entrants from Asia. These new players will be looking for a guaranteed large pharma revenue stream and a US base of operations. All this increased commercial manufacturing capacity bodes poorly for CMOs. But for drug developers, this is good news - increased capacity means lower prices. This is yet another reason not to lock in with a one-stop shop now - those who do will wind up paying today's prices for work that will almost certainly be cheaper in the future.

The Triumph of Ethics: A good recession flushes out the sludge of mankind - the Bernie Madoffs - but sometimes it also reveals the best. Medarex CEO H. Pien was selling his company to BMS. As CEO, obviously he knew about the sale in advance. That's why he's considered an insider, and as such, his shares are traded differently so they won't reflect any inside knowledge. He had set up a schedule ahead of time to sell shares on a regular predetermined basis throughout the year. Still, by a strange loophole, it would have been within the letter of the law for him to withdraw this schedule at any time. He chose the high road and did not withdraw the schedule, to his own personal detriment. He lost $250,000, but gained a priceless quotient of respect and reputation. Here at Xcelience, we have always believed in putting our principles first. We will find creative solutions to help a client save money, but we will never cut corners and compromise a molecule's chances of success. Some of our competitors take these risks on a regular basis, and while they took some business from us early in the recession with lower prices, I'll admit to a touch of glee that those clients are coming back to us now.

Biotech Increasingly Partners with Large Pharma: Is your small biotech aiming to take its own drug all the way to commercial? Odds are it's not going to go all the way alone. What biotech firms need is lots of money, and large pharma has it. What large pharma needs is promising new drugs, and small biotech has them. Biotech will not be able to get most of its money from venture capitalists anymore. They will need to partner with large and mid-size pharma. Investment banker Leerink Swann recently reported that the average 1-day premium for biotech acquisitions was an overwhelming 84.2% in 2008 after averaging just 28.7% from 1999 to 2007. Most of this premium is being paid to the smaller companies like Medarex (90% by BMS). Genentech received only 16%. So if you work for a small biotech, your CEO and his or her backers are more and more likely to sell the product or company before you have to produce at large scale - it's simply the fastest way to get the molecule to man in the current market.

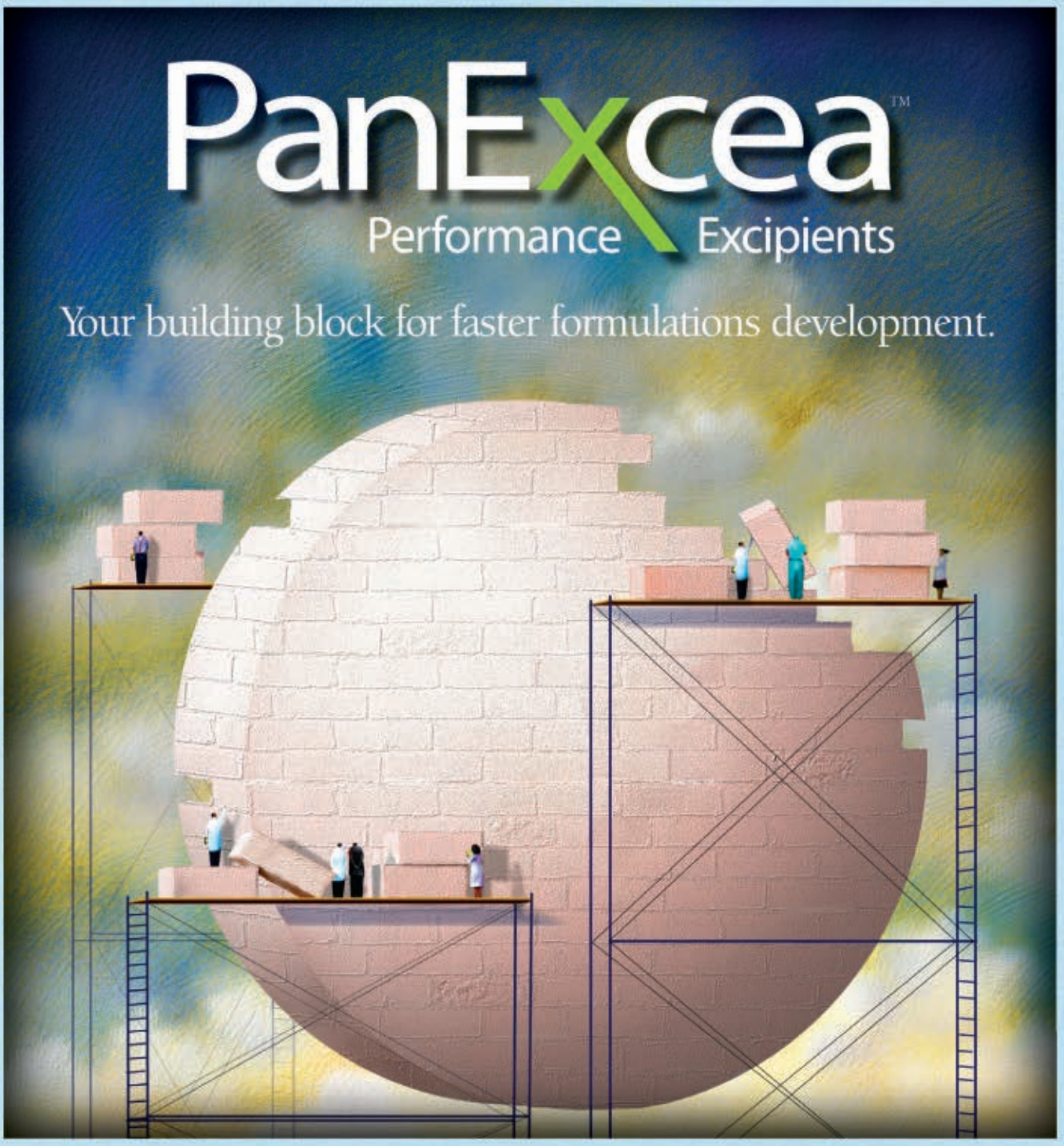
The Disappearing Employee: Right now, my desk is thick with great resumes from competitors who have lain off staff. As I said before, we are proud not to have had to make any large-scale lay-offs of employees. As well as affecting morale, it would've cut capacity, and now that business is coming back, we are running at or near capacity much of the time - something we couldn't have done if we'd laid off. I'm hiring now because the pipeline is beginning to fill up again, but also because I don't believe this wonderful labor pool is going to last. Am I the only one who sees this? Employees throughout the past few months have been burnt. If they haven't lost jobs outright, they probably felt they were staring over the precipice, waiting to take the fall. People are in shock and don't want to work for big companies anymore, where they're just a number that can be hacked at any moment for the sake of the bottom line. When jobs become more plentiful, look for a labor pool that's pickier - they will want to work for and with people they know and trust. I hope our loyalty to our staff throughout this crisis will help us on that front. Successful companies in the face of this hiring trough, which is going to be a lot harder than the 2006- 2007 drought, will be those who are transparent with their employees about what's going on in the company and encourage communication between management and employee and employee and client. This is the age of Twitter - when people feel what they do and say should matter.

Each of these trends is just a small part of the fabric of the new world to which we must adapt. I will say it again though - this is not a radically different world brought on by the recession. It is the same constantly evolving world it's always been. And you know what? The same laundry list of actions that got you through all the other hard times is all you really need to adapt to the new times, provided you are aware of these and other trends and using them to your advantage. Just apply good hard work, cost efficiency, service your client, and stick to your principles. The rest will follow. ◆

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).



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BIOAVAILABILITY ENHANCEMENT

Eligen® Vitamin B12 & the SNAC Carrier for Oral Delivery

By: Nicholas J. Hart, MBA

INTRODUCTION

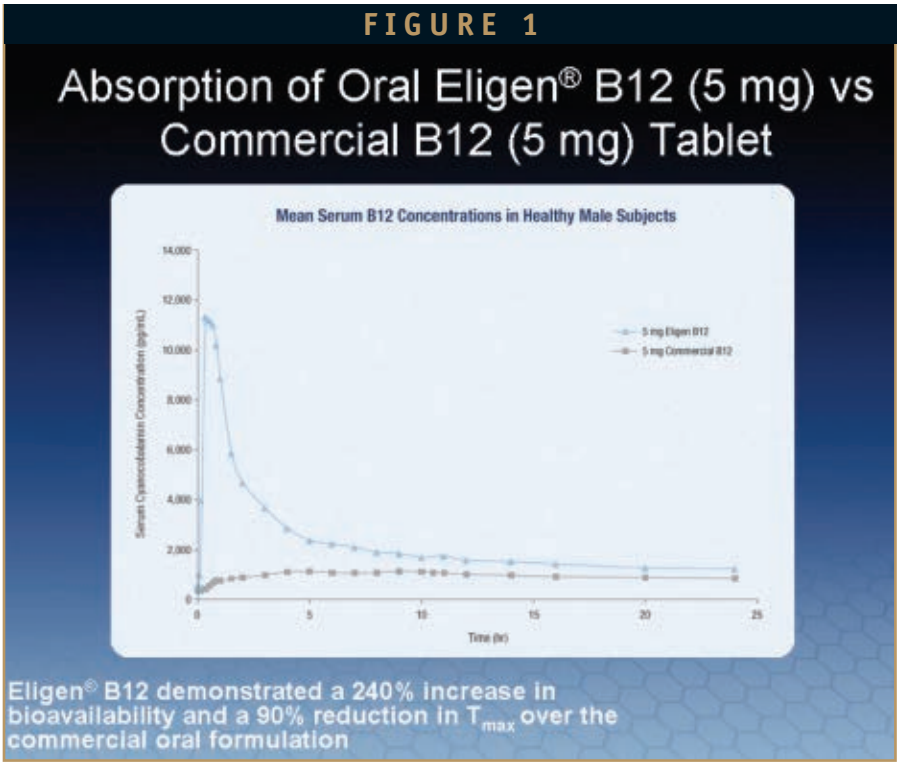
Emisphere Technologies is a biopharmaceutical company based in Cedar Knolls, NJ, that focuses on a unique and improved delivery method for therapeutic molecules and nutritional supplements using its proprietary drug delivery platform, the Eligen® Technology. The key benefit of Eligen Technology is that it improves the ability of the body to absorb small and large molecules with poor oral bioavailability, many of which are currently delivered by injection. The Eligen Technology can also be applied to routes of administration other than oral, such as buccal, rectal, inhalational, intra-vaginal, or transdermal. Based on the promise of this technology, Emisphere currently has agreements with Novartis Pharmaceuticals for oral delivery of salmon calcitonin combined with an Eligen carrier for the treatment of osteoarthritis and osteoporosis, and with Novo Nordisk for the oral delivery of a GLP-1 analogue for the treatment of type 2 diabetes.

ELIGEN® VITAMIN B12 & THE SNAC CARRIER

Emisphere has more than 4,000 carriers, 2,500 of which are covered by existing patents and patent applications. One such carrier; Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate (SNAC) has recently been reviewed by an independent panel of scientists and will soon be available for use in the US market in combination with nutrients added to food and dietary supplements to improve their bioavailability.

The company plans to commercialize its Eligen Technology in 2010 since it achieved Generally Recognized as Safe (GRAS) status for SNAC in the US in July/August 2009. GRAS status establishes the SNAC carrier as exempt from pre-market approval. The technology provides a

FIGURE 1



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platform for combining SNAC, the first commercially available Eligen carrier, with other substances, such as vitamins and nutrients. The initial combination for commercialization will include vitamin B12 with SNAC and will be known as Eligen B12.

Vitamin B12 delivered through injection is an effective and tested cure for patients suffering from a deficiency of the vitamin. Treatment schedules vary widely but usually consist of initial loading doses followed by monthly maintenance injections. There are, however, a number of challenges associated with injections. They are inconvenient, require physician office visits, and can be painful. Further, there is a potential for injuries (needlesticks) and infections. As a result of these compliance drawbacks, patients may not receive the proper amount of B12 at the times they should. In addition to injections, vitamin B12 supplements are available in tablet form. While convenient to take, only a fraction of the supplement can be absorbed orally through current pill formulations, and in some cases in patients with absorption problems, almost no vitamin B12 is absorbed.

There is a large market in both types of B12 units: tablets for oral supplementation and maintaining adequate serum levels (550 M US and 3B+ ex US); and injections for treatment (30 to 40 M US and 220 M ex US). The competition in the B12 marketplace exists in two forms. The injectable market, in which injections of B12 are given to treat deficiency, takes the form of a typical generic prescription pharmaceutical market where non-branded, established products are sold on the basis of lowest cost or are sold in conjunction with a manufacturer's other products for efficiencies in pricing. The non-injection B12 market (tablets, patches, nasal sprays, buccal, etc) more closely mimics the vitamin supplement market where products are sold on the basis of cost (low cost, high volume) or are sold on the basis of absorption, efficacy, or some other additional health benefit. Eligen Technology is based on increasing the bioavailability of difficult-to-absorb compounds and by circumventing the current absorption process. Eligen B12 is well suited to compete in both arenas. It is as bioavailable as the injection, yet has the sustainable advantage of being delivered orally in tablet form.

RESEARCH STUDY RESULTS

In a study involving healthy volunteers presented in March 2009 at the American Society of Clinical Pharmacology and Therapeutics Annual Meeting, Eligen B12 as compared to standard commercial vitamin B12 demonstrated a tenfold increase in peak

FIGURE 2

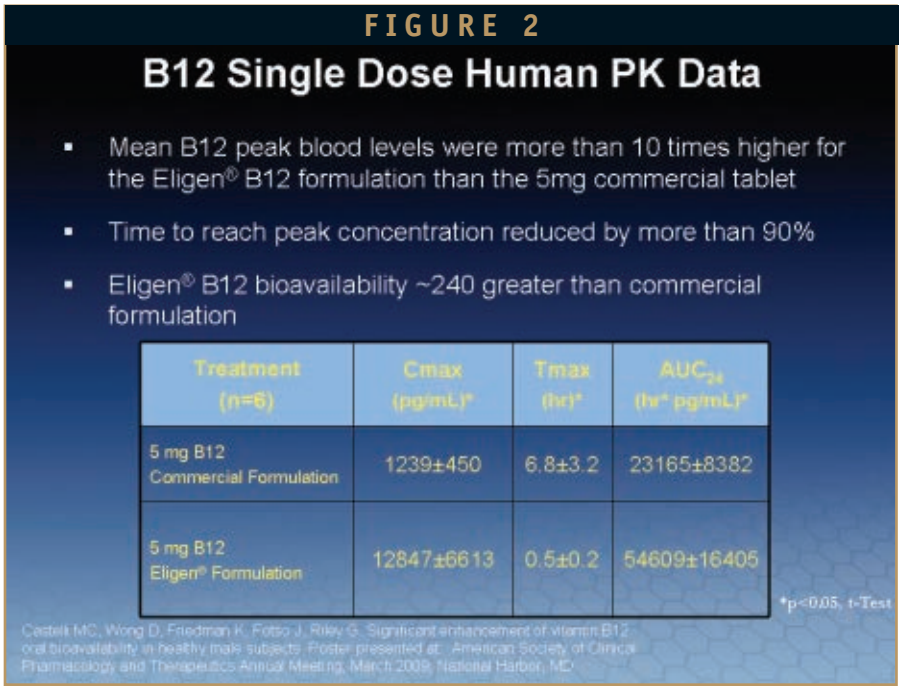


FIGURE 3

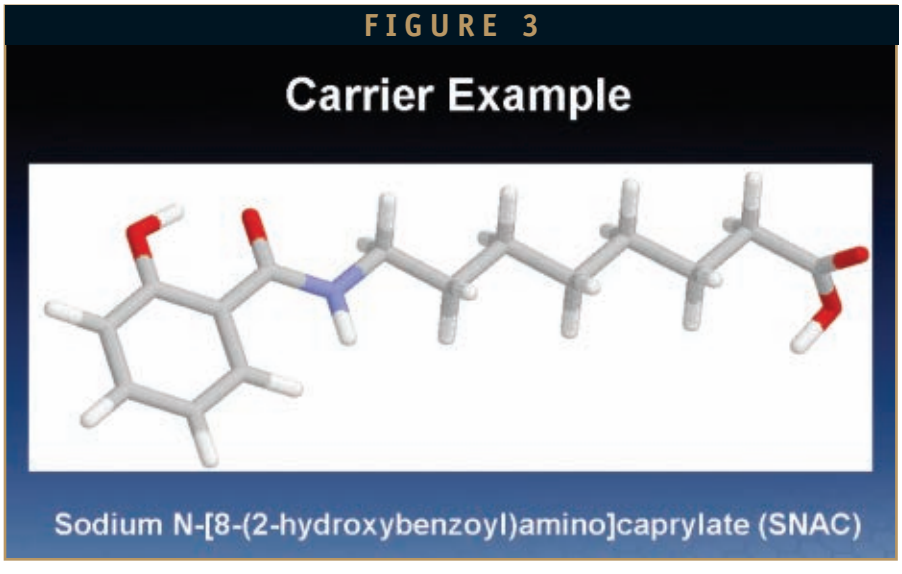
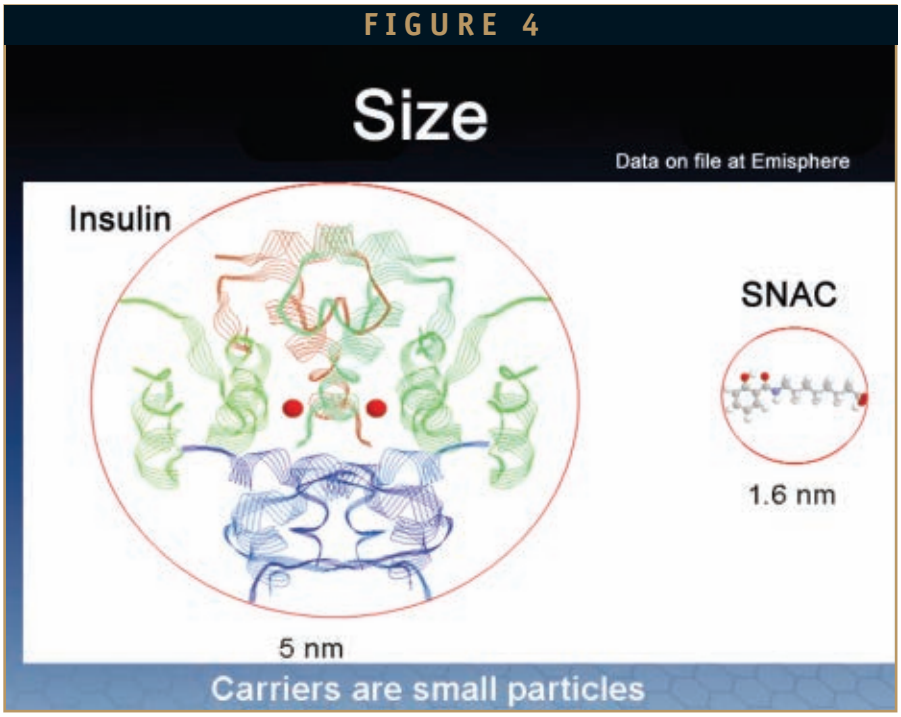


FIGURE 4



serum concentration of vitamin B12 (12847 pg/mL versus 1239 pg/mL), a 240% higher AUC (54609 pg/mL versus 23165 pg/mL), and a decrease in Tmax of 90% (0.5 hr versus 6.8 hrs).

WHY START WITH ELIGEN® VITAMIN B12 USING THE SNAC CARRIER?

Emisphere has two important goals in bringing Eligen B12 to the market. The first is to commercialize its advanced technology, and the second is to maximize the value of Eligen B12 first in the US and then worldwide. It is clear there is a place for this product and technology, and Emisphere is poised to fill a very large unmet need in the market. Eligen B12 has the potential to help millions of individuals who have trouble with vitamin B12 absorption or who just want to know they are getting the appropriate amount through supplementation.

The company's strategy for choosing the vitamin B12 market as its entry point to commercialization is that vitamin B12 is notoriously difficult to absorb, and its deficiency can lead to significant health-related problems, one of the most serious and common is pernicious anemia. Other health problems associated with B12 deficiency include fatigue, weakness, loss of appetite, and if left untreated for some time, progressive neurological degeneration starting with numbness and tingling in the hands and feet and leading to neuropathy, confusion, and dementia.

Additionally, the risk of B12 deficiency increases with age, those over age 60 are at significant risk, due to a decrease in the production of intrinsic factor (a protein synthesized in the parietal cells of the stomach) and is also associated with many exogenous influences that are increasing prevalent today. Some factors influencing B12 absorption, and in many cases deficiency, include gastric ailments like Crohn's and Celiac disease, chronic intake of pharmaceuticals to treat other conditions like proton pump inhibitors, diabetes medications, etc, as well as gastric bypass surgery and chronic alcohol intake.

The choice to use SNAC as the carrier with vitamin B12 derives from the fact that Emisphere has had a great deal of experience with this carrier having used it for many years in combination with various other pharmaceutical compounds. Because of this previous work with SNAC and pharmaceutical compounds in both animal and human work, there exists an abundance of toxicology and other safety data paving the way for a comprehensive review package. Additionally, the physical characteristics of SNAC and those of vitamin B12 are aligned in such a way as to facilitate a simple mixture of the two and ultimately demonstrated efficiency of delivery of vitamin B12.

