Drug Delivery Technology®

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

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FEATURING

SPECIALTY PHARMA
Strategies For Business Development

Our 5 Commitments

to the pharmaceutical industry

promoting Compliance

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lowering Costs

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Increased Absorption and Bioavailability
Liquids naturally offer faster and increased absorption and availability of active ingredients.

Increased Profit Potential
Add up all the advantages. Expect higher sales...and high margins!

Multi-Phase System
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Less Odor and Less Irritation
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Tamper Proof Sealing
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Unique Appearance
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Compounds
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Patent Pending US-2005-0008690-A1

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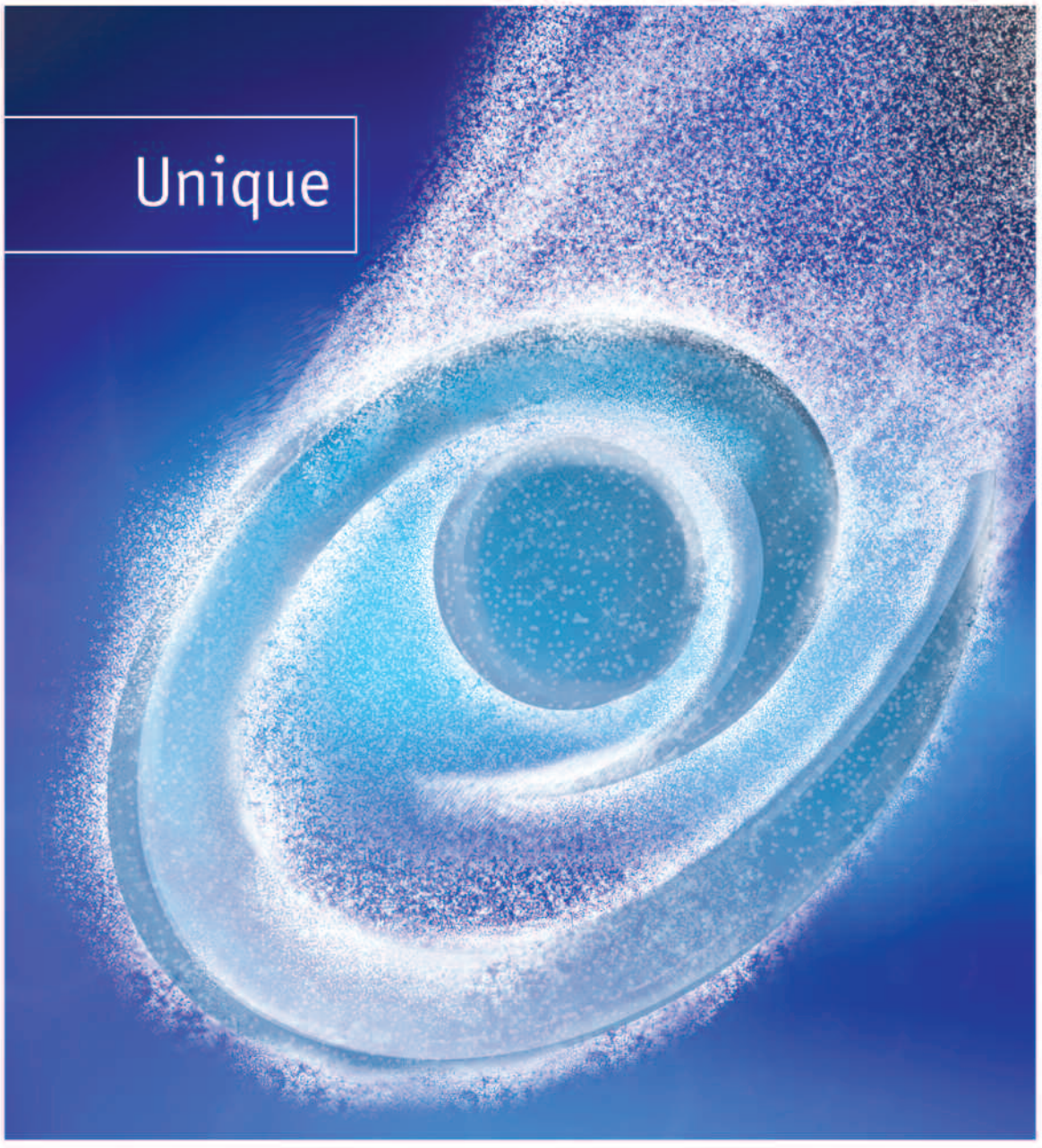

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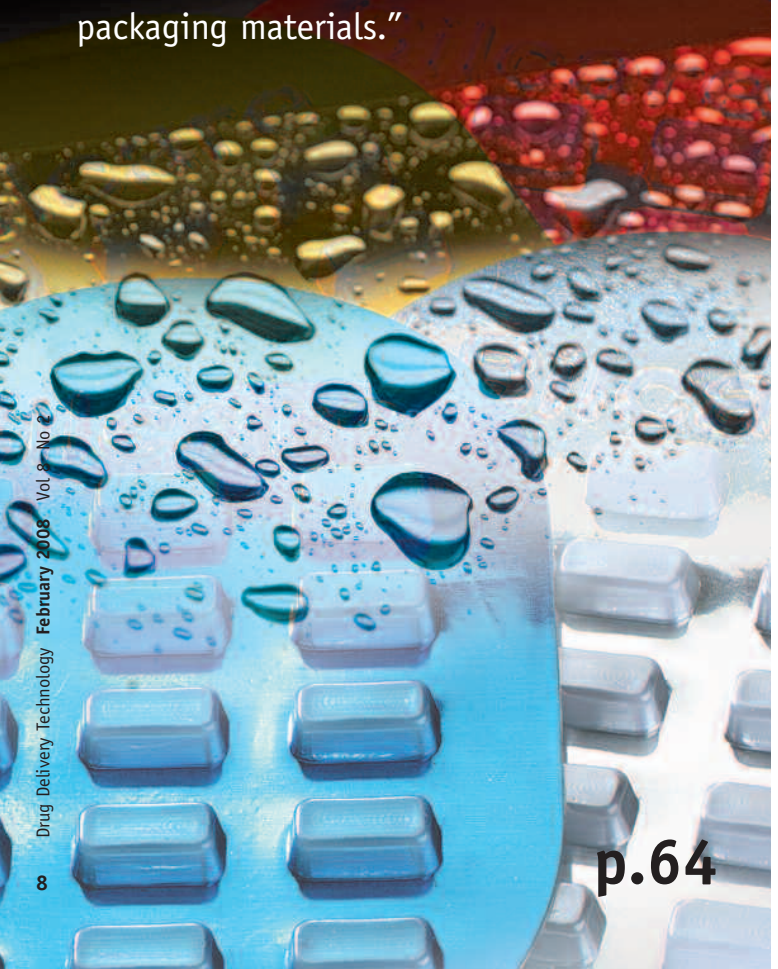

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Market News and Trends

Nektar Commences Phase II Trial of NKTR-118; Commences Phase II Clinical Development Program for NKTR-102

Nektar Therapeutics recently announced the start of its Phase II study for NKTR-118 (PEG-naloxol), an oral treatment being developed to treat opioid-induced constipation (OIC) and other clinical manifestations of opioid-induced bowel dysfunction (OBD). The double-blind, randomized, dose-escalation trial will evaluate the efficacy, safety, and tolerability of NKTR-118 in patients experiencing constipation while receiving opioid therapy.

NKTR-118 is being evaluated as an oral therapy to treat OBD and OIC, which are serious and debilitating conditions resulting from the use of opioids for pain management. NKTR-118, which is a PEGylated form of naloxol, was designed to selectively target peripheral opioid receptors to alleviate constipation associated with opioid therapy, while reducing the drug's penetration across the blood-brain barrier (BBB) and into the CNS in order to preserve opioid analgesia.

The Phase II trial for NKTR-118 is a multi-center, placebo-controlled, dose-escalation trial (5 mg, 25 mg, 50 mg, or 100 mg). Patients experiencing OIC will be randomized 1:1 to NKTR-118 or placebo in addition to their opioid treatment. Therapy will be administered orally once-daily (QD) over a 5-week treatment period. The primary efficacy endpoint of the trial will be the increase from baseline in spontaneous bowel movements per week (SBMs per week). Additional endpoints include monitoring of other symptoms of OBD, which will include the Patient Assessment of Constipation Symptoms (PAC-SYM) outcomes tool, and other quality-of-life measures. Maintenance of opioid analgesic effect will be assessed by measuring changes from baseline in mean daily opioid requirements and daily pain scores. Safety and tolerability will be assessed, and pharmacokinetics of the drug will be evaluated. The trial will be conducted in approximately 50 centers in North America and Europe.

NKTR-118 is an oral drug that combines Nektar's advanced small molecule PEGylation technology platform with naloxol, a derivative of the opioid-antagonist drug, naloxone. In preclinical studies, Nektar's PEGylation technology has been shown to reduce penetration of drugs across the BBB, an important potential advance for NKTR-118 and possibly many other small molecule therapies. The peripheral opioid antagonist NKTR-118 targets opioid receptors within the enteric nervous system, which mediate OBD, a symptom complex resulting from opioid use that encompasses constipation, bloating, abdominal cramping, and gastroesophageal reflux. Constipation is the hallmark of this syndrome, and is generally its most prominent component. Currently, there are no specific drugs approved or specifically indicated to treat OBD or OIC. NKTR-118 has been studied in two Phase I trials evaluating the safety, tolerability, and pharmacokinetics of single and repeated-dose administration of the drug. In a proof-of-principle Phase I trial, single oral doses of NKTR-118 antagonized morphine-induced delay in gastrointestinal transit time, demonstrating the potential of the drug to relieve constipation caused by opioid treatment. This effect was seen to increase in a dose-dependent fashion, reaching maximal effect at 125 mg. Further, no diminution of morphine-induced miosis, a CNS effect, was observed at single oral doses of NKTR-118 that produced a maximal effect on gastrointestinal transit time. NKTR-118 was well-tolerated and rapidly absorbed with dose proportional pharmacokinetics over single-dose ranges of 8 to 1,000 mg.

Nektar also announced the start of its Phase II clinical development program to evaluate NKTR-102 (PEG-irinotecan) as a potential treatment for colorectal cancer. NKTR-102 is Nektar's lead oncolytic candidate using the company's innovative small molecule PEGylation technology platform.

The Phase II program is designed to evaluate the safety and efficacy of NKTR-102 (PEG-irinotecan) for the treatment of patients with solid tumors. The first study in the program will investigate NKTR-102 in combination with cetuximab as a second-line colorectal cancer treatment in irinotecan-naive patients as compared to treatment with standard irinotecan in combination with cetuximab. The colorectal study is composed of two sequential stages. The Phase IIa is an open-label, dose-finding trial in multiple solid tumor types that are refractory to standard curative or palliative therapies. The Phase IIb is an open-label, randomized, double-arm study in patients with second-line metastatic colorectal cancer, and study participants will be randomized in one of two arms of the trial (1:1), to receive either NKTR-102 and cetuximab or standard irinotecan and cetuximab. The Phase IIb stage is expected to begin in mid-year 2008 and will be conducted in over 40 centers worldwide. The primary endpoint of the Phase IIb trial is progression-free survival. Secondary endpoints include response rate, response duration, overall survival, standard pharmacokinetics, and incidence of toxicities, including diarrhea and neutropenia.

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Market News and Trends

Diamyd Files US IND for Phase I Trial for Novel Chronic Pain Therapy

Diamyd Medical recently announced it is submitting an IND for NP2, the company's first drug candidate in its Nerve Targeting Drug Delivery System (NTDDS) gene therapy platform, to the US FDA. Pending a favorable review by the agency, Diamyd plans to initiate a Phase I clinical study.

NP2, developed by the company's US subsidiary, Diamyd, Inc., produces enkephalin locally in the targeted sensory neurons to block pain signals before they are transmitted through the spinal cord to the brain. This may reduce or eliminate the need for systemic pain treatment and avoid associated side effects.

"We have made significant progress in advancing NP2, the first of several product candidates, toward the clinic", said Michael Christini, President of Diamyd, Inc. "With NP2, we have laid the groundwork for the rapid development of additional drug candidates, such as the NTDDS-GAD product, to treat pain in diabetes. The ability to deliver and express gene products directly in neurons that project into the spinal cord is extremely innovative and provides Diamyd with numerous possibilities to treat pain and other peripheral nervous system diseases."

The proposed Phase I clinical trial will be conducted at the University of Michigan in Ann Arbor. Dr. David Fink, Professor and Chair of the Department of Neurology, at the University of Michigan, will be the principle investigator. The trial will be designed as a dose-escalation study to test the safety of NP2. In total, 12 patients who suffer from severe cancer-related pain are planned to be enrolled with the option to expand the trial to enroll up to 24 patients pending the initial results.

"We are excited about the progress of the NTDDS program in Pittsburgh", said Elisabeth Lindner, CEO of Diamyd Medical. "Potential therapies for diabetes complications, including neuropathic pain, is of strategic interest for Diamyd Medical and complements nicely our Diamyd diabetes vaccine, for which an application to initiate a Phase III trial was recently submitted to the FDA".

Diamyd Medical owns the exclusive worldwide license rights to a portfolio of patents for the Nerve Targeting Drug Delivery System (NTDDS). This system is based on a replication incompetent viral delivery system that can express numerous therapeutic genes. The NTDDS has a natural affinity for nerve cells. Diamyd's initial NTDDS projects are focused upon peripheral and central nervous system applications. To that end, Diamyd seeks to combine the natural biology of the NTDDS (local nerve targeting) with therapeutic agents that are naturally found in the body and have a known therapeutic effect (eg, GAD or enkephalin for treatment of pain, and neurotrophic factors for nerve damage). Thus, Diamyd believes that NTDDS proposes a new and broad class of nervous system disease therapies.

Diamyd's NTDDS pain products will target patients who suffer from chronic pain caused by many diseases and conditions. In the US, nearly one third of the population experiences severe chronic pain at some point in life. According to the American Pain Society, only one in four patients with chronic pain receive adequate treatment. Approximately 1.7 million people in the US and as many as 38 million worldwide suffer from moderate-to-severe neuropathic pain associated with back pain, diabetes, HIV/AIDS neuropathy, spinal cord injury, post herpetic neuralgia, and trigeminal neuralgia. Incidence in the US is anticipated to grow more than 5% annually due primarily to the greater rates of diabetes coupled with improved diagnosis. The neuropathic pain market is poorly served by current therapeutics and thus, is suitable for first-to-market products.

PDL BioPharma & Biogen Idec License the Rights to Develop Volociximab in Ophthalmic Indications to Ophthotech

Ophthotech Corp., a privately held biopharmaceutical company focused on developing ophthalmic therapies for back-of-the-eye diseases, Biogen Idec Inc., and PDL BioPharma, Inc. recently announced they have entered into an exclusive worldwide licensing agreement for an anti-angiogenesis antibody to treat Age-Related Macular Degeneration (AMD). Under the terms of the agreement, Biogen Idec and PDL have granted Ophthotech worldwide development and commercial rights to all ophthalmic uses of volociximab (M200). Volociximab is an investigational monoclonal antibody targeting α5β1integrin, a key protein involved in the formation of blood vessels, a process known as angiogenesis. Biogen Idec and PDL will each receive an equity position in Ophthotech as well as a combination of development milestone payments and royalties on future product sales. Other terms, including financial terms related to the agreement have not been disclosed.

"α5β1integrin is a critical survival factor for proliferating endothelial cells involved in angiogenesis," said Samir Patel, MD, President and CEO of Ophthotech. "The preclinical studies to date provide very strong support for developing volociximab for ophthalmic indications. It represents a potential breakthrough for the treatment of AMD."

"There remains a significant unmet need in treating AMD, and we're pleased that Ophthotech, founded by leaders in the development of new therapeutics for this disease, has chosen to explore the potential of volociximab in AMD," said Faheem Hasnain, Executive Vice President, Oncology and Rheumatology Strategic Business Unit, Biogen Idec.

"We believe the anti-angiogenesis properties of volociximab, coupled with Ophthotech's expertise in developing ophthalmic therapies, provides an excellent opportunity to maximize volociximab's value," said L. Patrick Gage, PhD, PDL's interim CEO.

Separately, Biogen Idec and PDL are co-developing volociximab in solid tumor cancers, and the companies retain rights in all other indications pursuant to their September 2005 collaboration agreement.

AMD is the leading cause of blindness for people over the age of 55 in the US and Europe. There are two forms of AMD, namely dry and wet AMD. The wet form is characterized by the growth of new blood vessels into the central region of the retina. These new vessels cause severe visual loss due to retinal damage caused by subsequent leakage and scar formation. Anti-VEGF therapies and photodynamic therapies have been approved for wet AMD. Dry AMD accounts for up to 90% of all cases of AMD. There is no approved therapy for dry AMD, which afflicts 8 million patients in the US and an additional 8 million in Europe. Visual loss in dry AMD is typically not as severe as wet AMD, however, over time, dry AMD can progress to the wet form of the disease.

Ophthotech Corp. is a biotechnology company focused on developing and commercializing therapies for back-of-the-eye diseases. Ophthotech plans to develop a pipeline of compounds with strong scientific foundations for the treatment of AMD and bring them to market in an accelerated manner. In August 2007, Ophthotech announced a $36-million Series A venture financing and two separate in-licensing deals with Archemix Corp and (OSI) Eyetech, Inc. Ophthotech's venture investors include SV Life Sciences, HBM BioVentures, and Novo A/S.

Biogen Idec creates new standards of care in therapeutic areas with high unmet medical needs. Founded in 1978, Biogen Idec is a global leader in the discovery, development, manufacturing, and commercialization of innovative therapies.

PDL BioPharma, Inc. is a biopharmaceutical company focused on discovering, developing, and commercializing innovative therapies for severe or life-threatening illnesses.

Market News and Trends

Generex Biotechnology Announces Generex Oral-lyn Marketing Launch Activities Made by the Company's Marketing & Distribution Licensee in India

Generex Biotechnology Corporation, a leader in drug delivery for metabolic diseases through the inner lining of the mouth, recently announced that Shreya Life Sciences Pvt. Ltd., the Company's marketing and distribution licensee in India, is rolling out its marketing launch activities for Generex Oral-lyn in the Indian market. The Company previously announced this past November that it had received regulatory approval to sell Generex Oral-lyn in India by the Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services, Government of India.

The first effort in this marketing launch campaign involves presentations about Generex Oral-lyn to Indian key opinion leaders and endocrinologists in India at closed-door meetings in Mumbai, India. The presentations involve Generex's expert medical and marketing teams and will focus on all drug-handling matters concerning Generex Oral-lyn for type 1, type 2, and IGT (Impaired Glucose Tolerance) populations. Generex Oral-lyn is a prandial (mealtime) insulin and provides safe and effective glucose control for up to 2 hours after each meal. Generex Oral-lyn is a convenient and pain-free alternative to insulin injections and could encourage prandial insulin therapy among those patients who presently avoid injections. Missed injections for patients with type 1 diabetes mellitus can eventually lead to health complications, including heart condition, stroke, blindness, amputation, and kidney failure, to name a few.

Generex Oral-lyn is a prandial insulin that allows for easy self-administration, precise dosage control, and easy titration, which allows for finer individual control. As such, Generex Oral-lyn also makes an ideal supplement at meal times for patients with type 2 diabetes mellitus in addition to basal or combination therapies based on blood glucose measurements.

India has a significant and growing number of people with diabetes. According to the Diabetes Atlas 2007, there are approximately 40.8 million diagnosed patients with diabetes in India. There are also an estimated 35.9 million people who have pre-diabetic conditions which, if not properly treated and managed, could lead to full-blown diabetes. Generex believes that early intervention with insulin therapy could delay the onset and progression of diabetes and its numerous complications.

Shreya Life Sciences Pvt. Ltd. is a leading Indian-based pharmaceutical company. Shreya is the fifth largest distributor of insulin in the Indian insulin market and ranked 38th in Indian Pharma Market (as per CMARC market research). Shreya has interests in both pharmaceutical and biopharmaceutical products in key therapeutic segments, including cardiology, neuropathy, and diabetes. The company has business operations in India, Russia, the Commonwealth of Independent States, and African countries.

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

Market News and Trends

Azopharma Product Development Group & Accu-Break Pharmaceuticals Announce Strategic Alliance Partnership

Privately-held Azopharma Product Development Group, Inc. and Accu-Break Pharmaceuticals, Inc. (ABP) recently announced the signing of a strategic alliance agreement in which Azopharma will become the "center of excellence" for developing products based on ABP's innovative Accu-Break TM patented tablet technologies, which allow for accurate and individualized dosage adjustment.

"ABP's patented Accu-Break technologies create an inactive break layer in tablets, allowing them to be broken into accurate partial doses," said Dr. Allan Kaplan, CEO of ABP. "By breaking at the inactive layer, accurate dose splitting can be guaranteed because the active layer remains undisturbed. The Accu-Break technologies have important implications for pharmaceutical companies as well as physicians and their patients."

"These new patented technologies will help pharmaceutical companies in many ways," added Phil Meeks, Azopharma's CEO. "From creating new products utilizing these novel technologies to gaining competitive market share by modifying existing products, we expect the pharmaceutical companies to be greatly affected by the Accu-Break technologies."

For pharmaceutical companies, the Accu-Break technologies also provide a solution for formulation challenges, such as separating incompatible active ingredients to allow for the development of unique combination therapy products. For physicians, the Accu-Break technologies allow for greater flexibility in dose adjustment and greater safety in the dose titration process. For patients, the Accu-Break technologies are designed to assist them in following dosing instructions for splitting tablets with ease and accuracy.

"We are excited to be the center of excellence for the development of products using Accu-Break technologies," said Mr. Meeks. "Our expertise in formulation and in total product development makes us the ideal partner for ABP."

Accu-Break technologies are US patented until at least 2025, and the strategic alliance agreement is for 5 years between Azopharma Product Development Group and ABP in which Azopharma will provide sales and marketing support for Accu-Break technologies. The patented tablet technologies can provide solutions for pharmaceutical companies as well as physicians and patients in overcoming issues associated with tablet breaking and dose splitting.

The company's capabilities and services include Azopharma Contract Pharmaceutical Services (integrated product development and CTM manufacturing for all dosage forms), ApiCross Drug Delivery Technologies (proprietary drug delivery platforms to solve difficult molecular challenges), Cyanta Analytical Laboratories (analytical chemistry and inhalation services from development to quality control testing), AniClin Preclinical Services (preclinical services in support of early product development), IQsynthesis (synthetic chemistry services from discovery to clinical API supplies including large-scale API synthesis), and AvivoClin Clinical Services (human clinical pharmacology services for Phase I/II/III clinical trials). All Azopharma PGO facilities are FDA registered and inspected, DEA approved, and client audited on a regular basis.

PII Acquires Pharmaterials Ltd.

Pharmaceutics International, Inc. (PII) recently announced it has acquired Pharmaterials Ltd, an international leader in preformulation and formulation development. This acquisition will extend the business development initiatives and increase the value of the service offerings of PII.

"PII offers a very wide range of cGMP production and formulation development services that have been expanded through alliances in drug delivery ventures," said Steve King, Senior VP of PII. "This acquisition of Pharmaterials will enable PII to provide a complete service for our customer base. We have a very high regard for Pharmaterials and are pleased to add their services to our offerings."

"PII is a company that provides an excellent service to their wide client base," added Professor Graham Buckton, Chief Executive and Founder of Pharmaterials. "They have a state-of-the-art facility with a staff of over 300 providing formulation and manufacturing services. The success that they have seen is based on providing value to their customers, which is the same philosophy at Pharmaterials. Working together, we will be able to provide preformulation, polymorphism, salt screening, and co-crystal services to PII's existing customers. In addition, they can provide new options in cGMP transfer to enhance services at Pharmaterials."

PII is a contract formulation development, Clinical Trail Materials (CTM), and commercial manufacturing company based in Hunt Valley, Maryland. Founded in 1994, PII can manufacture most solid and semi-solid dosage forms for use in clinical trials and commercial sale. These services are complemented by full analytical and regulatory support. The 170,000-sq-ft cGMP facility contains on-site manufacturing suites, analytical laboratories, and 30,000 sq ft of additional warehouse space. The company has a balanced client base of major multinational and virtual pharmaceutical companies that are primarily focused in the US and Europe.

Pharmaterials Ltd is a technology-driven contract research organization specializing in the optimization of drug substance physical forms and formulations to facilitate the development of low solubility and poorly permeable drug substances. With partnerships that span the globe, Pharmaterials works with a range of organizations, including start-up, mid-size, and multinational companies. Founded in January 2000 by Professor Graham Buckton, the company has exponentially expanded through implementation of an organic business model. Pharmaterials is housed in state-of-the-art laboratories and offices in Reading, UK, and has offices in Tokyo to support their increasing Japanese client base.

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

Market News and Trends

Bentley Announces Initial Filing for Spin-Off Drug Delivery Business

Bentley Pharmaceuticals, Inc. recently announced that its newly formed subsidiary, CPEX Pharmaceuticals, Inc., has filed an initial registration statement on Form 10 with the Securities and Exchange Commission (SEC) in furtherance of Bentley's plan to separate its drug delivery business from Bentley. Completion of the proposed spin-off is subject to numerous conditions, including final approval by Bentley's Board of Directors and the effectiveness of the registration statement on Form 10, which is subject to review by the SEC.

Bentley plans to spin off the drug delivery business in CPEX Pharmaceuticals as an independent, publicly traded company. Bentley plans to implement the spin-off through a taxable stock dividend of all CPEX Pharmaceuticals common stock to Bentley shareholders. CPEX Pharmaceuticals plans to seek a listing on the NASDAQ Capital Market under the ticker symbol CPEX, and Bentley will continue to trade on the NYSE under its current ticker symbol BNT. Upon completion of the plan, Bentley will focus on the generics pharmaceutical business. Until CPEX Pharmaceuticals can fully establish its own operations, Bentley will provide transitional services, including managerial, operational, and administrative support, for a period of up to 24 months.

"Filing the Form 10 with the SEC is an important milestone for the planned spin-off of CPEX," said James R. Murphy, Chairman and CEO of Bentley. "We are pleased with our progress and believe we are on track to complete the spin-off in a timely manner."

CPEX Pharmaceuticals will focus on developing innovative drug delivery technologies based on the company's unique CPE-215 permeation-enhancement technology. This technology has been validated through commercialization of Testim, a testosterone gel marketed by Auxilium Pharmaceuticals, and is also currently being used to develop Nasulin, an intranasal insulin product. Following the consummation of the spin-off, CPEX Pharmaceuticals will be based in Exeter, NH, and will employ approximately 20 individuals.

Next Safety Breakthrough in Pulmonary Drug Delivery to Bring Numerous In-Hospital Treatments to the Home

Next Safety, Inc., a leader in developing pulmonary drug delivery devices, recently announced verification of a significant breakthrough in pulmonary science that provides high efficacy delivery of drugs to the lungs.

Advanced optical characterization techniques performed by a third-party laboratory showed that 99.8% of the droplets delivered by Next Safety's pulmonary drug delivery devices were between 1 and 3 microns in diameter, and the droplets separated sufficiently in space and time to be absorbed into the alveoli of the lungs. The company has already demonstrated more rapid delivery of nicotine to the bloodstream through the lungs than possible with cigarettes. Four of the 10 largest global pharmaceutical companies have expressed interest in the company's pulmonary business.

Next Safety expects to begin a bidding process for its pulmonary business in early 2008. Next Safety's immediate and ongoing research studies focus on the pulmonary delivery of nicotine, albuterol, tobramycin, and long-chain peptide and protein molecules. Nicotine delivery and other clinical findings from brain imaging and arterial blood studies conducted in partnership with a major US medical institution will be announced in the first quarter of 2008.

"Previous nicotine replacement products have helped millions of smokers worldwide. However the delivery mechanisms of these products cannot equal the power of nicotine delivered through the smoked cigarette. The next step in nicotine replacement treatment is the ability to deliver nicotine directly to the lung and brain, in the same manner as a cigarette, without the 4,000 harmful chemicals in tobacco," said Matthew Bars, MS, CTTS, an expert in nicotine addiction, key opinion leader and consultant to the pharmaceutical industry and Next Safety, Inc. Mr. Bars is the Director of the New York City Fire Department's Tobacco Cessation Program.

"Pulmonary delivery of "clean" nicotine would become the gold standard of nicotine-replacement therapies. The Next Safety pulmonary nicotine delivery device has the potential of saving the lives of hundreds of millions of smokers worldwide," added Mr. Bars.

DSM & the FDA Join Together for Innovative Partnership in PAT

DSM Pharmaceuticals Inc. and the Food and Drug Administration (FDA) have recently signed an agreement to collaborate on a project involving Statistical Quality by Design Methodology during Pharmaceutical Manufacturing. Dr. Barry Gujral of DSM and Dr. Maziar Kakhi of the FDA will jointly work to build mathematical models using Quality by Design, Statistical Process Control, Design Space, and Risk Analysis methodologies.

The goal of this project is to recommend changes that support the Pharmaceutical Manufacturing sector's focus on proactively managing manufacturing processes. This will further enable the Pharmaceutical sector to reduce waste, enhance efficiency, and manufacture drugs with improved consistency and quality. The project is in line with the Process Analytical Technology Initiative the FDA released in September 2004 to bring more innovations in Pharmaceutical Manufacturing.

"This initiative with the FDA is a big step toward developing more innovative processes in the manufacturing of pharmaceuticals and will benefit current and future customers by improving efficiencies in the manufacturing process," said Terry Novak, President and Business Unit Director for DSM Pharmaceuticals Inc.

DSM Pharmaceuticals, Inc. a business unit of DSM Pharmaceutical Products, is a global provider of custom manufacturing services to the pharmaceutical and biopharmaceutical industries. The company's breadth of manufacturing services include the areas of steriles, orals, and topicals, including dose form manufacturing, scheduled drugs, clinical manufacturing, fill finish manufacturing, and lyophilization services.

DSM Pharmaceutical Products is a global provider of high-quality custom contract manufacturing services to the pharmaceutical and biopharmaceutical industries. DSM Pharmaceutical Products provides contract manufacturing services, including advanced intermediates, APIs, amino acids and derivatives, mammalian cell culture production (fed-batch and perfusion) of monoclonal antibodies, proteins, vaccines, finished dose manufacturing of solid dose, scheduled drugs, liquids, aseptic liquid and lyophilized products. From clinical to commercial services, DSM focuses the right resources on providing the highest level of service and quality while applying innovative solutions to satisfy customers' unique manufacturing and development needs.

Sol-Gel Signs $24.7-Million Deal for Dermatology Drug Delivery

Sol-Gel Technologies Ltd. recently announced it has entered into a development and licensing agreement with a leading US pharmaceutical company for the development and commercialization of a major dermatologic product. Under the terms of the agreement, Sol-Gel Technologies will receive $24.7 million, composed of an initial non-refundable payment as well as additional payments upon the successful completion of various milestones. The US partner will fund the product's development, and Sol-Gel will be entitled to receive royalties from net sales.

"This collaboration is further confirmation of the value of Sol-Gel's unique technology and an important step in our goal of becoming a leading provider of advanced encapsulated solutions and controlled drug delivery for the pharmaceutical industry," said Dr. Alon Seri-Levy, Co-founder and CEO.

"As Sol-Gel has retained the right to market this product outside of North America, we look forward to marketing it together with additional partners in the rest of the world," added Daniela Mavor, Senior VP for Business Development.

Sol-Gel Technologies Ltd. is a private company based in Bet Shemesh, Israel. The company provides innovative drug delivery solutions and life-cycle management opportunities using patented, sol-gel-based encapsulation systems in silica. The technology enables new and stable combinations of active pharmaceutical ingredients resulting in improved efficacy and usability.

"By applying Sol-Gel's technology, pharmaceutical companies can extend and improve current product lines," commented Tamar Ciehanover, Chairperson of Sol-Gel.

"Sol-Gel's pipeline includes a new generation of anti-acne kits, targeting the $1-billion acne therapy market and other dermatology products that have been significantly improved by Sol-Gel's proprietary drug delivery technology."

Sol-Gel was founded in 1997 to commercialize a breakthrough technology developed by Co-founder Prof. David Avnir of the Hebrew University of Jerusalem. Prof. Avnir currently is the Chairman of the International Sol-Gel Society. Sol-Gel has been funded by a distinguished group of Israeli and international investors, including JVP (Israel), Argonaut (US), DSM (Netherlands), Evergreen (Israel), Challenge (Israel), Millenium (Israel), Jesselson (Israel), and Stata (US).

COMBINATION UPDATE

The Future of Inhaled Insulin

By: Christine M. Ford, MBA

Pfizer may have recently abandoned efforts to market and sell Exubera®, but the concept of an inhaled insulin product is far from extinguished. In fact, Pfizer's exit from the market is only heating up competition among companies like Eli Lilly and Mannkind Corp. who are all working on developing similar inhaled insulin products.

While future approvals of inhaled insulin products may not meet with as much fanfare as the 2006 FDA approval of Exubera did, an easier-to-use and potentially more effective technology for insulin delivery is sure to create renewed excitement in the market. And with three new inhaled insulin products expected to be commercialized in the next 2 to 4 years, the $3-billion injected insulin market is still very much up for grabs.[1]

On the flip side, inhaled insulin is likely to be priced three to five times higher than conventional parenteral drugs. In addition, there is a lack of data on the pulmonary side effects caused by inhaled insulin beyond 3 years.

FEW VIABLE DELIVERY METHODS

What makes prospects for a successful inhaled insulin delivery method both challenging and exciting is the fact that as a very large protein molecule, insulin is very difficult to deliver. Patients have been clamoring for a non-parenteral form of insulin for years, yet other routes of delivery, such as through the nasal passage or stomach, have proven not to be viable.

The reason delivery through the lungs appears to be so promising is because the lungs provide a large surface area and ready absorption. By contrast, the nasal passage has a relatively small surface area and nasal membranes provide poor transport. Worse yet, even a mild cold or stuffiness could alter the dosage. As a result, patients could receive too high or low of a dose without knowing it. Insulin delivery through the stomach is equally stymied. In addition to the fact that acidity and digestive enzymes in the stomach and intestines render insulin molecules ineffective, intestinal membranes provide poor transport for the large insulin molecules.

INHALED INSULIN PRODUCTS ON THE HORIZON

The key players in today's inhaled insulin market promise to overcome many of the drawbacks of Exubera. These drawbacks include an inability to deliver precise doses, questionable effects on lung function, a large, indiscreet device size, and appropriateness for only large doses of insulin, which prohibits some type 2 diabetes patients from using it.

FIGURE 1

Mannkind Corporation

MannKind Corporation is in the final stage of clinical trials for its Technosphere® Insulin product (Figure 1), and is set to apply for federal approval to sell the drug for type 1 diabetes treatment by the end of 2008. According to the company, what sets Technosphere Insulin apart from the competition is that it works faster than any other insulin on the market, even those that are billed as fast-acting. This allows the drug to better control the spikes in blood sugar levels that occur after a meal.

FIGURE 2

FIGURE 3

Eli Lilly

Eli Lilly is expected to submit its AIR® Insulin product (Figure 2) for approval in 2009, which is currently undergoing Phase III clinical trials as a potential treatment for both type 1 and type 2 diabetes. Eli Lilly, which is developing the product alongside drug delivery specialist Alkermes, has been working on developing an inhaled insulin product since 2001. Alkermes will be the exclusive commercial manufacturer of insulin powder for AIR Insulin. Roughly the size of a marker pen, the AIR Insulin device is smaller than the Exubera device, which is 12 inches when open. It has not yet produced the same questionable effects as Exubera on lung function. As an illustration of both companies' confidence in the market potential of the inhaled insulin system, Eli Lilly has signed a new agreement with Alkermes for the manufacture of its AIR Insulin product. Eli Lilly is also investing in the creation of a second manufacturing line at Alkermes' commercial-scale production facility, expanding the plant's powder production capacity to meet expected post-launch requirements.

Novo Nordisk

On January 16, 2008, Novo Nordisk announced it will discontinue its experimental AERx Insulin Diabetes Management System (Figure 3), which uses a breath-guidance system that only delivers insulin to the lungs when breathing is correct, using strips with liquid insulin. This makes dosage adjustments possible to the nearest unit. However, the AERx system (about the size of a paperback book) was the only inhaled insulin system currently in clinical trials that uses a liquid formulation, requiring the insulin to be refrigerated. The company said its product was "unlikely to offer significant clinical or convenience benefits over injections of modern insulin with pen devices." Novo Nordisk was developing the inhaler with Aradigm Corp.

RENEWED HOPE FOR EXUBERA

Exubera may also be back in the running. Nektar Therapeutics, which licensed Exubera to Pfizer, is looking for a new partner in an effort to keep the product on the market.[2] Nektar has been developing a smaller, improved inhaler in response to e-mail messages from patients desperate to keep using Exubera.

MAKING LIVES BETTER

The purpose of medicine is not only to save lives, but to improve the quality as well. With 14.6 million Americans suffering from diabetes, including 176,500 under the age of 20, the advent of a needle-free insulin delivery system will come as a relief to families that must deal with injections, especially those with type 1 diabetes.[3]

While inhaled insulin products have their drawbacks, the potential benefits of this insulin delivery approach outweigh product negatives, especially as next-generation products come to market to offer faster-acting, safer, and more convenient inhaled insulin delivery.

The fact that prior ideas, such as insulin patches, swallowed insulin in special pills, and insulin pumps, never proved practicable, make it clear that inhaled insulin is the world's best hope for a faster-acting, needle-free insulin delivery system. Exubera proved an inhaled insulin delivery system was possible. Now other companies just need to demonstrate that this delivery method is better and more effective.

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BIOGRAPHY

Ms. Christine M. Ford is Event Director of PharmaMedDevice (www.pharmameddevice.com). Since joining Reed Exhibitions in 1991, she has been involved in a variety of conference and event management positions within a range of event portfolios, including technology, life sciences, and manufacturing. Ms. Ford served as Reed Exhibitions' Director of Business Development from 2000-2005, working on a variety of launch and acquisition projects. Since 2004, she has focused the majority of her business development work within the life sciences and healthcare industries, including the PharmaMedDevice launch. She earned her MBA from the University of Connecticut and her BS from Fairfield University. She can be reached at (203) 840-5391 or cford@reedexpo.com.

Progress in Swellable & Low-Density Excipients for Prolonged Gastric Retention

By: Avani Amin, MPharm, PhD; Tejal Shah, MPharm; Dhaivat Parikh, MPharm; and Mohit Shah, BPharm

Drug delivery systems formulated to prolong the gastric retention of drugs have gained popularity in the pharmaceutical market. Gastro-retentive drug delivery systems (GRDDS) offer several advantages for drugs acting locally in the stomach (antacids, antibiotics against H. pylori); drugs having a narrow absorption window in the stomach or upper small intestine (L-Dopa, furosemide, riboflavin); drugs unstable at intestinal or colonic environment (captopril); and drugs exhibiting low solubility at higher pH (diazepam, verapamil).[1,2]

Gastro-retentive systems are designed for a variety of drugs, and various technologies are flooded in the market. Patented technologies of various companies are also available for gastro retention. The technologies for GRDDS in the international market are summarized in Table 1 and are based on the following: low-density floating systems (including effervescent and non-effervescent systems), swelling and expandable systems, bioadhesive or mucoadhesive systems, and high-density systems.

The floating, swellable, and bioadhesive techniques have proved superior results over the other technologies. The excipients used in the formulation of GRDDS are the backbone of these technologies, and their performance is directly related to the effectiveness of the excipients. Researchers have fully explored the mucoadhesive polymers.[3,4] Thus, the scope of this article is to provide an update on excipients used for providing gastro-retentive properties based on swelling and floating. The recent technologies using excipients based on superporous hydrogels (SPH), lipid-based carrier matrices, and foam-based technologies are briefly discussed further.

FIGURE 1

Swelling of a marketed superporous hydrogel (Aquagel™)

SUPERPOROUS HYDROGELS

The three-dimensional network of hydrophilic polymer chains that have the capability to absorb water and swell without disruption of the overall structure are called hydrogels. They are held together by covalent bonds, hydrogen bonding, or ionic interaction, and are a type of cross-linked polymers, such as polyacrylic acid, polyacrylamide, poly(N-isopropyl-acrylamide), poly(ethylene oxide), poly(hydroxyethyl methacrylate), polyvinylpyrrolidone, poly(vinyl alcohol), and carboxymethylcellulose. Hydrogels are useful in the formulation of drug delivery systems and biomedical devices. Hydrogels have the ability to absorb water, and if the water content absorbed exceeds 95% of the total weight, it is called a Superabsorbent hydrogel. The imbibition of water by the hydrogel creates a space in the structure which is known as effective pore size. The pore size of the hydrogels varies from 10 to 100 nanometers for microporous and 100 nanometers to 10 micrometers for macroporous hydrogels. Conventional hydrogels demonstrate a very slow process of water absorption, and sometimes the dosage form may need

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several hours to reach a state of equilibrium. Hence, the drug delivery may sometimes be prematurely evacuated, leading to ineffectiveness of the dosage forms.

Hydrogels that have the ability to create effective pore sizes larger than 10 micrometers are known as Superporous hydrogels (SPH). The structure of this type of hydrogel allows the interconnected pores to form an open type of cell structure, which facilitates rapid absorption of water by capillary forces. SPH having an average pore size greater than 100 micrometers swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size (swelling ratio ~100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. The SPH absorbs water very rapidly, making them fully swollen; however, this gives them very poor mechanical properties. To improvise the hydrogel characteristics, various types of hydrogels have been prepared and are classified as generations.[5,6]

The first generation SPH (conventional superporous hydrogels or CSPH) are prepared by addition of a monomer, initiator, and cross-linker. The monomer is polymerized to form superporous hydrogel having a large pore size. The most commonly used monomers are acrylamides and various salts of acrylic acid. The other commonly used agents are ammonium persulfate/diamine (as an initiator), diacrylates (as a cross-linker), bicarbonates (as a foaming agent), acrylic acid or other acids (as a foaming aid), PEO-PPO block copolymer (as a foam stabilizer), and water (as a solvent). However, the CSPH are brittle and also fragile against bending, compression, or tensile strength. The mechanical property of the CSPH may be improved by increasing the concentration of cross-linking agent or by adding a composite material.

TABLE 1

Company	Technology	Type	Marketed Product
Depomed	AcuForm™	Polymer-based	Glumetza™ (metformin) ProQuin® XR (ciprofloxacin) Gabapentin GR (in Phase-III clinical trials)
Intec Pharma	Accordion Pill™	Expandable film, filled in capsule	-
Sun Pharma	Gastro Retentive Innovative Device (GRID)	Coated multi-layer floating & swelling system	Baclofen GRS
Merrion Pharma	Gastro-Intestinal Retention System (GIRES™)	Gas-generating inflatable pouch in capsule	-
Ranbaxy	-	Polymer-based	Cifran OD (ciprofloxacin) out-licensed to Bayer
Flamel	Micropump®	Gastro retention with osmotic system	Coreg® CR (Carvedilol) out-licensed to GSK
Roche	Hydrodynamically Balanced System (HBS)	Matrix-forming polymer-based floating system	Madopar HBS (L-Dopa + Benserazide)
Roche	-	Floating capsule	Valrelease (Diazepam)
GlaxoSmithKline	-	Floating alginate raft	Liquid Gaviscon® (Antacid)
Akina Inc.	Aquagel®	Super porous hydrogel	-

*** The companies' official websites may be referred to for further details of the technologies.**

Gastro retentive technologies available in the international market

The second-generation SPH (superporous hydrogel composite or SPHC) consist of a swellable filler (ie, a composite material) along with other agents mentioned earlier. It has the capability of absorbing a solution of monomer, cross-linker, initiator, and other components. During the synthesis of SPH, the absorbed monomers and cross-linker, along with those that were not absorbed, all participate in the polymerization, leading to the formation of an interpenetrating polymer network. Most of the superdisintegrants, such as cross-linked Ac-Di-Sol®, Primojel®, and Crospovidone®, are utilized as a composite material for the preparation of SPHC. Out of which Ac-Di-Sol exhibits the best improvement in swelling rate and mechanical property. The mechanical property of the SPHC can be further improved by acidification of the ionizable groups of the polymer, which then enables SPHC to withstand stresses of gastric contraction.

The third generation SPH (superporous hydrogel hybrid or SPHH) is developed to improve the mechanical and elastic properties. Instead of the swellable filler, the SPHH employs a water-soluble counterpart (hybrid agent) that can form a cross-linked structure, such as interpenetrating polymer network by physical or chemical cross-linking. Elasticity and spongy nature are the unique properties of the SPHH. They are resistant to various kinds of stresses, such as compression, tension, bending, and twisting, and they are not easily breakable when stretched. SPHH of alginate polyacrylamide were reported by Omidian et al to withstand compression forces up to 25 N, while the SPHC could not even resist a force of 2 N.[7]

SPH have the ability to withstand pressure induced by stomach motility, shape-retention capacity, flexibility, high-swelling capacity within a fraction of minutes, and higher mechanical strength. SPH are widely used for the GRDDS and absorb water via a capillary wetting action rather than diffusion, which cause extremely fast swelling of the dried hydrogel such that the swelling ratio is more than 100. The swelling

behavior of a commercially available SPH (Aquagel™ by Akina Inc.) is depicted in Figure 1.

Gastric motility plays a crucial role in deciding the effectiveness of the SPH. In an experiment in dogs, the SPH remained in the stomach for more than 24 hours in fasted conditions.[8] SPH were initially developed for GRDDS, but later on due to their high swelling, water absorption, and improved mechanical property, they were also useful for alternative applications in pharmaceuticals and agriculture.

LIPID CARRIER MATRIX

Recently, lipids have gained attention as an alternative to polymers for the development of sustained-release dosage forms because of their numerous advantages (no additional solvent requirement for solubilization of drug, ease of availability, biocompatibility, biodegradability, absence of toxic impurities, and preventing adverse effects of drugs by coat formation). Gelucires® belong to the family of lipid-based excipients used for oral drug delivery comprising of a mixture of glycerides with PEG 1500 esters of long-chain fatty acids. They exhibit both hydrophobic as well as hydrophilic properties due to presence of glycerides and polyethylene Glycol (PEG) esters, respectively. Gelucire is available in various grades differing in melting point and HLB values, which influence specific behavior in gastrointestinal fluid in context of hydrophilicity or hydrophobicity and floatability. The higher the ratio of PEG esters to glycerides, the higher the hydrophilicity of the base. Gelucire containing only PEG esters (Gelucire 55/18 and 44/14) are used to enhance solubility, while Gelucire containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01, and 39/01) are utilized for development of sustained-release dosage forms. However, only 39/01 and 43/01 grades of Gelucire are considered effective carriers for providing floating sustained drug delivery due to their dual property (hydrophobicity and low density).[9-11]

Some researchers have explored their properties for the preparation of gastroretentive dosage forms. Chauhan et al prepared sustained-release floating matrices of risedronate sodium using lipids, such as Precirol® ATO 5(HLB = 02), Compritol ATO 888(HLB = 02), and Gelucire 39/01.[11] Among the three, Gelucire 39/01 exhibited good floating properties and retarded the drug release. However, matrices prepared with other lipids did not exhibit a sufficient floating property even though all were hydrophobic in nature. The reason mentioned by the researchers for the sustained-release floating property of Gelucire 39/01 was attributed to its low density compared to the other lipids Precirol and Compritol used in the study. The same group (Shimpi et al) has explored the use of Gelucire 43/01 for the design of multi-unit floating systems of diltiazem HCl.[12] They studied the effect of drug-to-Gelucire ratio and observed that drug release was retarded with an increase in the ratio. However, no significant difference in floating property was observed with change in the ratio. The formulations also showed initial burst drug release. To overcome it, release retardant additives like glyceryl monostearate (GMS), hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and Sterotex were investigated. Gelucire:GMS did not exhibit floating. Gelucire:HPMC and Gelucire:Sterotex showed faster drug release compared to plain drug:gelucire granules. Gelucire:EC systems (1:0.5) showed floating with retarding of drug release. Patel et al also developed multi-unit floating granules of Ranitidine HCl with Gelucire 43/01 and similarly observed floating behavior.[13] This clearly indicates that hydrophobicity with a low density of lipid plays a crucial role in imparting floating sustained-release behavior.

FOAM-BASED TECHNOLOGY

Foam-based technology has also been used for the formulation of GRDDS. This technique is based on the incorporation of at least one porous structural element that yields floatability. Streubel et al had developed floating systems based on a similar technology (low density foam particles).[14] The highly porous, hydrophobic polypropylene foam powder (Accurel® MP) with open-cell structure that acts like a microsponge carrier for the drug and polymer (Eudragit, ethyl cellulose, or polymethyl methacrylate) was used. The floating microparticles consisting of foam powder were prepared by adsorbing drug and polymer on the foam using an o/w solvent evaporation method. The polymer partially covers the pores and the entrapped air within the system is removed slowly upon exposure of aqueous media and provides floating for an extended period of time. However, it should be noted that the foam only acts as a carrier for the floating system, whereas release pattern of drug from the system is mainly dependent upon the type and concentration of polymer. The majority of the formulations showed initial burst release of drug, which

significantly reduced with increasing amounts of polymer.

Based on a similar approach, the same group developed the floating matrix tablet consisting of foam powder, drug, matrix-forming polymers (HPMC, Carbopol, Na-alginate, corn starch, guar gum), and filler. Incorporation of foam powder into matrix tablets not only provides the low density systems (0.69 to 0.98 g/cm^3), but also significantly reduces the lag time for floating.[15] Sharma et al also developed multi-particulate floating-pulsatile systems using porous calcium silicate (Florite RE®).[16]

This discussion has been intended to provide an overview of swellable and floating excipients, which have demonstrated good potential to enhance the performance of a GRDDS. ◆

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Mr. Mohit Shah is a Research Scholar and has earned his BPharm from Sardar Patel University. He is perusing his MPharm in Pharmaceutics from the Institute of Pharmacy, Nirma University of Science and Technology. He is actively working in the area of gastro-retentive drug delivery systems.