SNAC DEVELOPMENT PROCESS & MECHANISM OF ACTION

The mechanism through which SNAC facilitates the absorption of its partner molecule is believed to be a passive transport mechanism (ie, not receptor-mediated). Absorption of a substance following ingestion is determined largely by the physicochemical properties of the substance itself, such as molecular weight, solubility, pKa, and lipophilicity, as well as its ability to withstand the harsh chemical and biological environment within the gastrointestinal tract.

For substances lacking the properties required for efficient oral absorption, SNAC, when combined with the target substance, forms a weak, noncovalent complex that enables absorption of the target substance while preserving its chemical integrity.[1] Studies have shown that these carriers enable systemic absorption primarily via transcellular pathways, without compromising the integrity of the intestinal epithelium.[2-5] A benefit of transcellular absorption is that it allows for the target molecule to be absorbed, while other molecules in the surrounding area, the absorption of which may be unwanted or even dangerous, are not as easily absorbed.

The association between the carrier and the target substance is thought to cause partial unfolding of proteins, thereby exposing hydrophobic residues and causing an increase

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in the lipophilicity of the target molecule, facilitating transport across cell membranes.[6] Other actions of Eligen carriers that contribute to the protection of the target substance in the gastrointestinal environment include buffering of the local pH in the stomach and inactivation of digestive enzymes, such as pepsin and chymotrypsin. Due to the weak association between the carrier and the target substance, the interaction reverses spontaneously with dilution upon entering the systemic circulation.

SUMMARY

With the publication of two studies in the July/August issue of the International Journal of Toxicology describing the toxicology of SNAC, Emisphere's SNAC achieved GRAS status for its intended application in combination with nutrients added to food and dietary supplements. Because there is such a heightened interest in increasing the bioavailability of some difficult-to-absorb compounds, including some vitamins and nutrients, Emisphere has been approached by several nutritional supplement, general health, and food companies to assess the likelihood of success in combining various nutritional compounds with SNAC or other Eligen carriers. Success in this instance is determined by increasing the bioavailability of the target compound.

Emisphere's Eligen Technology will be commercialized with the first application being SNAC used with vitamin B12; Eligen B12. In addition to using SNAC with B12, it is likely that it may also be used with other vitamins and nutrients that are difficult to absorb. This can happen with Emisphere's own proprietary products or in conjunction with partnerships with other nutritional supplement, general health, or food companies. Emisphere is poised for increasing use of its technology, which will have the potential to help many companies and, with an increase in bioavailability and a decrease in the need for some injections, will potentially aid millions of patients worldwide.

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BIOGRAPHY

Nicholas J. Hart serves as Emisphere Technologies' Vice President of Strategy and Development, responsible for planning all company commercial development, including Emisphere's Eligen® Technology. He has significant launch experience at manager, director, and therapeutic area levels. Mr. Hart is the former Leader of the Contraception Therapy Area and Executive Leadership Team member at Organon, part of Schering Plough Corporation. Also at Organon, he served as Senior Director/Executive Director of Marketing of the Women's Healthcare Franchise; Director of CNS Marketing, and Associate Director of Specialty Products. Prior to Organon, Mr. Hart held various marketing and sales positions with Novartis, Sankyo Parke Davis Pharmaceuticals, and Bristol-Myers Squibb. Mr. Hart is a graduate of West Point and earned his MBA in Finance, International Business from New York University Stern School of Business.

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Dendritic Polyguanidilyated Translocators for Ocular Drug Delivery

By: Chandrasekar Durairaj, PhD, and Uday B. Kompella, PhD

ABSTRACT

Drug delivery to the eye is challenging due to the presence of various permeability limiting biological barriers. These barriers, in addition to reducing the extent of drug delivery to the anterior segment, severely limit the treatment options for treating diseases of the back of the eye. However, with the discovery of novel materials and delivery systems, there is hope for enhanced ocular drug delivery. Dendrimer-based delivery systems in particular have gained popularity in recent years due to their nano-size, monodispersity, and abundance of surface functional groups that facilitate drug loading and/or targeting. The following describes a novel class of polyguanidilyated dendrimers capable of membrane translocation as well as drug solubilization and discusses their potential for enhancing ocular drug delivery.

INTRODUCTION

Although scientific advancements are identifying new molecular targets and therapeutic agents for treating various diseases of the eye, the biological membranes remain as key barriers for drug delivery to the intraocular targets. Novel materials and delivery systems are currently being investigated for their ability to overcome the membrane barriers that limit drug delivery. Dendrimers belong to a novel class of drug carriers that can potentially enhance transport of drugs across various cellular barriers.[1] Dendrimers are hyperbranched polymers capable of encapsulating various drug molecules through electrostatic, hydrophobic, or hydrogen-bonding interactions.[2] Further, the numerous functional groups available on the surface of dendrimers can be utilized for conjugating ligands for target-specific drug delivery.[3,4] Dendrimers with innovative chemical architectures based on poly(amidoamines) (PAMAM), poly(ethyleneimine) (PEI), amino acids, and peptides offer various advantages.[1] This following discusses the drug delivery and membrane translocation potential of non-peptide, polyguanidylated dendritic structures that were designed and synthesized in recent years.[5]

CHEMISTRY OF DENDRITIC POLYGUANIDLYATED TRANSLOCATORS (DPT)

Synthesis of a DPT involves a two-step approach.[5] The first step involves synthesis of a precursor containing three guanidine groups starting from a core of tris-(hydroxymethyl) aminomethane as shown in Figure 1. The second step involves coupling of the precursors to a core molecule. Coupling of two units of the precursor to 3,5-diethoxycarbonylbenzoic acid derivative results in a g6 dendrimer containing six guanidines (Figure 2a). The nomenclature for DPTs is different from the conventional dendrimers in that g stands for guanidine group and the number six stands for the number of guanidine groups. By coupling three units of the precursor to a derivative of tris-(hydroxymethyl) aminomethane yields a g9 dendrimer containing nine guanidines (Figure 2b). For a g9 dendrimer, a different core is used compared to g6. Thus, the conventional nomenclature of G0➤Gn, where n indicates generation of the branches on the same core molecule is inappropriate for DPTs. Similar to g6 and g9, a g12 dendrimer (Figure 2c) can be prepared from four precursor units. The end group in the core of g6,

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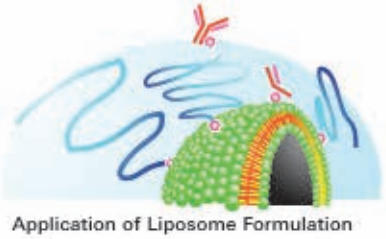

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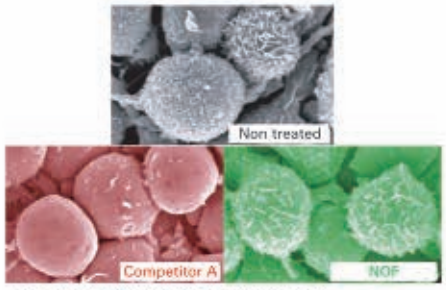

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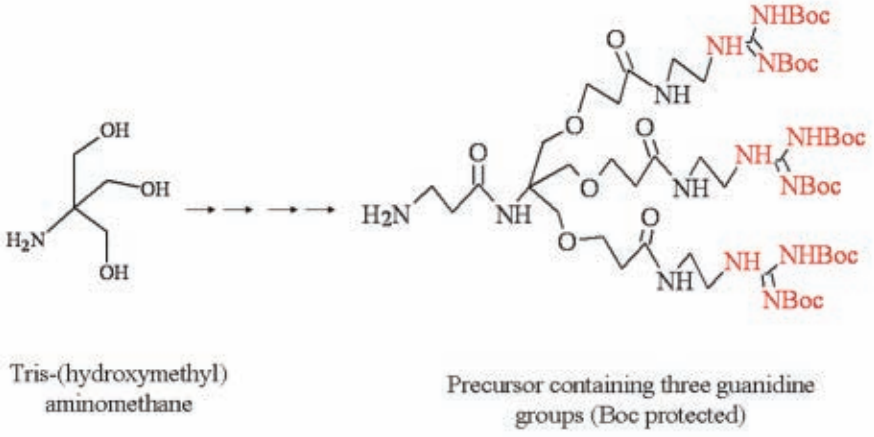
g9, and g12 dendrimers can be capped with acetyl group or derivatized with a trackable fluorescein moiety. The advantage of DPT architecture is its flexibility and steric features that can be potentially exploited for drug delivery.

EFFICIENT UPTAKE OF DPT DENDRIMERS BY CELLS

Cell uptake studies in HeLa S3 cells indicated efficient uptake of fluorescent g3, g6, g9, and g12 dendrimers. Fluorescence activated cell sorting (FACS) analysis showed a concentration-dependent linear increase in the percent uptake of these dendrimers into HeLa S3 cells.[5] Of the dendrimers tested, g6, g9, and g12 dendrimers exhibited enhanced uptake, indicating that a minimum of six guanidine groups are needed for efficient cellular uptake. Uptake patterns observed for these three dendrimers were similar, suggesting that six guanidine groups are sufficient to achieve excellent translocation in this cell line. Dose-dependent uptake of fluorescein conjugated g9 dendrimers revealed that the half-maximal concentration for cellular uptake was 1.5 ± 1 micromolar after 4-hr incubation in HeLa S3 cells. Further, results from time-course FACS and deconvolution image analysis confirmed similar translocation efficiency for fluorescein conjugated g9 dendrimer and fluorescein labeled Tat peptide (Figure 3). Finally, the cytotoxicity tests confirmed non-toxic nature of g9 dendrimer up to 50 micromolar following 4-hr treatment, indicating the potential safety of this class of dendrimers.

FIGURE 1



Synthesis of a precursor containing three guanidine groups for the preparation of dendritic polyguanidylated translocators.

DPT DENDRIMERS DELIVER MACROMOLECULES ACROSS CELLULAR BARRIERS

To overcome current limitations in ocular drug delivery, a carrier should deliver the payload (either small molecules or macromolecules) across biological barriers. In order to explore the potential of DPT in delivering protein molecules, g3, g6, and g9 dendrimers were conjugated to a green fluorescent protein mutant (GFPcys) containing an N-terminal cysteinyl green fluorescence protein preceded by a hexa-histidine C-terminal tag.[5] Further, a Tat (49-57) peptide tagged with GFP and plain GFP were used as controls for comparing the translocation efficiency of DPT dendrimers. FACS analysis indicated that up to 75% of GFP conjugated g3, g6, and g9 dendrimer entered HeLa S3 cells at the end of 4-hr incubation (4 micromolars), while GFP alone did not enter the cells to a significant extent. Further, FACS analysis of cellular uptake at different doses indicated similar uptake for GFP-g9 dendrimer and GFP-Tat peptide. These results suggest efficient translocation of GFP-DPT dendrimer conjugates similar to the Tat conjugates. Thus, DPT dendrimers can potentially be used to deliver macromolecules across biological barriers.

CHALLENGES & OPPORTUNITIES IN OCULAR DRUG DELIVERY

Topical administration of eye drops, the most commonly used route for treating anterior segment eye diseases, has the disadvantage of very low bioavailability (typically less than 5%) due to rapid eye drop drainage and short corneal contact time.[6] The cornea is the main biological barrier for topical drug delivery to the anterior segment of the

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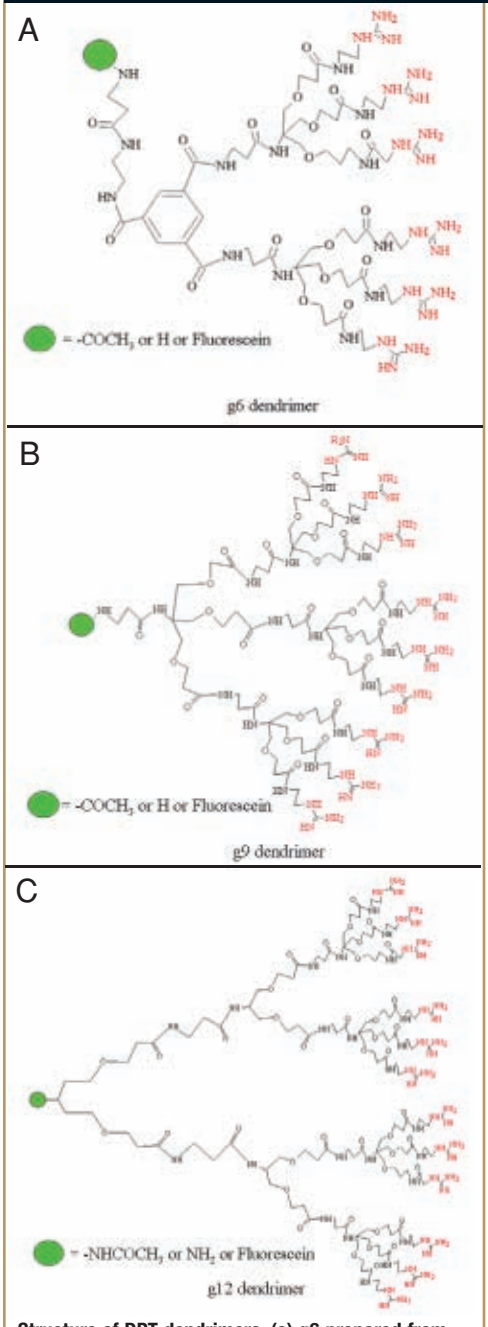
FIGURE 2A-C



Structure of DPT dendrimers. (a) g6 prepared from two precursor molecules, (b) g9 prepared from three precursor molecules, and (c) g12 prepared from four precursor molecules. The end group (shown in green) can be a free amino group for coupling with other molecules, acetylated to prevent interactions, or attached with a fluorescent molecule to enable tracking of the dendrimer.

eye. It is made up of three key layers, including epithelium, stroma, and endothelium. The superficial layer of corneal epithelial cells have tight junctions that hinder transport of hydrophilic molecules, with transport efficiency reducing significantly beyond a molecular size of 500 Da.[7] Stroma is a fibrous tissue composed mostly of water and collagen fibrils, and the corneal endothelium is a monolayer of cells with large intercellular junctions. Literature analysis clearly indicates that corneal epithelium is the principal barrier for drug delivery to the anterior segment of the eye.[8] If DPT dendrimers enhance corneal epithelial uptake of drugs similar to what is observed in HeLa cells, they would be beneficial in enhancing drug delivery to the anterior segment of the eye.

From an eye drop, there is little or no access for drugs to the back of the eye. Therefore, invasive intravitreal injections are in use or under development for treating vision threatening back-of-the-eye diseases, including age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa.[9] Although intravitreal injections can deliver drug to the retina for effective therapy, low molecular weight drugs as well as macromolecules exhibit short half-lives, ranging from a few hours to a few days, necessitating the development of long-term delivery approaches that are less invasive to the eye globe.[10] Due to the high incidence of adverse effects encountered with systemic administration and the invasive nature of intravitreal injections, transscleral drug delivery is a potentially safer alternative to treat posterior segment diseases.[11-13] Further, transscleral routes, such as subconjunctival and sub-tenon routes of administration, result in higher drug levels in the tissues of the posterior eye when compared with topical drops.[14] We have recently demonstrated that a single subconjunctival injection of carboplatin-loaded PAMAM dendrimer nanoparticles effectively treat transgenic murine retinoblastoma with no associated toxicity.[15] With the advantages of high cellular uptake and efficient translocation efficiency, DPT dendrimers are promising delivery systems for transscleral delivery. However, additional studies will be required to determine whether DPT dendrimers offer a similar or greater advantage in transscleral delivery of anticancer agents.

IDEAL CHARACTERISTICS OF OCULAR DRUG DELIVERY SYSTEMS

Some of the desired characteristics for a topical ocular drug delivery system include the following:

- Carry a high payload of drug in physiological solution (eye drop) without any irritation and deliver a large fraction of dose per administration.
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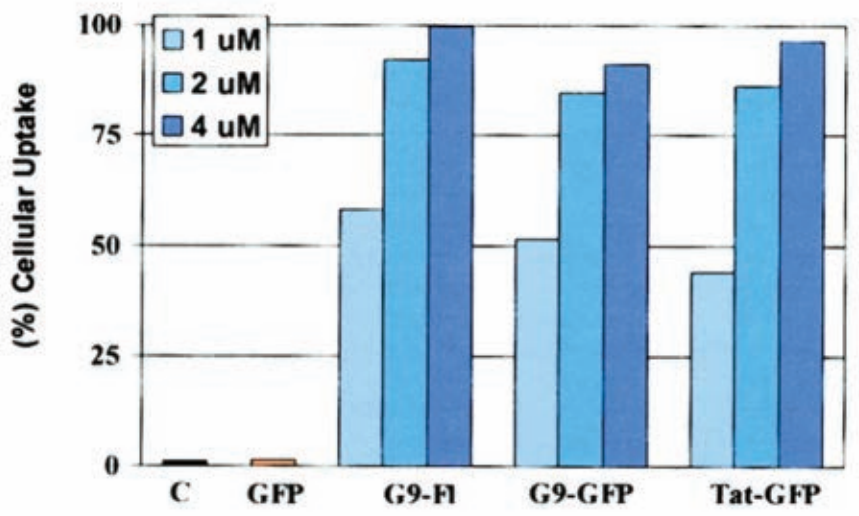
protecting it from degradation.

- Prolong the drug release, thereby reducing the number of instillations.
- Penetrate across the ocular barriers.
- Provide functional groups for coupling with targeting moieties/imaging agents/other carriers.

SOLUBILITY ENHANCING PROPERTY OF DPT G6 DENDRIMER

In our continuing effort to develop better delivery systems for effective drug delivery for treatment of various ocular diseases[16-20], we investigated the potential ability of DPT dendrimer (Visionary Therapeutics Corporation, Richmond, VA) for delivering ocular drugs. Because ophthalmic drop dosage forms require high drug solubility to deliver high drug payload in small volumes, our preliminary investigation was focused on the intrinsic property of a g6 DPT dendrimer for enhancing the solubility of three ophthalmic drugs: gatifloxacin (zwitterion), ketorolac tromethamine (negatively charged), and tropicamide (positively charged).[21] Equilibrium drug-solubility studies in the presence of 1 and 10 mg/ml dendrimer were carried out in isotonic phosphate buffer saline (pH 5.65, 6.30, and 7.37) followed by analysis by HPLC. The g6 dendrimer was highly soluble (> 200 mg/ml) at all three pH conditions and permeated completely through a 3,000 MW cut-off membrane, indicating its molecular, nano-form. The g6 dendrimer increased the solubility of all three drugs in a pH-dependent manner. The maximum solubility increase was observed for gatifloxacin (three-fold at pH 6.3) followed by ketorolac and tropicamide (two-fold at pH 5.65). Isothermal titration calorimetry studies also confirmed the > 1 stoichiometry of drug association with each g6 dendrimer molecule.

FIGURE 3



Dose-dependent translocation efficiency of the G9-conjugates. HeLa S3 cells were treated for 4 hours at 1, 2, and 4 micromolar of each conjugate and were treated for 4 hours and analyzed by FACS for cellular fluorescence. C = control cells; GFP = green fluorescent protein; G9-F1 = fluorescein-conjugated g9; G9-GFP = GFP-conjugated g9; Tat-GFP = Tat(49-57) fused GFP protein. The plot shows the average from triplicate experiments. (Reproduced from Biopolymers, Vol.76, p.87 © 2004 Wiley Periodicals, Inc., with permission of John Wiley & Sons, Inc.)

G6 DENDRIMER INTERACTS WITH DRUG MOLECULES BY IONIC, HYDROPHOBIC & HYDROGEN-BONDING INTERACTIONS

The nature of interaction between the g6 dendrimer and the ocular antibiotic gatifloxacin was investigated by isothermal titration calorimetry (ITC) and Fourier-transformed infrared spectroscopy (FTIR). Competitive ITC inhibition studies in the presence of sodium chloride (ionic interaction inhibitor) or Triton-X (hydrophobic interaction inhibitor) indicated ionic and hydrophobic interactions, respectively, between gatifloxacin and g6 dendrimer.[21] Further, FTIR studies indicated ionic interactions (between guanidine groups of g6 dendrimer and carboxylic group of gatifloxacin) and hydrogen bonding (between amide bonds in branching units of dendrimer and electronegative atoms in gatifloxacin) in the complex.

SUMMARY & FUTURE DIRECTIONS

In summary, dendritic polyguanidilyated translocators or DPTs belong to a novel class of dendrimers

useful for efficient delivery of therapeutic agents across biological barriers. These dendrimers exhibit efficient cellular uptake comparable to Tat peptide. By complexation with these dendrimers or chemical conjugation to the core, delivery of therapeutics across biological barriers can be enhanced. Our recent investigations indicated that these dendrimers are capable of enhancing solubility of low molecular weight topical ophthalmic drugs. Thus, DPTs are promising delivery systems for enhancing ocular delivery of small molecules as well as macromolecules.

ACKNOWLEDGEMENTS

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TOPICAL DELIVERY

Topical Regional Neuro-Affective (TRNA) Therapy: Novel Ground-Breaking Triptan Drug Delivery for Treating Migraines

By: Ronald Aung-Din, MD

INTRODUCTION

Current short-comings in triptan therapy for migraine may now be overcome by the concept of topical regional neuro-affective (TRNA) therapy. This novel, proprietary (European Patent No. 1 435 945, granted Febraury 2008) triptan delivery is unique in providing therapeutic benefit while avoiding both systemic and cerebral blood. Drug blood levels are unnecessary as therapeutic effect is achieved by direct serotonin agonist (triptan) action on unmyelinated cutaneous free nerve-endings below the skin surface (stratum corneum) at the back of the neck (Figures 1 and 2).[1]

There exist free nerve-endings in the skin at the upper posterior cervical region (the back of the neck at the hairline, BONATH) as components of peripheral nerves of the region. These comprise branches of cervical nerve roots, C1-C4, which constitute the tract and nucleus of the Spinal (Caudal) Nucleus of the Trigeminal Nerve System (TNS), the Migraine Generator responsible for the migraine process within the cervical cord and brainstem. Roughly estimated, there is in the order of hundreds of thousands to millions of free nerve-endings in the approximate 12- to 14-cm square area of this anatomy that feedback to the trigemino-cervical neural complex.[2-4,9]

MIGRAINE PATHOPHYSIOLOGY & NEUROANATOMY

To appreciate TRNA technology, review of migraine pathophysiology and the region's neuroanatomy is in order (Figure 3). Migraine is believed the result of neuronal hyperexcitability within TNS. TNS provides pain and sensory input from the face, head and neck, sinus cavities, and intracranial dura and vessels. Migraine may be triggered by disturbances within these peripheral TNS components with subsequent involvement of central structures, resulting in typical symptoms of an attack. Certain odors or irritants stimulating the sinuses, neck muscle tension, changes in barometric pressure, sleep loss, stress, and other triggers can precipitate migraine. As TNS and other CNS structures become involved, head pain, nausea, and light and noise sensitivity become prominent. Cutaneous allodynia or unpleasant sensations of the skin affecting the face, scalp, and back of the neck is an early indication of the start of migraine. These symptoms represent neural irritation at the cutaneous free nerve-ending level within peripheral components of TNS.[3-6]

Triptans, as serotonin agonists, are thought to treat migraine symptoms by inhibiting neural transmission to central TNS structures and down-regulating neuronal hyperexcitability within TNS. Other events include dural vascular constriction with reduced permeability and diminished chemical inflammation. TRNA therapy allows expeditious triptan TNS down-regulation through direct peripheral afferent neural input from cutaneous free nerve-endings. This feedback down-regulation of CNS efferent neural output through peripheral afferent input activation is the same as in vagal nerve stimulation (VNS) for the treatment of seizures, headache, and depression. As CNS efferent activity is modulated, clinical symptoms of neuronal hyperexcitability as seizures or migraine are reduced.[7]

In addition to that by TNS, CNS afferent input from cutaneous free nerve-endings from BONATH is provided by the vagus nerve and the sympathetic nervous system through cervical neural connections within the soft tissues of the neck via vagal and sympathetic ganglia. The result is afferent neural input from skin at BONATH to TNS and other CNS structures involved with the migraine process providing enhanced feedback attenuation of clinical symptoms. The CNS and skin are both derived from the same embryological tissue (neuroectoderm), accounting for the rich neural connections between these two areas.

From the viewpoint of mechanism, TRNA may be seen as a combination of VNS and botulinum toxin (Botox) injection. TRNA is similar to VNS in functioning through afferent neural activation. Like Botox injection, TRNA drug action takes place at the peripheral

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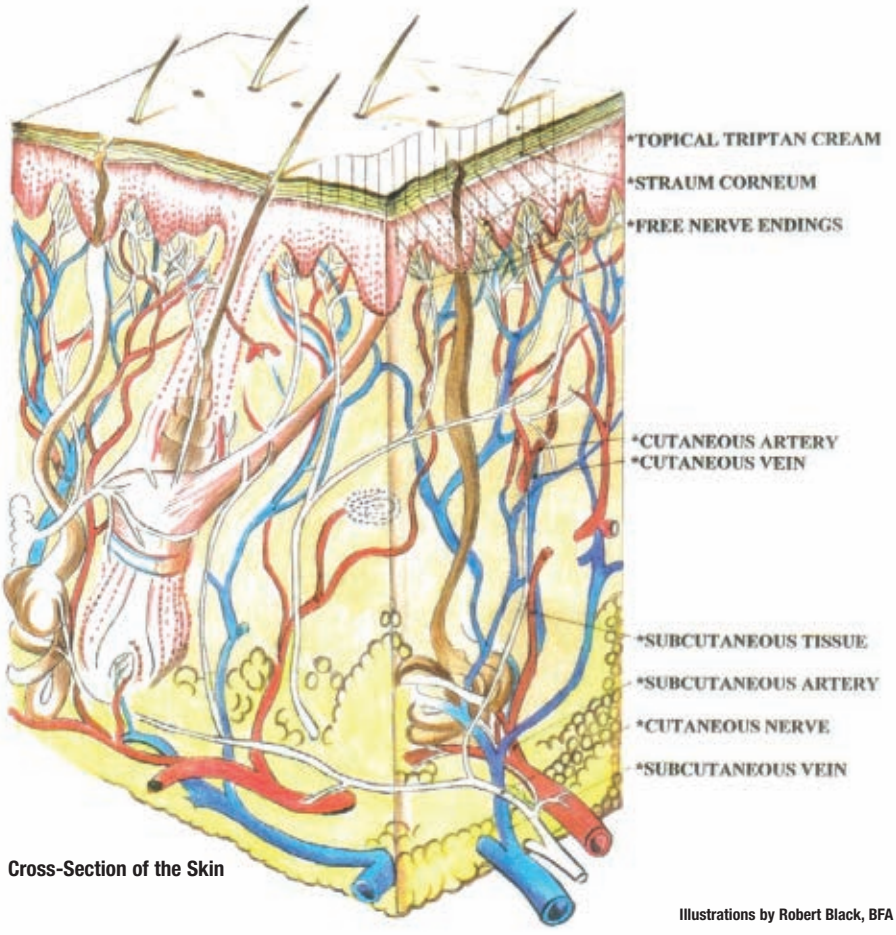
neural synapse. However, in contrast to VNS where surgical isolation of the vagus nerve at the anterior neck is required for direct afferent stimulation, cutaneous free nerve-endings below the skin surface at BONATH are utilized in TRNA for the same purpose. While Botox effect is at the neuro-muscular junction; in TRNA, it is at the sensory neuron receptor level.[8,9]

MIGRAINE: EXTENT OF THE PROBLEM & CURRENT TRIPTAN THERAPY

Despite significant advances in the understanding and treatment of migraine, a therapeutic void exists. Notwithstanding their efficacy and impact on migraine therapy, short-comings are apparent with triptans. Cost, tolerability, and overall acceptance contribute to the fact that much of the migraine population continues to rely on OTC products. Worldwide triptan use has not been as expected with seven same-class drugs on the market. The belief among some migraine sufferers is: considering the high cost of triptans, until the availability of something significantly more effective, safer, and convenient to justify change, OTC products are adequate. As migraine is not life-threatening but temporarily disabling, that logic seems difficult to argue.[1,8,10] Migraine headache affects some 28 million individuals in the US. The disorder is estimated to occur in 15% to 18% of women and 6% to 8% of men. Over 10% of the world population is afflicted by this medical condition. The World Health Organization (WHO) Task Force on Headache ranked migraine as one of the most disabling of chronic conditions; with attacks equating in disability to quadriplegia, psychosis, and dementia. Affected individuals are often young, productive, and in the prime of their lives; implying significant socio-economic impact.[11,12]

FIGURE 1



Cross-Section of the Skin

Illustrations by Robert Black, BFA

Introduced in the 1980s, triptans were developed to abort migraine attacks through their specific serotonin agonist action. They proved highly effective and significantly altered the approach to migraine treatment. With triptans, migraineurs were enabled to treat headaches without the need to see a doctor or go to the emergency room. Injections and treatments requiring healthcare professionals had been the usual practice for severe episodes. Patients were now capable of aborting attacks within a reasonably short (30 to 60 minutes) period of time and return to a relatively functional status. There was freedom to deal with migraine without the constraints of the healthcare delivery system.[7]

The success of triptans as a class was evidenced by six additional entries to market

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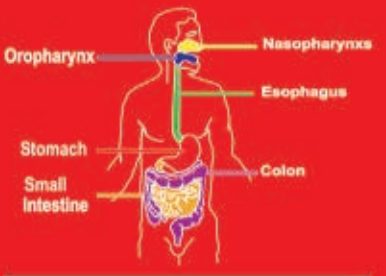

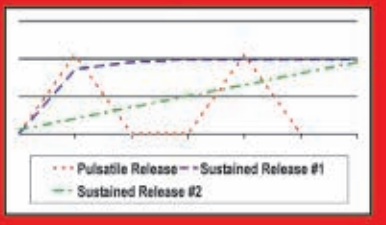

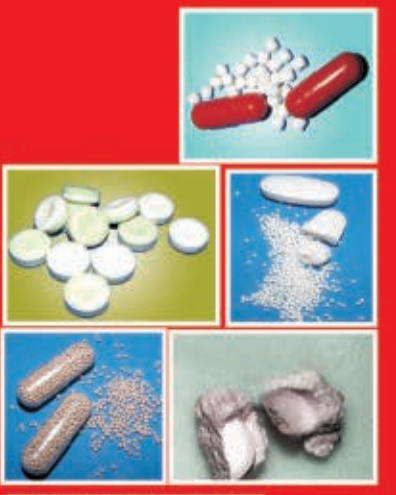

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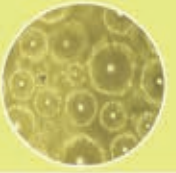

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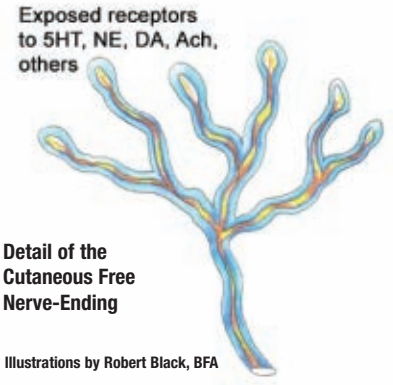
FIGURE 2



after the first triptan, sumatriptan (Imitrex®): almotriptan (Axert®), frovatriptan (Frova®), zolmitriptan (Zomig®), naratriptan (Amerge®), rizatriptan (Maxalt®), and eletriptan (Relpax®). Sumatriptan is currently available as a tablet or in combination with the NSAID naprosyn (Treximet®), nasal spray, and subcutaneous injection. The other triptans are tablets except zolmitriptan, which also comes as nasal spray. Rizatriptan and zolmitriptan are available as plain or orally dissolvable tablets (ODTs).[1,13,14]

WHAT MIGRAINEURS WANT

In repeated surveys of migraine patients, rapid pain and symptom relief leads desire from therapy; followed by absence of recurrence, tolerability, convenience, and cost. The sumatriptan injection, although relatively rapid in onset, is associated with a higher incidence of side-effects and recurrence from drug bolus effect. The systemic and cerebral triptan effects of chest tightness, tingling of the face and extremities, lethargy, mental clouding, and fatigue are accentuated. Many also object to feeling a rush with the injection. Injections are considered invasive and viewed as inconvenient. Nasal spray is also generally not a preferred treatment for migraine. It may be associated with an objectionable taste as drug drips down the back of the throat.[10,15,16]

The pill is the most used form of triptan. However, the oral route may not be the most appropriate considering the clinical and pathological peculiarities of migraine. In addition to prominent head pain, significant gastrointestinal (GI) symptoms may occur during a migraine attack: nausea, vomiting, diarrhea, indigestion, and bloating. Patients are reluctant to take an oral drug when experiencing significant nausea and vomiting. Further, when vomiting occurs after pill ingestion, the question of repeating a dose arises. GI transit is impaired during the migraine process, delaying absorption of oral drugs. Studies also indicate absorption of oral triptans may be delayed by the presence of food in the digestive tract. Some orally ingested triptans are significantly metabolized by hepatic first-pass, affecting eventual drug blood levels. In the case of sumatriptan (Imitrex), nearly 85% of an oral dose is lost through hepatic first-pass metabolism.[17]

THE PROBLEM WITH SYSTEMIC DELIVERY OF TRIPTANS

All current triptan delivery relies on eventual presence in systemic and cerebral blood for therapeutic effect. Side effects are related to their presence in the circulation. Symptoms of chest tightness and numbness and tingling of the lips and extremities may be confused with those associated with more serious heart disease. This is further complicated by the fact that triptans have been demonstrated to cause vasocontriction. As a class, they are contraindicated with coronary artery disease, Prinzmetal's angina, and uncontrolled hypertension. They are likewise not advised in complicated migraine varients, such as hemiplegic and basilar migraine as these sub-types are associated with cerebrovascular vasocontriction and potential for stroke.[15-17]

The opinion of some headache experts is that overall triptan use has been limited by the potential for adverse events. Physicians are particularly reluctant to prescribe this drug class to older patients. Cardiac clearance may be recommended for such individuals prior to triptan use.[15,16]

IMPROVING TRIPTAN EFFECTIVENESS

In consideration of current limitations in triptan therapy, measures have been taken to enhance therapeutic benefit and widen use. To improve effectiveness of the plain sumatriptan tablet, it has been combined with the non-steroidal anti-inflammatory agent (NSAID), naprosyn (Treximet, GSK). NSAIDs are thought to block TNS synaptic central transmission. As non-selective cyclo-oxygenase (COX) inhibitors, the synthesis of prostaglandin, essential in the inflammatory component of migraine, is thought to be prevented.[1]

Studies are also underway with a transdermal sumatriptan patch (NuPathe) in an effort to maintain prolonged therapeutic blood levels of drug. However, with sustained triptan blood levels, issues with side effects and tolerability remain.[18]

THE UNIQUE MECHANISM OF TRNA TRIPTAN THERAPY

The author has applied triptans (eg, sumatriptan/Imitrex and frovatriptan/Frova), which are formulated as cream (12.5 mg sumatriptan in 0.5 ml) compounded in a dermal penetration-enhancing medium, to the BONATH of human patients. Through direct

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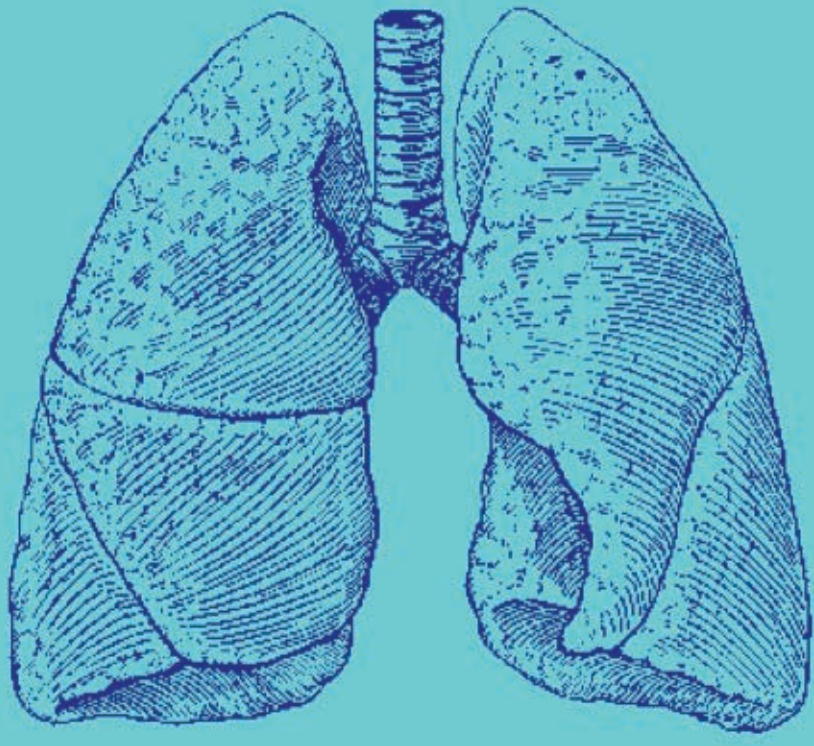

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effect on serotonin receptors of cutaneous free nerve-endings, afferent neural input is provided to TNS, effectively aborting the migraine process. As drug effect is achieved through neural connections than by bloodstream; clinical benefit is realized rapidly (10 to 15 minutes) and without the usual side effects of triptans.[19-21]

All current triptan delivery, whether injection, oral, nasal spray, or transdermal patch, ultimately require active drug in blood, exposing patients to side effects and other potential complications of systemic triptan therapy.[15,18]

TRNA DIFFERS FROM THE TRANSDERMAL PATCH

Although both are applied to the skin, TRNA triptan therapy differs from the systemic transdermal patch in that topically applied TRNA drug need only traverse the stratum corneum of the skin to reach cutaneous free nerve-endings for therapeutic effect. In contrast, the transdermal patch requires a drug concentration gradient for active drug to enter blood vessels in the subcutaneous tissue and dermis. These are at relative greater distance from the skin surface than the free nerve-endings (Figure 1). Further, after entry into the bloodstream, drug is required to be transported to the brain through cardiac output. As active drug is found in both systemic and cerebral blood, drug effect is not isolated to areas of migraine pathology, and extraneous effects are encountered. In contrast, in TRNA therapy, specific TNS pathways are affected through afferent neural connections from cutaneous free nerve-endings and upper cervical nerve roots. As therapeutic response is determined by rate of neural impulse than blood flow, clinical benefit is realized more rapidly with TRNA triptan delivery.[5,6]

TABLE 1

TRNA Versus Systemic Delivery (oral, injection, transdermal patch)

TRNA	Systemic
Direct affect on CNS through free nerve-endings and peripheral nerve connections.	Relies on therapeutic drug blood levels at CNS target sites.
Not rely on dermal, systemic, or cerebral blood flow for effect.	Drug enters systemic blood for effect after delivery by injection, patch, or as pill.
Rapid and prolonged drug effect as regional administration allows high tissue saturation of drug.	Therapeutic effect dependent on GI absorption, hepatic first pass, cardiac output, and cerebral blood flow.
Side-effects minimized without drug in systemic and cerebral blood.	Prone to systemic and CNS side effects.
Drug-drug interactions and metabolism/excretion negligible: may be considered "green."	Interactions with concomitant drugs and issues of metabolism and excretion.
Mechanism: analogous to electrical capacitor with charge build-up and discharge.	Mechanism: diffusion across concentration gradients and analogous to filling a reservoir to achieve a therapeutic level --- fluid dynamics.

The analogy is of an electrical capacitor discharging after charge build-up (TRNA) compared to a fluid reservoir filling to a required therapeutic level (transdermal patch). Finally, with TRNA therapy, the specific placement of active drug, as acute use single-dose cream or sustained delivery patch, at the BONATH is key in capitalizing on the unique relationship of the region to TNS with respect to providing important afferent input. On the other hand, the systemic transdermal patch may be placed anywhere on the body as anatomical location is irrelevant to its mechanism of action. As dilution in blood is not a consideration with topical regional delivery, active drug dose requirements are also much lower (Table 1).[18]

As alluded, the principles of TRNA therapy may also be applied to a sustained release patch and other depot drug delivery systems administered to the BONATH, with the only requirement of availing active drug to the cutaneous free nerve-endings for therapeutic effect. Conditions characterized by persistent, recurrent headaches, such as menstrual migraine, would benefit from such applications.

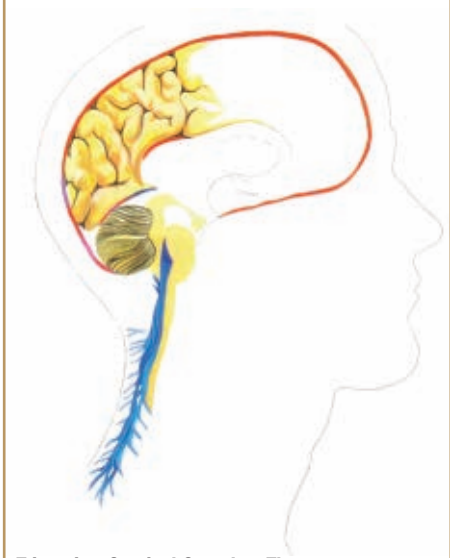
TRNA technology may be considered environmentally friendly or green. With negligible to no active drug in blood, there is lack of metabolism and excretion into the environment. Likewise, there is no concern for drug-drug interactions with concomitant medications.