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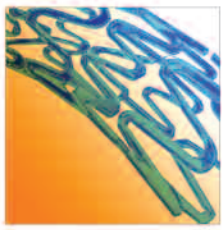

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Breaking Through the Stent-Coating Process

By: Robert R. Andrews, MBA, MS, and James B. McClain, PhD

According to the American Heart Association, heart disease is the leading cause of death in the US, killing almost double the number of people that cancer, car accidents and AIDS kill combined.[1] For this reason, innovative therapies and devices to treat heart disease are in high demand.

In 2003, drug-eluting stents emerged as a breakthrough solution for Acute Coronary Syndrome (ACS), one of the many causes of heart disease. This technology was anticipated to use drug therapy to address the persistence of early restenosis with bare metal stents and injury to the vessel wall associated with traditional percutaneous coronary intervention (PCI) treatments, such as balloon angioplasties. Drug-eluting stents were rapidly adopted by physicians, accounting for over $5 billion of the biomedical device market's annual sales in 2006.[2]

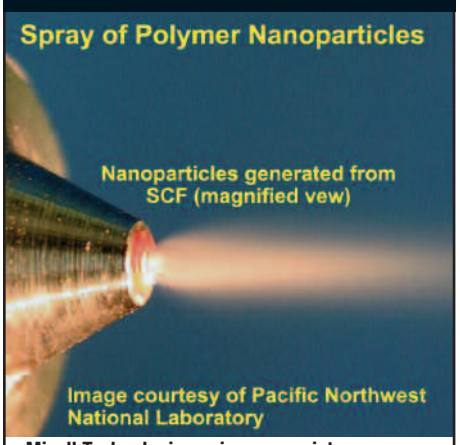
Recently, drug-eluting stents have been plagued by concerns about long-term product safety. Although the FDA issued a statement in 2006 stating that drug-eluting stents are safe, they noted recent data suggesting a small but significant increase in the rate of death and myocardial infarction possibly due to late stent thrombosis.[3]

Micell Technologies, Inc. has developed a unique, proprietary, multi-layered coating technology that can create drug-eluting coatings for medical devices with better uniformity, enhanced control over drug placement, morphology and elution, and improved manufacturing process control. These improvements have the potential to provide substantial clinical benefits to the next-generation of drug-eluting stents. The company partnered with the Commercial Equipment Group of Foster-Miller to develop an automated, commercial-scale manufacturing process to incorporate the new coating technology into drug-eluting stents faster and more effectively.

CURRENT CHALLENGES WITH DRUG-ELUTING STENTS

Patients suffering from ACS have long been treated with PCI. By inserting a stent into an occluded or narrowed coronary artery to restore blood flow to the heart, doctors avoid exposing already vulnerable heart patients to invasive open heart surgery yet achieve the same therapeutic effects. Patients benefit from reduced surgical risk, faster recovery, and a less painful procedure.

FIGURE 1



Micell Technologies unique, proprietary supercritical fluid multi-layered coating technology uses low temperatures and is an entirely dry process.

While first-generation bare-metal stents virtually eliminated many of the complications associated with abrupt artery closure after balloon angioplasty, issues with restenosis (or reblocking) of the stent persisted. While restenosis can occur through several mechanisms, most importantly it is thought to result from an inflammatory cellular response in the vessel wall that induces tissue proliferation around the angioplasty site. Although the rates were somewhat lower, bare-metal stents still experienced reblocking (typically

at 6 months) in about 25% of cases, necessitating a repeat procedure.[4] Although drug-eluting stents have been successful in eliminating early restenosis, doctors have recently become concerned about the rising number of cases of patients experiencing complications from late stent thrombosis (typically years after stent implantation) with drug-eluting stents.

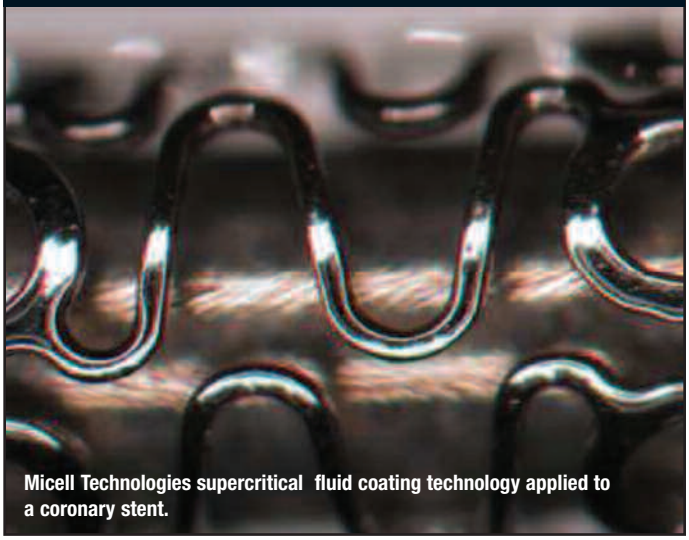
The results of several studies tracking the health of patients who received drug-eluting stents were released in September 2006 at a major international meeting of cardiologists, The World Congress of Cardiology in Barcelona. These studies suggested higher levels of late stent thrombosis, or blood clots, and other problems than had previously been reported with drug-eluting stents.

In September 2006, the FDA released a statement regarding its position on the public's growing concerns with drug-eluting stents, indicating that while the studies presented at the Barcelona meetings raised important questions, the data were not sufficient to fully characterize the mechanism, risks, and incidence of DES thrombosis, and that a more formal evaluation of the data in these studies was necessary. The statement went on to say that "at this time, the FDA believes that coronary DES remain safe and effective when used in patients having clinical and coronary anatomic features similar to those treated in the pivotal trials conducted by the manufacturers for FDA approval."[5]

In December 2006, the FDA held a public meeting of the Circulatory System Devices Advisory Panel, where it was stated that currently approved drug-eluting stents were associated with a small increase in stent thrombosis compared to bare metal stents that emerges 1 year post-stent implantation. A number of factors, including potential polymer/drug toxicity, physician placement, off-label use, and lack of compliance with anti-platelet therapy post-stent implantation, have all been considered as contributing factors to the recent increases seen in late stent thrombosis. Participants of the Advisory Panel provided recommendations, including conducting further studies with longer term follow-up to ensure the safety of DES.[6]

Research is continuing to determine what factors related to drug-eluting stents may lead to complications in some patients a year or more following implantation. Researchers are re-examining patient selection guidelines to determine which patients may fare better with older bare metal stents. Others are investigating hypersensitivity reactions in some patients that may lead to inflammation and contribute to blood clots and other serious complications. And researchers are developing new types of stents and coatings that may reduce or eliminate the risk of late stent thrombosis. Improved

FIGURE 2



Micell Technologies supercritical fluid coating technology applied to a coronary stent.

FIGURE 3

Coronary artery drug-eluting stent.

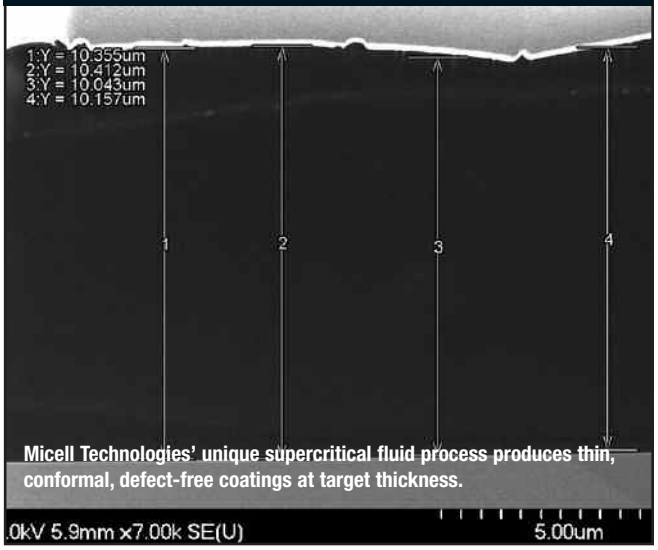
FIGURE 4

Scanning electron micrograph of Micell Technologies' supercritical fluid coating technology applied to a coronary stent.

FIGURE 5

Scanning electron micrograph of Micell F. Micell Technologies' unique high-precision, flexible, and adherent coating.

FIGURE 6



Micell Technologies' unique supercritical fluid process produces thin, conformal, defect-free coatings at target thickness.

technologies that address thickness and uniformity of polymer coatings, together with control over drug morphology, elution, and placement within the coating, will play an important role in the ability of next-generation drug-eluting stents to address the current clinical challenges.

AN IMPROVED COATING PROCESS FOR IMPROVED PATIENT CARE

Micell Technologies has created a unique, proprietary, multilayered coating technology designed for delivering advanced therapeutics to the surface of medical devices with the potential to create clinically superior next-generation drug-eluting stents.

Micell's patented process can create coatings that allow for independent placement of multiple drugs into microenvironments inside the surface coating of devices. This feature enables the drug to be "dialed-in," meaning that the distribution of the drug in the coating can be manipulated to control the elution profile.

In addition, multiple drug combinations, such as antirestenosis and anti-coagulant therapies, can be added in a single drug-eluting stent, providing the opportunity for sequential therapies and the potential for improved clinical performance.

Using benign supercritical fluids, Micell's technology provides a more gentle coating process that does not expose drugs to harsh environments. Entirely dry and solvent-free, Micell's technology uses moderate temperatures to retain the structure, morphology, and potency of therapeutic agents. Additionally, more uniform, flexible, and adherent polymer coatings can be created using Micell's solvent-free system due to the elimination of lengthy drying times and lack of exposure to harsh solvents.

Lastly, Micell's unique process reduces exposure to potential solvent hazards and minimizes disposal issues related to hazardous waste.

KEEPING MANUFACTURING IN MIND

While the features of Micell's stent-coating process were designed to facilitate improved clinical performance in the next generation of drug-eluting stents, a feasible manufacturing process was essential to enable commercialization of this technology. For this reason, Micell partnered with the design and engineering firm Foster-Miller early in the development process so that manufacturing needs would be considered from the initial stages of

the project.

Combining Micell's expertise with Foster-Miller's engineering, materials, and manufacturing know-how created a powerful team and a wealth of information about regulatory and quality standards, emerging technologies, and manufacturability. This reduced the risk of designing an un-manufacturable device, or one doomed to regulatory failure, and facilitated the development of an efficient, novel process.

Foster-Miller capitalized on several unique features of Micell's technology to design a proprietary manufacturing process that can coat a batch of stents in less than 5 minutes.

The homogenous, unidirectional process developed by the Foster-Miller – Micell team decreases production time and streamlines operations, accelerating product time-to-market, and offering advantages in terms of manufacturing throughput and associated costs.

Process control is also enhanced in this proprietary system, allowing the coating process to be monitored and measured at multiple points. The drug dosage can be metered in real-time to maximize the quality and consistency of drug placement. The companies' partnership created a seamless transition from design to manufacturing, moving the project from the laboratory to a process platform that could support preclinical and clinical trials, and ultimately commercial product manufacturing. Foster-Miller also helped its partner secure intellectual property protection by assigning Micell all rights to the manufacturing process.

LOOKING TO THE FUTURE

Preliminary data suggest that Micell's unique drug-eluting stent technology may provide improved clinical benefits to ACS patients. Although coronary drug-eluting stents have been targeted as the first application for Micell's proprietary technology, the process' flexibility promises future applications. The technology can be applied to a variety of combination devices, and is compatible with numerous drugs and a wide range of durable and bioabsorbable polymers. Small molecules, peptides, proteins, hormones, and other heat-sensitive agents can be used with Micell's proprietary process, providing new therapeutic options for drug-eluting coatings. The next applications may include drug-eluting orthopedic devices and novel drug delivery systems.

In the competitive medical market, drug coating will continue to be an important part of creating more effective, safer medical devices. Micell's unique coating process offers significant advances in technology and has the potential to redefine surface modification of medical devices using drug-eluting coatings. ◆

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BIOGRAPHIES

Mr. Robert R. Andrews is Medical Division Manager for the Commercial Group at Foster-Miller Inc., a QinetiQ North America company. He has 30 years of medical device experience managing product development and operations. He has 11 issued US medical device patents. He earned his MBA from Bryant College and his BS and MS in Plastics Engineering from The University of Lowell. Mr. Andrews has authored several articles for various medical industry publications. He can be contacted at (781) 684-4639 or randrews@foster-miller.com.

Dr. James B. McClain serves as Chief Technology Officer and is one of the Co-founders of Micell Technologies. He has published many articles in leading scientific journals, including Science, Nature, and the Journal of the American Chemical Society, and is listed as author on more than 50 US patents. Dr. McClain earned his BS in Chemical Engineering from Lehigh University in Bethlehem, Pennsylvania, specializing in Polymeric Materials Engineering. He also attended the University of North Carolina at Chapel Hill, earning his PhD in Chemistry on the characterization of polymeric materials and surfactants dissolved in supercritical fluids. He can be contacted at (919) 313-2111 or jmcclain@micell.com.

MBO Discussion Series

The Born-Again Entrepreneur

By: Derek G. Hennecke, MBA

I was a corporate guy. When the head office told me what to do, I did it. As General Manager of a CRO in Tampa, Florida, that's pretty much how I saw myself. That's what I'd been for 20 years. So I was completely blind-sided when 13 months after relocating to Florida to head up a formulation development services company, my boss took me aside during a routine management meeting and informed me that the head office had decided to sell off my division.

My head reeled. My first thought was, "could we convince upper management to keep us?" But no matter how hard I tried to pick it apart, the overall strategy of the mother company was sound. They were going to narrow their focus and concentrate on fewer areas of expertise.

It made sense. Twenty years of experience in Holland, Egypt, Mexico, Canada and America had shown me a thing or two about our sponsors, the drug development specialists. They were looking for quality and compliance, followed by a combination of speed, responsiveness and communication. My company was trying to be everything to everyone, and the industry was strewn with the bodies of companies that followed this strategy.

Our sponsors were sophisticated and wanted to cherry pick the best services from a variety of companies. They weren't looking for a big Wal-Mart of drug development. Such a strategy couldn't even offer up economies of scale in our service-oriented business. Specialization was the key; do one thing, and do it exquisitely. The company had thought this out...unfortunately.

My next move, I'll confess, was for the condition of my résumé. I had a family to support. Head office needed me for just 6 months to oversee the sale of my plants (I had another in Seattle and one near Montreal). They said they'd find something else for me, but a company that's focusing on its core is shrinking. There would be few relocation opportunities. I was a corporate guy, and I sure as heck knew how to read between the lines of a departmental announcement.

As a corporate guy, it never once occurred to me to be their buyer. Heck, they'd just contracted me to help sell the company, not to buy it. I'll never forget the moment the obvious hit me. I walked into the Executive Renaissance Forum for Entrepreneurs. I'd belonged to this group for a while – they helped me think outside the box as I was implementing my turnaround. When I told them my news (silently hoping that one of them might have a job lead for me), their first question was, "So are you buying it?" These were serial entrepreneurs, and in there own words, "If you swim with sharks, everything starts to look like a meal." My corporate disaster was to them — blood in the water.

Once I recovered my balance, I began to realize that just maybe I wanted to do this. But I had no clue where to start. How would I value my division? I'd never thought of my division in those terms. Would the rest of management join me? Would the employees be on my side? Was my plan for the company strong enough to sail alone? What would cutting the corporate ties cost us? Where does one go to find money on that scale?

My wife was very supportive. She comes from a family of entrepreneurs and has stood behind every bold move we've ever made as a family. It's critical to have your family on board — you're

all on the line, and it sure is good to have a shoulder to cry on as you go along.

For me the defining moment was telling our Vice President of Sales and Marketing, Randall Guthrie, that the company was on the block. He had only started with this division 2 months before from another part of the company, and I was concerned about his reaction to the news. Randall had over 25 years of experience in the industry and had worked for some of the largest and most reputable CROs. He's a real go-getter, highly driven, and knows everybody in this field. I wouldn't be able to do this without him. What would he say? I'll never forget his knee-jerk reaction: "Well, can we buy it?" That cinched it right there.

I'm going to write my story for you over the next six articles. I'm doing this because I want you to have it in the back of your head in case the boss ever pulls you aside. Maybe you don't even need the boss to hit you over the head. Maybe you work for a company where you can see that your group would be better off without the head office, and you could make them an offer.

Organizing this management buy-out (MBO) was the single best career decision I ever made. Whether or not it's the best decision for you is something only you can ascertain — but maybe this chronicle will help you decide. MBOs are the least common form of sale. Why? Because management is full of corporate guys, not entrepreneurs. And when the company goes on the block, the entrepreneurs come out of the woodwork. Investment management companies are called in. They know everything there is to know about these deals and they line up the sharks, who begin to circle in the water around your company. These guys do a couple of deals like ours over breakfast without even flinching. To the management, however, this deal is the biggest thing that has ever happened in their lives. It's a change of vocation, a new kind of leadership, a career risk on the scale of Mount Everest, and it's probably going to involve their life savings. There aren't a lot of managers willing to take this on.

Now contrast this against another fact. In most cases, MBOs are the best possible outcome for the company. Think about it. Who is better equipped to know and understand the business; to guide it through a change in ownership? Who better has the trust and commitment of the employees? Who else do the customers know they can rely on through all the coming changes? The mother company knows this intuitively. The investment companies know this from experience. This is management's ingrained advantage (and most managers don't even know it's there).

What the other bit management rarely understands is that the capital isn't as tough to get as you might think. In 1980, there was $10 billion in private equity and that has been steadily rising ever since. Since 2005, there has been over $100 billion a year. Right now there is more capital available than ever before. Imagine all those wealthy people who are over-invested in real estate, the stock-market, and are looking to diversify. They could be very interested in shares of a promising, privately owned MBO. They know the advantages of an MBO, and they generally agree that there is a shortage of good managers to invest in; all you need to do is convince them that you are one.

To this end, you need a solid business plan convincingly demonstrating how your management team can rake in the profits in a way that the mother company could not. I can't emphasize this enough. The mother company's plan wasn't working; otherwise they wouldn't be selling. Your plan has to convince the banks, private equity, your employees, your family, and your loyal sponsors. For me, the business plan was the one piece of the puzzle I had confidence in. The management team had been working to improve results for months, and the quality of work in the group was outstanding. A good CRO comes down to only a couple of things: a good customer-oriented scientific staff that is focused on quality and speed, and a sales force that can go out there and deliver the message. We had both.

Our results had been negative for a couple of years, but the turnaround was showing slow and steady results. Positive results were on the horizon. Management projections of a profit aren't enough to significantly raise the price tag on a company like ours. Investors want to see some serious black before they lay out a lot of green. That meant our price would be low, while my confidence in the future was high. Well, mostly. Any change as big as this, no matter how logical and well-reasoned is bound to cause wild fluctuations in spirit. But I had a plan. Maybe even a good one. And I was clinging to it. Sure, I was a corporate guy, but I was about to be baptized into a whole new world. I would become a born-again entrepreneur, and I was going to need some serious help. ◆

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).

FORMULATION FORUM

Formulating Proteins and Peptides: Designing for Delivery

By: Cindy H. Dubin, Contributor

Protein and peptide therapeutics have become an important class of drugs due to advancements in molecular biology and recombinant technology. There are more than 100 biopharmaceutical products approved and generating revenue of more than $56 billion dollars, according to researchers at Lipocine Inc., a Salt Lake City, Utah-based drug delivery company. A safe, effective and patient friendly delivery of these agents is the key to their commercial success.

Currently, most proteins are administered parenterally; various delivery strategies and specialized companies have evolved over the past few years to improve delivery of proteins and peptides. Polymeric depot and PEGylation technologies have overcome some of the issues associated with parenteral delivery. Considerable research has been focused on non-invasive routes, such as pulmonary, oral and transdermal, to increase patient compliance.

Yet, delivery via non-invasive routes remains challenging due to their poor absorption and enzymatic instability. In the case of oral administration, for example, the barriers to peptide bioavailability after oral administration are intestinal membrane permeability, size, intestinal and hepatic metabolism and lastly solubility. Structurally modifying the compound or site-specific delivery are just some of the approaches being used to overcome limitations via oral delivery.

While there is much excitement surrounding the potential of proteins and peptides, the complex structure of these therapeutic substances require special formulation and delivery strategies, creating special challenges for drug developers and their formulation technology and delivery device partners.

One formulation trend is emerging: Designing for delivery has become the goal of many formulators when it comes to proteins and peptides. According to Dr. Tom Tice, Vice President of Research for Brookwood Pharmaceuticals, Inc., a subsidiary of SurModics, Inc., "The drug delivery folks have had their technologies around and were just waiting to deliver proteins and peptides. We are now developing proteins and peptides that match to the existing delivery systems and as a result we get better dosing regimens, improved stability, optimized solubility, and optimized formulation manufacturing."

Patricia Haller, PhD, Director, GMP Manufacturing and Process Development at American Peptide Company, Inc., says that small modifications in the peptide sequence or counter-ion can alter their compatibility with existing delivery systems without compromising the affinity and potency of the peptide drug. "These requests from clients are not uncommon and can be accommodated during manufacture," she says.

AMERICAN PEPTIDE COMPANY, INC. — CONCENTRATING ON THE COUNTER-ION

According to Scott Caton, Senior Manager, GMP Quality Control for American Peptide, the number-one challenge in helping clients with formulation is the solubility of hydrophobic peptides. Much of these solubility issues come from the general chemistry of the peptide, but there are steps within manufacturing that can increase solubility. One of these steps is the type and concentration of the counter-ion. The specific concentration of the counter-ion can be difficult to control, but understanding the minimum counter-ion concentration needed to be soluble can help with formulation development.

"Clients are looking at us to help them in the early stages of their formulation hurdles. They are carefully looking at several different issues that directly affect the stability and solubility of their API," says Shawn Shirzadi, Vice President, Quality. "Clients are coming to us in various stages of the drug development process. Most of our clients are in Phase I and Phase II of development, although we have some late-development stage clients. The early-stage clients are where a majority of the formulation-related questions and concerns come from. Some clients do not have experience with peptides or formulation development. Based on our experience with peptides and the drug development process, we help our clients with these questions and their development work through stability and forced degradation studies, impurities identification and solubility issues."

"Most of our clients are in the development of cancer fighting therapeutics," says Gary Hu, Vice President, Sales and Marketing. "With all the published genome mapping information available, clients are able to find and develop specific peptides that target new technologies to help combat cancer. The other area of therapeutic development is dealing with autoimmune diseases."

The peptides that American Peptide manufactures contain a counter-ion or they are requested as a specific salt form. The most common counter-ion is acetate. An additional counter-ion sometimes requested is TFA, says Mr. Caton. In some peptides, the varying concentration of acetate directly affects solubility.

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Therefore, work within process development and the consistent value of acetate in the manufacturing process can be greatly beneficial to the client. In addition, having any residual TFA in an acetate salt peptide can be hazardous to the client's formulation process. This may cause solubility difficulties and/or stability issues based on a change in the pH or chemistry of peptide. An additional concern regarding any residual TFA for an acetate salt form or other salt form stems from regulatory issues and concerns for the patient's reaction to higher levels of TFA.

BROOKWOOD PHARMACEUTICALS, INC. — WAITED FOR PROTEINS AND PEPTIDES

Brookwood scientists have been key participants in many areas of microencapsulated product development, from work with contraceptive steroids in the 70s, to LHRH peptides in the 80s. Brookwood Pharmaceuticals is a drug delivery company that provides its proprietary polymer-based technologies to companies developing improved pharmaceutical products. The company has particular strength in proprietary injectable microparticles and implant technology, both of which are based on biodegradable polymers, to provide sustained drug delivery. Active ingredients microencapsulated at Brookwood include small molecules, peptides, proteins and nucleic acids.

This past August, Brookwood was acquired by Surmodics, Inc., a provider of surface modification and drug delivery technologies. By combining SurModics'proprietary, internally developed Eureka™ biodegradable polymer family with Brookwood's proprietary drug delivery platforms and capabilities, the two expect to offer a novel technology well suited for systemic drug release products. According to Dr. Tice, Eureka offers stability maintenance to a protein after it is administered. "You need to maintain stability with these larger molecules to ensure that the protein properly interacts with its target."

On the peptide side, Brookwood takes a solution-oriented approach to formulation through synergistic capabilities and technologies, depending on the peptide and the customer's target drug profile. Customers benefit from enhanced capabilities and services such as research-scale peptide synthesis for backbone and side chain modifications, evaluation of available drug delivery technologies, large-scale peptide drug substance production, formulation feasibility studies and development of microencapsulation processes, drug excipients manufacturing (phospholipids, polymers and biomaterials), drug product formulation, and manufacturing of clinical supplies and final drug delivery product.