CLINICAL EXPERIENCE WITH TRNA TRIPTAN THERAPY

In the 8 years of development, sumatriptan and tizanidine TRNA therapy has been used in over 300 patients, leading to the publication of five papers at

FIGURE 3

Illustrations by Robert Muller



Trigemino-Cervical Complex: The Neuroanatomical Basis of Migraine

International Headache and Clinical Research Meetings. Observations with TRNA in established migraineurs with prior traditional triptan use indicated onset of relief of headache and other migraine symptoms occurred in the majority within 10 minutes of topical sumatriptan (12.5 mg sumatriptan) compounded cream application. Headache response (moderate/severe to mild/none) was achieved in the majority within 30 minutes; less than 10 minutes in 30%. No significant side effects, in particular triptan effects, were noted.[19-21]

Topical tizanidine (Zanaflex) alone or in combination with sumatriptan has also been investigated with TRNA technology in both migraine and tension-type headache with similar positive results. Studies are currently underway to evaluate the utility of this novel delivery process with other CNS-active drugs. The dopamine agonist apomorphine is being studied in Parkinson's disease and essential tremor with initial findings of significant clinical response to TRNA therapy.[22-24]

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BIOGRAPHY

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HOT-MELT EXTRUSION

Properties of Modified-Release Pellets Prepared by Hot-Melt Extrusion

By: Sandra U. Schilling (PhD student) and James W. McGinity, PhD

INTRODUCTION

The interest in multiple-unit dosage forms providing modified drug release in the gastro-intestinal tract stems from their beneficial pharmacokinetic properties and high flexibility in formulation development.[1] Particles that are small enough to pass through the pylorus have been shown to spread more uniformly in the intestinal tract independent of gastric emptying and feeding state. Thus, drug absorption is maximized while plasma level fluctuations and intra- and inter-subject variability in bioavailability are reduced. In contrast to monolithic dosage forms (including film-coated tablets), high local concentrations and dose dumping are avoided. Blending of pellets containing different drugs or providing different drug-release rates allows the simultaneous delivery of incompatible drugs and the creation of tailored release profiles.

Hot-melt extrusion is a well-established process that is widely applied in the plastic, rubber, and food industries. More recently, the process has been adapted for the preparation of polymer-based pharmaceutical products, including implants, tablets, powders, and films. The pharmaceutical applications of hot-melt extrusion have generated a growing interest as evident from the surge in numbers of patents, scientific publications, and marketed drug products. This technology has also been the subject of numerous reviews.[2-5] Hot-melt extrusion allows the manufacture of modified-release matrix pellets in a continuous and efficient process offering potential for scale-up. Subsequent processing steps, including film coating and the use of organic or aqueous solvents, are avoided, making the process amenable for hydrolysable drugs and reducing the time and effort associated with the coating procedure and solvent removal.

HOT-MELT EXTRUSION TECHNOLOGY & TRADITIONAL METHODS OF PELLET PREPARATION

Traditional methods of pellet preparation involve multiple steps and require the use of water or organic solvents. Popular techniques, including wet-mass extrusion/spheronization, granulation, or balling, utilize binder solutions or dispersions in combination with kneading and compaction forces to generate spherical or semi-spherical particles. Alternatively, pellets may be prepared by layering of core seeds or by spray-drying. Modified-release properties are mainly achieved by subsequent application of a functional coat in case of reservoir-type pellets, or may be provided by the dissolution properties of the matrix material itself (matrix pellets). Although

FIGURE 1

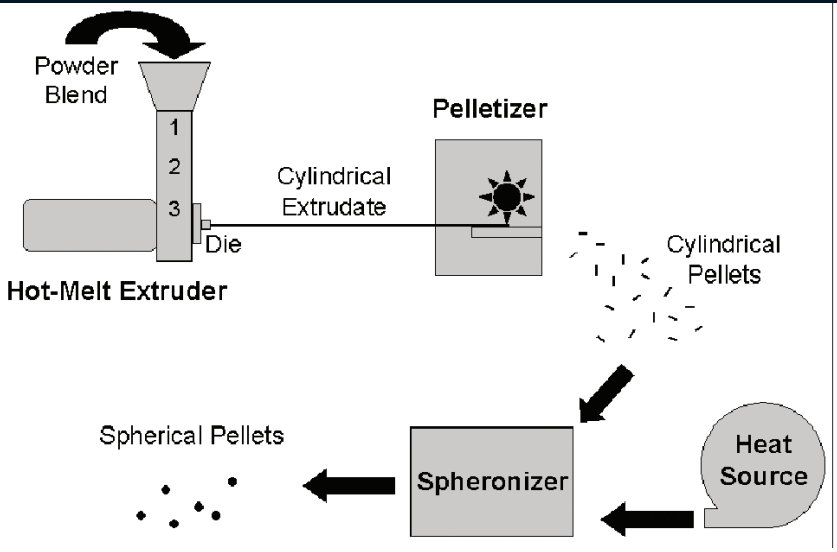

Diagram of a lab-scale hot-melt extrusion, pelletization, and spheronization process. Reproduced with permission from reference 10.

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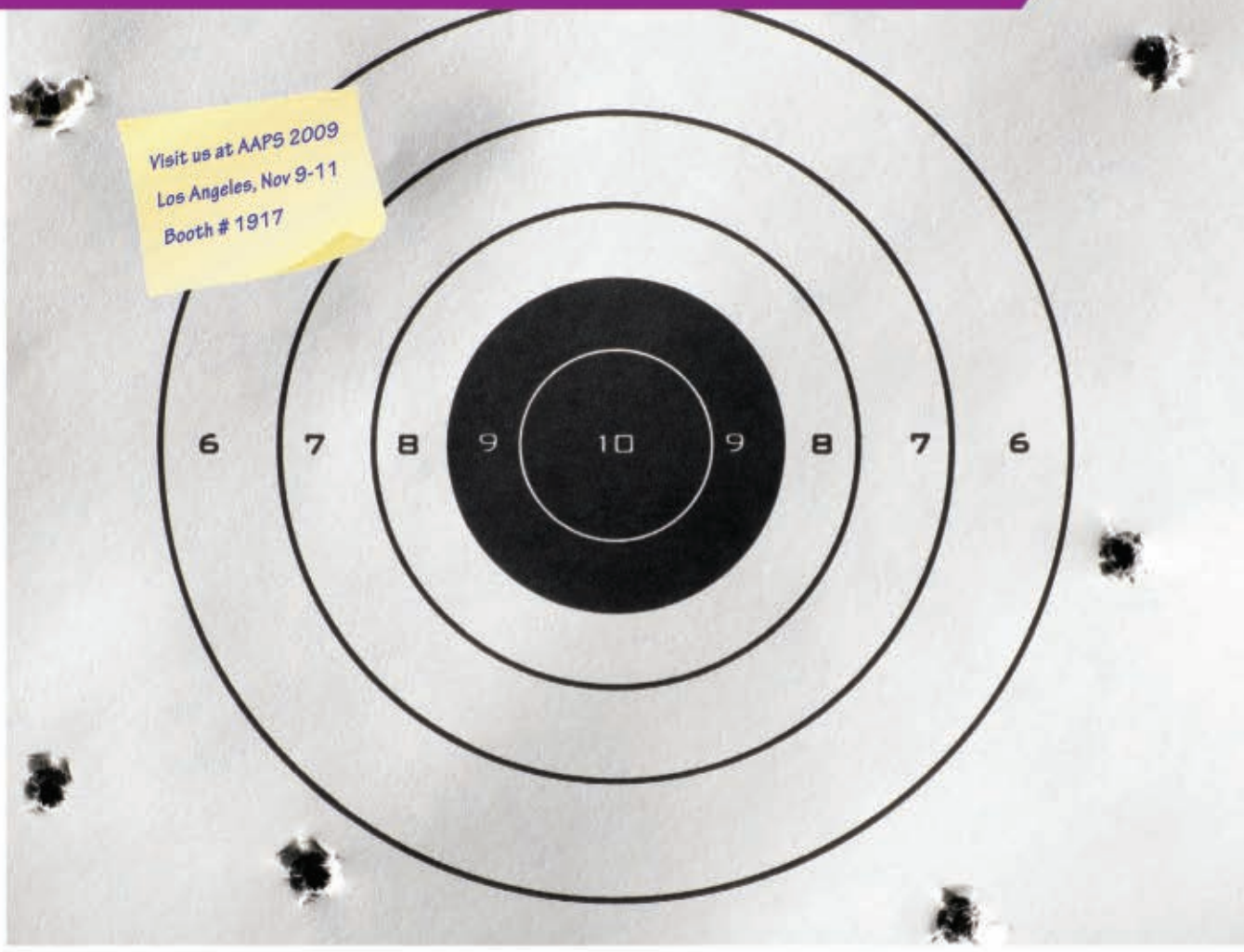

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HOT-MELT EXTRUSION

film-coating is well established and widely used, this procedure is labor intensive and costly because it requires the careful optimization of multiple steps, including film-coating, drying, and curing. The preparation of matrix pellets instead reduces the number of production steps and may overcome challenges associated with film-coating. Sustained release from wet-mass extruded pellets is usually limited to poorly soluble compounds whose release is mainly controlled by the erosion kinetics of the matrix material.[6] Thermal methods, such as melt granulation or spray-congealing, may be used to sustain the release of soluble drugs by embedment into a lipophilic matrix based on lipids, waxes, or fatty acids.[7,8]

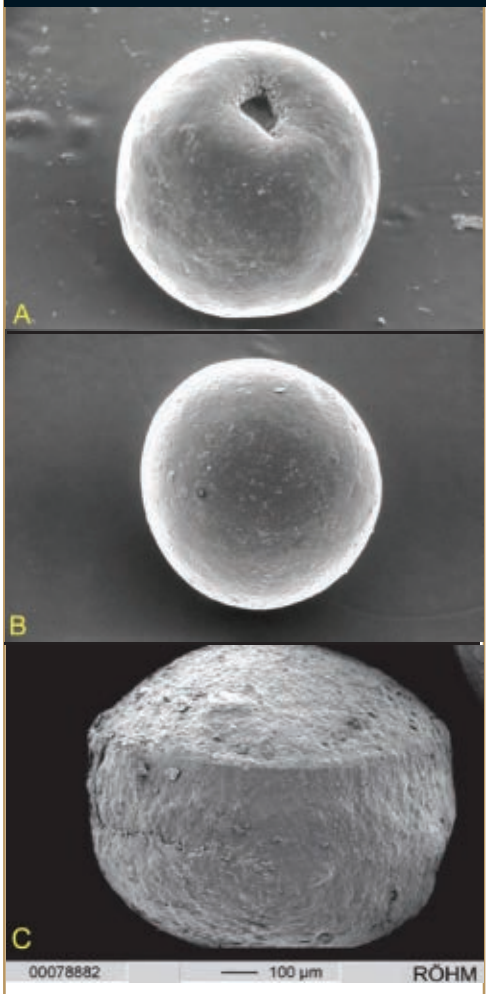
During hot-melt extrusion, a powder blend comprising the drug, a thermoplastic carrier, and optional processing aids is transported inside a heated barrel by either one or two rotating screws. The material undergoes zones of increasing temperature and pressure inducing the softening or melting of one or more blend components. Particle deaggregation and intense mixing is provided by shearing of the material, resulting in a uniform distribution of non-melting particles in the carrier matrix to yield a highly homogeneous dosage form. The diameter and cross-sectional geometry of the extruded pellets is mainly controlled by the design and orifice size of the product-shaping die. Because most carriers are viscoelastic polymers, the material may undergo partial elastic recovery upon die exit known as "die swelling," resulting in an increase in cross-sectional area of the extrudate. Numerous formulation factors, including polymer type, drug-to-polymer ratio, and type and level of plasticizer, influence the extent of elastic recovery and hence pellet diameter. A careful selection of the extrusion parameters, including size of the die orifice, processing temperature, screw speed, and constant velocity of material output, enables the extrusion of strands with constant and highly reproducible diameter. The produced pellets show a narrow particle size distribution, and tight particle size fractions may be obtained at high yields compared to traditional wet-mass extrusion methods.[9]

Several technologies have been developed to accomplish downstream pelletization and spheronization of the extrudate in a continuous or semi-continuous manner. In-line pelletizers are composed of rotating knives that cut the extruded strands into cylindrical pellets either after cooling (strand pelletizers) or directly at the die upon exiting in the softened state (die face pelletizers). Young and co-workers developed a lab-scale process for the production of spherical pellets whose set-up is outlined in Figure 1.[10] After exiting the extruder through a cylindrical die, the polymeric strand exhibited a uniform diameter of 1.22 ± 0.03 mm and was cut into cylindrical pellets employing a Randcastle strand pelletizer RCP-2.0. Spheronization was accomplished in a traditional benchtop Caleva Model 120 spheronizer at elevated temperature. As illustrated in Figure 2a and 2b, the surface morphology of the pellets was influenced by the spheronization time. Indentions on the pellet sides representing the cut surfaces were reduced and eliminated by extended spheronization time. A recently developed micro pelletizer combines the shaping, cutting, and spheronization of the extruded material in one device to produce spheroid pellets (Figure 2c).[11,12] The extruded strands exit through a die plate with concentric holes, are cut in the hot stage by a rotating knife, and immediately spheronized in a circulating air stream by impingement against the pelletizer housing.

CHARACTERIZATION OF THE FORMULATION & THE FINAL PRODUCT

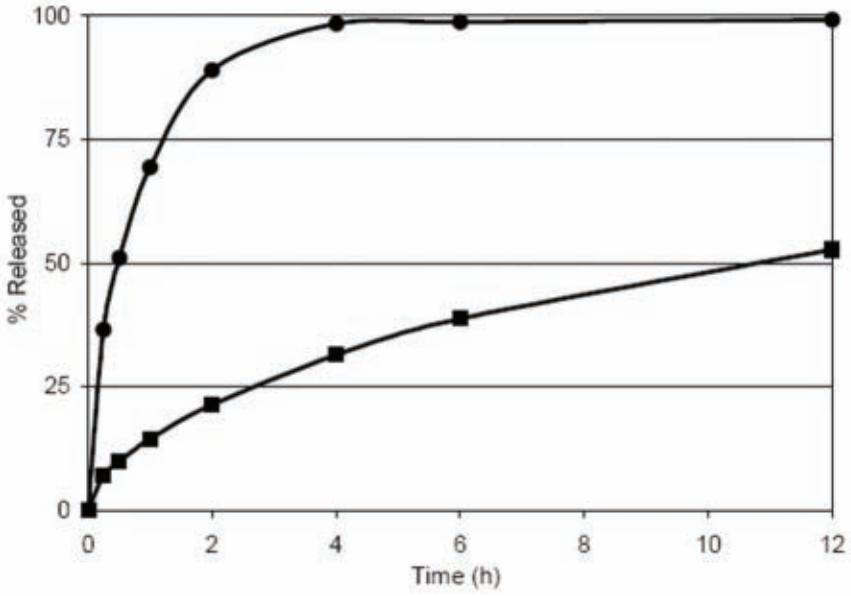
The preparation of modified-release pellets by melt extrusion requires the presence of a thermoplastic carrier, which softens or melts during thermal processing. Most suitable carriers, including polymers, lipids, or waxes, are amorphous or semi-crystalline materials exhibiting a characteristic glass transition temperature (Tg) and/or melting point. Typically, the temperature in the melting zone must be set to 15°C to 60°C above the Tg of amorphous polymers to efficiently decrease the melt viscosity of the extruded material.[4] The incorporation of

FIGURE 2A-C



Scanning electron microscopy images of hot-melt extruded pellets.
(A) pellet after spheronization for 45 min (1.2 mm diameter); preparation according process in Figure 1; image in reference 10.
(B) pellet after spheronization for 80 min (1.2 mm diameter); preparation according process in Figure 1; image in reference 10.
(C) pellet obtained by a micro-pelletizer as disclosed in reference 11; (1 mm in diam eter); image in reference 12. Reproduced with permission.

FIGURE 3



Dissolution in pH 1.2 medium of pellets prepared by two different techniques. (●) Wet-mass extrusion; (■) Hot-melt extrusion. (USP 27, apparatus 2, 900 ml, 37°C, 100 rpm, n = 3). Reproduced with permission from reference 9.

plasticizers into the formulation may be required to reduce the processing temperature when polymers with high Tgs and melt viscosities are utilized as carriers. Polymer-plasticizer compatibility and plasticization efficiency in the form of Tg reduction can be experimentally determined by modulated differential scanning calorimetry or mechanical analysis. The extruded matrix pellets may be characterized in a similar fashion to pellets prepared by traditional methods.[13] Important pellet properties that influence the drug release and feasibility for downstream processing include particle size and particle size distribution, geometric shape, surface area and morphology, pellet density, matrix porosity, mechanical strength, and friability. In addition, the chemical stability of the drug and the excipients should be closely monitored because the materials may undergo thermally induced degradation during the extrusion process. Elevated processing temperature and miscibility with the carrier may further promote drug melting and solubilization in the matrix, potentially leading to the formation of metastable drug modifications or supersaturated amorphous systems after cooling. To identify potential physical instabilities during storage, the crystalline state of the drug and the dissolution properties of the pellets should be studied at accelerated storage conditions.

HOT-MELT EXTRUDED PELLETS PROVIDING SUSTAINED DRUG RELEASE

Matrix pellets with sustained drug release properties may be prepared by hot-melt extrusion of drugs with water-insoluble carriers, including polymers, waxes, or lipids. The release of water-soluble drugs from hot-melt extruded pellets is mainly controlled by the permeability and dissolution behavior of the carrier and by the amount of soluble components in the formulation. As opposed to pellets prepared by traditional wet-massing techniques, diffusion through pores initially present in the matrix is minimized due to the low porosity of melt-extruded matrices.[14]

Pellets with increased drug loads may be successfully prepared under preservation of the controlled-release properties. As demonstrated for a formulation containing 30% theophylline (Figure 3), pellets with sustained-release properties could be successfully prepared by hot-melt extrusion, while wet-massed pellets failed to prolong the drug release.[9] Electron microscopic images of pellet cross-sections showed the effect of the processing method on the pellet porosity (Figure 4). Melt-extruded matrices were highly coalesced and void of pores, while wet-massed pellets remained as porous agglomerates of distinct particles.

Follonier and co-workers investigated four polymers [ethyl cellulose, cellulose acetate butyrate, poly(ethylene-co-vinyl acetate), and Eudragit® RS PM] as thermoplastic carriers for the sustained release of diltiazem hydrochloride, a freely soluble model drug at loads of 30% to 70%, from hot-melt extruded matrix pellets.[15,16] The rate and extent of drug release was dependent on the carrier polymer, the pellet particle size, and the drug load. All formulations yielded sustained-release profiles with biphasic dissolution characteristics: an initial burst release due to dissolution of drug at the pellet surface, followed by a slow, diffusion-controlled phase. Hydrophilic polymers and swelling superdisintegrants were added to the formulation to suppress the initial burst by gel formation and to promote complete drug release by increasing the matrix porosity in the second phase.

Miyagawa and co-workers demonstrated that a twin-screw extruder may be used for the preparation of cylindrical sustained-release pellets based on carnauba wax.[17] The generation of high pressures in the melting zone enabled processing at temperatures below the wax melting point. Soluble and swellable polymers increased the drug-release rates in a concentration-dependent manner by promoting crack and pore formation in the matrix. Granules based on glyceryl palmitostearate could be successfully prepared with a single-screw extruder when the ratio between melting wax and non-meltable filler was optimized.[18]

Brabender and co-workers developed mini-matrices formulated with ethyl cellulose

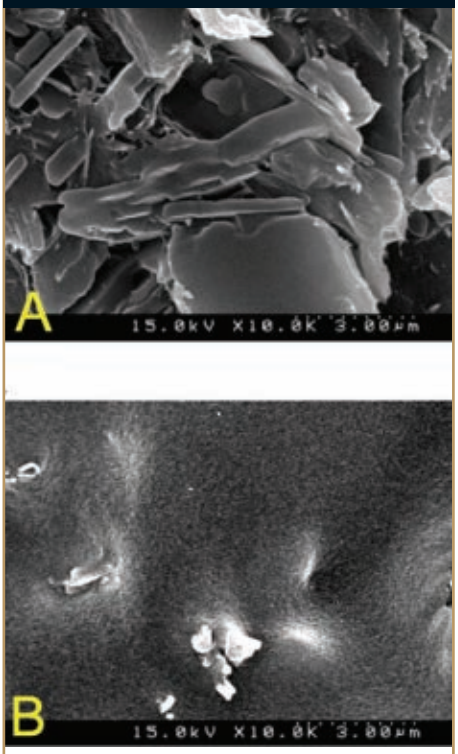
as the thermoplastic carrier and release-retarding agent for the sustained release of ibuprofen.[19] Although high drug loads of 60% were used, the release from the ethyl cellulose matrices was very slow, with only 20% drug released in 24 hours. The addition of hydrophilic polymers was necessary to enhance the drug-release rate. In contrast to hydroxypropyl methylcellulose compacts, higher viscosity grades increased the dissolution rate to a larger extent, attributed to their higher swelling capability, which promoted water penetration into the matrix. When xanthan gum was used instead of hydroxypropyl methylcellulose, the initial burst release was eliminated, and drug-release profiles approaching zero-order release could be obtained due to the rapid formation of viscous gels.

HOT-MELT EXTRUDED PELLETS PROVIDING DELAYED DRUG RELEASE

According to the current USP, the drug release from delayed-release articles is limited to no more than 10% in acidic medium pH 1.2 over 2 hours. As previously pointed out for sustained-release pellets, drug at the pellet surface is exposed to the release medium, and the pellets show a burst release during the initial acidic stage of the dissolution test. High drug loads and small pellet particle size increase the fraction of drug in the matrix devoid of the control by an enteric polymer, resulting in failure of the USP requirement for the maximum release in acid. As previously demonstrated for hot-melt extruded matrix systems based on Eudragit® L100-55, pellets extruded through a 1.2-mm die and containing 20% theophylline released more than 25% drug in 2 hours at pH 1.2, compared to 10% drug release from melt-extruded tablets with a diameter of 6 mm.[20] As disclosed in patent application WO 2008/101743, the permeability of enteric polymers can be reduced by utilizing blends with an insoluble polymer.[21] The release profiles in Figure 5 show that matrix pellets containing 50% drug exhibited enhanced gastric resistance when anionic Eudragit® FS 30D in the spray-dried form was extruded as a physical mixture with insoluble Eudragit® RS PO.[22]

Additional challenges arise from the thermal properties of most enteric polymers. The temperature window between glass transition and thermal degradation is oftentimes small, so that the use of plasticizers becomes indispensable. Efficient plasticization is further required to lower the melt viscosity and reduce the elastic recovery or die swelling of the polymer as the preparation of small pellets involves an extrusion of softened material through die holes with diameters of 1 mm or less. Plasticizers exhibiting aqueous solubility may leach from the pellet or promote water penetration into the matrix, resulting in increased drug release by diffusion through the porous network during the acidic stage. As shown in a previous study, cellulosic polymers with enteric properties (Aqoat® LF and HF) exhibited good thermal processibility, and small pellets could be produced at moderate temperature and high yields by hot-melt extrusion. However, the matrix permeability was too high, as more than 10% of the drug content was released during the initial 2 hours in acid. Pellets prepared with methacrylic polymers (Eudragit® S100 and L100) and containing up to 40% drug showed minimum drug release in acid and were compliant with the USP requirement for the acidic stage, but required the addition of high plasticizer amounts to reduce the processing temperature and avoid thermal instabilities. The release properties were dependent on the type and level of the used plasticizer, and only plasticizers with low or moderate aqueous solubility were adequate to preserve the gastric resistance of the polymer matrix.[23] Alternatively, film-coating was demonstrated to be a suitable method to provide melt-extruded sustained-release pellets with pH-dependent drug-release properties that remained stable at accelerated storage conditions.[24]

FIGURE 4

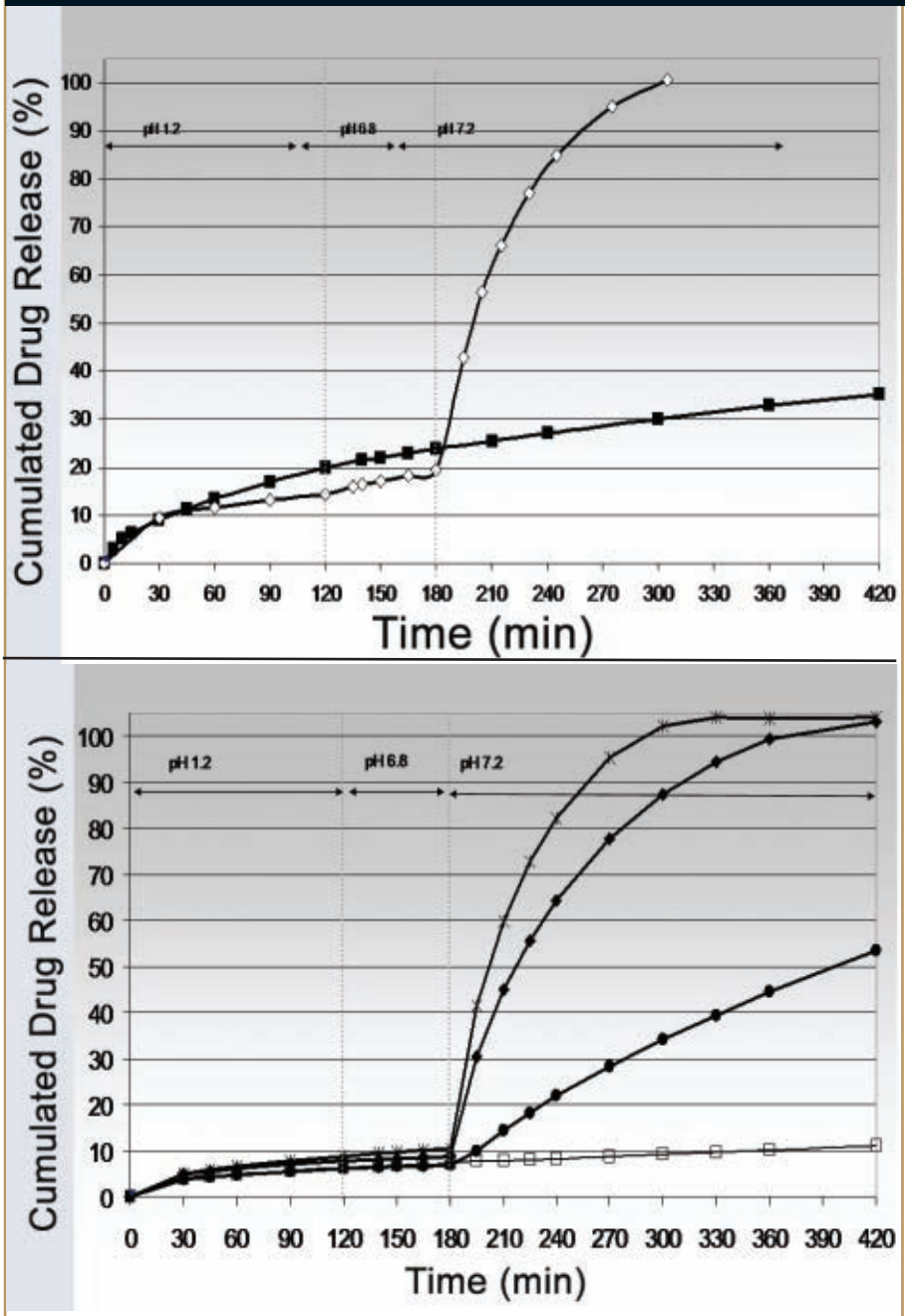


High-magnification SEM micrographs of the cross-section of pellets produced by two different techniques. (A) wet-mass extrusion; (B) hot-melt extrusion. Reproduced with permission from reference 9.

DOWNSTREAM PROCESSING

Downstream processing of multiple-unit systems into monolithic, multi-particulate dosage forms becomes necessary to ensure patient compliance and dosing accuracy. The two most common techniques include the filling of multi-particulates into capsules or the compression into tablets. Capsules are more cost intensive than tablets and may be less secure due to their higher susceptibility to tampering. Capsule shells are further hygroscopic and provide little protection to light, oxygen, and moisture. Direct compression of pellets into multi-particulate tablets has gained popularity, but remains technologically challenging.[25] Compaction

FIGURE 5A & B



Dissolution profiles from pellets (1 mm) prepared with 50% theophylline and (✧) 50% Eudragit FS 30D (dry polymer); (■) 50% Eudragit RS PO; (x) 40% Eudragit FS + 10% Eudragit RS PO; (◆) 30% Eudragit FS + 20% Eudragit RS PO; (●) 20% Eudragit FS + 30% Eudragit RS PO; (❑) 10% Eudragit FS + 40% Eudragit RS PO. Reproduced with permission from reference 22.

forces during tableting can fracture the film of functionally coated pellets and result in the loss of gastric protection. The requirement of large amounts of cushioning agents to absorb compaction forces and physically separate the pellets during compression limits the amount of pellets that can be loaded into the tablet.

Hot-melt extruded matrix pellets potentially exhibit higher robustness than coated particles toward downstream processing procedures, which is attributed to their mechanical strength, low friability, and the circumstance that the release performance is independent of the intactness of a functional coat. Because wet-massed pellets represent agglomerates of distinct particles and are often porous, they mainly fail by adhesive or cohesive fracture or crack propagation of flaws when subjected to compression forces.[26] On the other hand, hot-melt extruded dosage forms are highly coalesced matrices exhibiting low porosity and being held together by intermolecular forces and physical entanglement between polymeric chains. These strong cohesive forces and the lack of pores are responsible for the high mechanical strength of melt-extruded pellets.[23] As demonstrated by Young and co-workers, multi-particulate tablets of acceptable hardness and low friability could be prepared by direct compression of 50% hot-melt extruded pellets with tableting excipients.[27] Furthermore, the release properties of the unprocessed pellets could be reproduced after tableting, independent of the compaction force, pellet-to-filler ratio, and tableting excipient when the rapid disintegration of the tablet was ensured. As illustrated in Figure 6, the pH-controlled release profiles of the initial pellets and the compacted pellets were superimposable when compression forces up to 15 kN were utilized. Higher forces (20 kN) produced tablets with a slower release in acidic medium attributed to extended disintegration times.

CONCLUSIONS

Hot-melt extrusion represents an efficient and continuous method to produce pellets with modified-release properties providing sustained or delayed drug release in the gastrointestinal tract. Many drawbacks associated with traditional

preparation techniques may be overcome, and the resulting matrix pellets offer advantages over reservoir-type pellets in terms of mechanical robustness and stability of the dissolution performance during downstream processing and storage.

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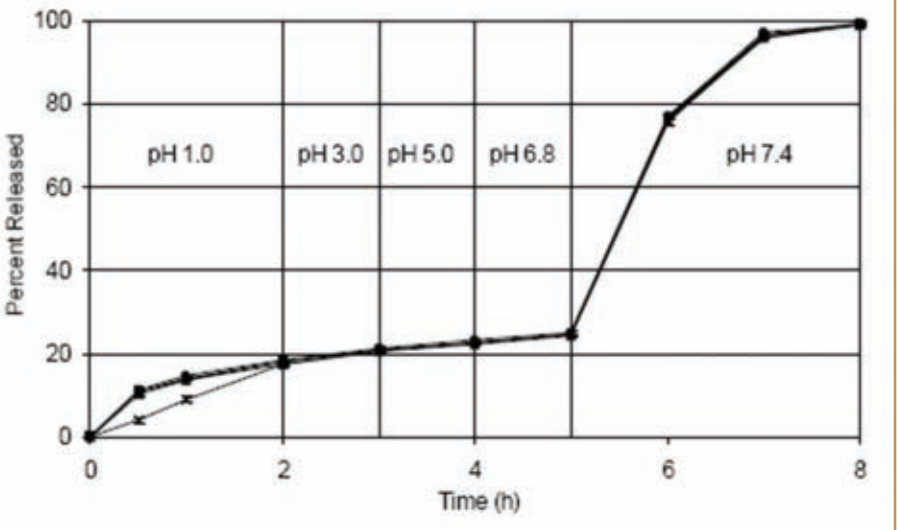
FIGURE 6



The influence of compression force on the theophylline release profile of compressed hot-melt extruded pellets using 50% pellet content and MCC as the filler excipient. (●) initial pellets; (◆) 5 kN; (■) 10 kN; (▲) 15 kN; and (x) 20 kN. (USP 27 Apparatus 3, 250 mL, 37°C, 20 dpm, n = 3). Reproduced with permission from reference 27.

BIOGRAPHIES

Ms. Sandra U. Schilling is currently a graduate student in the Division of Pharmaceutics at The University of Texas at Austin. Her PhD research focuses on the implications of plasticization on the properties of hot-melt extruded delivery systems providing modified drug release. She has published articles in international pharmaceutical journals and has presented her work at several national and international scientific conferences. Prior to entering the PhD program, she earned her licensure as a pharmacist from the Freie Universitaet in Berlin.

Dr. James W. McGinity is Professor of Pharmaceutics in the College of Pharmacy, The University of Texas at Austin. He earned his BS in Pharmacy at the University of Queensland, Australia, and his PhD in Pharmaceutics from the University of Iowa. Dr. McGinity's research interests and publications are focused on solid dosage forms, aqueous film coating of pellets and tablets, powder technology, materials science, transdermal systems, hot-melt extrusion, and controlled and targeted drug delivery systems. Hot-melt extrusion technology has been investigated as a pharmaceutical process to prepare transmucosal films, transdermal patches, tablets, granules, pellets, and fast-dissolving oral dosage forms. Dr. McGinity is an author or co-author on over 175 scientific publications and he has been issued 23 US patents. He is an AAPS Fellow and is the US Editor for the *European Journal of Pharmaceutics and Biopharmaceutics* and a Charter Editorial Advisory Board Member of Drug Delivery Technology magazine.

MUCOADHESIVE DELIVERY

Clotrimazole Controlled-Release Chitosan Films for Local Delivery in Oral Candidiasis

By: Bhupendra G. Prajapati, MPharm, and Madhabhai M. Patel, PhD

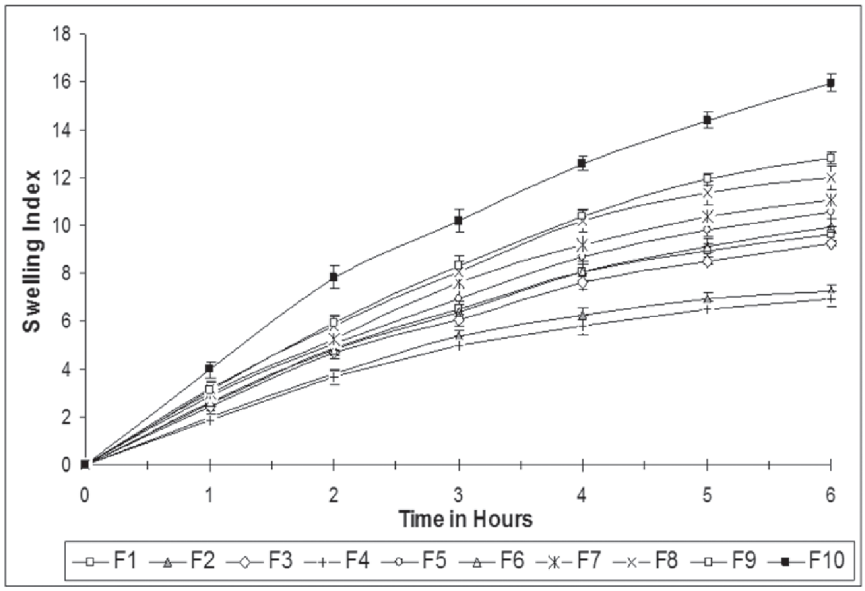
ABSTRACT

Topical delivery of antimicrobial agents is the most widely accepted approach, and the present study aims at prolonging active drug concentrations in the oral cavity. As most antifungals do not posses an inherent ability to bind to the oral mucosa, this is best achieved through improved formulations using mucoadhesive polymers in the formulation. The antifungal agent, clotrimazole (CLZ) was used as the model drug to design a formulation containing chitosan for local delivery. Films of chitosan were prepared containing 0.5% of CLZ via the solvent casting method. The prepared films were cross-linked with 0.1% and 0.2% of tripolyphosphate (TPP) to prolong the drug release. The chitosan CLZ films were studied for film thickness, swelling index, in vitro drug diffusion, and in vitro permeation. Physico-mechanical parameters of chitosan films were found to maintain their structure throughout the study period. Releases of CLZ from non-cross-linking films were 92.8% ± 1.1% and 94.2% ± 1.0%, respectively, compared to cross-linked films (0.2% TPP) 66.4% ± 0.9% and 60.5% ± 1.2%, respectively, in 5 hours. A controlled release was observed with cross-linked film formulations with 2% chitosan and 0.2% TPP for 7 hours. There was no lag time observed in release of CLZ from all the medicated films. The optimized formulation, cross-linked with 0.2% TPP showed 86.9% ± 1.1% CLZ release in 7 hours, 10.5 ± 0.5 g of mucoadhesive strength, 168 ± 2 minutes of ex vivo mucoadhesive time, and 155 ± 5 folding endurance. The in vitro drug permeation showed good correlation coefficient of 0.9976.

INTRODUCTION

Successful eradication is a major problem in drug delivery for fungal infections in the oral cavity due to the dilution and rapid elimination of topically applied drug by the flushing action of human saliva. Thus, the kind of drug delivery system and route are important considerations to prolong retention of the drug in the oral cavity. In recent years, biodegradable polymeric systems have gained importance in the design of surgical devices, artificial organs, materials for orthopaedic applications, drug delivery systems with different routes of administration, carriers for

FIGURE 1



Swelling Index of Chitosan Films

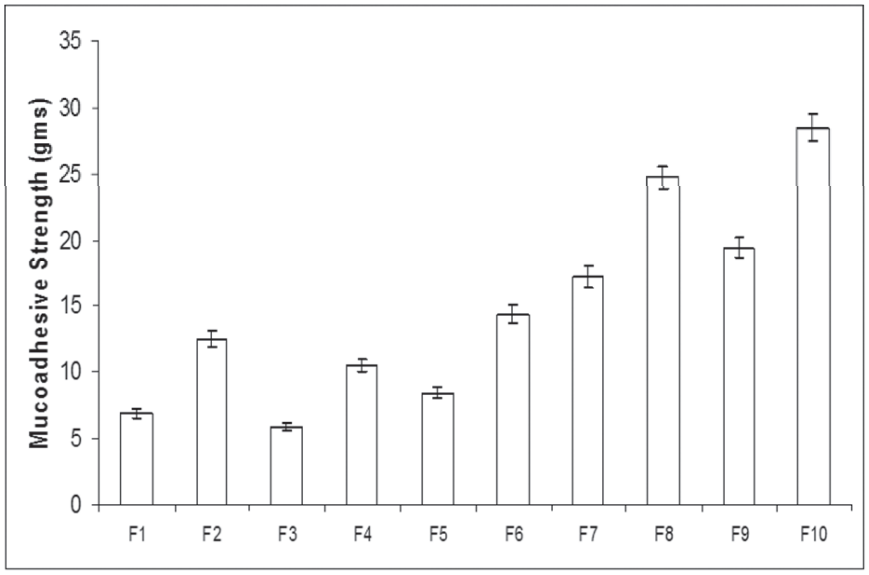
immobilization of enzymes and cells, and as biosensors and ocular inserts. These polymers are classified as synthetic or natural. Natural polysaccharide-based polymers represent a major class of biomaterials, which include agarose, alginate, carageenan, and chitosan.[1,2] The bioadhesive polymer in formulation may also reduce the frequency of application and the amount of drug administered, which might improve patient compliance and acceptance.

Chitosan is derived from chitin, a type of polysaccharide present in the hard exoskeletons of shellfish-like shrimp and crab.[3] Chitin, in fact, is one of the most abundant polysaccharides found in nature, making chitosan a plentiful and relatively inexpensive product. Chitosan is the N-deacetylated product of the polysaccharide chitin.[4] Chitosan has several advantages, such as minimal foreign body reaction, mild processing conditions (synthetic polymers often need to be dissolved in harsh chemicals; chitosan will dissolve in water based on pH), controllable mechanical/biodegradation properties (such as scaffold porosity or polymer length), and availability of chemical side groups for attachment to other molecules.[5] Chitosan has already been investigated for use in the engineering of cartilage, nerve, and liver tissue.[5-7] Chitosan has also been studied for use in wound dressings and drug delivery devices.[8,9]

Chitosan is gaining increasing importance in the pharmaceutical field due to its good biocompatibility (following intravenous and oral administration) and its non-toxicity and biodegradability.[10] From a technological point of view, chitosan has also been demonstrated to be a promising matrix carrier for sustained drug release, and possesses excellent film-forming properties.[11,12] Chitosan is biologically safe and has been proposed as a bioadhesive polymer for oral mucosal delivery.[13] Studies showed that chitosan hydrogels prolong both retention times on the oral mucosa and drug release from gels.[14] In addition to its bioadhesive properties, chitosan inhibits the adhesion of Candida albicans to human buccal cells, and thus helps prevent the development of mycosis.[15]

The aim of the present study was to design a formulation of chitosan film for oral mucosal delivery of the antifungal agent CLZ. Film formulation of chitosan incorporating CLZ was developed and investigated for swelling index, mechanical properties (eg, thickness and folding endurance), bioadhesive strength, mucoadhesion time, in vitro drug release, and in vitro permeation.

FIGURE 2



Mucoadhesive Strength of Chitosan Films

MATERIALS

Chitosan 221 was obtained from the Siber Hegner (India), CLZ was received as a gift sample from the Helios Pharmaceuticals Ltd (India), TPP (USA) was used as a cross-linking agent, and all other chemicals were of analytical grade.

METHODOLOGY

Chitosan gels of 1% and 2% concentration containing 0.5% of CLZ were prepared by allowing chitosan to swell in 1% lactic acid overnight to form a gel. Medicated and non-medicated films of chitosan were prepared via the solvent casting method. The prepared gels were homogenously mixed with 5% glycerol (plasticizer). Prepared films

TABLE 1

Ingredient (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
CLZ	-	-	0.5	0.5	0.5	0.5	0.5	0.5	-	-
Chitosan	1	1	1	1	2	2	1	2	1	2
TPP	0.1	0.2	0.1	0.2	0.1	0.2	-	-	-	-
Glycerol	5	5	5	5	5	5	5	5	5	5

Composition of chitosan films

were cross-linked with 0.1% and 0.2% TPP.[15] The films were packed in aluminium foil and stored in an airtight glass container to maintain the integrity of the films. Table 1 shows the composition of different chitosan films.

Folding Endurance

Folding endurance of the films was determined by repeatedly folding one film at the same place until it broke or folded up to 200 times at the same place without breaking.[16] The entire test was performed in triplicate.