"We have had the technology in our PLG polymer and have been waiting for scientists to develop the proteins and peptides that could be delivered with PLG," says Dr. Tice. "But as existing peptides had solubility and physical property issues, synthetic peptides are being designed to eliminate these characteristics." Brookwood has partnered with Genzyme Pharmaceuticals to finalize the design of the physical and chemical properties of the peptide to match the delivery system, known as the Design for Peptide Delivery℠ program.

Brookwood is able to modify the physical and chemical properties of peptides for optimal drug delivery. "This enables us to design the peptide to do what we want it to do and makes it easier to formulate," Dr. Tice says.

Chemical modification includes: minimizing aggregation and adsorption; modulating hydrophobicity/hydrophilicity; optimizing charge distribution; and introducing non-solubilizing elements.

Improved physical properties include: modulating acetate counter ion content and optimizing bulk density.

NEKTAR THERAPEUTICS — MAKING DRUGS BETTER THROUGH PEGYLATION

Nektar uses its proprietary PEGylation technology as a platform for both large and small molecules. "In the areas of proteins and peptides, there remains a great deal of opportunity to make these drugs better through the use of PEGylation," says Mary Bossard, PhD, Director of Biopharmaceutical Research. "Most recently, we made great progress in the area of hemophilia with a PEGylated Factor-IX program. Our internal team performed the initial preclinical research on this molecule, establishing proof of concept and identifying the opportunity. We then partnered with the leader in hemophilia, Baxter, who will develop this program, which can represent an important advance for hemophilia patients. This builds on our partnership for PEGylated Factor XIII and other blood clotting factors. So hemophilia has become a become a big focus for us."

Most proteins require frequent shots or in the case of hemophilia, patients still required infusion therapies. This means there are still many opportunities for once-weekly subcutaneous delivery or even longer alternatives to the prospect of daily shots, says Dr. Bossard. Nektar supplies the PEG for Neulasta (pegfilgrastim) for Amgen. "This drug is a perfect example of a second-generation drug that improved the parent drug from daily weight adjusted dosing to a standard injection once per chemotherapy cycle."

In the areas of proteins and peptides, site-specific PEGylation and the use of engineered sites to place the PEG are very popular, she says. "As far as peptides go, oral delivery is still the ultimate goal and PEGylation may help us get there. We are also looking at small-molecule PEGylation, an area that is to date largely unexplored, and is becoming a very hot area. If we can improve the PK and delivery of small molecules, we may be able to ultimately improve their efficacy as well as had been done with the PEGylation of proteins in the past."

Newer drugs close to market are often adding in an engineering component in their design. The PEGylated antibody fragment under development by UCB given the trade name CIMZIA® for Rheumatoid Arthritis and Crohn's disease is an excellent example, says Dr. Bossard. The protein component of the antibody fragment can be produced in a microbial setting, which is cheaper than conventional mammalian cell coupling and this protein fragment is engineered for

attachment of Nektar's custom PEG. In this case, the final product is a new drug to compete with traditional anti-tumor necrosis factor (TNF) antibody treatment.

3M DRUG DELIVERY SYSTEMS — ELIMINATING THE NEEDLE AND SYRINGE?

With the continued rapid growth of biotherapeutics, proteins and peptides are being developed across a wider range of therapeutic areas at 3M Drug Delivery Systems. Rather than focusing on a specific therapeutic area, 3M looks for opportunities to leverage our inhalation, transdermal, and microneedle drug delivery technologies to provide increased value across all relevant therapeutic areas, says Timothy A. Peterson, Technical Manager.

However, vaccine delivery is certainly one area of emphasis for 3M's microstructured transdermal system (MTS). "This technology is particularly well suited to vaccine delivery because it provides targeted delivery to the immune responsive cells present within the skin, offering the potential for enhanced immunogenicity. The MTS technology is also applicable to a variety of antigen types, including protein antigens, which are typically less immunogenic than other antigen types such as inactivated virus," says Mr. Peterson.

"Another part of our vaccine offering is our small molecule toll-like receptor (TLR) 7 and TLR8 agonists that have shown potent vaccine adjuvant activity in a number of systems," he adds. Being small molecules, these TLR7/8 agonists can be delivered by multiple routes of administration unlike other classes of TLR agonists that are generally much larger. "Our lead compound, resiquimod, is available at manufacturing scale and has undergone extensive evaluation both preclinically and clinically. We are looking to license these compounds on a nonexclusive basis to a number of vaccine companies."

Development partners come to 3M at a variety of stages within the development process. Mr. Peterson says: "In some cases, our partners are interested in a new delivery system for a protein/peptide that is already marketed in another dosage form. In other cases, we are working with partners that are trying to get their protein/peptide into an initial clinical trial and want to start the development process with a delivery system that maximizes their likelihood of success."

3M is leveraging core technology in microstructured materials and processes to create targeted vaccine delivery systems as well as systems for systemic delivery of macromolecules. 3M's Microstructured Transdermal System (MTS) is a microneedle system for transcutaneous or intra-dermal drug delivery. MTS bypasses the barrier properties of the stratum corneum and provides a means to deliver a variety of molecules that ordinarily would not penetrate

the skin, including vaccines. MTS enhances the efficacy of vaccines by targeting the antigen presenting cells within the skin, thereby improving delivery efficiency and reducing dose requirements. In summary, MTS is a painless, easy-to-use system with the potential to greatly improve the delivery of vaccines.

"3M's expertise in microreplication, precision molding, precision coating, microfluidics, and GMP manufacturing underlies the technology and enables the production of robust, economically viable MTS systems," says Mr. Peterson.

3M also offers inhalation drug delivery systems for delivery of proteins and peptides to the lungs. 3M introduced the first commercial metered dose inhalers (MDIs) 50 years, and while it still provides the same familiar user interface for patients, virtually all aspects of MDI technology ranging from the container system to the valve to the propellant based formulations have been redesigned and optimized over the years, making today's MDI a relevant technology for delivery of peptides and proteins to the lung, says Mr. Peterson.

In addition to MDI technology, 3M is also developing dry powder inhalation (DPI) technologies that will expand the range of proteins and peptides that can be delivered to the lung by increasing the high end of the dosing range and improving both delivery efficiency and reproducibility.

When it comes to formulaion, Mr. Peterson says foremost among the challenges is the need to protect the stability of the protein or peptide during the dosage form manufacturing process and throughout the shelf life of the drug product. The severity of this challenge can vary greatly depending on the specific properties of the protein/peptide, but in general, heightened concern about the stability of the active ingredient is one of the key challenges that distinguish formulation development of proteins/peptides from small molecules.

Bioavailability is another concern. New drug delivery systems for proteins and peptides are often compared to existing injectable delivery systems which generally provide relatively high bioavailability. Combine this with the high cost of many of the protein/peptide APIs and some new formulations/delivery systems can become cost prohibitive if a certain minimum level of bioavailability is not achieved. Since most delivery alternatives will not provide an increase in bioavailability, the delivery system must provide therapeutic advantages sufficient to compensate for any reduction in the efficiency of drug utilization and provide an overall improvement in the value proposition associated with the therapeutic.

The heightened concern about protein/peptide stability quite often means that processes must to be adapted or redesigned to protect the API. A simple example from inhalation drug delivery are the processes used for obtaining active ingredient in the 1-5 micron size range necessary for efficient delivery to the lungs. While most low molecular weight drugs can be size reduced through a jet milling micronization process, many proteins and peptides would not survive such a high shear process without degradation. As a result, more gentle particle generation technologies, such as spray drying, have been developed to protect the stability of the more labile proteins and peptides, explains Mr. Peterson.

With respect to efficient utilization of the protein/peptide, it is important to not only optimize the bioavailability of the protein/peptide to the patient, but also to minimize the amount of API utilized in the drug product manufacturing process. For example, within the field of vaccine delivery, microneedle delivery systems are being evaluated that have enhanced immunogenicity when compared to SC or IM injections because they deliver the vaccine in closer proximity to antigen presenting cells within the skin. However, this advantage could be wiped out or reduced if the processes used for coating microneedles with vaccine formulation were significantly less efficient than a syringe filling process. Mr. Peterson says: "At 3M, we focus our efforts to ensure that the overall API utilization starting with the first dosage form manufacturing process through to the absorption of the API in patients is as efficient as possible, thereby improving the economics for our biopharmaceutical partners."

The greatest opportunity in protein and peptide delivery systems is the replacement of the needle and syringe. Although the needle and syringe works quite well as a delivery system in many cases, the collateral problems that arise as a result of its use (needle phobia, pain, barriers to self-administration and needle disposal to name a few) leave a big window of opportunity for alternative delivery systems.

"3M intends to develop inhalation and MTS systems that cost effectively deliver on the promise of eliminating the needle and syringe and provide real patient patient benefit," says Mr. Peterson. ◆

BIOGRAPHY

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

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MUCOADHESION ENHANCEMENT

Enhancement of Mucoadhesion by Blending Anionic, Cationic & Nonionic Polymers

By: Rita J. Majithiya, MPharm; Amit J. Raval, MPharm; Manish L. Umrethia, MPharm; Pradip K. Ghosh, MPharm; and R.S.R Murthy, MPharm, PhD

ABSTRACT

Formulation of an efficient mucoadhesive drug delivery system needs careful consideration of critical formulation-related parameters. This study was aimed to investigate the effect of the combination of nonionic (HPMC), cationic (chitosan), and anionic (Carbopol 934) mucoadhesive agents on the mucoadhesive characteristics of the dosage form. Mucoadhesive tablets containing nonionic [hydroxypropylmethylcellulose (HPMC)], cationic (chitosan), and anionic polymer (Carbopol) at different ratios were prepared by direct compression using clarithromycin as a model drug. The in vitro bioadhesive properties were evaluated by a shear stress measurement and detachment force measurement using rat stomach membrane and a modified balance method, which showed that HPMC possessed the best mucoadhesive strength when used alone. When used in combination with the other polymers, an additive or synergistic effect on the mucoadhesive property was observed. Maximum mucoadhesive strength was observed with the formulation having chitosan: Carbopol (1:4). A combination of chitosan and HPMC showed an additive effect on the mucoadhesive potential of the formulation. A synergistic effect on the mucoadhesive potential was found in the Carbopol and chitosan combination on rat stomach mucosa. A similar finding was also observed when a combination of Carbopol and HPMC were used. Swelling studies indicated a correlation of swelling capacity and the mucoadhesive potential for the formulation consisting of the polymers alone. However, when used in combination, a significant correlation was not observed between swelling capacity and mucoadhesion. Thus, it can be concluded that suitable blending of nonionic, cationic, and anionic polymers is needed for a better mucoadhesive property in mucoadhesive delivery systems.

INTRODUCTION

The use of mucoadhesive polymers as a means of delivering therapeutically active drugs, including proteins and peptides, to/via mucosal membranes has been the focus of attention in recent years.[1-5] For the purposes of drug delivery, a bioadhesive has been defined as a synthetic or biological material that is capable of adhering to a biological substrate or tissue.[6,7]

Mucoadhesive drug delivery systems localize the drug at a desired site and are therefore considered a better approach to design drug delivery systems to organs like the buccal, nasal, and vaginal cavity. Throughout the past decade, research was particularly focused on the delivery of mucoadhesive dosage forms in the gastrointestinal tract, which is the most favorable route of delivery with regard to patient compliance and ease of application. Because many drugs are absorbed only from the upper small intestine, localizing oral drug delivery systems in the stomach or duodenum would significantly improve the extent of drug absorption. The intimate contact with an absorption surface as offered by mucoadhesive delivery systems may increase the local permeability of even high molecular weight drugs, such as peptides and proteins. Mucoadhesive polymers are natural or synthetic hydrophilic macromolecules, which contain numerous hydrogen bond-forming groups. These polymers will hydrate and swell in contact with an aqueous medium, and as a result, adhere to the mucosal surfaces. Mucoadhesive drug delivery systems consisting of polymer and drug in matrix form could be prepared using mucoadhesive polymers, natural or synthetic hydrophilic macromolecules containing numerous hydrogen bond-forming groups. The objective of the present investigation was to study the adhesion strength of various mucoadhesive polymers, including nonionic (HPMC), cationic (chitosan), and anionic (Carbopol), using shear stress measurement and detachment force measurement techniques. Mucoadhesive strength of tablets prepared using the aforementioned mentioned polymers alone and in combinations was assessed. The investigation is also aimed to optimize the best possible combination of the mentioned polymers for formulating mucoadhesive delivery systems with maximum mucoadhesive and therapeutic potential.

EXPERIMENTAL

Materials

Clarithromycin U.S.P. was obtained as a gift sample from M/s Sun Pharmaceuticals Advanced Research Centre, Baroda (India). Chitosan (molecular weight of 650,000,

degree of deacetylation of 81.5%, viscosity of 150 cps) was obtained from Central Institute of Fisheries Technology, Cochin (India). Hydroxypropylmethylcellulose K4M (HPMC) and Carbopol 934 P were procured from Hi-media lab Pvt Ltd., Mumbai (India). All other chemicals were of analytical reagent grade and were procured from local suppliers.

Preparation of Mucoadhesive Polymer Tablets

The test polymers used included Carbopol 934, hydroxypropylmethylcellulose K4M (HPMC), and chitosan. Flat-faced tablets with a diameter of 12 mm, weighing 100 mg each were prepared. Various tablet formulations containing test polymers either alone or in various combinations of the polymers and a fixed amount of model drug (clarithromycin) were prepared by direct compression using a rotary tablet compression machine (Table 1). Compression force was adjusted so as to get the tablet hardness of four newtons.

TABLE 1

Batch	Ratio of various polymers used in the formulation of mucoadhesive tablets				Weight required for detachment in rat stomach membrane (W_b)	Force required for detachment in rat stomach membrane (F_b)
	Chitosan	HPMC	Carbopol	Drug	gm (Mean ± SD)	Newton (Mean ± SD)
X	1	-	-	1	3.47 ± 0.27	3.40 ± 0.26
Y	-	1	-	1	11.76 ± 0.66	11.54 ± 0.65
Z	-	-	1	1	10.51 ± 0.98	10.31 ± 0.96
A1	0.8	0.2	-	1	6.05 ± 0.49	5.94 ± 0.48[x,y]
A2	0.6	0.4	-	1	7.52 ± 0.91	7.38 ± 0.89[x,y]
A3	0.5	0.5	-	1	8.95 ± 1.01	8.78 ± 0.99[x,y]
A4	0.4	0.6	-	1	9.95 ± 0.78	9.75 ± 0.76[x]
A5	0.2	0.8	-	1	10.82 ± 1.20	10.61 ± 1.18[x]
B1	0.8	-	0.2	1	9.71 ± 0.59	9.53 ± 0.58[x]
B2	0.6	-	0.4	1	11.75 ± 0.76	11.53 ± 0.75[x]
B3	0.5	-	0.5	1	12.42 ± 0.33	12.18 ± 0.32[x,z]
B4	0.4	-	0.6	1	13.85 ± 0.51	13.59 ± 0.50[x,z]
B5	0.2	-	0.8	1	17.63 ± 0.93	17.30 ± 0.91[x,z]
C1	-	0.2	0.8	1	17.59 ± 0.52	17.26 ± 0.51[y,z]
C2	-	0.4	0.6	1	14.77 ± 0.76	14.49 ± 0.75[y,z]
C3	-	0.5	0.5	1	13.11 ± 0.67	12.86 ± 0.66[z]
C4	-	0.6	0.4	1	12.35 ± 0.59	12.12 ± 0.58
C5	-	0.8	0.2	1	10.70 ± 0.02	10.50 ± 0.02

[x](P < 0.05, with respect to batch X) [y](P < 0.05, with respect to batch Y) [z](P < 0.05, with respect to batch Z)

Detachment force of mucoadhesive tablets containing varying ratios of Carbopol, chitosan, and HPMC. Data are represented as mean ± S.D. (n = 4).

Preparation of Model Mucosa

The model mucosa used for assessment of mucoadhesion was rat stomach membrane. Fasted wistar rats (200 to 250 g) were anesthetized with sodium pentobarbitone and sacrificed. The stomach was removed, cut longitudinally, and emptied of food. The inner surface was washed with JP XII 1st fluid at a rate of about 20 ml/min for 10 minutes until the mucosa was clean. The tissue was used within 2 hours following dissection.

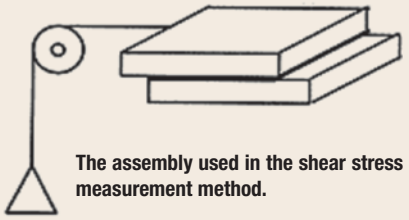
In Vitro Mucoadhesion Testing

The in vitro adhesion testing was done based on the principles of shear stress measurement and detachment force measurement.

SHEAR STRESS MEASUREMENT METHOD: Shear stress measurement studies were carried out as described by Rao et al.[8] Two smooth, polished glass blocks were selected. One block was fixed with the adhesive Araldite onto a glass plate that was fixed on a table. The level was adjusted with a spirit lamp. The upper block was tied to a thread that passed down through a pulley, the end of which was tied to a pan (Figure 1). A drop of polymer solution was placed at the center of the fixed block surface, and the second block was placed on it (100 g of pressure was applied). After keeping it for fixed time intervals of 5, 10, 15, and 30 minutes, the weights were added to the pan. The weights required to pull the block or to make it slide down from the base block represent the adhesion strength, that is, the shear stress required to indicate the adhesion strength (Figure 2).

DETACHMENT FORCE MEASUREMENT METHOD: Detachment force method was used to study in vitro mucoadhesion of different polymers. The modified balance method was used to assess the tendency of mucoadhesive materials to adhere to mucosal membrane.[9] The left pan was replaced with a Teflon block B ring hung by a number of metallic rings. The mucosal membrane was attached to Teflon block A, and the tablet was attached to Teflon block B using an adhesive and was lowered on block A kept in jacketed glass beaker filled with the test medium [JP XII 1st fluid (pH 1.2) at 37°C]. The right pan of the balance was replaced with a light weight beaker. Two sides of the balance were balanced by keeping suitable weight on the right-hand pan. Removal of weight from the right-hand side lowered Teflon block B, resulting in the attached tablet to rest on the membrane attached to block A. After contact time of 4 minutes, weight was increased in the beaker on the right-hand pan by addition of water until the tablet became detached from the membrane. The excess weight to the right-hand side gave the mucoadhesive strength of the tablet. The force

FIGURE 1



The assembly used in the shear stress measurement method.

in newtons (F_D) was calculated and was used as a parameter for adherence (Table1). This experiment was run four times on each batch of polymer tablets prepared.

In Vitro Swelling Studies on Bioadhesive Tablet

Swelling time is an important characteristic for bioadhesion. The swelling rate of the tablet was evaluated using 1% w/v agar plate.[10] The average weight of three tablets of each formulation was calculated (W1) by placing the tablets on a gel surface in a petri dish, which was incubated at 37 ± 0.1°C. After absorbing excess water on the surface of swollen tablets using filter paper, the tablets were weighed at time intervals of 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 7.5, 8.5, and 9 hours, and the average weight (W2) was calculated. The Swelling Index was calculated using the following formula:

$$\text{Swelling Index} = \frac{W2 - W1}{W1}$$

Statistical Analysis

All the data were expressed as mean + S.D. Detachment force data were analyzed by one-way analysis of variance (ANOVA), followed by tukey's multiple comparison test. Differences were considered to be statistically significant when $p < 0.05$. Statistical analyses were performed using Instat Version 3 (Graph pad Software).

RESULTS & DISCUSSION

Shear Stress Measurement Method

The results of the shear stress measurement in terms of weight (Wss) required to break the adhesion with mean and standard deviation for various polymers with different contact times are shown in Figure 2. Mean values of four experiments for each polymer was considered. It can be seen that increasing contact time for adhesion increased the force required to break adhesion for all the polymers, indicating an increase in the adhesion strength with the time of contact. From the results in Figure 2, it can be observed that of all the polymers, HPMC was found to have greater adhesion, and the order of adhesion strength of polymers is chitosan < Carbopol < HPMC.

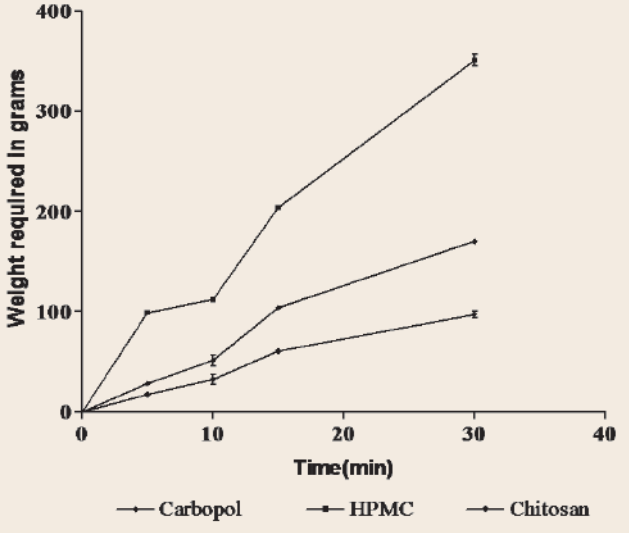
Detachment Force Measurement Method

The detachment force in newtons (F_D) and the corresponding weight (W_D) required to detach various batches of tablets prepared using different ratios of chitosan, HPMC, and Carbopol adhered to rat stomach are shown in Table 1. As seen from the results, it is evident that in comparison to both chitosan and Carbopol alone, HPMC had greater mucoadhesive strength on rat stomach mucosa, and the results obtained from detachment force measurement studies are in agreement with that obtained from shear stress measurement. However, tablet batches prepared using different ratios of cationic, anionic, and nonionic polymers showed no correlation between Wss and F_D. Among all the batches prepared, batch-B5 with 1:4 ratio of chitosan and Carbopol has shown the greatest mucoadhesion.

It can be observed from Table 1 that the detachment force required for batches A1 to A5 (chitosan and HPMC blend) was significantly ($P < 0.05$) greater than that required for batch X (chitosan only), whereas the force required for batches A1 to A3 was significantly ($P < 0.05$) lower than that required for batch Y (HPMC only). Thus, an increase in concentration of HPMC and a corresponding decrease in concentration of chitosan resulted in increased mucoadhesive strength in terms of force required for detachment. It is clearly evident from the results that when HPMC and chitosan are used in combination, they exhibit an additive effect on mucoadhesion.

In general, mucoadhesion is considered to occur in three stages, ie, wetting, penetration, and mechanical interlocking between polymer and mucus membrane. It is understood that mucoadhesive polymers could interact with mucus glycoprotein by forming physical and chemical entanglements, followed by hydrogen bonds with sugar residues on oligosaccharide chains that result in the formation of a strengthened mucus gel network that allows the formulations to remain adhesive for an extended period of time. HPMC is a long-chained, nonionic polymer and so its mucoadhesion is attributable to the formation of physical bonds or hydrogen bonding with the mucus components. HPMC possesses a large number of hydroxyl groups that are responsible for adhesion. Formation of hydrogen bonds between the hydrophilic functional groups of the mucoadhesive polymers and the mucus layer or the mucosal surface is a prerequisite for extensive and longer mucoadhesion. The increased sites for bond formation can explain

FIGURE 2



Shear stress measurement of polymers in terms of weight (Wss) used to prepare mucoadhesive tablets. Data are represented as mean ± S.D. (n = 4).

the increase in bioadhesion with an increase in concentration. Chitosan is a polycationic polymer; a positively charged hydrogel is formed in an acidic environment that could develop additional molecular attractive forces by electrostatic interactions with negatively charged mucosal surfaces or the negatively charged sialic acid groups of the mucus network. Also, it is a linear polyamine in which the amino groups are readily available to interact with negative surfaces. The higher mucoadhesive potential observed with formulations containing only HPMC is probably due to the controlled rate of hydration of HPMC as a nonionic polymer. This could in turn prevent the tablet from quick over-hydration and formation of slippery and weak mucilage, which could be easily removed from the mucosal surface. Chitosan may be forming weaker, more easily fractured gels due to its comparatively low molecular weight in addition to very high rate of swelling, resulting in low mucoadhesive strength.

The results of mucoadhesive strength obtained from tablets prepared using different ratios of chitosan and Carbopol show a synergistic effect on its mucoadhesive strength. An increase in Carbopol concentration resulted in a significant increase in mucoadhesive strength. As evident from Table 1, detachment force required for batches B1 to B5 (chitosan and Carbopol blend) was significantly ($P < 0.05$) higher than that required for batch X (chitosan only). This is also evident in the case of batches B3 to B5 in which F_D is significantly ($P < 0.05$) higher than that required for batch Z (Carbopol only). The F_D for batches B1 to B5 is greater than the sum of the contribution of both the polymers on a weight fraction basis. It can therefore be concluded that a combination of Carbopol and chitosan synergistically increases the mucoadhesive potential of the formulation. It is evident from these observations that a combination of chitosan and Carbopol up to a 1:1 ratio resulted in a maximum synergistic effect on mucoadhesion.