Content uniformity

Drug content uniformity was determined by dissolving the film through homogenization in 100 mL of an isotonic phosphate buffer (pH 6.8) for 7 hours with occasional shaking. The drug content was then determined after proper dilution and analyzed for drug content at 270 nm using a UV-spectrophotometer. The entire test was performed in triplicate.

Swelling Study

The films were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37°C ±1°C. At regular 1-hr time intervals until 6 hours, the films were removed from the petri dish, and excess surface water was removed carefully using filter paper. The swollen films were then reweighed (W2), and the swelling index (SI) was calculated. The entire test was performed in triplicate.

Surface pH Study

Surface pH study was performed to investigate the possibility of any side effects in vivo in the human oral cavity. As an acidic or alkaline pH may cause irritation to the oral mucosal layer, the objective was to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg et al was used to determine surface pH of the films.[17] The films were allowed to swell by keeping them in contact with 1 mL of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was noted down by bringing the electrode in contact with the surface of the films and allowing it to equilibrate for 1 minutes. The entire test was performed in triplicate.

Ex Vivo Mucoadhesive Strength

A modified balance method was used for determining the ex vivo mucoadhesive strength.[18] Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The 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 and hung in a glass beaker filled with phosphate buffer pH 6.8, at 37°C ± 1°C such as the buffer surface just touches the mucosal surface. The oral film was stuck to the lower side of the rubber stopper with cyanoacrylate adhesive. Two sides of the balance were balanced with 5-g weight on the right-hand pan. A 5-g weight was removed from the right-hand pan, which lowered the pan along with the film over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to the weight) was added slowly with infusion set (100 drops/minute) to the right-hand pan until the formulation detached from the mucosal surface. The detachment force gave the mucoadhesive strength of the film in grams. The entire test was performed in triplicate. The following are the equations used for force of adhesion and bond strength.

Equation 1.

$$\text{Force of adhesion (N)} = \frac{\text{bioadhesive strength}}{1000} \times 9.81$$

Equation 2.

$$\text{Bond strength (Nm}^{-2}) = \frac{\text{force of adhesion (N)}}{\text{surface area of film (m}^2)}$$

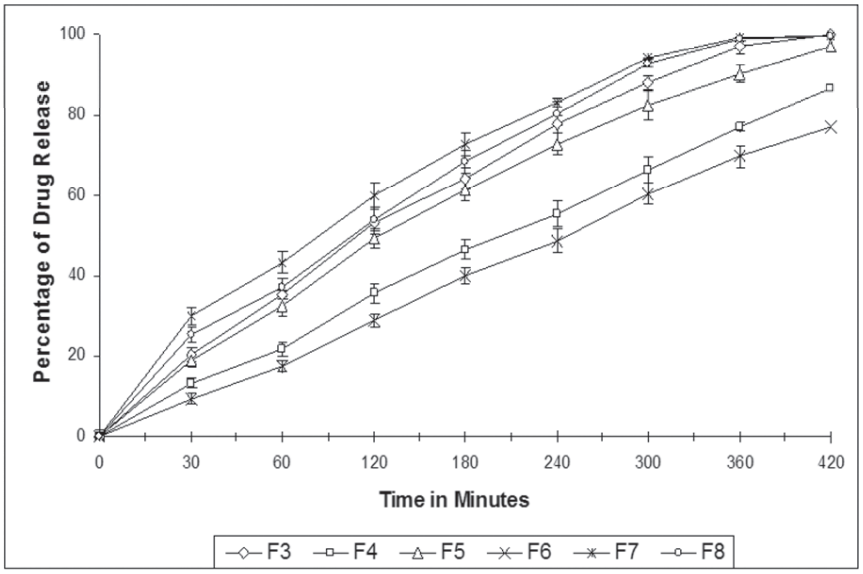
Ex Vivo Mucoadhesion Time

The ex vivo mucoadhesion time was measured following application of the films on freshly cut sheep buccal mucosa.[18] The fresh sheep buccal mucosa was fixed in the inner side of a beaker, about 2.5 cm from the bottom, with cyanoacrylate glue. One side of each film was wetted with 1 drop of phosphate buffer (pH 6.8) and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 200 mL of phosphate buffer (pH 6.8) and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and film adhesion was monitored for 12 hours. The time required for the patch to detach from the sheep buccal mucosa was recorded as the mucoadhesion time. The entire test was performed in triplicate.

In Vitro Drug Release

In vitro drug release of drug from film formulations was studied using the USP XXIII rotating paddle method.[19] The dissolution medium consisted of 200 mL of phosphate buffer pH 6.8. The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The films were attached to the glass disk with instant adhesive (cyanoacrylate). The disk was fixed at the bottom of the dissolution vessel. Samples were withdrawn at predetermined time intervals and replaced with fresh medium.[20] The samples were filtered through 0.45-micrometer Whatman filter paper and analyzed (Shimadzu, SPD-10 A VP, Japan) at 270 nm. The entire test was performed in triplicate.

FIGURE 3



Cumulative Drug Release From Chitosan Films

In Vitro Drug Permeation

The in vitro drug permeation study of CLZ was studied through the sheep buccal mucosa using a Keshary Chien type glass diffusion cell at 37°C ± 0.2°C. Fresh sheep buccal mucosa was mounted between the donor and receptor compartments. The film was placed with the core facing the mucosa and the compartments clamped together. The donor compartment was filled with 1 mL of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. A 1-mL sample was withdrawn at predetermined time intervals and analyzed for drug content at 270 nm.

RESULTS & DISCUSSION

The prepared chitosan films containing CLZ were found to be ideal for use as carriers for drug delivery, after being evaluated for properties like thickness, folding endurance, and drug content (Table 2). Thicknesses of films increased as the content of polymers increased in the film from 1% to 2%.

The optimum swelling behavior of films is necessary for uniform and prolonged release of drug and effective mucoadhesion. The swelling index gives the indication of drug release when it is due to water intake of polymeric preparation. The mucoadhesive strength and time are important parameters

TABLE 2

Batch Code	Thickness (mm)	Drug Content	Surface pH	Mucoadhesion Time (min)	Folding Endurance
F1	0.30 ± 0.01	-	6.32 ± 0.21	304 ± 2.2	191 ± 9
F2	0.44 ± 0.01	-	6.23 ± 0.04	468 ± 1.8	221 ± 3
F3	0.33 ± 0.01	98.90 ± 0.3	6.30 ± 0.03	256 ± 1.4	174 ± 8
F4	0.31 ± 0.02	99.01 ± 0.4	6.02 ± 0.14	168 ± 2.1	155 ± 5
F5	0.46 ± 0.02	99.21 ± 0.3	6.42 ± 0.04	367 ± 1.9	193 ± 6
F6	0.49 ± 0.01	99.54 ± 0.2	6.51 ± 0.05	202 ± 3.7	175 ± 4
F7	0.32 ± 0.01	99.00 ± 0.6	6.31 ± 0.09	593 ± 2.4	189 ± 8
F8	0.48 ± 0.01	99.95 ± 0.3	6.24 ± 0.05	673 ± 1.8	232 ± 3
F9	0.28 ± 0.01	-	6.41 ± 0.08	694 ± 2.3	201 ± 8
F10	0.48 ± 0.01	-	6.22 ± 0.02	876 ± 3.4	267 ± 12

Note: Mean ± SD and n=3

Physico-Mechanical Properties of Chitosan Films

regarding the residence of the formulation on the mucous membrane, which can be useful for controlled drug delivery to a local site. The in vitro drug release and permeation study indicate the total amount of drug release in specific time. The surface pH of prepared films was found to be in the range of 6.02 to 6.51, which may not cause any irritation (Table 2). The swelling study results indicated absence of any changes in shape; however, changes in thickness were observed due to swelling of the polymer. The chitosan film formulation showed the swelling index ranging from 10 to 28 in 6 hrs. The swelling study of chitosan in CLZ non-cross-linked films (F7 to F10) indicated that the rate of swelling was directly proportional to polymer content (Figure 1). However, the chitosan CLZ films cross-linked with TPP (F1 to F6) showed the decrease in swelling index compared to non-cross-linked film with the same amount of chitosan (F1 and F9). Even as the TPP increased, a decrease in swelling index was observed from 9.62 ± 0.31 to 7.24 ± 0.25 for F1 and F2, respectively. Of the drug containing films, the most prolonged swelling was observed in formulation F6 (9.96 ± 0.28 in 6 hours), and it still continued to swell. Both drug and TPP gave negative effect on swelling property of films (F1 to F8), although later they showed significant effect in reduction of the swelling index.

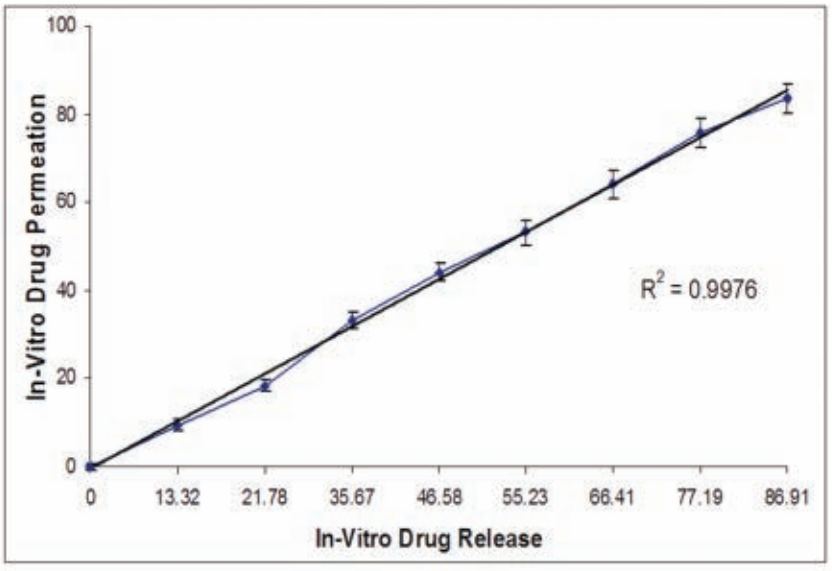
Mucoadhesion may be defined as the adhesion between a polymer and mucus. In general, mucoadhesion is considered to occur in three major stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors, such as molecular weight of polymers, contact time with mucus, swelling rate of the polymer, and biological membrane used in the study. In this study, sheep buccal mucosa was used as a biological membrane for mucoadhesion. The films containing higher proportion of non-cross-linked chitosan showed good mucoadhesive strength in 8 minutes of contact time. The plain film with neither drug nor cross-linking agent containing higher proportion of chitosan (F10) exhibited the highest bioadhesive strength (28.5 ± 1.1 g). However, all the non-cross-linked films exhibited good mucoadhesive strength with sheep buccal mucosa compared to cross-linked films F7 to F10 ranging from 17.2 ± 0.8 to 28.5 ± 1.1 g. Even incorporation of drug had a slight negative effect on mucoadhesive strength (Table 3). The results of folding endurance indicated that higher amounts of chitosan lead to higher folding endurance: 201 ± 8 and 267 ± 12 in plain films F9 and F10, respectively. Cross-linking agent and incorporation of drug in films had a slightly negative effect on mechanical properties. The lowest folding endurance was observed in the F4 formulation (155 ± 5).

In formulations with CLZ, the highest mucoadhesion time was observed in non-cross-linked films F8 with 2% chitsoan; 673 min ± 1.8 min and shortest time in F4; 168 min ± 2.1 min, which indicates that polymer concentration had a positive effect and cross-linking agent had negative effect on mucoadhesion time (Table 2).

The drug-release rate decreased with increasing amount of chitosan in the non-cross-linked formulations; F7 and F8 after 3 hours of dissolution 72.9% ± 3.5% and 68.7% ± 3.1%, respectively (Figure 3). This may be due to higher viscosity of the swell films, which produces resistance to release the drug, and hence slower dissolution. However, in the case of cross-linked films, the drug-release rate decreased as the amount of cross-linking agent increased (F3 to F6). The comparison of the different batches with similar amount of chitosan, cross-linked and non-cross-linked with similar amount of TPP, showed (F3 with F5 and F4 with F6) that TPP had a significant negative effect on release compared to simply increasing the amount of chitosan. Overall, drug release was directly related to swelling of formulations, and that may also be a proposed mechanism of drug release by dissolving the drug in absorbed fluid. So higher concentrations of chitosan in formulations F1 to F8 swell slower and consequently give rise to slower or prolonged release of drug. Maximum in vitro drug release from prepared film was found in F7 (90.27% ± 3.57%), and it was prolonged in the F6 (77.19% ± 2.75%) over a period of 6 hours. All films remained intact during the 6-hour period in the dissolution study.

Formulation F4 containing 1%

FIGURE 4



Correlation of In Vitro Drug Release & In Vitro Drug Permeation of Chitosan Film Containing CLZ

TABLE 3

Batch Code	Mucoadhesive Strength (g)[a]	Force of Adhesion (N)	Bond Strength (Nm^{-2})
F1	6.9 ± 0.3	0.0676	336.32
F2	12.5 ± 0.6	0.1222	608.20
F3	5.9 ± 0.3	0.0575	286.04
F4	10.5 ± 0.5	0.1028	511.55
F5	8.4 ± 0.4	0.0826	411.00
F6	14.4 ± 0.7	0.1411	701.92
F7	17.2 ± 0.8	0.1686	839.08
F8	24.5 ± 0.9	0.2421	1204.68
F9	19.4 ± 0.8	0.1905	947.93
F10	28.5 ± 1.1	0.2792	1389.19

[a]Mean ± SD, n=3

Mucoadhesive parameters of chitosan films

polymer and cross-linked with 0.2% TPP was optimized as it showed moderate swelling, good mucosal residence time, and prolonged drug release. This formulation showed 86.91% ± 1.09% CLZ release in 7 hours, 10.48 ± 0.5 g of mucoadhesive strength, 168 ± 2 minutes of ex vivo mucoadhesive time, and 155 ± 5 folding endurance.

The optimized formulation was further studied for in vitro drug permeation. The CLZ permeation in 7 hours through sheep buccal mucosa was 83.72% ± 3.34%. Good correlation was observed between in the in vitro drug release and in vitro drug permeation study with correlation coefficient of 0.9976 (Figure 4), which was statistically significant at 5% confidence level.

CONCLUSION

The study of chitosan film formulations indicating prolonged drug release was achieve by cross-linking chitosan film with TPP, which can be a useful carrier for local mucosal drug delivery for buccal, nasal, vaginal, and rectal drug delivery of antimicrobial agents.

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BIOGRAPHIES

Bhupendra G. Prajapati earned his MPharm in Pharmaceutics and Pharmaceutical Technology. He has been working as an Assistant Professor at the S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva, North Gujarat, India. He has 7 years of experience in academic/industry. He claims on his name more than 30 national and international presentations as well as publications. He secured research, travel, as well as staff development grants from national and state government for different areas.

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DRUG DELIVERY Executive

Jean-Luc Herbeaux, PhD
Head of Business Line Pharma Polymers

Evonik Degussa Corporation

"Last year, we announced the expansion of our value proposition to better match our customers' value chain. We expanded our offering to include services, such as custom-tailored formulation development, clinical batch manufacturing, process technology support, and development of highly sophisticated drug release profiles matching customer requests. By combining over 50 years of EUDRAGIT® formulation science and savoir-faire and newly developed expertise, we help our customers accelerate their most complex product development projects."

Evonik Pharma Polymers: A Company in Transition

Evonik Industries, a global market leader in specialty chemicals, offers a broad portfolio of products and services to the pharmaceutical market. Pharma Polymers, a business line within the Chemicals Business Area of Evonik, has a leading position in the manufacture and supply of functional coatings for the pharmaceutical industry. EUDRAGIT® acrylic polymers are used for enteric coatings, sustained-release formulations, immediate-release, and protective applications for oral solid dosage forms. Dr. Jean-Luc Herbeaux has been at the helm of the Pharma Polymers Business Line, the house of EUDRAGIT®, since the beginning of 2009. Dr. Herbeaux, who joined Evonik Industries (formerly known as Degussa) in 2000, worked for the RohMax Oil Additives business line, specializing in lubricant additives before joining Pharma Polymers. Drug Delivery Technology recently interviewed him to discuss how Pharma Polymers is working with customers to meet drug delivery challenges in the global market.

Q: Can you discuss the main differences between your previous assignment and your current job.

A: The automotive industry in which RohMax primarily operates has been hit hard by the global crisis. Even before last year's economic storm, the automotive industry was mostly driven by cost optimization and exhibited anemic growth. In this low-growth, cost-obsessed environment, offering solutions that promote value-addition is a true challenge. Nevertheless, RohMax Oil Additives has been very successful in creating value for shareholders and customers alike by offering innovative approaches, such as additive solutions for fuel efficiency enhancement while preserving strong operational effectiveness. Comparatively, the pharmaceutical industry offers higher organic growth and plenty of energy for creative and innovative approaches. Yet, companies have to be creative and resourceful to increase their short-term maneuverability due to limitations associated with the long-time-to-market. Regardless, the fundamentals for sustainable success remain essentially the same: solutions to customers and operational excellence.

Q: What impact does the current difficult world economic situation have on the Pharma Polymers' business?

A: The pharmaceutical industry has shown some resilience to the crisis. Published data show that the market only experienced a moderate reduction in growth. Some of the pharmaceutical players may have experienced greater swings as consumers switched to budget brands, i.e., private labels and generics. In our business, this last trend created significant geographic shifts in demand. We also have experienced the effect of stricter cash management at our customers, with order forecasts becoming a lot more short-sighted. These trends have made forecasting more of a challenge, but our strong commitment and preparedness to provide customers with high levels of supply reliability has enabled us to cope with these developments.

Q: How will Evonik proceed with its strategy for the future?

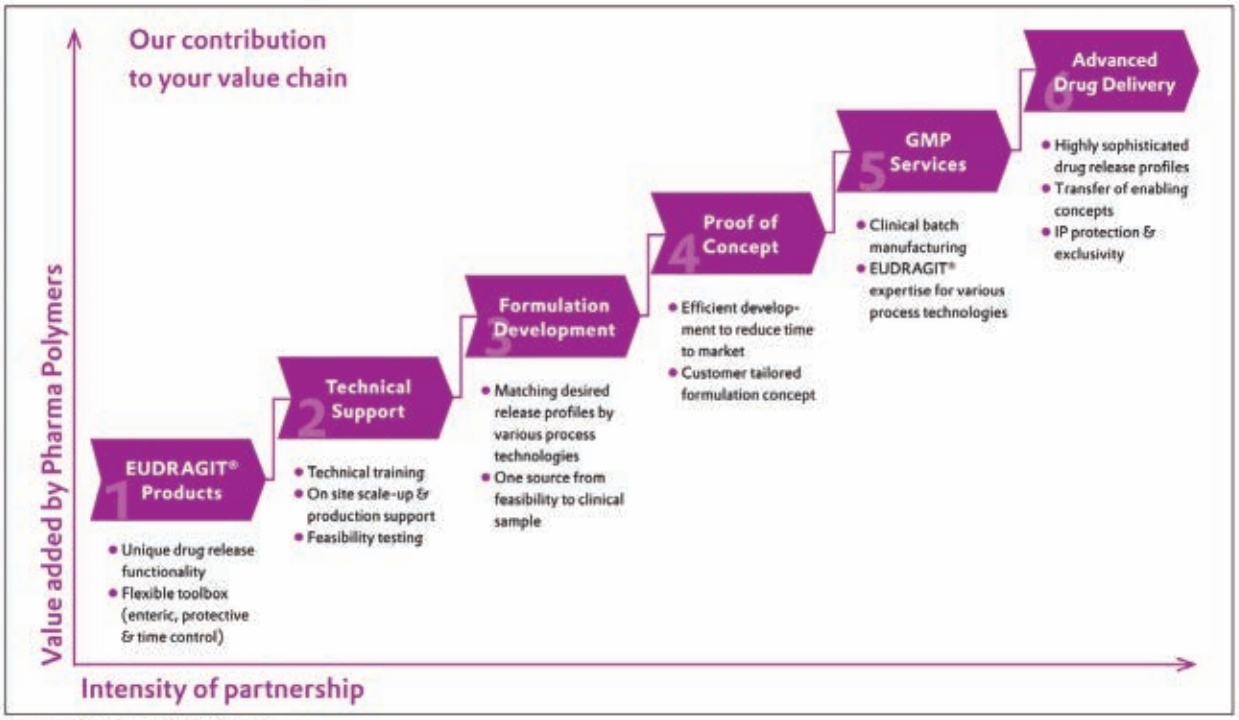
A: I sometimes reflect on what it could be like to be 18 again and know what I know today - coupling the wisdom of decades of experience with fresh legs and an almost unlimited energy pack to explore and grow tirelessly. This bold combination is what Evonik Pharma Polymers yearns to achieve as a business–relying on the strength of more than 50 years of experience in the pharmaceutical functional excipient business while building on new energy and ambition to become an even stronger strategic resource to our customers.

There is no doubt that the pillars of our past success, namely operational excellence, effective customer support, and superior product technology and services, are and will continue to be essential elements of our success. But our new legs will take us further. Last year, we announced the expansion of our value proposition to better match our customers' value chain. We expanded our offering to include services, such as custom-tailored formulation development, clinical batch manufacturing, process technology support, and development of highly sophisticated drug-release profiles matching customer requests as shown in the Value Chain graphic. By combining over 50 years of EUDRAGIT® formulation science and savoir-faire and newly developed expertise, we help our customers accelerate their most complex product development projects.

Q: What are the main challenges associated with this shift?

A: Moving further into the pharmaceutical industry value chain beyond polymer supply for coating and matrix applications and basic technical support does not happen overnight. One of the most elementary "brakes" is market perception. Market players need time to change perceptions developed over many years. Moreover, if most managers out there are like me, they must feel somewhat wary of any new capability claims. Today's tendency for disinformation and hype creates skepticism toward even the earnest statements. This being said, I am glad to report that our prudent and committed approach is starting to pay off, and a perception shift is now visible.

Another aspect, which I would qualify more as an opportunity than a challenge, has to do with the necessary level of partnership with our customers to offer them true value. Most of our service offers are custom designed to fit the needs of the customers. This requires a higher level of intimacy with our customers, which can only be achieved with increased proximity. We must be present where our customers need us most and actively listen to better serve. This translates in continuous efforts to become more international and local in our listening, thinking, and execution. The strengthening of our global technical service laboratory network with recent expansions of our R&D service centers in India and in China supports this orientation. Add to this the newly planned expansion of our laboratory facilities in Tsukuba, Japan, and you will understand the



Pharma Polymers Value Chain

true measure of our commitment to local expert service.

Q: Will innovation play a major role in this strategy?

A: At the risk of being obvious, innovation is what will allow us and our customers to remain differentiated from the competition. And differentiation is value. We have started a number of programs in the area of innovation management process and corporate culture to boost our ability to innovate not only technically but also in business matters. New innovative approaches and products are in the works, some of which will be ready to hit the market as early as next year. It is one of the management team's constant targets to increase the speed and the breadth of our innovation.

Q: What is essential for the continued growth for Pharma Polymers in this?

A: Pharma Polymers is blessed with a strong and dedicated group of employees who feel ownership for the success of the company. As markets and challenges become more complex, it becomes increasingly important that our employees operate as a global unit with superior communication, cooperation, and support. We believe this is best achieved in a culture that promotes constructive elements, such as performance orientation, fulfillment via empowerment, and cross-regional and cross-functional teamwork. The resulting boost in employees' morale, engagement, and alignment is what powers our battery pack for further exploration and growth and makes us an even greater resource for our customers. Evonik Pharma Polymers has always been a great company to be associated with whether as a customer, a partner, or an employee, and I am fully committed to strengthening its attractiveness. ◆

Technology Showcase

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

Development Services

Azopharma Product Development Group, The Total Product Development Company™, is dedicated to providing clients with comprehensive product development services from discovery through commercialization. Azopharma maximizes communication and minimizes downtime by bundling services from key sections of the drug development process, including the Preclinical, CMC, and Clinical phases. Our capabilities include Full NCE Development, Full IND Development, Full NDA Development, Full ANDA Development, and Full Medical Device Development. Whether it's a stand-alone service or a comprehensive program, Azopharma has the solution to fit your needs! Our group of companies includes Azopharma Contract Pharmaceutical Services, AniClin Preclinical Services, and AvivoClin Clinical Services. For more information, contact Azopharma Product Development Group at (954) 433-7480, development@azopdogroup.com, or visit **www.azopodogroup.com.**

Film Coatings

BASF's Kollicoat® grades can be employed as film coatings with controlled-release agents, for instant-release, enteric, or sustained-release applications. Our polymer compounds deliver maximum quality in terms of function, stability, and appearance. Kollicoat is extremely cost effective because relatively little is required to achieve great results. In addition, Kollicoat can be used with all standard coating equipment. This simplifies the production process, accelerates spraying, and reduces the time and effort involved in cleaning equipment after use. Kollicoat® IR creates a robust, glossy film of exceptional flexibility, which increases tablet stability, reliably protecting the active ingredients. At the same time, the film remains highly water-soluble. And significantly enhanced process ability helps cut the cost of producing coated tablets. For more information, contact BASF at pharma-ingredients@basf.com or visit **www.pharma-ingredients.basf.com.**

Prefillable Delivery Systems

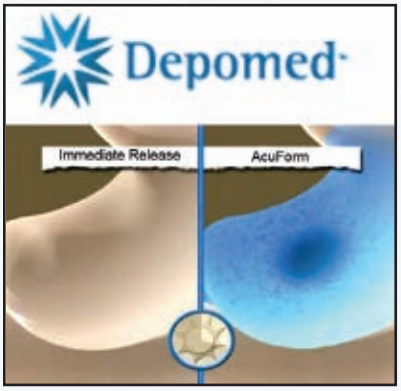
BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. BD offers a range of products, including glass and plastic prefillable syringes, a nasal spray system, and a variety of self-injection systems. We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

Technology Showcase

Capsule Filling & Sealing

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

Upper GI Delivery



AcuForm is Depomed's unique, patented, polymer-based technology designed to optimize drug delivery. AcuForm allows for targeted, controlled delivery of pharmaceutical ingredients to the upper GI tract, the preferential absorption site for many oral drugs. Unlike immediate- and some extended-release formulations that pass through the upper GI tract within approximately 3 hours following ingestion, AcuForm's unique swelling polymers allow the tablet to be retained in the stomach (gastric retention) for approximately 8 to 9 hours. During this time, the tablet's active ingredient is steadily delivered to the upper GI tract at the desired rate and time, without the potentially irritating burst of drug that often occurs with other formulations. For more information, visit Depomed, Inc. at **www.depomedinc.com.**

Development & Manufacturing

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

Bioavailability Enhancement

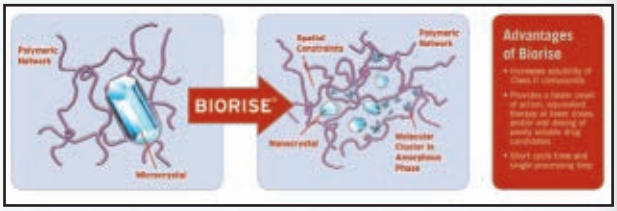
Elan Drug Technologies' NanoCrystal® technology is a drug enablement and optimization technology applicable to poorly water-soluble compounds. Improved bioavailability provided by the NanoCrystal technology can result in the following benefits: increased rate of absorption, reduction in fed/fasted variability, improved dose proportionality, rapid formulation development, and reduction in required dose with smaller and more convenient dosage forms. Five products incorporating the technology are now launched in over 100 markets worldwide with over $1.8 billion in market sales achieved in 2008. With over 1,300 patents/patent applications worldwide, it has been optimized and simplified from over 15 years in development. Applicable to all dosage forms, it has been manufactured at commercial scale since 2001. For more information on our range of technology solutions, contact Elan Drug Technologies at edtbusdev@elan.com or visit **www.elandrugtechnologies.com.**

Technology Showcase

Particle Engineering

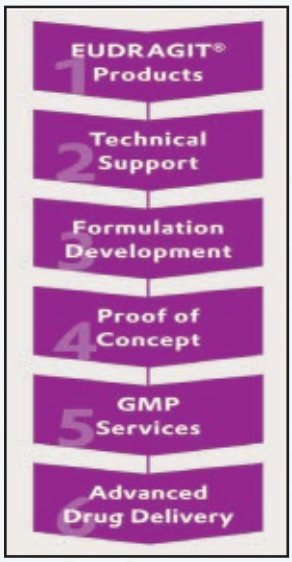
Enavail provides particle engineering expertise for increasing the bioavailability of proteinaceous compounds and poorly water-soluble drugs. Enavail's core technologies are focused on two key areas: a) producing high surface area, non-degraded powder forms of labile proteins and b) generating crystalline or amorphous forms of poorly water-soluble compounds, providing high potency and greatly enhanced dissolution. Our company's proprietary particle design capabilities include novel, validated, and scalable technologies for use with multiple routes of administration (oral, pulmonary, intranasal, parenteral). A highly controllable "bottom up" approach is taken, creating precise particle size and morphology. Enavail offers custom solutions to partners from initial drug screening (microgram to gram quantities) through to final product development. State of the art research and GMP manufacturing facilities are located in Austin, Texas. For more information, contact Enavail at (512) 697-8161 or **visit www.enavail.com.**

Bioavailability Enhancement



Biorise® increases the "intrinsic dissolution rate" of poorly water-soluble drugs, thereby enhancing their bioavailability and/or onset of action. Eurand's proprietary Biorise and Diffucaps® technologies can be applied to enable formulation of insoluble drugs and to improve the rate and extent of absorption of drugs from oral dosage forms. Diffucaps is a multiparticulate system that provides flexible dosage strength, required PK profile, and optimal release profiles for single drugs and drug combinations. The Diffucaps drug-release system can also be used in combination with other Eurand technologies to enhance drug solubility in the GI tract. For more information, visit Eurand at **www.eurand.com** or email us at partners@eurand.com.

Pharma Polymers



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

Wireless Data Collection

Total Tech
"Creation Thru Innovation"

Total Tech Medical, LLC, is the innovator of COMMAND CONTROL MODULE™ utilizing live non-in vivo data analysis and collection - one of the most exciting advances in remote medical data collection and chemical analysis in several decades. Through the integration of cutting-edge medical devices, software, engineering, and wireless technology, Total Tech Medical offers the ability to substantially minimize the time and expense involved in bringing new drugs to market. By providing live data collection capabilities, patient activity and adherence can be logged continuously, resulting in cleaner, more accurate data. This groundbreaking technology can also be integrated into a broad range of applications, such as chemical sensory devices (transdermal chemical detectors, specimen sample detectors, etc), bio-sensory devices (cardiac, diabetic, epileptic), and countless others. For more information please contact Total Tech Medical, LLC at (973) 551-2189 or visit **www.totaltechmedical.com.**

Technology Showcase

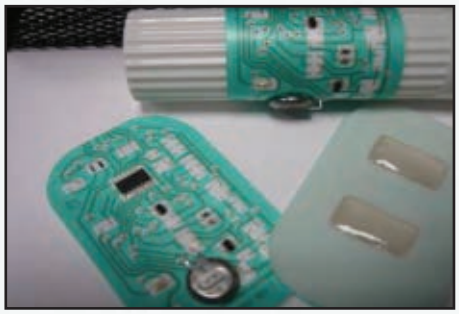
Manufacturer & API Specialist

Hovione is an international group dedicated to the cGMP development and manufacture of APIs, serving exclusively the pharmaceutical industry. With FDA-inspected plants in Europe, the Far East, and the US, Hovione is committed to the highest levels of service and quality. With a 50-year track-record, Hovione offers advanced technologies as well as APIs for all drug delivery systems, from oral to injectable and from inhalation to topical applications. Specializing in complex chemistry and particle engineering, Hovione offers all services related to the development, manufacture, and preformulation of both NCEs and existing APIs for off-patent products. Our aim is to do well what is difficult, to give our customers what they cannot find elsewhere. For more information, visit Hovione at **www.hovione.com.**

Combination Capsule Technology

InnerCap offers an advanced patent-pending multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions to problems affecting pharmaceutical companies, patients, and healthcare providers. The delivery system will be licensed to enhance pharmaceutical and biopharmaceutical products. It is a very effective way to deliver multiple active chemical compounds in different physical phases with controlled-release profiles. The delivery system provides the pharmaceutical and biopharmaceutical industries with beneficial solutions to the industry's highly publicized need to repackage and reformulate existing patented blockbuster drugs with expiring patents over the next 5 years. For more information, contact InnerCap Technologies, Inc., at (813) 837-0796 or visit **www.innercap.com.**

Iontophoretic Patch



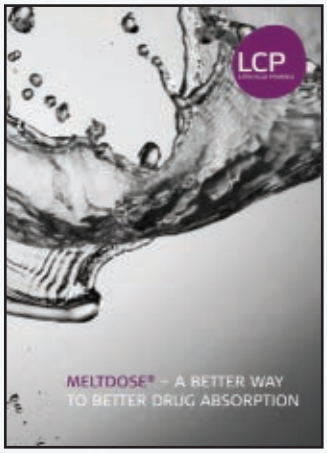
Isis Biopolymer, Inc. is expanding the capabilities of active transdermal drug delivery with its breakthrough product, the Isis Patch. The first compact, wireless, active iontophoretic patch to be fully programmable by healthcare professionals, the Isis Patch enables physicians to control activation, monitor use, and adjust drug delivery to each patient. Proprietary hydrogels allow dosing of multiple drugs, as well as a wide variety of drugs. A smaller, softer, and more flexible design resembles a band-aid, while hypoallergenic, skin-friendly polymers eliminate irritation and enable the patch to be worn for up to 7 days with superior adherence to the skin. Isis Biopolymer's lower cost, environmentally friendly manufacturing process reduces the cost of conventional iontophoresis by much as 50%. For more information, contact Isis Biopolymer at (401) 921-6873 or visit **www.isisbiopolymer.com.**

Airless Bottle

LABLABO's new EasyFoil bottle is fitted with a pouch consisting of an aluminum multilayer film rolled up and welded around a superior ring and an inferior cup, both produced in a thick plastic material. The film is composed of an exterior PET layer and an interior PP or PE layer wrapping a central aluminum layer of 12 microns in thickness. Depending on the nature of the product used, the internal layer choice will be PP or PE, the ring and cup being produced in the same material with a sufficient thickness to provide a perfect barrier, especially against oxygen or UV. EasyFoil accepts the most viscous products (> 100.000 cps) and the most fluid (alcohol) and offers excellent restitution, the bottle could be used upside-down, precise dosage delivery, or containment of the pouch at a stand still position, an ideal packaging for transdermal applications. For more information, visit Lablabo at **www.lablabo.com**, or e-mail l.khoury@lablabo.fr.

Technology Showcase

Absorption Enhancement



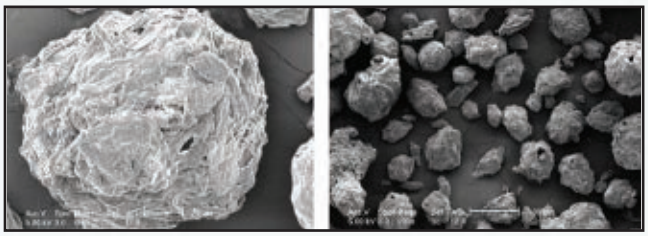
LCP is an emerging specialty pharmaceutical company focused on certain cardiovascular indications and organ transplantation. It currently has one product on the market, seven clinical development programs covering five product candidates, and three product candidates in preclinical development. Its first commercialized product, LCP-FenoChol, has received FDA approval for sale in the US under the brand name Fenoglide™ and is marketed in the US by Sciele Pharma. Fenoglide and its other development compounds are based upon its unique drug delivery technologies. The proprietary MeltDose® platform enhances the absorption of poorly soluble drugs. Applying MeltDose technology creates new versions of existing drugs with improved oral bioavailability, improving efficacy, allowing for lower dose, and in some cases, reducing food effect and/or potential side effects. For more information, visit LCP at **www.meltdose.com.**

Transdermal & Oral Films

LTS Lohmann Therapy Systems

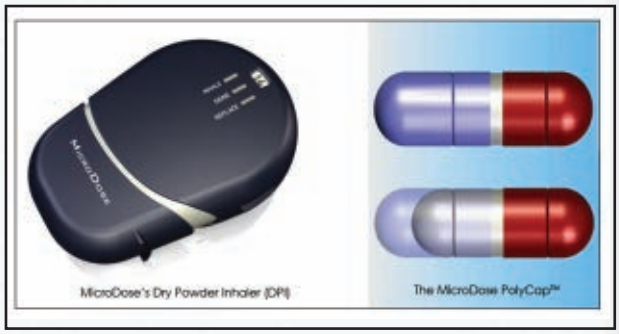
LTS Lohmann Therapie-Systeme AG is a world-class developer and manufacturer of transdermal systems, oral film drug delivery systems, and adhesive laminates. We use leading-edge technology to manufacture developed products on a large and cost-effective commercial scale. LTS develops products from inception through commercialization in our facilities in Germany and the US under GMP conditions, both approved by the FDA and European Authorities. Our partners include many of the world's successful pharmaceutical, consumer healthcare, medical device, and diagnostic companies. Our resources include research & development, clinical pharmacology, technology transfer, analytical, regulatory affairs, quality assurance, operations, and product support. For more information, contact LTS Business Development at ltsgroup@ltslohmann.de or visit **www.ltslohmann.com.**

Performance Excipients



Mallinckrodt Baker recently launched PanExcea™ MHC300G performance excipient, a homogeneous particle that serves as a filler, binder, and disintegrant for immediate-release applications. Manufactured using novel particle engineering technology, the granular spherical excipient provides multifunctional performance capabilities that enable efficient and cost-effective drug development and manufacturing. PanExcea MHC300G lowers the total cost of ownership for the drug formulator by facilitating direct compression of even the most difficult APIs. It offers extensive API compatibility and variable API load capability to increase formulation flexibility. PanExcea MHC300G, which can be used as a building block or as a complete excipient, provides formulation development flexibilities and efficiencies, and enables implementation of Quality by Design (QbD) initiatives. For more information, contact Mallinckrodt Baker at (800) 943-4747 or visit **www.MallBaker.com/PanExcea.**

Pulmonary & Oral Delivery



MicroDose Therapeutx is pioneering the creation of next-generation products utilizing its proprietary technologies. MicroDose's Dry Powder Inhaler (DPI) and PolyCap™ combination oral dose capsule system promise to dramatically improve efficacy and compliance. MicroDose's next-generation DPI is a state-of-the-art electronic inhaler providing superior delivery for both small and large molecules to the lungs. It provides a platform technology that is low cost, reusable, and environmentally friendly, which can support a full pipeline of products. MicroDose's PolyCap System is a proprietary approach that enables the rapid development of FDC therapies in a single dose, but separated by a physical barrier. Utilizing the proven strengths of capsules and the advantages of a barrier system, it allows for more rapid development timelines and lower regulatory requirements. For more information, contact MicroDose Therapeutx at (732) 355-2100 or visit **www.mdtx.com.**

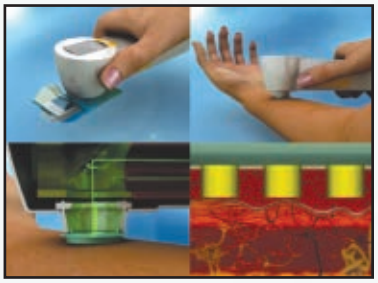
Technology Showcase

Functional Phospholipids

from the biosphere to outer space.
NOF CORPORATION

NOF has several solutions for the targeted delivery of any kind of drug with its unique and advanced technologies. The company's Functional Phospholipids are its top-tier drug delivery system excipients for targeting liposome formulations and lipid micelles. Its current customers have been using NOF phospholipids for oncology, neurology, metabolic diseases, and other therapeutic areas. NOF has also been developing prototype DDS liposome formulations with transferrin, mainly used for tumor cell targeting for oncology. The main product line of Functionalized Phospholipids includes Activated Phospholipids (Maleimide Phospholipid and Calboxyl Phospholipids), Activated PEG-Phospholipids (Maleimide PEG-Phospholipids, Calboxyl PEG-Phospholipids and Amino PEG-Phospholipids), and Fluorescent Phospholipids. Custom-made phospholiids are also available. For more information, contact NOF America Corporation at 914-681-9790 or visit **www.phospholipid.jp.**

Intraepidermal Delivery



P.L.E.A.S.E.® (Painless Laser Epidermal System) is a novel transdermal delivery method for high molecular weight drugs. A hand-held laser device creates controlled aqueous micropores in the epidermis. Due to the special 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 medical personnel or patients, who can use the device without supervision. A special laser source ablates outer skin tissue painlessly in a highly controlled and accurate fashion. Features and benefits include very short pulses that practically eliminate thermal damage; fast and accurate ablation of skin tissue; and scanner optics allowing for flexible formation of pore arrays. For more information, contact Pantec-Biosolutions at +423 377 13 90 or visit **www.pantec-biosolutions.com.**

Development & Delivery Solutions

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

Delivery & Specialty Pharma

Penwest has a family of patented drug delivery technologies with a proven track-record (TIMERx®, Geminex®, SyncroDose™, and GastroDose®), all of which are available for product development. Products based on these technologies have been approved and marketed around the world. Our most recent success is Opana® ER, a pain product with $100 million+ sales in its first year of launch. Our technologies are well-suited for drugs with solubility, bioavailability, or site-specific delivery issues. The formulation flexibility and range of potential delivery profiles, coupled with a successful track-record of product approvals, is what attracts companies to TIMERx technologies for reinvigorating their products and extending exclusivity. For more information, please e-mail bizdev@penwest.com or visit **www.penwest.com.**

Technology Showcase

Safe Dispensing

The Cartridge Pump System (CPS) by Pfeiffer is committed to excellent patient safety and reducing time to market in the face of increasingly stringent regulations. Designed by an in-house team of experts, this modular system offers microbiological integrity that makes it suitable for protecting and administering preserved and unpreserved products. A metal-free fluid path makes it ideal for oxidizing formulations and for protection from crystallization. Since spray pump delivery brings the container closure and drug dispensing systems into direct contact, safe dispensing is thus assured. Its excellent spray performance enables dose uniformity over the device's entire lifetime, even with irregular use. Complemented by the highest service standards, the CPS is the new benchmark on the global market for multidose sprays. For more information, visit Pfeiffer of America at **www.pfeiffer-group.com.**