Carbopol is a cross-linked, anionic, hydrophilic polymer. In acidic pH , its swelling behavior is attributed to an uncharged carboxylic group that get hydrated by forming a hydrogen bond with imbibing water and hence extending the polymer chain. Earlier work with Carbopol polymers has clearly indicated that it is the availability of these carboxyl groups that determines bioadhesion.[11] Carbopol has a very high percentage (58% to 68%) of carboxylic groups that gradually undergo hydrogen bonding with sugar residues in oligosaccharide chains in the mucus membrane, resulting in the formation of a strengthened network between the polymer and mucus membrane. Thus, Carbopol having a high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins. At the same time, it may also be adopting a more favorable macromolecular conformation and accessibility of its hydrogen bonding groups.

Carbopol is reported to demonstrate a concentration-dependent adhesive property. Therefore obviously, increasing the concentration of Carbopol in the formulation consisting of a combination of Carbopol and chitosan showed increased mucoadhesion. Furthermore, addition of chitosan to Carbopol (batches B2 to B5) showed increased mucoadhesion as compared to batch Z. This increase in mucoadhesion may

FIGURE 3A

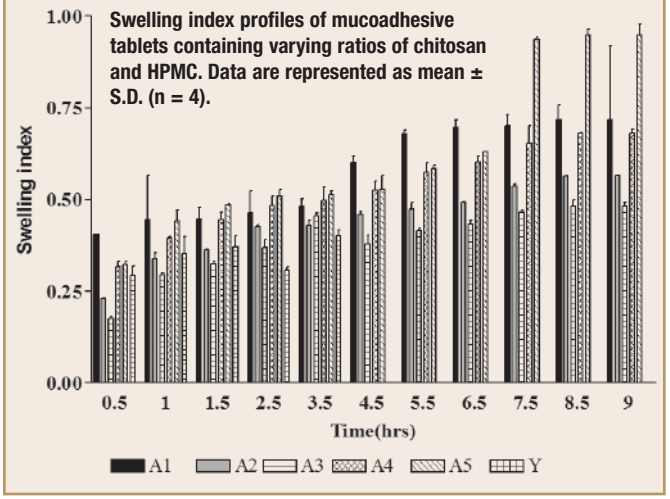


FIGURE 3B

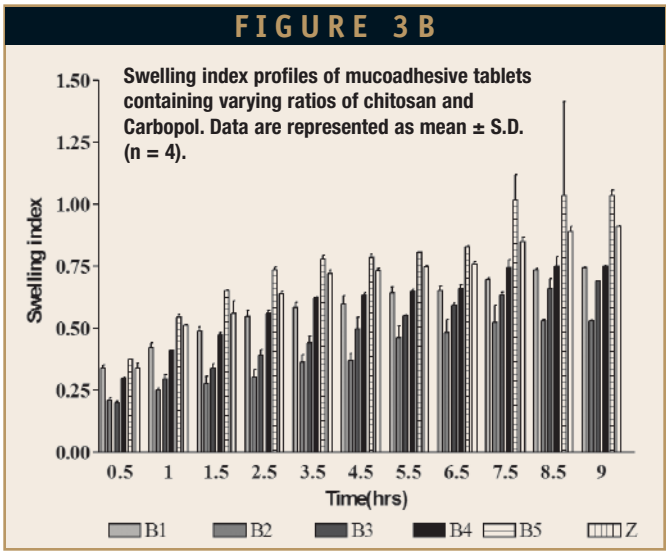
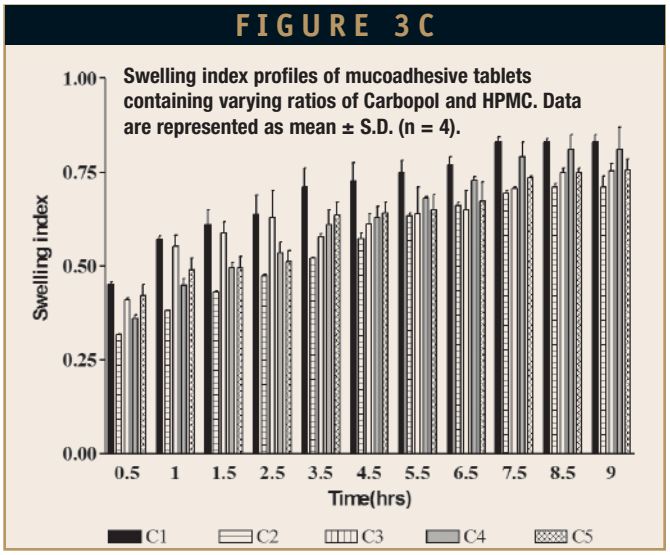


FIGURE 3C



be attributed to electrostatic interaction of positively charged amino groups of chitosan with negatively charged sialic acid of mucus membrane in addition to hydrogen binding of Carbopol with mucus membrane. Thus, both polymers acted synergistically to enhance mucoadhesive potential. The groups responsible for hydrogen binding in the oligosaccharide unit of the mucus membrane are more in number as compared to that responsible for electrostatic attraction (sialic acid groups). Therefore, mucoadhesive potential increased continuously upon increasing Carbopol concentration, but there was limited significance on mucoadhesive potential upon increasing the chitosan concentration beyond 50%.

Similar results were obtained from tablets prepared using different ratios of Carbopol and HPMC. As seen in Table 1, an increase in concentration of HPMC and a simultaneous decrease in concentration of Carbopol resulted in a reduction in mucoadhesive strength; however, all the batches showed better mucoadhesion as compared to batch Y (HPMC only) and batch Z (Carbopol only). Detachment force required for batches C1 to C2 was significantly ($P < 0.05$) higher than that required for batch Y; similarly, detachment force for batches C1 to C3 was significantly greater than that required for batch Z. Thus, Carbopol and HPMC synergistically increase the mucoadhesive potential, with Carbopol having a more pronounced effect on increasing the mucoadhesive potential.

The results are in agreement with other studies in which detachment force measurement studies carried out on sheep intestinal mucosa showed significant increase in the force required to detach the formulation as the concentration of Carbopol increased.[12] It is reported that compared to anionic polymers (Carbopol), nonionic polymers (HPMC) tend to form weaker gels with mucus, which may be ascribed to less available hydrogen bonding sites.[13,14] Therefore, as the percentage of Carbopol increases, percentage of carboxylic acid also increases, resulting in stronger hydrogen bonding.[11] Apart from the aforementioned, it seems that the initial water-absorbing capacity for Carbopol (30 minutes) is higher compared to HPMC, and both polymers expand and relax due to stresses introduced by penetration of water. Thus, upon increasing Carbopol concentration, more water penetrates, resulting in disentanglement and relaxation of polymers and thereby increasing access to hydrogen-bonding sites of polymers. However, it may be due to the same high water absorption capacity that Carbopol alone shows lower mucoadhesive potential compared to HPMC, due to over-hydration resulting in the formation of slippery mucilage and thereby reducing mucoadhesion strength. As HPMC has a lower water-absorbing capacity, addition of HPMC to cCarbopol results in prevention of slippery mucilage formation. Thus, the polymers Carbopol and HPMC act synergistically to enhance overall mucoadhesive potential of the formulation.

In Vitro Swelling Studies

Adhesion was reported to be affected by hydration.[15] Hydration of the mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. In the case of tablets applied in the dehydrated state, which is most convenient, it is essential that sufficient water be available so that rapid hydration takes place and a flexible rubbery state occurs. The capillary force arising when water from the space between the mucosa and the polymer is taken up by a dry system may be considerable.[16] It is of great importance that the mucoadhesive material will develop a bond with only minimum applied force. When the bond is formed, reduction in the rate of swelling due to water uptake from the tissue surface may only prolong the association of the tablet with the mucosa. Removal of water from the underlying mucous layer by the hydrating polymer may increase the cohesive forces of mucus. This plays a vital role in the establishment of an effective mucoadhesive bond.[17]

Water uptake tests are of great significance, as variation in water content causes a significant variation in the mechanical properties of formulations, especially those composed of hygroscopic components. The capacity of the formulation to take up water is an important intrinsic parameter of the polymeric system in consideration of the mucoadhesion of the formulation on the mucosal surface.

Formulation X containing chitosan alone was found to disintegrate within 30 minutes, and the rate of swelling was very high, which may be one of the reasons responsible for the lowest mucoadhesion strength observed for the same formulation. Further, it can be observed from Figure 3A that formulation Y (HPMC alone) showed a higher rate of swelling as well as lower water-absorbing capacity compared to the formulations containing mixture of chitosan and HPMC. When chitosan is in excess as seen in formulations X and A1, excess NH_2 groups are ionized, which results in loosening of the network as a result electrostatic repulsion between the polymer and decreased hydrogen bonding possibility caused by charged NH_3+ species. Protonation favors hydration and unfolding of cross-linked polymeric structures, and therefore, swelling and hence a higher water-absorption capacity is seen with batches X and A1, which may be one of the reasons for lower mucoadhesive potential of these batches. With batches A2 and A3, as concentration of chitosan is reduced, water-absorption capacity reduces with minimum water absorption capacity seen with batch A3 (chitosan to HPMC ratio 1:1). For batches A4 an A5, further increase in concentration of HPMC results in increased water-absorption capacity because in the case of HPMC, water uptake capacity increases with increase in concentration. Swelling of HPMC is attributed to disruption of hydrogen bonding among polymer chain and polymer chain relaxation. When water penetrates into solid HPMC, it inserts into H-bond between polymer chains, as more and more water comes between chains, forces between chains diminish.

Formulation Z (Carbopol alone) showed higher water-absorption capacity compared to HPMC alone, combination of chitosan and Carbopol (except batch B5), and all combinations of Carbopol and HPMC. A very high water-absorption capacity of Carbopol may be one of the reasons for its lower mucoadhesive

potential compared to HPMC alone. Carbopol will remain in un-ionized form at pH 1.2. Excess of Carbopol will therefore result in excess of the COOH group, but when used in combination with chitosan, NH_2 of chitosan is not available for hydrogen bonding as chitosan would be in a protonated state and hence exhibit a tightening of the network due to low probability of hydrogen bonding. Swelling seems to occur in the case of Carbopol due to a relaxation response of polymer chains due to stresses introduced in the presence of swelling medium. Batch B1 shows higher water-absorbing capacity due to the similar phenomena as described earlier, occurring as a result of excess the NH_2 groups. The lowest swelling is seen with batch B2. Batch B3's water-absorbing capacity was found to be increased with an increase in concentration of Carbopol. Among formulations containing a combination of Carbopol and HPMC, the highest water-absorbing capacity was seen with batch C1. Water-absorbing capacities of other combinations were such that no correlation could be established between the effect of concentration of Carbopol and HPMC on the overall water-absorption capacities.

The data obtained from the swelling study shows that for the formulations prepared using a combination of different polymers, water-absorbing capacities do not play a significant role in deciding its mucoadhesive potential; rather polymer properties of individual polymers play a significant role in the mucoadhesive potential of formulations. However, in the case of formulations containing polymer alone, it was found that a very high water-absorption capacity and rate of swelling resulted in lower mucoadhesive potential as it resulted in quick over-hydration and formation of a slippery and weak mucilage, which could be easily removed from the mucosal surface.

CONCLUSION

The combination of cationic polymer (chitosan), anionic polymer (Carbopol), and nonionic polymer (HPMC) was found to be suitable for increasing mucoadhesion of the mucoadhesive dosage form. Best mucoadhesion was found with a combination of anionic and cationic polymers at the optimized ratios. These polymers act complementary to each other. Formulations containing higher proportions of Carbopol showed increased mucoadhesive potentials. Thus, the variation in their ratios could be manipulated as per the desired mucoadhesive potential.

ACKNOWLEDGEMENT

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BIOGRAPHIES

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CAB COATING FILMS

Permeability Study on Cellulose Acetate Butyrate Coating Film

By: Jinghua Yuan, PhD; Doug Dunn, Nancy M. Clipse, and Ray J. Newton, Jr., PhD

INTRODUCTION

Cellulose acetate butyrate (CAB) belongs in the cellulose ester family. CAB could be used for tabletting as a matrix material or taste-masking when combined with cellulose acetate (CA) and hydroxypropyl cellulose, and has been reported in patents for semi-permeable membranes in osmotic drug delivery systems.[1-4] Particularly, CAB could be used in extended release formulations due to its more hydrophobic nature. Little work has been reported related to the permeability of CAB films. Recently, a group of researchers from Alza conducted a study to characterize CAB membrane properties with respect to performance of OROS® systems. Typically, the release rate of drugs from an OROS is controlled by semi-permeable membranes composed of cellulose acetate. They found that "the CAB membrane matched the CA membrane in robustness but had superior drying properties, offering particular advantages for thermolabile formulations."[5] The objectives of this study were to investigate the effects of formulation variables on CAB coating film performance, to examine CAB lot-to-lot variation effects on the permeability of the coating films, and to compare the permeability of CAB coating film with those of CA-coating film within a similar formulation and under the same coating processing conditions.

MATERIALS

Cellulose acetate butyrate CAB-171-15NF and cellulose acetate CA-398-10NF/EP (Eastman Chemical Company) were used in the study. The typical physical properties of CAB are listed in Table 1. A coating formulation included CAB-171-15NF or CA-398-10NF/EP (CA), polyethylene glycol 3350 (PEG 3350, Sigma Aldrich) as the plasticizer (Pz), acetone (high purity solvent, B&J Brand, Burdick & Jackson), and deionized water (NANOpure water system, Barnstead) as the solvent system. The model tablets to be coated consisted of 98.5% of POLYOX water-soluble resins with a molecular weight of 5,000,000 (Dow Chemical); 0.5% of colorant (Sensient Technologies Corp.), and 1% of magnesium stearate (Mallinckrodt Baker Inc.). All of the materials were used as received.

METHODS

Preparation of Model Tablets

POLYOX with a molecular weight of 5,000,000, blue dye, and magnesium sterarate were

blended in a v-blender (The Patterson Kelly Co. Inc.) for 3 minutes with the intensifying bar on for 15 seconds. The mixture was then compressed into 250-mg tablets on a rotary tablet press (D3B 16 Station, Manesty) under a 400-pound compression force.

Preparation of CAB Coating Solution

A CAB coating solution, with 6 wt% solid content was prepared by dissolving Pz, if any, in water for 1.5 hours, then most of the needed acetone was added. Finally, CAB was added gradually while stirring. After all CAB dispersed, stirring continued for another 2 hours. A calculated amount of acetone was added to compensate the loss due to evaporation during the dissolving process. Twelve formulations listed in Table 2 were investigated.

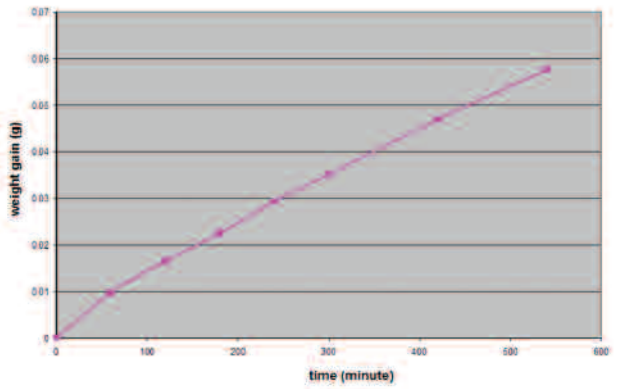
Procedures of Performing CAB Coating

800 g of tablets were coated with a CAB coating solution in each run. All of the coating runs, with a theoretical coating weight of 10 wt% relative to the tablet weight, were performed in a pan coater (COMPU-LAB, Thomas Engineering, Inc.) with one spray gun under the processing conditions indicated in Table 3. All of the coating formulations were repeated twice.

Measurement of the Permeability of CAB Coating Film

The permeability of CAB coating film was determined by performing a water uptake test. Eight tablets from each run were randomly selected and tested in 1000 ml of deionized water at 37°C using a standard USP disintegration tester. At selected time intervals, the tablets were taken out, dried gently with a tissue, and weighed. The water uptake at time t is the tablet weight at time t minus the tablet weight at time zero (tablet weight before testing). The testing was terminated after 9 hours. The average value of eight tablet results was used in the analysis.

FIGURE 1



Water uptake of CAB-coated tablets changes with time.

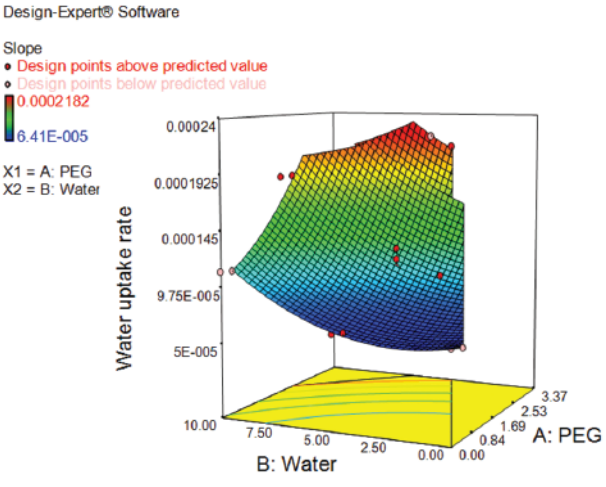
TABLE 1

Property	Range
Viscosity (sec)	14-24
Acetyl (wt%)/ DS	29.5 / 2.0
Butyryl (wt%) / DS	17.0 / 0.7
Hydroxyl (wt%) / DS	1.1 / 0.3
Melting Range (°C)	230-240
Glass transition temperature (Tg, °C)	152

Note: 1. Properties reported here are typical of average lots. Eastman makes no representation that the material in any particular shipment will conform exactly to the listed properties. 2. DS: Degree of Substitution. 3. Tg is obtained from the second heating scan by DSC.

Typical physical properties of CAB-171-15NF

FIGURE 2



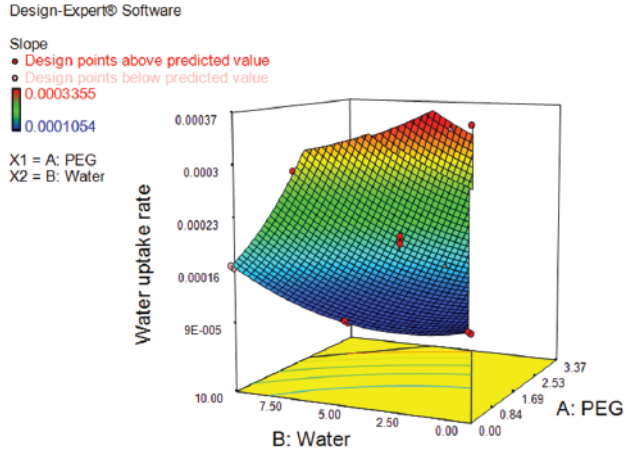
Water uptake rate changed with Pz and water in the beginning of the testing.

TABLE 2

Formulation ID	CAB (g)	PEG 3350 (g)	Water (g)	Acetone (g)	PEG/CAB Ratio	% Water
1	71.05	8.95	66.67	1186.66	0.13	5.00
2	71.05	8.95	133.33	1120.00	0.13	10.00
3	80.00	0.00	0.00	1253.33	0.00	0.00
4	80.00	0.00	66.67	1186.66	0.00	5.00
5	71.05	8.95	66.67	1186.66	0.13	5.00
6	62.02	17.98	66.67	1186.66	0.29	5.00
7	71.05	8.95	40.00	1213.33	0.13	3.00
8	62.02	17.98	53.33	1200.00	0.29	4.00
9	71.05	8.95	66.67	1186.66	0.13	5.00
10	80.00	0.00	133.33	1120.00	0.00	10.00
11	62.02	17.98	133.33	1120.00	0.29	10.00
12	71.05	8.95	66.67	1186.66	0.13	5.00

Coating formulation investigated

FIGURE 3



Water uptake rate changed with Pz and water in the second region of the testing.

TABLE 3

Factor	Condition
Equipment	12 " Pan coater (COMPU-LAB, Thomas Engineering)
Nozzle	35100-ss
Substrate	250-mg tablets
Pan charge	800 g
Inlet temperature	25°C
Air flow rate	175 cfm
Pan rotate speed	15 rpm
Atomized air pressure	15 psi
Spray rate	20 ml/min for 5 min; increased to 25 ml/min for another 5 min; and maintained at 30 ml/min for the rest of the run

Coating processing conditions

RESULTS & DISCUSSIONS

Pz & Water Effect on the Permeability of CAB Coating Film

CAB-coated tablets were tested in deionized water to determine water uptake as a function of time. It was observed that the water uptake rate is greater in the first hour, then the uptake rate decreases slightly and is maintained at the rate for the rest of the testing. Figure 1 shows an example of water uptake changing with time.

The observed shift in water uptake rate may be due to a change in the mechanism of water transport through the coated film. In the beginning of the experiment, water starts to penetrate the film by occupying the pores in the film; water may start to diffuse through the film simultaneously, but at a very low rate. When all pores are filled with water, water penetrates through the film only by diffusion. Because the diffusion step is slow, the water uptake rate decreases. After the first hour, the water uptake rate remains constant at the diffusion-controlled rate.

Based on the fact that the water uptake rate changes within the testing range, two models were established to fit the experimental data. Design Expert® software (Design Expert V7, Stat-Ease, Inc.) was employed to analyze the data. The water uptake rates are predicted as follows:

For the first region (about the first hour), water uptake rate (g/min)	For the second region (beyond the first hour), water uptake rate (g/min)
+6.50370E-005 -1.05288E-006 * PEG -4.91641E-006 * Water +2.54453E-006 * PEG * Water +1.02019E-005 * PEG^2 +9.62682E-007 * Water^2	+1.07750E-004 -6.48804E-007 * PEG -7.22356E-006 * Water +3.73240E-006 * PEG * Water +1.53744E-005 * PEG^2 +1.29684E-006 * Water^2

Here, PEG and water are the corresponding concentration in the formulation in %.

The models indicate that Pz and water level affect the permeability of CAB coating significantly, which is illustrated in Figures 2 and 3. Figure 4 shows an example of the model-predicted results and

experimental data. The agreement between the prediction and experimental data is clearly shown.

CAB Lot Variation Effect on the Permeability of CAB Coating Film

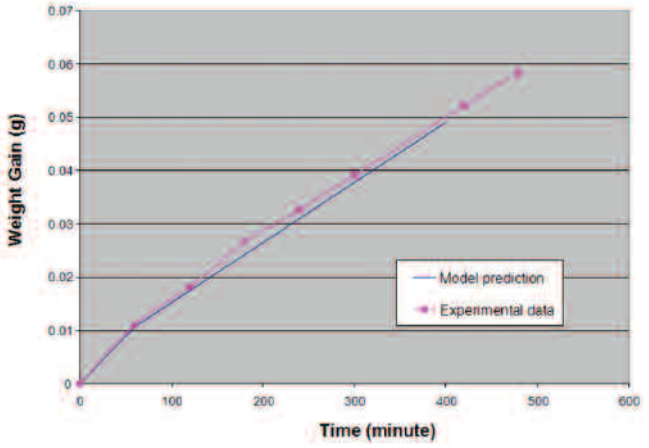
To examine the effects of variation in CAB lot on the permeability of CAB coating films, three CAB lots were selected. Table 4 lists the product information of three CAB lots. The same model tablets were coated with these three CAB lots under the same coating conditions as previously described with an exception of atomized air pressure being 20 psi instead of 15 psi used in other coating runs. The coating formulation was Pz/CAB = 13%, water = 5% (formulation No. 1 in Table 2).

For each lot of CAB, two separate coating runs were performed. Water uptake experiments were conducted with eight randomly selected tablets. The average value was reported. Figure 5 displays the water uptake results.

To determine the lot-to-lot variation, statistical analysis was performed on center points in the experimental design. There were four center points in the design; formulations Nos. 1, 5, 9, and 12. Table 5 lists the water uptake data variation at 500 minutes. The variation was calculated as: variation = (run^2 – run^1)/ run^1 x 100%.

The variation results from the center point formulation indicate that the water uptake difference at 500 minutes between two runs could be up to 7% for the same coating formulation under the same coating conditions. The water uptake variations of three CAB lots between two runs are also listed in Table 5. The data suggest that the variation of lot-to-lot is within the experimental errors. Therefore, it is concluded that the variation of CAB lots in the studied range doesn't significantly impact on the permeability of the coated films.

FIGURE 4



Comparison of model-predicted results and experimental data. Formulation: Pz/CAB = 13%; water = 5.00%.