Knowledge Management

PharmaCircle™

PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (847) 729-2960 or visit **www.pharmacircle.com.**

Contract Service Provider

PharmaForm doesn't just provide its clients with creative solutions; it creates successful partnerships. As a pharmaceutical contract service provider, it offers a wide range of formulation, drug product development, manufacturing, analytical testing and stability services, patent litigation support services, and product platform licensing opportunities. Its formulation scientists have core expertise and experience in improving solubility of poorly soluble compounds. One such available technique to clients is Evaporative Precipitation into Aqueous Solutions (EPAS), a process that causes the formation of nano-sized particles that can help enhance bioavailability of a poorly soluble compound. PharmaForm's state-of-the-art facility is registered with the FDA and the DEA and is cGMP/GLP Compliant. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com.**

Intranasal Delivery System

The µco™ system is a novel intranasal drug delivery system developed by SNBL, Ltd., consisting of a mucoadhesive powder carrier and user-friendly delivery device. Effectiveness of the µco system has been shown in clinical studies. Granisetron administered by the µco system showed a similar PK profile to IV injection (around 100% BA) in Phase I and dose response of clinical efficacy in patients on highly emetogenic chemotherapy in Phase II, while showing excellent safety profile. The µco system is a promising drug delivery system for various drug compounds, including small molecules and peptides. Further, the µco system is expected to be applicable to intranasal vaccines and is currently under further investigation. The system is available for out-licensing, as well as SNBL's pipeline of products using the µco system (granisetron, triptan, fentanyl, etc). For more information, e-mail SNBL Ltd. at info@trltd.co.jp or visit **www.trltd.co.jp/.**

Technology Showcase

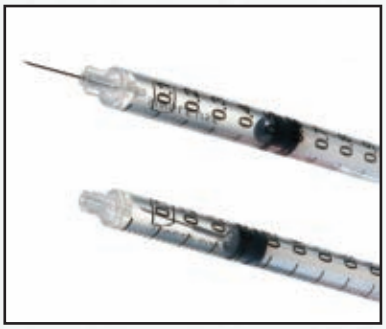
ODT Excipient System

SPI Pharma recently announced the launch of Pharmaburst® 500. Using proprietary technology with superior organoleptics, Pharmaburst 500 will raise the bar in terms of performance and economics that formulators have come to expect from a quick-dissolve dosage form. Studies show that Pharmaburst 500 outperforms all of its direct competitors with respect to product functionality and organoleptics. It is easy to use, cost-effective, and readily formulated with various actives to make robust orally disintegrating tablets (ODTs). The finished ODT can be manufactured internally rather than through outsourcing. The Pharmaburst® platform was the first off-the-shelf, patented, co-processed ODT excipient system introduced in the pharmaceutical market. For more information, visit SPI Pharma at **www.spipharma.com.**

Performance Excipients

Pharmaceutical excipients produced by Stepan Company feature outstanding performance characteristics for use in the development of medical delivery systems including topical formulations. NEOBEE® Medium Chain Triglycerides are odorless, colorless, and naturally derived. Their low viscosity and polar nature facilitates handling under low-temperature processing conditions and promotes improved dispersibility, spreading, and dissolution of actives. ONAMER® M (Polyquaternium-1) exhibits unique antimicrobial activity, is extremely mild, and exhibits very low toxicity to host cells, allowing ONAMER® M to function in a wide range of medical device applications, including surgical scrubs, surgical preps, and other topical formulations requiring a broad spectrum of antimicrobial efficacy. For more information, contact Stepan at (201) 712-7642 or visit **www.stepan.com.**

Prefilled/Clinical Safety Syringes



Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply with needlestick prevention laws and encourage single-use and safe disposal practices outside of healthcare settings. The products feature a passive (automated) needle retraction mechanism allowing operators to control the speed of needle retraction directly from the body into the barrel of the syringe. The Unilife Ready-to-Fill Syringe features a glass barrel and is compatible with the manufacturing procedures used to fill standard prefilled syringes. The Unitract 1-mL Insulin Syringe is FDA certified and now being manufactured in the PA facility. For more information, contact Unilife at (717) 938-9323 or visit **www.unilife.com**

Drug Development

Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose®, which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality. For more information, contact Xcelience at (608) 643-4444 or visit **www.xcelience.com.**

Minimizing Cardiovascular Liabilities Throughout Drug Development

By: Alain Stricker-Krongrad, PhD, Chief Scientific Officer, and Stephen Wilson, Senior Research Scientist, Charles River

Introduction

The various effects of pharmaceuticals on the cardiovascular system are currently a major topic of interest throughout the drug development industry. This cardiovascular focus is primarily due to the fact that drugs–even those not specifically designed to directly affect cardiovascular function–can easily alter this fragile but vital organ system. As a result, specialized precautions must be taken throughout a drug discovery and development program. These precautions require the conduct of specific studies that can increase the overall complexity and require additional risk/benefit assessments. Potential cardiovascular toxicities can become more evident as a lead candidate enters the later stages of drug development.

Potential Cardiovascular Toxicities

A primary issue for drug development involves the interruption of the heart's electrical cycle due to blocking the human ether-à-go-go related gene (hERG) channel. The hERG channel ensures that potassium is removed from cells while the heart is repolarizing. If the hERG channel is blocked, the amount of time it takes for the heart muscles and myocytes to prepare for the next heart beat becomes prolonged. The classic biomarker for assessing potential hERG block is the QT interval from the electrocardiogram (ECG). Such QT prolongation can often be fatal, causing Torsade de Pointes.

Several drugs have been removed from the market or are saddled with marketing restrictions and labeling requirements due to QT prolongation effects. As a result, it is imperative to assess QT liability early in the discovery and development process. There are a number of *in vitro*, *ex vivo*, and *in vivo* assays that can be used to identify potential QT liabilities. These assays can provide data that allow for the identification of potential toxicities early in the development process. As a result, researchers can focus effort and resources on compounds without QT liabilities.

Although an important part of cardiovascular toxicity, QT prolongation is only one potential liability. The cardiac system has a number of potential toxicity targets, including heart rate, conductivity, contractility, and many others, all of which are important areas of research. Drugs that cause changes in heart rate or impact the force of contraction of the left ventricle can result in very serious conditions, potentially culminating with mortality.

Front loading the development program with assays to identify potential cardiovascular risks is an important tool for minimizing investment in unsafe compounds and bringing safer drugs to market. In addition, early cardiovascular assessment expands the amount of data available when selecting doses and designing regulated preclinical studies and early clinical trials.

Safety Pharmacology

After discovery and early phase preclinical work has been completed and a lead compound has been identified, the program moves into preclinical safety testing, which includes toxicology and safety pharmacology studies. Safety pharmacology evaluates potentially undesirable pharmacodynamic effects of a test article on physiological function at the therapeutic range and above.[1] Regulatory bodies, such as the FDA, require a thorough assessment of the core battery of organ systems, which includes cardiovascular, respiratory, and central nervous system for new chemical entities. The results from the safety pharmacology studies are integral in setting doses and identifying end points that may require additional monitoring.

The field of safety pharmacology uses a two-tiered approach to assessment of the core battery. The first tier encompasses the standard end points, while second-tier assessments, or follow-up studies, are conducted to further assess the mechanism or

ramifications of a potential physiologic alteration caused by a test article. The standard end points for the assessment of the cardiovascular system include heart rate, ECG, blood pressure, and body temperature. These parameters are usually collected via telemetry, which allows for the data to be collected from conscious, unrestrained animals. Assessment should include the time after dosing when the physiologic change occurs, the duration of the effect, and the magnitude of the alteration. In addition, the physiologic changes should be correlated to systemic exposure of the drug by collecting concurrent samples or comparing results to a previously determined toxico-kinetic profile.

The standard cardiovascular safety pharmacology study provides ample opportunity to identify potential drug-related changes on heart rate, systemic blood pressure, ECG morphology, and ECG intervals; however, these studies cannot identify every potential cardiovascular liability of a drug. For example, monitoring left ventricular pressure can add an additional level of complexity to a study (more invasive surgery, increased costs), but the data collected can be key to identifying significant toxicities. Pimobendan, a phosphodiester III (PDE-III) inhibitor, increases myocardial contractility and causes some vasodilation. When pimobendan is administered, no significant alterations occur in heart rate or systemic blood pressure. When left ventricular pressure is monitored, an increase in contractility can be measured.[2] The increased contractility can lead to a proarrhythmic state (greater propensity for arrhythmias).[3]

Cardiovascular safety pharmacology is typically assessed in a single-dose, crossover design (all animals receive all doses). The inclusion of cardiovascular end points for large molecule biologics on toxicology studies is fairly standard, and this is typically the manner in which cardiovascular end points are monitored for large molecule biologics.[4] It is critical that the methods employed are sensitive enough to detect pharmacologically induced changes in the monitored parameters, and the results must be useful in the design of clinical studies by identifying specific end points that require monitoring in the clinic or limits on the doses that can and will be administered.

Clinical Assessment

In assessing preclinical data for use in clinical studies, it is important to understand what was actually observed. Many of the assays used in preclinical work are good predictors for QT prolongation (for instance, *in vivo* and hERG assays), but none are completely failsafe. Cases in which the preclinical data has predicted an absence of QT liabilities and the clinical studies have revealed the opposite occur at some frequency.

Many clinically available or investigational non-cardiovascular drugs and cardiovascular non-antiarrhythmic drugs have been identified as being able to delay cardiac repolarization.[5] Due to the large number of drug classes that can have deleterious effects, safety considerations should be directed at the early detection of undesirable cardiac repolarization at the early clinical phases of drug development. Although the degree of QT prolongation is an imperfect biomarker for pro-arrhythmic risk, QT liability is a valid and important cause for concern in drug safety, so more rigorous screening for potential QT prolongation is often needed. In addition, more detailed monitoring might be warranted in order to ensure that any idiosyncrasies of data are fully evaluated. For instance, a moderate decrease in blood pressure that occurs immediately after an intravenous bolus might be reason enough to monitor those participants more closely or have them cared for in specific ways during the clinical trial. This could include such seemingly insignificant actions as having participants receive the drug while sitting in a chair to minimize the chance of light-headedness or falling. In fact, a solid analysis of the data could reveal similar small alterations that can be undertaken to modify a clinical design for better success.

Another aspect of preclinical and clinical data that needs careful attention is the pharmacokinetic and pharmacodynamic profile of both humans and the animal models used in the preclinical study. For example, if it takes enormous concentrations of a compound to bring about QT liability in an animal model, and the clinical trial is set up for only microdosing, then the chances of QT liability are actually quite low. As a result, the investigational approach for a particular drug should depend on the pharmacodynamic, pharmacokinetic, and safety characteristics of the product, as well as on its intended clinical use. The clinical assessments should include the testing on QT interval as well as the collection of cardiovascular adverse events.

Due to the aforementioned considerations, drugs are expected to receive a clinical electrocardiographic evaluation early in clinical development, including a single trial dedicated to evaluating their effects on cardiac repolarization, the so-called thorough QT/QTc (TQT) study.[6] Many regulatory agencies mandate the TQT study regardless of what the preclinical data for a compound suggests, although some clinical factors can be considered that reduce the need for such a study.

The TQT study focuses on therapeutic doses and is based on a Phase IIa proof-of-concept supra-therapeutic dose approach, including the use of patient randomization, blinding, and concurrent placebo control group. The drug dosing should incorporate a reasonable dose-response range. A short-term upper dosing should have substantial multiples of the anticipated maximum therapeutic exposure. In many cases, metabolic inhibition can be used to achieve a high systemic level. Plasma concentrations of the drug (parent and metabolites) should be monitored at peak and trough at a minimum. Assay sensitivity also needs to be demonstrated. As a result, a positive control is routinely added (for instance moxifloxacin, an antibiotic that causes QT prolongation). In addition, careful considerations should be given to reduce QT/QTc intrinsic variability, as well as the use of parallel or crossover group study design.

Because the TQT study is intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, it is necessary to evaluate

both QT and corrected QT (QTc) to correct QT for the effect of heart rate. Many correction formulae are available; some are population-based corrections, such as Fridericia's or Bazett's, or inter- or intra-subject corrections based on linear regression analyses of QT to RR intervals relationships. Other approaches, such as the use of QT dispersion (maximum minus minimum QT intervals within a subject) to assess drug-induced alteration in ventricular repolarization have not yet been validated as risk indicator of pro-arrhythmia.

The threshold level of regulatory concern is around 5 ms. The evaluation is accomplished by calculating the largest time-matched mean differences in QT/QTc between post-drug and baseline versus placebo and baseline. The hope is that the one-sided (upper) 95% confidence interval around the mean effect can be shown to be less than 10 ms at every time point. In fact, a change of less than 5 ms is no risk, a change of 6 to 10 ms is unlikely risk, and a change of 11 to 15 ms is a possible risk, basically meaning that any changes over 10 ms will be flagged as an area of concern.

As a result, in order to make these studies work and accurately assess whether a risk of QT prolongation is present or not, the confidence interval must be minimized. This is accomplished by first minimizing the QT/QTc variation that is not due to the drug by screening or qualifying the individuals who will participate in the study (eg, avoiding enrollment of individuals who have a long-QT syndrome or hereditary long-QT intervals), ensuring that study conditions are uniform for all patients (minimizing stimuli, using a fixed-meal schedule) by keeping heart rate constant as much as possible, and using ECG acquisition technology that will provide the needed sensitivity (eg, continuous 12-lead data monitoring). Aside from minimizing the confidence interval, the number of data points and patients must be maximized at each ECG extraction time point by retaining enrolled participants and preventing lost data points.

Summary

Cardiovascular safety is an important part of any drug development program. A number of assays are available to identify potential toxicities during the discovery process, which can minimize time and resources spent on compounds with cardiovascular risks. Safety pharmacology studies, conducted during the preclinical safety portion of the drug development program, offer an opportunity to assess a wide array of potential cardiovascular liabilities. These studies are crucial in identifying potential functional changes that may impact dose selection and the addition of non-standard monitoring during clinical studies. In addition, it is important to confirm that the methods used during nonclinical assessments demonstrate sensitivity to clinically relevant changes and the results can be utilized by clinicians in the design of human trials. In early clinical trials, safety considerations should be directed primarily at the identification of a change in QT or QTc interval duration, as a marker of a risk of pro-arrhythmia. A specific and detailed clinical electrocardiographic evaluation should be conducted, including a single trial dedicated to evaluating effects on cardiac repolarization, focusing on supra-therapeutic doses and including the use of patient randomization, blinding, and concurrent placebo control group. If a risk of drug-induced pro-arrhythmia is identified by such a trial, expanded electrocardiographic safety evaluation during later stages of drug development will have to be considered. ◆

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Executive Summary

Allen Barnett, PhD
CEO, Kinex Pharmaceuticals

Kinex Pharmaceuticals: Novel Targeted Oncology Therapies for a Variety of Tumors

Kinex has the technology to discover and develop selective non-ATP competitive inhibitors of kinase-signaling pathways. As a proof-of-concept, Kinex is currently developing a small molecule inhibitor of src signaling and tubulin polymerization called KX2-391 (KX-01). It has just completed Phase I clinical trials with a good safety profile and pilot efficacy. Plans are in progress to initiate Phase II studies this year in at least two tumor types. One will include hormone-refractory prostate cancer, and either one of the leukemias (AML) or breast cancer (tamoxifen-sensitive and/or insensitive, triple-negative) are being strongly considered as the second tumor type. KX-01 worked against every type of human tumor tested *in vitro* and *in animal* xenograft models implanted with human tumor tissue. A second development candidate, called KX-02, is on an IND path, with Phase I clinical trials scheduled for early 2010. It is a highly lipophilic drug with exceptional brain penetration (76% of plasma levels) and potent effects on glioblastoma cell growth *in vitro* and *in vivo*. It also has a unique effect in causing the complete disappearance and lack of re-appearance of glioblastomas in more than 50% of the animals tested. Kinex has also launched several new discovery programs with potential success in immuno-inflammatory diseases, such as rheumatoid arthritis. CEO Allen Barnett recently spoke with *Specialty Pharma* magazine regarding the opportunities and challenges presented by developing new cancer drugs employing novel mechanisms of action.

Q: ***What is the history and background behind the formation of Kinex?***

A: Kinex was formed in 2004 based on technology developed at the University at Buffalo, The State University of New York. There were four cofounders as the only staff at the start, all with significant experience in pharmaceutical development and biotechnology. An outsourcing strategy was developed to keep overhead costs to a minimum. To date, funding has come from angels and governmental sources.

Q: ***You have said that PharmaDirections represents a new paradigm in drug product development. What leads you to believe that a new paradigm is needed?***

A: As Big Pharma companies increasingly depend on outside innovators to fuel their pipelines, we have seen an explosion of innovation and an accelerated progression of ideas from university labs into small companies. The new paradigm we are promoting extends this creativity and innovation into the drug development realm to maximize the potential of these exciting novel technologies.

For innovation to flourish, a diverse set of creative scientists needs to come together to exchange information and to build upon each other's ideas. Bureaucratic infrastructure has to be kept outside their realm to minimize the limitations to their time and thoughts. PharmaDirections provides the scientists and the team structure to foster this type of innovative development, and it also provides the project managers needed to facilitate execution through CROs.

The new paradigm is needed to ensure scientists can work together to create new technologies and new approaches, as well as optimal solutions to the challenges of drug development.

Q: ***Please go into more depth regarding your company's unique technology platform.***

A: The original technology was developed to design and synthesize substrate-competitive kinase inhibitors, using src (pronounced sark) as the initial target. This work began with a peptide backbone that was converted into a non-peptide following several synthetic iterations. After developing a library of these inhibitors, many of which were synthesized internally, this has served as a basis for finding lead compounds for other kinase targets. Substrate-competitive kinase inhibitors are more selective than ATP-competitive kinase inhibitors and thus have fewer side effects. Another advantage is that Kinex is one of the few companies to succeed in this area, and as a result, has an exceptionally strong patent portfolio based on the chemical structure, the holy grail of intellectual property position in pharmaceutical industry.

Q: ***What is your business model and what sets your company apart from others?***

A: Kinex has a three-part business plan to develop at least three development candidates and to take each of these to a clinical proof-of-concept stage before partnering. This would provide a strong pipeline that would be the basis for an IPO or some other liquidity event for our investors.

Kinex is unique because of several factors. It has succeeded in developing compounds that are target-selective and very potent. It has successfully employed a strategic business model that evolved from total outsourcing to (after modest hiring of several laboratory scientists) a mixture of external and internal activities. All development activities are outsourced, and most of its drug discovery work is in-house.

Finally, as of mid-2009, Kinex raised a total of $16 million and has the aforementioned two development candidates to show for the management team's cost effectiveness in drug discovery and development.

Q: ***Why would Kinex be an attractive investment and business partner?***

A: Kinex has continued to increase its value over the 5 years of its existence, from $7.5 to $20/unit. Because many of our investors have increased their investment during 5 sub-rounds of Series A, the price has involved only modest increases to make re-investment rewarding to them. Another attraction is that with two development candidates already achieved, Kinex is within a few years of an IPO or some other form of exit to liquidity. Lastly, Kinex is still keeping its G&A at a low level (< 15%) so that whatever money is invested goes almost entirely to fund R&D, which is the basis of a good investment.

Kinex has had a history of collaborating successfully with a number of outside groups in order to develop KX-01 and KX-02, so working with a partner is not a new experience. Also, our co-founders represent a wealth of experience (more than 50 years among the four of them) in Big Pharma, so we are quite familiar with how the industry works. This is an important factor for a collaboration of this type. Another potential partnering arrangement might involve a company with development expertise wanting to merge with a company like Kinex, with a very strong discovery team. This type of arrangement could work with the right company.

Q: ***Where will the next development candidate come from after KX-01 & KX-02?***

A: We have selected a series of several targets, all of which would lead to novel treatments for immuno-inflammatory diseases. There are currently structural leads for each target that came from our chemical library, and lead optimization is in progress.

Q: ***What are the biggest challenges facing Kinex going forward?***

A: From the very beginning, Kinex has faced the challenge of developing a drug with a unique mechanism of action. In the case of KX-01, we convinced the scientific community that we have novelty and superiority in preclinical models. Now, we have the task of demonstrating this clinically. In this regard, we are very encouraged by the Phase I results and are preparing to begin Phase II. It was extremely rewarding that Kinex's KX-O1 data was selected as American Society of Oncology's (ASCO) Best of ASCO 2009, a very prestigious award from the largest scientific and clinical society. In addition, Kinex was awarded a $1-million SBIR grant from the government (non-dilutive to the shareholders), which is another endorsement from the scientific community.

A second challenge is to achieve the same level of success in the immuno-inflammatory area as we have in the oncology area. Although there is no guarantee we will be successful, the addition of a newly developed technology platform called OPAL, which uses highly sensitive and novel photoaffinity labeling approaches that can be applied to drug target discovery and validation, will supplement our Mimetica platform, a method for designing and synthesizing small-molecule, substrate-competitive kinase inhibitors. So we believe our chances of success are relatively high. ■

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