TABLE 4

Test	Lot 1	Lot 2	Lot 3	Specification
ASTM-A Viscosity, sec	21.32	18.80	16.84	14.0-24.0
Butyryl by GC, wt%	17.06	17.48	17.31	16.5-19.0
Free Acidity by IC, %	0.0101	0.0147	0.012	< 0.1
Acetyl by GC, wt%	30.08	30.48	30.14	28.0-31.0
Hydroxyl by Titration, wt%	1.10	1.07	1.03	0.8-1.4
NF Water, wt%	0.81	0.93	0.90	< 5.0

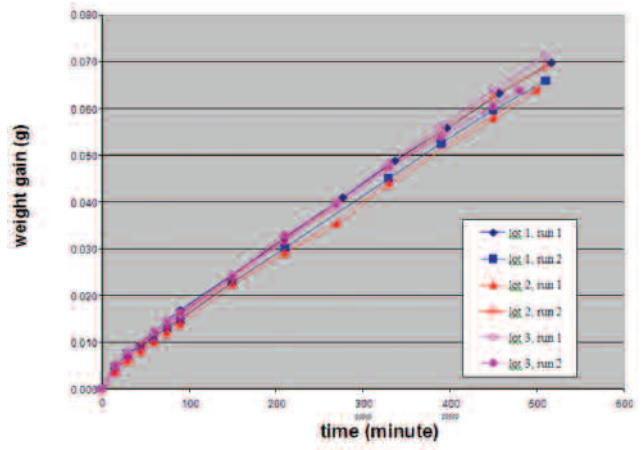
Product information of three CAB lots

TABLE 5

	Run 1	Run 2	Variation (%)
Center Point 1	0.060	0.064	6.7
Center Point 2	0.058	0.056	3.4
Center Point 3	0.061	0.062	1.6
Center Point 4	0.058	0.057	1.7
Lot 1	0.069	0.066	4.3
Lot 2	0.068	0.064	5.9
Lot 3	0.071	0.068	4.2

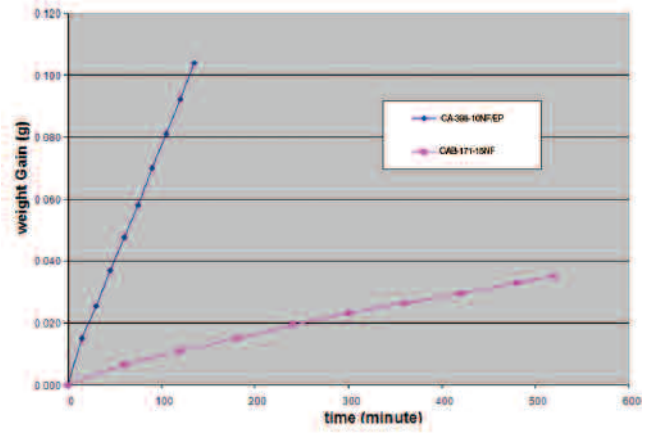
Statistical analysis of lot variations

FIGURE 5



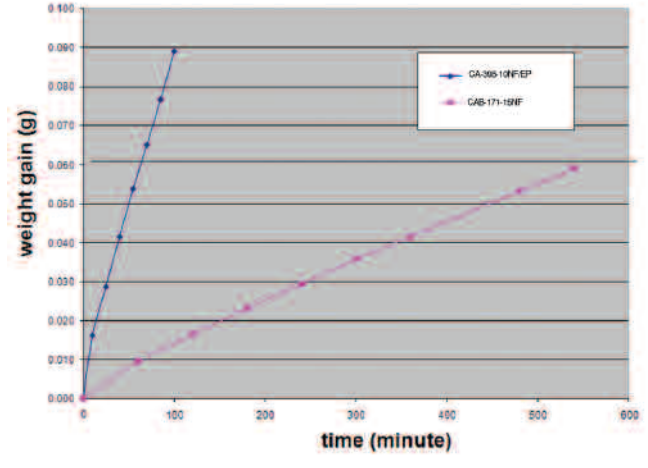
Water uptake results from three CAB lots.

FIGURE 6



Comparison of water uptake between CA and CAB coating. Formulation: Pz/polymer = 0%; water = 0.00%.

FIGURE 7



Comparison of water uptake between CA and CAB coating. Formulation: Pz/Polymer = 13%; water = 5.00%.

Comparison of Permeability of CA & CAB Coating Film

The model tablets were coated with CA or CAB using the same formulation, and the permeability of CA or CAB coating film was determined by water uptake tests. Figures 6 and 7 illustrate the results. It is not surprising that CAB coating has lower permeability due to its hydrophobic nature. SEM images show that no obvious differences in morphology of the coating films between CA and CAB (Figures 7 and 8). Hence, the difference in water uptake between CA and CAB coating are mainly determined by two factors: 1) the nature of the polymers (the more hydrophilic type of polymer CA would allow for faster water diffusion through the coating film, which gives higher water uptake) and 2) the differences in molecular weight of the polymers (CA has a lower molecular weight). At the same amount of coating weight, the lower molecular weight polymer has more free volume, which enables water diffusion through the film at a higher rate. Combining these two factors, it is expected that water uptake from CA coating film would be much higher than CAB coating film.

CONCLUSIONS

This study has demonstrated that formulation variables, such as Pz and water level will affect the permeability of the CAB coating films. It seems that PEG has a major influence. CAB lot variation doesn't seem to have a significant impact on the permeability of the coated films. Comparison of the permeability between CA- and CAB-coated films suggests that CA film is more permeable. It is possible to achieve desirable membrane permeability by selecting specific formulation variables and various types of polymers.

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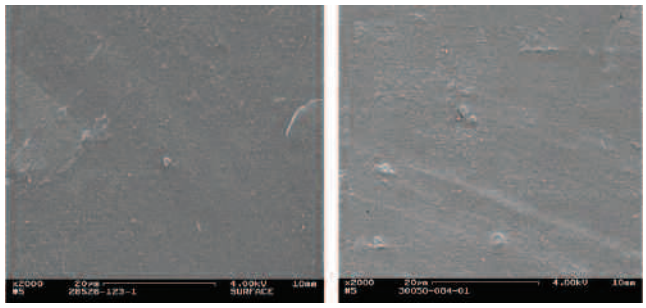
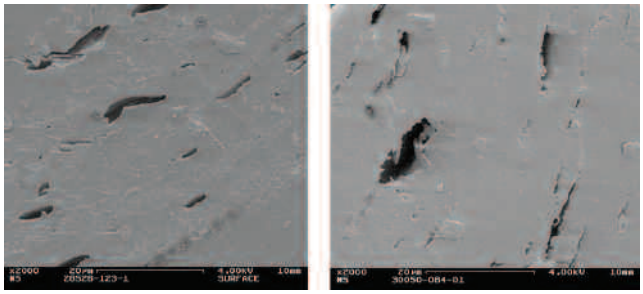
FIGURE 8



SEM surface images.
Left: CA coating film Right: CAB coating film.

FIGURE 9



SEM cross-section images.
Left: CA coating film Right: CAB coating film.

BIOGRAPHIES

Dr. Jinghua Yuan was appointed Principal Technical Service Representative for Eastman Chemical Company in 2002, responsible for pharmaceutical excipient products. Dr. Yuan has more than 20 years experience in formulation development and drug delivery systems. Prior to joining Eastman, Dr. Yuan worked as a Research Associate for both the School of Engineering at Purdue University and the Department of Chemical Engineering at the University of Virginia. She was also a lecturer and researcher for the Department of Chemical Engineering at Tianjin University in China. Dr. Yuan earned her BS in 1983, her MSc in 1986, and her PhD in 1989, all in Chemical Engineering from Tianjin University.

Mr. Douglas Dunn began his career at Eastman Chemical Company in 2005 with the Pharmaceutical Excipient Products group. Mr. Dunn has more than 25 years of laboratory experience, 18 of those in the pharmaceutical industry. Prior to joining Eastman, he worked as a Development Scientist for GlaxoSmithkline Pharmaceuticals in an R&D analytical laboratory. He mostly worked with the liquid dose team that saw several new products approved for market. Mr. Dunn earned an Associate of Science degree in Chemical Technology from Northeast State Technical Institute, Blountville, Tennessee, in 1981.

Ms. Nancy Clipse is a Lab Analyst, Performance Chemicals at Eastman Chemical Company, She has more than 40 years with Eastman Chemical and more than 20 years experience in formulation and drug delivery systems. She attended East Tennessee State University in 1968 and in 1982.

Dr. Ray J. Newton was appointed Group Leader of the Formulation Products Lab in the Technical Service Department, Eastman Chemical Company in 2004. Among other responsibilities, the Formulation Products Lab promotes Eastman's pharmaceutical excipient products through applications research and development. Prior to his current assignment, Dr. Newton's career has included a wide range of duties within Eastman, including R&D, manufacturing technical support, manufacturing supervision, and new business development. Dr. Newton earned his BS in 1974 from Lee University and his PhD in 1978 in Organic Chemistry from The University of Tennessee, Knoxville.

CNS DELIVERY

Delivery Across the Blood-Brain Barrier Using the CORVUS Peptide

By: Manjunath N. Swamy, MD, and Priti Kumar, PhD

ABSTRACT

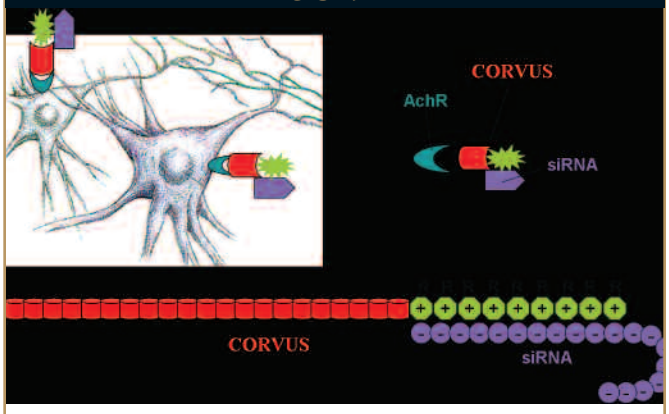
History has taught that drug molecular size is a critical factor as to whether drugs can enter the CNS and treat the myriad of CNS disorders. This is due to the infamous Blood-Brain Barrier (BBB). The BBB has created such difficulty in drug development that the basic concept is widely known and understood by lay persons outside of drug discovery and development. With a novel drug-targeting technology, researchers at the Immune Disease Institute in Boston have developed a strategy for selectively ferrying drugs across the BBB to the brain by IV injection. This strategy utilizes a small peptide carrier and holds promise for delivering a wide variety of molecules that cannot otherwise cross the BBB.

INTRODUCTION

The demand for new drug delivery strategies is clear based upon the many approved delivery technology-enabled products on the market, as well as the new nanotechnologies on the rise, reportedly reaching $26 billion by 2012.[1] As fewer novel druggable targets are identified, and increasingly fewer drugs coming from high-throughput chemical screening, drug delivery has become an important avenue for biotechnological and pharmaceutical companies to more efficiently bring drugs through clinical trials to the patients that need them. Nowhere is the importance of effective drug delivery more evident than in the maturing field of RNA interference (RNAi). Since the discovery of this powerful gene silencing mechanism, it has become abundantly clear that this technology holds great promise in the treatment of many diseases. The mediators of RNAi, small interfering RNA (siRNA) usually of 21 to 23 nucleotides in length, must act intracellularly. Potential side-effects of RNAi is also a cause for concern, increasing the importance of delivery only into cells of the target tissue. Therefore, delivery to specific target tissues and cellular uptake are key challenges to the implementation of RNAi therapy and for increasing the efficient progress of RNAi-based drugs to the marketplace.

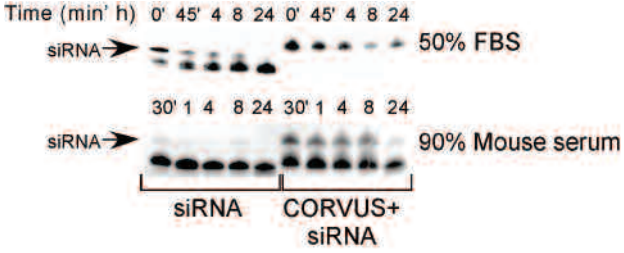
Additionally, companies are increasingly utilizing drug delivery solutions with existing drugs and to develop drugs that meet important unmet medical needs, such as hard-to-treat cancers and neurodegenerative disorders. Through repositioning of existing drugs to treat unmet

FIGURE 1



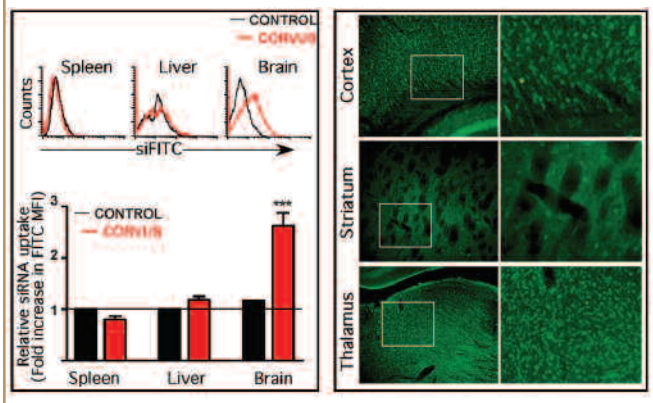
CORVUS design. Schematic representation of the CORVUS peptide binding to siRNA and the nicotinic acetyl choline receptor on neuronal cells.

FIGURE 2



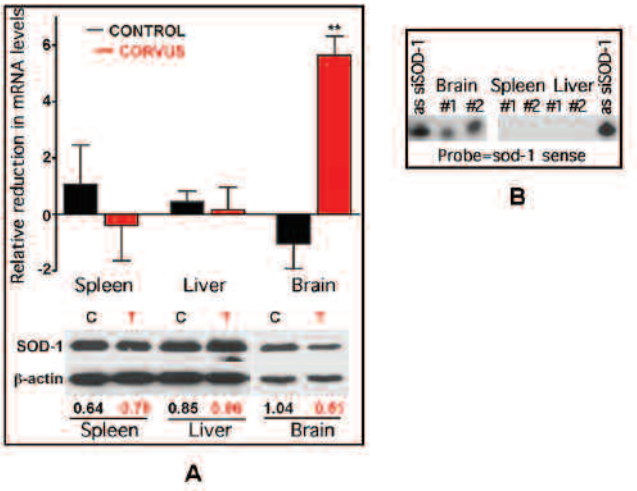
CORVUS binding confers partial protection from serum nucleases. Naked and CORVUS-complexed siRNA were incubated with sera at 37°C and aliquots taken at indicated times digested with proteinase K, electrophoresed on 15% polyacrylamide gels, and visualized with SYBR gold staining.

FIGURE 3



CORVUS delivers siRNA into the CNS.
A) Mice (n = 4) were iv injected with FITC-siRNA/peptide complexes and uptake by brain, spleen, and liver cells examined by flow cytometry. Representative histograms (top) and cumulative data (bottom) are shown.
B) Coronal sections of brain from FITC-siRNA/CORVUS injected mice were stained with anti-FITC antibody and examined by fluorescent microscopy. Images of FITC-positive cells in the cortex, striatum, and thalamus at lower (left panel) and higher magnification of boxed regions (right panel) are shown. Scale bar = 200 micrometers.

FIGURE 4



Brain-specific gene silencing by iv injection of CORVUS/siRNA complex.
(A) Balb/c mice (n = 3) were iv injected with SOD-1 siRNA/peptide complexes, and their brain, spleen, and livers examined for SOD-1 mRNA (top) and protein levels (bottom). The numbers below the western blot represent the ratios of band intensities of SOD-1 normalized to that of b-actin.
(B) Small RNAs isolated from different organs of RVG-9R/SOD-1 siRNA injected mice were probed with siRNA sense strand oligo. Antisense strand oligo was used as positive control (first and last lanes).

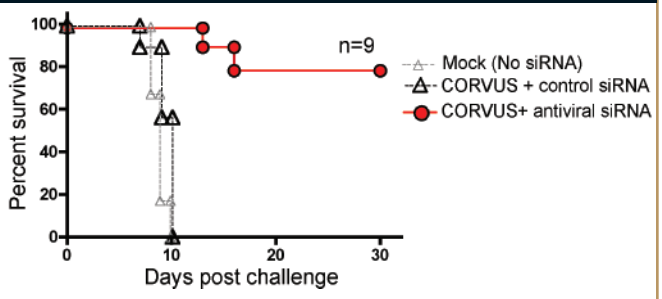
medical needs, using drug delivery and drug targeting, companies can yield more effective returns for the billions that have been invested in drug discovery and development.

CORVUS CNS DELIVERY

The BBB has been a challenge to drug discovery for generations and continues to slow the development of CNS therapeutics. The human brain contains on the order of 100 million capillaries with a surface area of ≈12 m^2, and nearly every neuron in the brain is supplied with its own capillary.[2,3] Thus, delivery of therapeutic molecules to neurons for the treatment of neurological diseases across the capillary endothelial cells would be a highly valuable method of drug delivery. However, the presence of the BBB, characterized by a tightly sealed layer of endothelial cells, precludes entry of most molecules from the vasculature into the brain parenchyma.[4] Small molecules on the order of 400 to 500 Da and some small lipid-soluble proteins can freely diffuse across the BBB; but transport of almost all larger proteins to the CNS occurs via receptor-mediated transcytosis.[5] Conventional methods for brain delivery have included direct stereotactic injection of therapeutic molecules, including siRNA into the brain tissue.[4,6] However, these methods only result in localized delivery around the injection site, with no widespread effects within the brain, and are also too invasive for human therapy. If one could overcome the BBB, intravenous (iv) administration would provide the ideal non-invasive means for delivery throughout the brain.

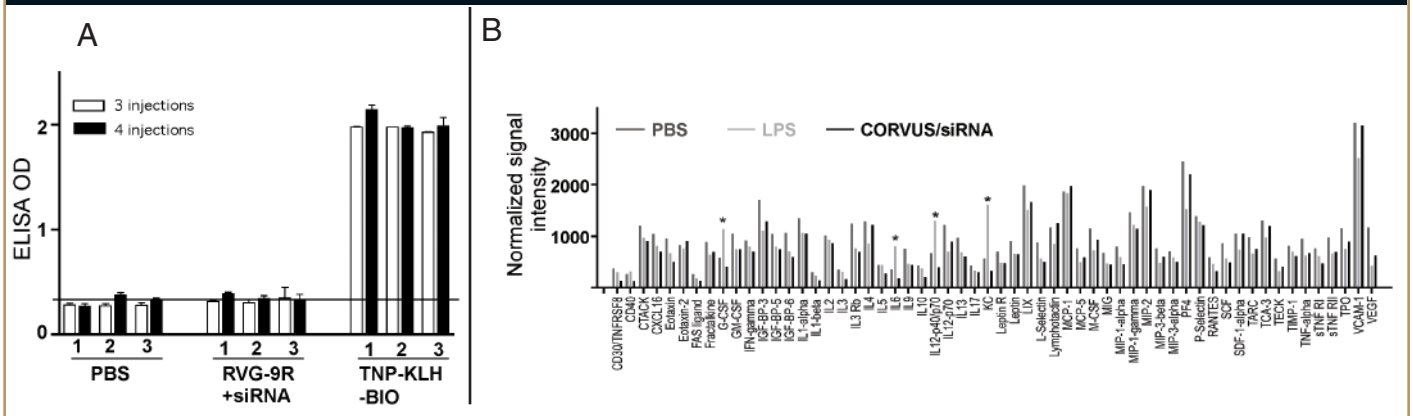
Because neurotropic viruses do cross the BBB to infect brain cells, a similar strategy could probably be adopted to transport drugs to the CNS. The Rabies virus shows a high degree of neurotropism in vivo, and the cellular entry mechanisms have been well characterized.[7,8] The envelope glycoprotein of Rabies virus (RVG) specifically interacts with the nicotinic acetylcholine receptor (AchR) on neuronal cells for productive infection.[7] In fact, a short 29 aa peptide derived

FIGURE 5



Intravenous treatment with antiviral siRNA/CORVUS complex protects mice against JEV encephalitis. JEV-infected mice (n = 9) were treated intravenously with control or antiviral siRNA complexed to CORVUS daily for 4 days and monitored for survival.

FIGURE 6



CORVUS-siRNA complex does not induce antibodies or inflammatory cytokines.
A) Mice (n = 3) were injected with siRNA complexed to CORVUS or for positive control, with the immunogenic TNP-KLH-biotin peptide on days 0, 3, 10, and 22 and serum samples collected on days 21 and 30 tested for the presence of antibodies to CORVUS or biotin by ELISA.
B) Sera obtained 1 day after the fourth CORVUS/siRNA injection were tested for the indicated panel of secreted cytokines and chemokines in an ELISA assay. Sera from LPS injected mice served as positive control. Asterisks indicate statistically significant differences.

from RVG has been shown to be sufficient to mediate binding to AchR.[9] However, to enable binding to siRNA, this peptide needs to be coupled to a positively charged carrier. Hence, the RVG was engineered in fusion with another short positively charged cell-penetrating peptide, nona-d-arginine (Figure 1), with the added advantage that the d-form of this peptide is resistant to most serum proteases whose substrates are naturally occurring proteins made of L- amino acids.[10] This chimeric peptide called CORVUS (previous referred to as RVG in Nature) was then investigated for its ability to deliver siRNA into brain cells in mice.

Since CORVUS binding protected siRNA against degradation by serum nucleases for up to 8 hours is an important feature to be considered for potential in vivo usage (Figure 2). To test whether CORVUS can mediate entry into neuronal cells in vivo, FITC-labeled siRNA complexed to CORVUS was injected via the tail vein into Balb/c mice and single-cell suspensions obtained from the brain, spleen, and liver 10 hours after iv injection examined by flow cytometry. FITC fluorescence was detected in the brain only when the siRNA was complexed to CORVUS but not a control peptide of similar design. No FITC uptake was seen in the spleen or liver, suggesting that CORVUS allows brain-specific targeting (Figure 3A). Microscopic examination of mouse brain sections stained with anti-FITC antibody revealed the presence of FITC-positive cells in different regions of the mouse brain (Figure 3B).

To test brain-specific gene silencing, mice were treated with CORVUS complexed to siRNAs targeting an endogenous gene, Cu-Zn Superoxide Dismutase-1 (SOD-1), and SOD-1 mRNA and protein levels were measured by qPCR and western blotting, respectively. While no changes were detected in SOD-1 levels in any organ in animals treated with the control peptide, both SOD-1 mRNA and protein levels were significantly reduced in the brain, but not other organs in the test animals (Figure 4A). The presence of SOD-1 siRNA in the brain by Northern analysis confirmed that the observed knock-down was due to specific delivery of siRNA within the brain (Figure 4B).

RNAi therapy has tremendous potential in the treatment of acute neurological infections like flaviviral encephalitis. Mosquito-borne encephalitic flaviviruses like Japanese encephalitis (JEV) and West Nile (WNV) virus are among the most important examples of emerging and resurging pathogens in the world today.[11] Currently, no effective drugs are available to treat flaviviral infections, and vaccines are not available freely for large-scale application in countries of Southeast Asia, where annual epidemics result in more than 50,000 cases. Intracranial treatment with antiviral siRNAs have been shown to provide robust protection from fatal flaviviral encephalitis in mice.[12] However, a non-invasive iv treatment method would be optimal for clinical use. Therefore, it was of interest to test if iv treatment with CORVUS/siRNA complexes could protect mice from JEV-induced encephalitis. CORVUS peptide complexed to antiviral siRNA could protect almost 80% of the mice against a JEV (5LD50) challenge, while all control mice succumbed about 10 days after viral challenge (Figure 5). Repeated administration of CORVUS/siRNA complexes did not induce

inflammatory cytokines nor elicit an anti-peptide antibody responses in immunocompetent animals (Figures 6A & 6B), attesting to the viability of this delivery approach. Collectively, our work to date indicates that CORVUS will enable iv delivery of siRNA to silence gene expression within the brain.

CORVUS BENEFITS

The ability to ferry drugs across the BBB yields several value points for researchers in the biotechnology and pharmaceutical community. First, CORVUS promises to be a powerful transfection reagent to assist in various basic research applications. Unlike many of the existing transfection reagents, CORVUS will probably work for hard-to-transfect neuronal cells.

Second, CORVUS is a promising tool for validating gene targets in vivo. As the next logical step upon completion of an siRNA screening for identifying drug targets, CORVUS would potentially allow for rapid generation of in vivo data by enabling in vivo target validation of siRNA. Clinical failures are often due to side effects in non-target tissues or when drugs are not acting on their targets in amounts that allow efficacy. Targeted drugs have the potential to overcome both of these important problems relating to non-targeted drugs.

Finally, companies could design novel drug libraries that include the CORVUS technology for screening against existing and newly discovered CNS biological targets.

CNS MEDICAL NEEDS

CNS indications are some of the most valuable in all of drug development largely because they can lead to some of the most debilitating and expensive-to-treat diseases. Due to the challenges caused by the BBB, many of the CNS disorders remain unmet or lacking in a treatment without side effects. The value of proposition for treating unmet medical needs is very attractive, and many companies are actively discovering and developing therapeutics in this space.

In addition to the indications of Huntington's disease and viral encephalitis, other CNS indications in which therapies are needed include pain, stroke, hemorrhage, cancer, spinal cord injuries, and other neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases.

SUMMARY

CNS drug development has long been stifled by the BBB, resulting in countless failed programs and leaving many unmet medical needs. The CORVUS delivery technology is a novel delivery strategy to ferry drugs into the brain that can be used to treat a variety of CNS disorders. The technology is also a promising tool in other stages of CNS drug discovery and development, such as target identification and drug screening. With the increasing importance of drug delivery and targeting for various platforms, including RNAi, the timing of this innovative delivery strategy could not be better.

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BIOGRAPHIES

Dr. Manjunath Swamy is an Investigator at the Immune Disease Institute and an Assistant Professor of Pediatrics at Harvard Medical School. Dr. Swamy earned his MD from the All India Institute of Medical Sciences and Post-doctoral training at the Tufts-New England Medical Center. The Swamy lab is studying how T cell differentiation is orchestrated and how after stimulation, T cells decide to become either effector or memory cells.

Dr. Priti Kumar is a Post-doctoral Fellow at the Immune Disease Institute. Dr. Kumar earned her PhD from the Indian Institute of Science. The title of her doctoral thesis is: *Human Immune Responses to the Non-Structural Protein 3 (NS3) and the Envelope Glycoprotein of Japanese Encephalitis Virus: Interferon Gamma and Perforin Production by NS3-Specific T cells Correlate With Protective Immunity.*

Technology Showcase

Transdermal Delivery

Aveva Drug Delivery Systems owns proprietary transdermal formulation and manufacturing technologies. The broad range in technology and experience includes solubilized matrix, crystal dispersions, multi- or single-layer systems, membrane-controlled systems, specialized proprietary adhesives, and packaging technologies. These technologies can be optimized, not only for new drug entities, but also to build upon the proven success of transdermal products in various therapeutic areas. One focus area for Aveva is the treatment of chronic moderate-to-severe pain with sufentanil. Potent opioid compounds, like sufentanil, can have an important therapeutic role in the treatment of patients suffering from chronic pain using Aveva's drug-in-adhesive design. For more information, contact Robert Bloder at (954) 624-1374 or visit **www.avevadds.com.**

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Azopharma is a contract pharmaceutical development organization that helps turn ideas into cures with a complete spectrum of CMC solutions for pharmaceutical development. The company supports contract drug development for Solid Oral Dosages (tablets, capsules), Liquid Dosages (injectables, suspensions), Topical Dosages (creams, ointments, lotions), Inhalation Dosages (nasal, MDI, DPI), Drug Substance and Excipients, Biopharmaceuticals, and Medical Devices & Drug/Device Combinations. Its facilities in Miramar, Florida, are FDA registered and inspected, DEA approved, and client audited on a routine basis. The fully cGMP-compliant facilities are registered with the DEA for testing of all schedules of controlled drugs and have individual licensing for manufacture on an as-requested basis. For more information, contact Azopharma at (954) 433-7480 or visit **www.azopharma.com.**

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DSM Pharma Chemicals, a business unit of DSM Pharmaceutical Products, is a global provider of custom manufacturing services to the pharmaceutical industry. Services include advanced intermediates, such as unnatural amino acids and derivatives, registered materials, and active pharmaceutical ingredients. Our technologies include biocatalysis, homogeneous catalysis, fermentation, and chiral technologies. DSM delivers comprehensive custom manufacturing services to the spectrum of pharmaceutical companies, including emerging pharmaceutical companies and large pharmaceutical companies. From clinical to commercial services, DSM focuses the right resources on providing the highest level of service and quality, while applying innovative solutions to satisfy customers' unique manufacturing needs. For more information, contact DSM Pharma Chemicals at (973) 257-8011 or visit **www.dsmpharmaceuticals.com.**

Technology Showcase

Central Lab Services

Pacific Biometrics, Inc. (PBI) is announcing new Clinical Biomarker Services, which are designed primarily to support clinical development of biotherapeutics. These include validation of ligand-binding assays for immunogenicity testing by ELISA and MSD and multiplexing for novel biomarkers, in a regulatory-compliant environment. Established in 1989, PBI is a Specialty Central Laboratory with an established reputation as the premier lab with scientific expertise, reliable results, and outstanding client services for cardiovascular risk, diabetes, osteoporosis, arthritis, and inflammatory diseases. For more information, contact Pacific Biometrics, Inc. at (800) 767-9151 or visit **www.pacbio.com.**

Global Central Labs

PPD's global central labs fully support your drug development programs with extensive global reach; logistical expertise; highly customized and flexible services; strong and consistent science and therapeutic expertise; high-quality performance (98.5% data acceptance rate); efficient, accurate, and rapid sample collection; and state-of-the art laboratories with all relevant accreditations and certifications. Through strategically located facilities in North America and Europe, and with the use of sophisticated logistics and courier services, PPD provides clinical laboratory services to investigator sites in virtually every country of the world. PPD recently announced it has expanded its global central lab services into China through an exclusive agreement with Peking Union Lawke Biomedical Development Limited. For more information, contact Rob Danziger at (859) 442-1300 or visit **www.ppdi.com.**

Controlled Delivery Platform

SCOLR Pharma applies its patented CDT® Controlled Delivery Technologies to develop formulations for companies with pharmaceutical, OTC, and nutraceutical products. These elegantly simple technologies can be used for controlled-release periods for up to 24 hours and can be manufactured using readily available standard materials and conventional production equipment. SCOLR Pharma partners with companies under contractual arrangements that include licensing fees, royalties, manufacturing contracts, or other mutually agreed upon financial arrangements. SCOLR Pharma's CDT® has the many distinct advantages, including highly programmable (capable of a wide range of release profiles), easy to manufacture (employs conventional manufacturing equipment), cost effective (utilizes standard tableting excipients), higher payload (when compared to other technologies), and strong patent protection (full patent life and easy enforcement). For more information, visit SCOLR Pharma at **www.scolr.com.**

Packaging Material

ZEONEX Cyclo Olefin Polymer (COP) offers advanced, break-resistant packaging for protein-based, peptide-based biopharmaceuticals and high-viscosity drugs, as well as contrast media. Its "glass-like" transparency allows for easy inspection of the drug prior to and during injection without the concern of breakage. Because of its low water absorption and high purity, drugs can be stored for longer periods of time compared to other medical plastics. ZEONEX is optimal for protein- and peptide-based drugs because, unlike glass, it overcomes protein adsorption and pH shift of a diluents' concerns. The COP has superior moldability and can be molded for prefilled syringes, pen injector cartridges, and vials ranging from < 10 ml to > 250 ml. For more information, contact Zeon Chemicals at (877) 275-9366 or visit **www.zeonchemicals.com/zeonex_medical.aspx.**

Technology Showcase

Spray-Dried Dispersions

Bend Research is offering a new initiative to make available Pfizer's drug delivery technology for improving the clinical value of experimental compounds. The search for new medicines is made more difficult because many potentially valuable compounds have low solubility and low bioavailability. To overcome these challenges, Bend Research and Pfizer jointly developed the new, proprietary drug delivery technology relying on spray-dried dispersions (SDDs). The SDD technology has been successfully applied to more than 200 Pfizer compounds with low aqueous solubility. Further, improved oral bioavailability significantly above that of crystalline drug has been demonstrated in 17 clinical trials conducted by Pfizer, including one Phase III trial. For more information, contact Bend Research at (541) 633-0573 or visit **www.bendres.com.**

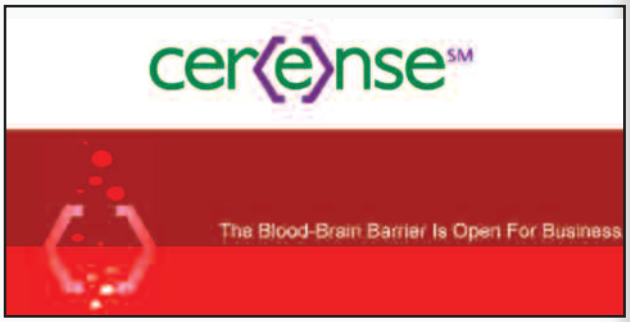
Controlled Release Technologies

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

Drug Delivery & Development

Galenix, a pharmaceutical drug delivery and drug product development company, includes 3 business units to manage the development process from the molecule to the registration of the medicinal product according to GMP Europe and FDA standards. Galenix Pharma is dedicated to clinical trial batch manufacturing and packaging and quality control. Galenix Development is a research and development company focusing on drug delivery systems, which include Microgix, Minextab, Minextab/Floating, and Mucolys. Galenix Innovations carries out technology surverys, innovating formulation design and feasibility studies for patented technologies used by pharmaceutical laboratories. Galenix runs its own drug product development programs from the sourcing and characterization of APIs to marketing and outlicensing to pharmaceutical companies. For more information visit Galenix at **www.galenix.fr.**

CNS Drug Assessment



Cerense℠ is the world's first integrated solution to release the value of your CNS portfolio by unlocking the blood-brain barrier (BBB) and measuring brain penetration. This is achieved through the combination of Genzyme Pharmaceuticals' patented CNS drug delivery technology and the unique expertise of Pharmidex to determine neuro-pharmacokinetics. Two major obstacles are recognized to inhibit the successful development of CNS medicines: (1) difficulties in getting compounds across the BBB and (2) difficulties in successfully measuring BBB penetration and neuro-pharmacokinetics. Cerense brings together a patented CNS drug delivery technology with world-class expertise in neuro-pharmacokinetics to overcome these twin obstacles and thus release the value of your CNS portfolio. For more information, visit Genzyme Pharmaceuticals or Pharmidex at **www.cerense.com.**

Technology Showcase

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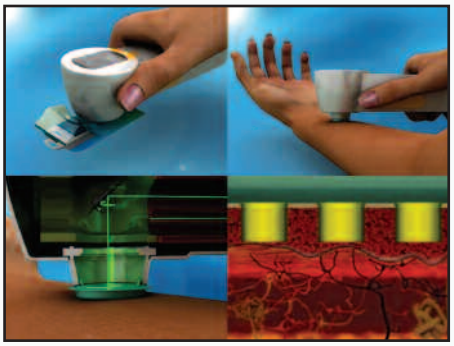
Intraepidermal Delivery



LEDDT™ (Laser Easy Drug Delivery Technology) 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.**

Pharmaceutical Product Development

Licensing opportunities for PharmaForm's patented transdermal and transmucosal delivery systems are available. PharmaForm's proprietary delivery platform is a versatile polymeric delivery system that can be applied to many drug candidates and product applications. The company's Drug Delivery Technology team is integrated with formulation development, analytical, materials, and manufacturing groups to develop and optimize transdermal systems. The Formulation and Product Development and Analytical groups work closely to plan and execute the numerous facets of system development activities. After formulation development, clinical assessment, and final formulation selection is complete, PharmaForm can scale-up your product for commercial manufacture. PharmaForm will combine its pharmaceutical expertise, formulation chemistry, and long history of know-how to develop a high-quality transdermal drug delivery system for your market application. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com.**

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AdvaTab® is a new generation of ODT technology that offers distinct advantages and unique applications – unparalleled taste, flexible dosing, modified release, and a robust tablet. AdvaTab can be combined with Eurand's leading Microcaps® taste-masking technology to provide an ODT with superior taste and mouth-feel. AdvaTab tablets dissolve rapidly in the mouth within 15 to 30 seconds, and the smooth mixture of carrier excipients and taste-masked drug granules is suitable for delivering high drug doses. Modified-release drug granules can also be incorporated into the AdvaTab dosage form to provide a fast-dissolve tablet with sustained-release properties. AdvaTab tablets can be packaged in either bottles or push-through blisters. For more information, contact Eurand at (937) 898-9669 or at **bizdev@eurand.com.**

DRUG DELIVERY Executive

IntelGenx Corp.
Innovative Drug Delivery Solutions

IntelGenx: Developing Next-Generation Orally Delivered Drugs

Horst G. Zerbe, PhD
President & CEO
IntelGenx Technologies Corp.

IntelGenx, headquartered in a suburb of Montreal, is a new participant in the approximate $60-billion drug delivery market, which has flourished in recent years. The company develops improved formulations of approved drugs using proprietary and novel technologies and has been successful in attracting early stage product partnerships with large pharmaceutical companies. Its two novel lead proprietary platform technologies include its Tri-Layer Tablet technology, which allows for the development of oral controlled-release products, and its Quick Release Wafer technology for the rapid delivery of pharmaceutically active substances to the oral cavity. Drug Delivery Technology recently interviewed Horst G. Zerbe, PhD, President and Chief Executive Officer of IntelGenx, to share his thoughts on the reasons why his company is primed for significant growth in the dynamic drug delivery industry.

"Our technologies also offer new financial opportunities for pharmaceutical companies with drugs that are approaching the expiration of their patent protection. By reformulating patented drugs to work with new, patent-protected drug delivery technologies, a pharmaceutical company can extend the life cycle of some its most important branded drugs, and do it at relatively little expense."

Q: Can you tell our readers more about IntelGenx?

A: IntelGenx is a drug delivery company specializing in novel oral delivery technologies. We have two proprietary platform technologies that are being incorporated with the pharmaceutical products of our development partners. We currently have 11 products, six of which are being developed in partnership with four companies.

Our oral delivery technologies offer new methods of delivering the active drug into the patient's system. Our oral film technology allows for instant release of an active drug to the oral mucosa. Our multi-layer tablet platform represents an inexpensive alternative to achieve quasi-zero-order release of a drug. In addition, it allows for multiple drugs to be released at different rates over time. These innovative qualities offer new therapeutic opportunities to the patient as well as the doctor.

Our technologies also offer new financial opportunities for pharmaceutical companies with drugs that are approaching the expiration of their patent protection. By reformulating patented drugs to work with new, patent-protected drug delivery technologies, a pharmaceutical company can extend the life cycle of some its most important branded drugs, and do it at relatively little expense. So our technologies are quite important to the growth of the pharmaceutical industry.

IntelGenx works with several pharmaceutical companies as development partners. Those companies will eventually become the holders of the drug license issued by the FDA, and they will market the final products. IntelGenx is not a distributor, but rather licenses the commercial rights to its products to competent partner

companies once the viability of the product has been demonstrated.

We have been in business since 2003, and in 2006, we obtained seed financing of $1.25 million. In the course of this financing, the company completed a reverse merger with a US shell company and began trading on the OTC Bulletin Board in 2006 under the ticker symbol IGXT. The number of projects in the company's portfolio has increased rapidly and currently stands at a total of 11. This strong growth required additional funding, and the company completed a secondary financing in 2007 in which we raised an additional $1.5 million.

IntelGenx is headquartered in Montreal, where it occupies a 3,500-sq-ft state-of-the-art R&D facility and currently has a staff of nine full-time employees, five of whom are scientists working on the bench.

Q: What accomplishments has your company made in the past year?

A: The most important tasks accomplished over the past 12 months were (1) securing the company from a financial standpoint, (2) stimulating growth by adding more projects and development contracts to our project portfolio, and (3) assembling an experienced management team. Today, we have a team of very motivated and experienced individuals.

My background is in industrial pharmacy. I have been involved with drug delivery for 27 years, working at Schwarz Pharma, 3M Pharmaceuticals, and Lohmann Therapy Systems. Our CFO, Gino Di Iorio, has more than 15 years of experience in publicly traded companies. Our VP of Business Development, Jim Wittenberg, has more than 20 years of experience in business development and market research, most recently as Director of Business Development at Schwarz Pharma. Our Director of R&D has more than eight years of experience in dosage form development and pharmaceutical analysis and is a co-inventor of most of the company's patents.

Q: Provide us more insight into the medical side of the company and the technology. What are some of the challenges and future possibilities?

A: We have two platform technologies we use to develop new products. One involves thin films. You may be familiar with breath-freshening films that you place on your tongue and dissolve instantly to clean your breath. We have film technology that is very similar to these films. It is a thin film that tastes good and, when placed on the tongue, disintegrates instantly in the oral cavity. We have started to formulate drugs with this film technology, which opens new therapeutic opportunities. There are no product prescription drugs on the market today that involve using a film as a means of delivery. There is one product being marketed for the treatment of coughs and colds in children that uses film technology. Other than that, there are no products using that type of technology.

Our oral film technology puts us very much at the forefront of development in this field. The advantage and uniqueness of this technology comes from the fact that it provides a very rapid onset of action. Usually, if you swallow a tablet, you have to wait maybe a half hour until any therapeutic effect kicks in. This can be significantly too late for certain indications.

For example, let's discuss a migraine headache. A migraine attack manifests itself within a couple of minutes. A conventional tablet could not prevent an attack. It could provide relief from the headache, but it could not prevent


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the attack from starting. That is something that could be achieved with the film. You build relevant blood levels so fast that the attack has no chance to manifest. That is a new therapeutic achievement, and there are other similar indications in which the film could also be used.

The second platform technology our company owns revolves around a layered tablet. The opportunities presented by that layered tablet technology, which is well protected by patents, are several-fold. For example, we can combine different drugs in one tablet to create a combination in an FDA-compliant format. Right now, we are working on a product combining an antidepressant with a nicotine antagonist for smoking cessation. That is a novel therapeutic principle, which we have achieved very elegantly with a layered tablet. We formulate the active ingredients into different layers and then provide them with different release profiles (one can be slow releasing and one can be fast releasing) to accommodate various therapeutic requirements. That's just one example of the unique capabilities of this multilayer technology.

The layered-tablet technology was initially developed to control the release of the active ingredients from the tablet matrix using a novel, patent-protected mechanism that we call "controlled erosion," which ultimately controls the rate of release of the active from an active, drug-containing matrix layer. That is also novel and offers high-value opportunities. This technology makes us highly competitive in the generic market, which is dominated, from a delivery technology standpoint, by tablets using osmotic systems that are very costly to manufacture. Our layered tablet technology provides a low-cost alternative for high-value, slow-release generics.

Q: In addition to these two innovative drug delivery platforms, are there other strengths supporting the company's growth?

A: We are constantly broadening our technology base and have recently added an oral muco-adhesive delivery technology to our technology portfolio. We perceive ourselves as a technology-driven company, and we are always on the look-out for new technologies or a logical extension of our current technology portfolio. At the same time, of course, we aggressively protect our intellectual property. Finally, we have management expertise. We have proven technology and have an understanding for the development risks involved, which in our case is very low.

Q: What should compel investors to include IntelGenx as part of their investment strategy?

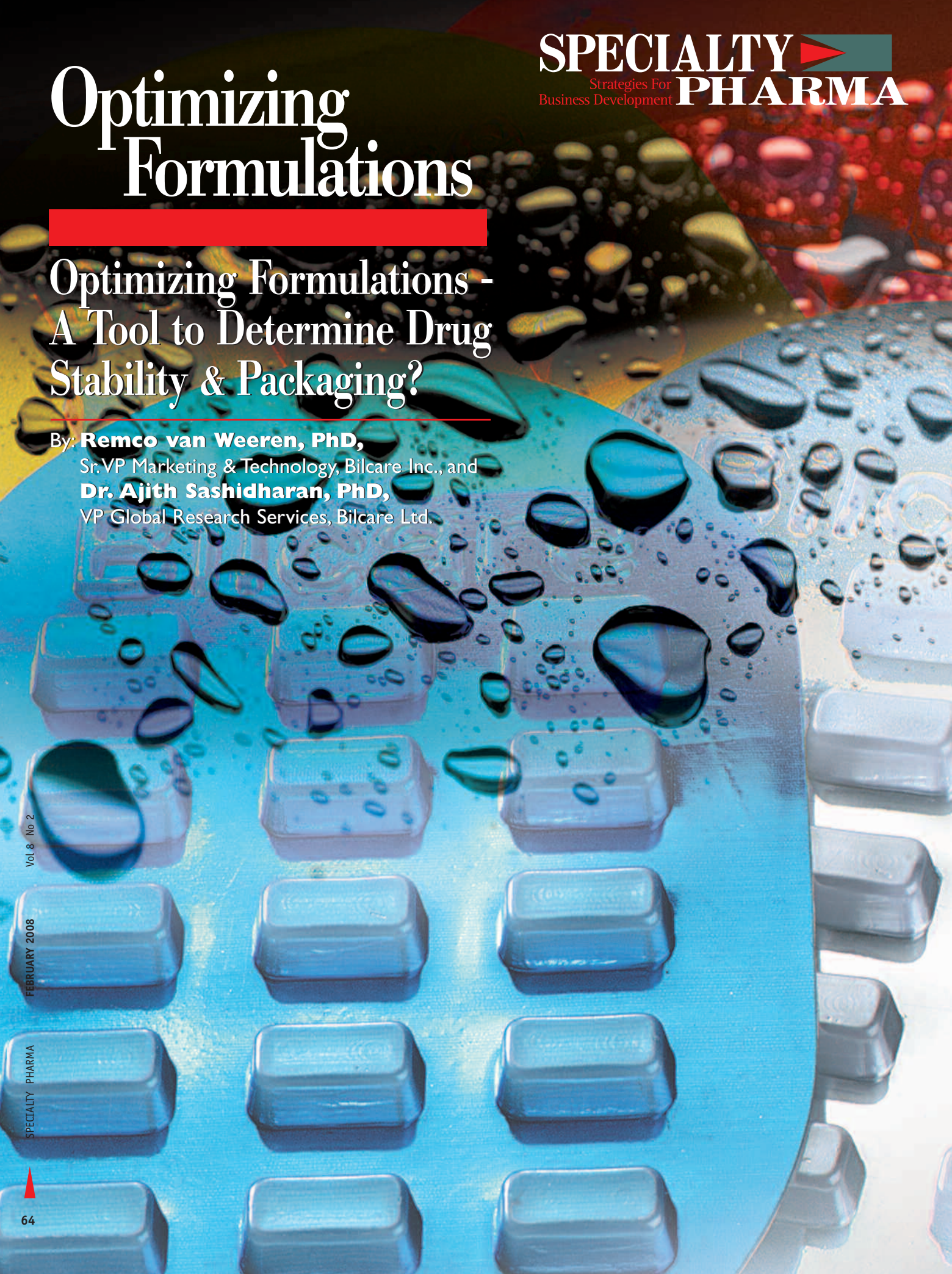
A: I believe what makes us interesting for an investor is our growth potential and the low-risk/high-reward ratio: the opportunity for high reward is big, and the risk is relatively low. Moreover, the timeframe is relatively short-term. We expect major revenue increases toward the end of 2008/early 2009. We have a solid business plan, we are meeting our development goals, and we offer very strong growth potential within the near-term. Our highest priority in the next 12 months is to get our first product out of our laboratory and into the marketplace. We expect this to happen in the first half of 2008. Keep an eye out for us! ◆

SPECIALTY PHARMA
Strategies For Business Development

Optimizing Formulations

Optimizing Formulations - A Tool to Determine Drug Stability & Packaging?

By: **Remco van Weeren, PhD,**
Sr. VP Marketing & Technology, Bilcare Inc., and
Dr. Ajith Sashidharan, PhD,
VP Global Research Services, Bilcare Ltd.



Introduction

The sensitivity of formulated drug is often described qualitatively as highly sensitive or less sensitive based on the active ingredients properties. Therefore, the difference in the sensitivity with change of formulations using the same active ingredients goes unnoticed. Formulation scientists would benefit if the small differences in the environmental sensitivity between the formulations were distinguishable, giving them leads to optimize the formulation in terms of stability and other required properties. Often, a conventional stability study in the final packaging format is the only way to understand the sensitivity or stability of the product and leaves little or no opportunity for the formulator to optimize the formulation for better stability.

Forced degradation studies are popular in the preformulation stage, but these are more focused on the impurity profiling for analytical method development and to develop the moisture absorption isotherms. Because these studies are concentrated on the ingredient properties, strengths of final formulation with respect to environmental stability is not determined or clearly distinguished in these studies. A new sensitivity profiling method was developed that looks at the final formulation beyond the chemical stability and diagnoses the external reasons for the deterioration of the characteristic properties of formulation, which is essential to serve its purpose for the patients. It quantitatively evaluates the effect of the environmental parameters on the deterioration of the product and looks not only at its chemical/assay properties, but also various physical properties, drug-release patterns, and the interaction with packaging materials.

This method quantifies the various sensitivity parameters of the formulation in an absolute scale of 0 to 10 based on the results of forced degradation experiments and thus gives the formulators a tool to measure the strength of their formulation in a scientific scale prior to finalizing it.

Shortcomings of Conventional Forced Degradation/Stress Testing Studies

There are no detailed regulatory guidelines that describe how to carry out stress testing, and it is often used synonymously with accelerated testing. As a result, the purpose of both stress testing and accelerated stability testing is to create a path for the product degradation and not to diagnose the causes for degradation. These two tests should be distinctly different. For identifying the factors affecting degradation, it is essential to define the testing protocols in such a way that to be able to understand the cause and effect aspects while accelerating the degradation process, it is only necessary to increase the severity of the parameters causing deterioration. In fact, the purpose of the accelerated stability studies is to fasten the degradation, while that of stress testing should be the understanding of the degradation process.

The ICH defines accelerated testing as the following:

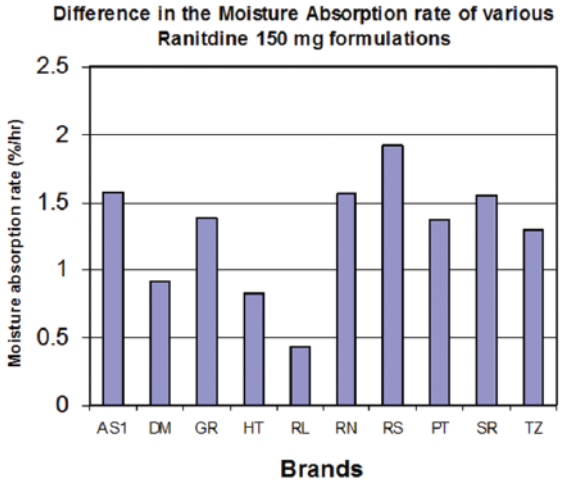
Studies designed to increase the rate of chemical degradation or physical change of an active substance or drug product using exaggerated storage conditions as part of the formal, definitive, storage program. These data, in addition to long-term stability studies, may also be used to assess long-term chemical effects at non-accelerated conditions and to evaluate the impact of short-term excursions outside label-storage conditions, such as might occur during shipping. Results from conventional accelerated studies are not always predictive of physical change.

The IHC defines stress testing as the following:

Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

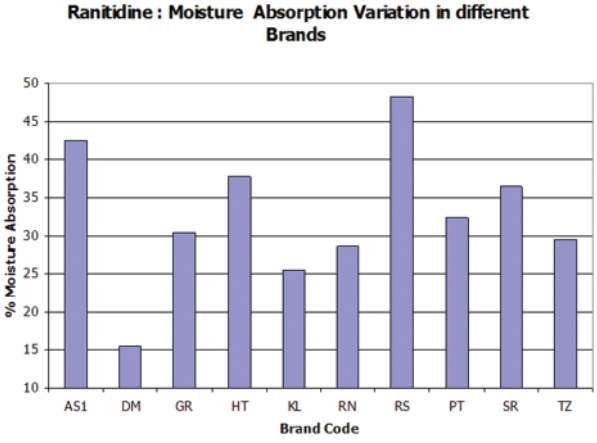
From a regulatory perspective, stress testing or forced degradation

FIGURE 1



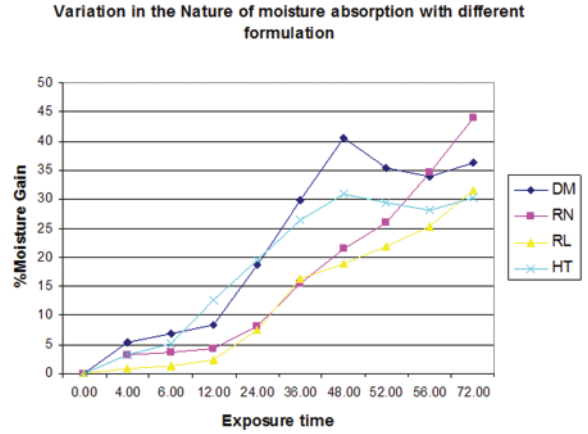
Moisture Absorption Rate of Various Ranitidine Formulations Exposed at 40°C and 75% RH

FIGURE 2



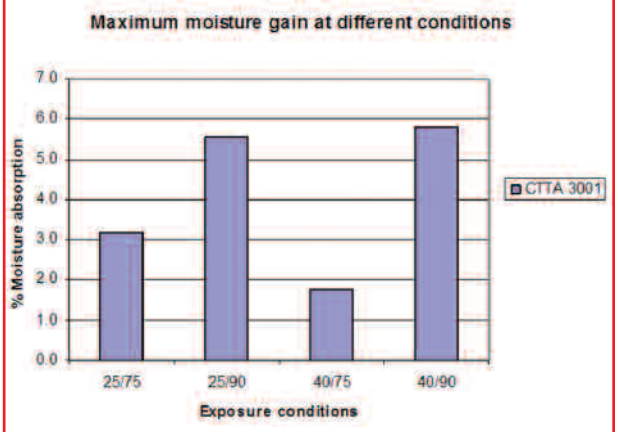
EMC of Various Rainitidine Formulations After Exposure at 40°C and 75% RH

FIGURE 3



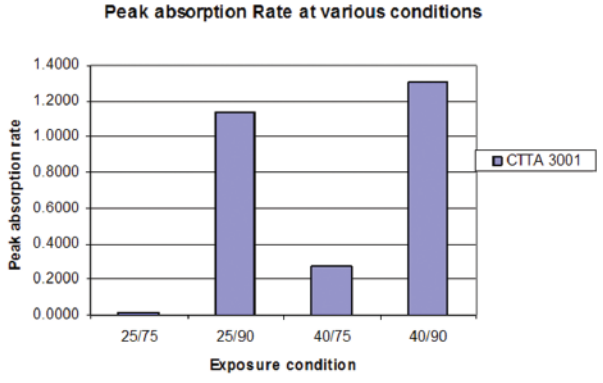
Moisture Absorption Path of Various Ranitidine Formulations When Exposed to 40°C and 75% RH

FIGURE 4



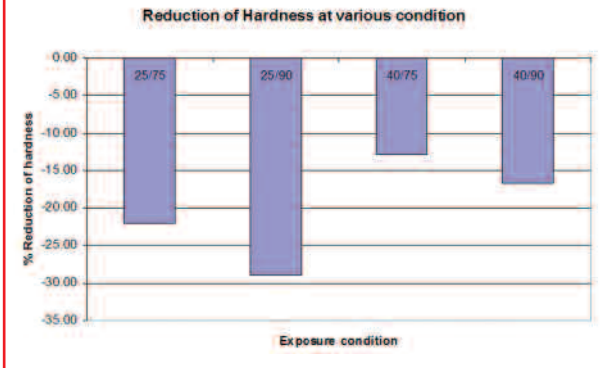
EMC of a Cefuroxime Formulation at Different Testing Conditions

FIGURE 5



Moisture Absorption Rate of a Cefuroxime Formulation Under Different Testing Conditions

FIGURE 6



Reduction of Hardness at Various Conditions

studies are a scientific tool to understand stability issues, and are inherently predictive in nature. Accelerated testing, on the other hand, is purely focused on whether or not stability is maintained at a pre-set condition.

Sensitivity Profiling Through BilcareOptima™

It is essential to look at a formulation beyond the chemical aspects to ensure the efficacy of the product to the patient. As an example, a chemically stable product without any visual degradation with time or upon exposure to humidity/light is normally categorized as a stable product. However, this product may not be effective if its drug-release property is affected by any environmental factor or if there is a tendency to liberate gases upon storage. In conventional stability studies, these factors are not studied critically, rather it is only assessed whether the determined values are within the specified limit at the end of the study.

BilcareOptima test the final dosage form under a range of different conditions, to determine the critical characteristics that affect the stability and quantify its severity on a scientific scale. Three batches of dosage forms are studied under various environmental conditions for a more precise understanding and the effect of the following parameters: hygroscopicity, dehydration, physical degradation, chemical degradation, drug-release pattern, hardness, photo sensitivity as a function of RH and temperature, gas liberation tendency, product packaging material interaction, and dimensional aspects.

Each of the properties is investigated for the influence of various environmental parameters and its impact on the stability and efficacy of the product. These evaluations lead to an exact determination of the critical property of the given oral dosage and influencing environmental parameter. It is further used to determine the threshold values and sensitivity scaling using a mathematical model. This information is used to predict the product behavior at different climatic conditions and decide the storage conditions, protection needs, and shelf life.

The sensitivity scale gives a quantitative picture about product sensitivity toward environmental parameters property-wise. The property-wise sensitivity data is allowed to come down to the most critical property. This also helps to understand the batch-to-batch and formulation-to-formulation variation and can be used to make differentiations among them.

Formulation Comparisons

Sensitivity profiling is a very effective tool to understand the difference in the stability of various formulations of the same ingredient and dosage. Normally, one often fails to identify the micro-differences in the formulation and ends up generalizing the formulations. However, when the micro-details are studied in a scientific way, it helps to identify the differences and understand the formulation better.

A study was conducted on the various brands (and hence different formulations) of Ranitidine using this method to understand the differences in hygroscopicty. Ranitidine is a highly hygroscopic product, and qualitatively, all Ranitidine tablets are rated in general as highly hygroscopic products without any differentiation. As a standard practice, hygroscopicity of a product is measured in terms of equilibrium moisture content (EMC).

Equilibrium moisture content is the highest level of moisture content a product can achieve at a specified condition. However, in all probability, a product in protective packaging never reaches that stage during its shelf-life. It is thus the absorption rate, nature and path of moisture absorption, and/or the effect of moisture under the influence of temperature and light that are the deciding factors for the stability in a packaged condition. These are seldom studied in forced degradation studies and hence, the performance of the formulations could not be predicted.

Figures 1, 2, and 3 show the moisture absorption rate, EMC, and nature of absorption path of different Ranitidine formulations at 150 mg when exposed at 40°C and 75% RH. It can be seen from these graphs that the EMC, absorption rate, and path are all distinctly different for the formulations. This shows that with the same ingredients and dosage level, the products exhibit

different moisture absorption capabilities, indicating that the shelf-life, storage conditions, and protection needs cannot be the same for all the formulations. This clearly puts a question mark to the accepted trend in the industry to follow the innovator or brand leader's packaging selection for the generic formulations that are approved after patent expiration.

The differentiation of the formulation is very critical for its optimization and is possible only when each formulation is subjected to detailed sensitivity profiling. There are also changes of behavior for similar formulations at different climatic conditions. An accelerated stability condition of 40°C/75% RH is standard for all the protocols. As described in the introduction, the accelerated stability conditions derived are only creating a path for faster degradation but are not predictive in nature of the product's behavior in different climatic conditions, especially for higher humidity conditions. Increasing the severity of the testing condition is not the solution, rather it will be misleading and complicated. It is important to understand the effect of each environmental parameter individually and in combination to ensure understanding of the degradation profile.

The results in Figures 4 and 5 show the effect of different climatic conditions on the hygroscopicity of a cefuroxime formulation. As can be seen in Figure 4, the EMC of the product at a 25/90 condition is significantly higher than at a 40/75. Scientifically, it is reasonable to assume that at an elevated temperature, the product undergoes simultaneous dehydration and hence EMC, which is the equilibrium between the hydration and dehydration phenomena, is lower. At lower temperatures, the dehydration process is negligible and hence the EMC levels are higher. This means that the product absorbs more moisture at high humidity areas than what we observed at accelerated conditions. A condition of 40/75 is the ICH "accelerated condition," while 25/90 is the standard condition for most of the coastal area in India and Mexico, which means that product deterioration could be significantly higher in these regions than one anticipated from the results of the accelerated stability studies.

Figure 5 shows that the rate of moisture sorption is influenced more by external humidity than temperature, which is contrary to the logic of the accelerated condition in which elevated temperature is used to increase the rate. One of the major physical properties affected by moisture absorption is the hardness of the tablet. Reduction in hardness might not be very critical for a product packaged in bottles, but it is very critical for a product packaged in blister packs as the product needs to be pushed against the lid foil to break the lid to take the product. The hardness of the product cannot fall below the push through force (PTF) required to open the blister.

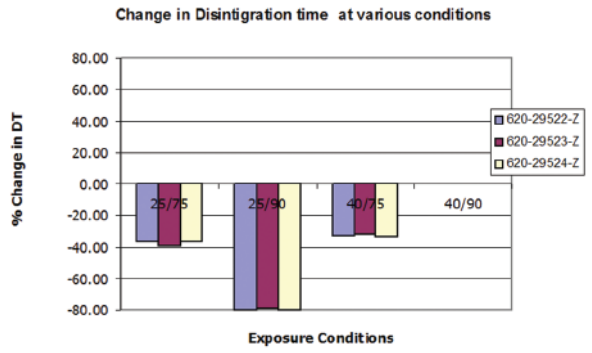
As can be seen in Figure 6, when the hardness is measured after 12 hrs of exposure in different conditions, the decrease in hardness is more pronounced at lower temperatures than at accelerated temperatures. This again shows even if the product hardness maintains the acceptable level upon accelerated study protocols, it could indeed drop below its acceptable level at ambient temperature conditions and thus the correlation results from the accelerated studies cannot be extended for all climatic conditions.

Figure 7 shows a similar discrepancy when studying disintegration times under the various conditions. This property is one of the factors influencing the drug-release property.

Summary

BilcareOptima is a forced degradation profile mapping protocol for a very quick determination of the critical parameter that determines the stability of a solid oral dose. It provides a quantitative picture about the sensitivity of important parameters toward the environmental factors, which enable the formulator to predict its behavior when exposed to various environments. This tool can be used to map the sensitivities of various similar formulations and understand the varied environmental dependencies of different formulations. In addition, it allows for a better prediction and understanding of stability than the standard accelerated testing protocol. ◆

FIGURE 7



Change in Disintegration Time at Various Conditions

Remco van Weeren, PhD

Sr. VP Marketing & Technology, Bilcare Inc.

Dr. van Weeren plays a lead role in developing and implementing Bilcare's strategies in North America as well as managing the company's operations and sales efforts. Most recently, he led the launch of Optima, Bilcare's innovative testing protocol that determines the optimal packaging for medicinal products. Prior to joining Bilcare, he served as a Market Manager for Honeywell's healthcare team. Dr. van Weeren earned his MS in Chemical Engineering from the University of Technology in Delft and his PhD in Materials Science and Engineering from Rutgers University. He can be contacted at (610) 422-3305 or remco.vanweeren@bilcare.com.

Ajith Sashidharan, PhD

VP Global Research Services, Bilcare Ltd.

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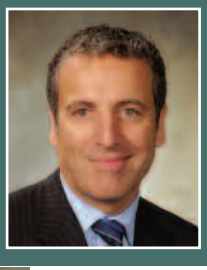
Central Lab Partnering

Mr. David Spaight

President, MDS Pharma Services



Dr. Agostino Fede

Senior VP of Global Central Labs, PPD

Ms. Lynn Kippenhan

VP Sales & Marketing, Covance Central Laboratory Services

Central Labs & Specialty Pharma: Hot Topics

By: Cindy H. Dubin, Contributor

The Central Laboratories market is now worth more than $1.5 billion a year and is vital to the successful development of new drugs, according to a recent industry report edited by Dr. Graham Hughes, an expert in pharmaceutical outsourcing. This is a truly global business dominated by major players. Choosing the right Central Laboratory and handling the relationship effectively is vital to the successful management of clinical trials, as is the complex business of getting samples from the patient to the laboratory, says Dr. Hughes. This Specialty Pharma exclusive roundtable discusses some of today's hot topics with leading players in the Central Lab arena. Participants here include David Spaight, President of MDS Pharma Services; Dr. Agostino Fede, Senior Vice President of Global Central Labs for PPD; and Lynn Kippenhan, Vice President, Sales & Marketing for Covance Central Laboratory Services.

Q: ***How are you adapting your lab to handle the increasing pressures of R&D and biomarker development?***

Mr. Spaight: In 2005, MDS Pharma Services determined that biomarker development would be core to our Central Lab activity. At that time, we established a Research and Development lab to support our focus on biomarker development. This lab is entirely dedicated to assay development, technology benchmarking, and basic lab work, such as regular reassessment of reference ranges, long-term stability testing, and cross-validations

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between platforms running esoteric biomarkers within the MDS Lab network across the world. We use a variety of specific tactics to address the increasing requirements related to R&D and biomarker development. We work in close partnership with pharma companies as upstream as possible in the drug development process. We partner with them to transfer techniques they have developed during early development stages of a new compound, and adapt them for high throughput testing as requested in Central Lab's activity. In addition, our clinical trial scientists are tightly involved in bid review so that alternative markers may be proposed when appropriate and feasibility of esoteric requests can be evaluated on the spot. Finally, development of standardized templates for validation, correlations, and between-site training are keys to speeding up the documentation process and allowing for timely transfers to several testing labs when multiple sites are requested.

Dr. Fede: We provide a range of services to clients for their biomarker development work from discovery through production in clinical operations. PPD's biomarker discovery sciences focus on the discovery of novel biomarkers for use in drug development. Biomarkers can accelerate critical path decisions in product development by providing key response data. In addition, we are continually expanding our partnerships with pharmaceutical companies by developing, analyzing, or validating specialized assays using a variety of high technology platforms and tools. While pharmaceutical labs usually oversee the identification and development of assays, they increasingly rely on us as compounds move through development. Phase II and III studies often require the analysis of thousands of samples, and we work closely with our clients during these phases to analyze and run assays to determine key indicators for a drug's efficacy. Our bioanalytical group is equipped to validate and test specialty assays that run on LC-MS and ICH platforms. Our global central lab routinely validates new assays on standard and specialized platforms. For inflammation and oncology indications, we routinely use flow cytometry to evaluate how drugs are impacting immune and cellular response. We also work closely with third-party labs for highly specialized testing needs as defined by our clients. In these situations, we can manage sample collection and logistics to ensure the stability of samples for testing. Additionally, we have the ability to provide long-term storage of de-identified samples for potential pharmacogenomic analysis that may later be needed to support regulatory submission.

Ms. Kippenhan: Covance Central Laboratory Services (Covance CLS) works very closely with our clients to better understand and meet their needs for biomarkers. To support our clients' drug development needs, Covance has a team of biomarker experts that offer consultation services to identify biomarkers that create unique value for clients. Covance has one of the most comprehensive lists of assays developed and validated. However, for more custom needs, our experts provide a full suite of biomarker assay development, validation, and biomarker testing services (both large and small scale) across the full drug development continuum. Covance is best positioned to meet not only the high volume needs of our clients, but also the need for specialty and esoteric assays from early proof-of-concept stage to commercial laboratory testing. Some service examples include: Preclinical through Proof-of-Concept (antibody development, assay development, validation and reporting, and biomarker testing), and Phase IIb through Commercialization (assay development, validation and reporting, assay production, and biomarker testing).

Q: ***What are you doing to strengthen client relationships to please them and increase your ROI at the same time?***

Dr. Fede: We begin work with clients as early as possible in the development process so that we fully understand their priorities, whether it is cost, speed, scalable processes, or a combination of these strategies. To meet our clients' needs, we offer a broad range of services that extend beyond reporting results. We provide protocol consultation and design, data analysis, performance metrics, and flexible reporting in addition to our in-depth therapeutic experience and ability to identify successful site recruitment strategies. Time is always an important consideration, and we look to create significant time savings for clients in the design and start-up phases and later in the database lock process. We create valuable partnerships with our clients by offering the flexibility they need to meet specific protocols, data reporting, and management information requirements.

Mr. Spaight: At MDS Pharma Services, we have strengthened client relationships through strategic client-focused teams that have a senior leader overseeing global activities for one client across all sites and all trials. In addition, we use Lean Sigma as a foundational tool to create efficient

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processes in collaboration with our clients. This strengthens the relationships on one hand, and increases ROI on the other. Most important, however, is the recent introduction of our sophisticated global study management system, Apollo, which increases the visibility of trial activities for our clients and at the same time, increases the efficiency of study management for both the client and MDS Pharma Services.

Q: ***How much more are you being called upon to manage your clients' relationships with niche labs?***

Mr. Spaight: In most global trials, sponsors are still inclined to outsource specific tests to esoteric or academic labs. However, MDS Pharma Services' central lab would be ideally positioned to run most of these tests. It would simply require that we get involved with a sponsor very early on in the planning and design phases of a protocol in order to validate new tests and perform extensive stability testing, allowing us to establish the most efficient logistical model possible.

Ms. Kippenhan: We do see an increasing client interest in more specialty and esoteric testing. However, Covance CLS has always had this capability and work with select referral laboratories (Qualified Labs) to handle certain unique testing needs of our clients, such as anatomical pathology, PK testing, and select low-volume biomarker needs. We have always believed in helping our clients with even their most unique needs and for this reason, we have well-established processes and procedures to handle the full array of requests, including specimen management, data management, and business management aspects.

Dr. Fede: Clinical study testing is becoming increasingly complex, which has increased our work with niche labs. Sophisticated testing of compounds in areas such as pharmacogenetics, pharmacokinetics, and protein analysis is now available. Pharmaceutical companies are trying to get the most out of their clinical data to avoid additional testing once a drug has already begun the regulatory approval process. We continue to expand our own lab services as the market dictates. For example, we developed new flow cytometry services because of the strong demand from infectious disease and immunology trials. Yet, we have several options for partnering with niche labs when needed. These options vary depending on the sponsor and the study. We can contract directly with a niche lab. In the proposal phase, we will identify and propose the lab with whom we plan to work unless specified by the client. In this case, we oversee the entire management of the lab, including sample handling and reporting. In some instances, sponsors may choose to select the partner and oversee the third-party lab. In this case, we may still be involved in sample handling and distribution of samples to the lab. Data may come back directly to us or to the sponsor. Regardless, we have strong relationships with referral labs, and we have dedicated personnel to manage and oversee technical and commercial arrangements with third-party laboratories.

Q: ***What are your and your partners doing from a technological and software perspective to ensure patient safety and enhance trials?***

Dr. Fede: We have developed a dynamic online interface that allows clients to access and analyze their laboratory results and project information. This interface has the ability to give clients and investigator sites the ability to customize their own interface or portal. For instance, a project dashboard captures key financial data and detailed metrics for each site and sample. In one screen shot, clients can view their data in real time, an extremely important tool to help them reduce the time of their trial while ensuring accurate data. The interface has several benefits, including ease of use, ongoing access to data at any time and location, customization for required information and greater visibility, and control and confidence in trial data. In addition, this truly global database allows all data to be stored in one place, regardless of the number and location of sites. Some features include customized queries, a report builder, and a repository of reports. We plan to add supplies and specimen inventory management, training, and study document repositories.

Mr. Spaight: At MDS, we recently launched a proprietary study management system as I mentioned earlier (Apollo) that we developed specifically for our Global Central Lab business. Apollo is a unified, web-based study management system that gives clients real-time global access to their study data, anytime. It strengthens the chain of custody – from specimen collection to central lab receipt, to testing and sample storage. And it's accessible virtually anywhere and any time, enabling

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MDS to respond quickly and efficiently to changes in client needs and study requirements. Apollo provides a single interface for all aspects of protocol management, including protocol specifications, kit building, sample reception and test ordering, query identification and resolution, customizable results flagging, report distribution, frozen sample management, data extraction, and invoicing. Apollo provides client study teams a host of features that enable greater control over all aspects of the study, improving efficiency and quality. These include a dashboard for a high-level overview of a trial, including automated kit expiry and test cancellation notification, alert/exclusion reports, and query notices regarding pre-programmed escalations; automatic detection of late or missing batch samples, third-party shipping list templates, automatic recall site notification, recall of frozen samples from affiliate laboratories, and global frozen sample inventory reports; and kit-building support, including latest bills of material, kit component inventories with specific lot numbers and expiry dates, and pre-labeled tubes for delivery to study sites.

Q: ***How have you and your clients been working to control logistics and transportation costs?***

Ms. Kippenhan: Covance CLS recognizes that costs for transportation represent a significant percentage of budget for global and complex clinical trials. For this reason, we strive to be as transparent as possible and provide clients with information about logistics options and associated costs early on during the bidding and study set-up phases of a trial. The two areas we see that increase logistics costs the most are secondary city locations of investigator sites and the use of premium couriers. When developing each client proposal, we first do everything possible to find less expensive methods that will not compromise the sample stability or the project timeline. For example, if secondary city locations need to be used to achieve enrollment, then we will work with sites to maximize the number of patients visiting those sites on the same day to allow for better consolidation of sample shipments, thus reducing cost. We also work diligently and continuously with our standard courier partners to achieve the needed level of service so as to minimize the use of expensive premium couriers. More than any other central lab, Covance has the largest volume of studies ongoing at any given time, which means we also have the highest volume of samples being moved around the globe everyday. This volume allows us to negotiate preferential service levels, meaning our clients' samples move most reliably and at very competitive prices.

Mr. Spaight: MDS' ability to effectively manage logistics and transportation issues is a leading driver of our Central Laboratory success. We know this represents a very high percentage of the budget for our sponsors, and are continuously seeking improvements in this area. Using Lean Sigma principles, we established a global standardized approach that defines how and when samples need to be shipped for all trials. This global standardization has resulted in a significant reduction of costs and workload for all the parties – Sponsors, Investigators, and our Central Lab.
At the same time, we recognize certain trials may have unique needs and therefore retain enough flexibility to address some study specifics. So, within the framework of our standard global process, we consider different transport services/solutions for different geographic locations, turn-around-time requirements, sample stability, etc., and make appropriate recommendations to the client. This ensures the best balance between costs and services to support the protocol.

Dr. Fede: We work closely with our clients and business development and finance departments on logistics planning and support to accurately and effectively match the cost/service requirements specific to each individual client or study. PPD carefully reviews study specifics, including sample stability requirements (temperature and/or packaging), courier performance data, and costs and transit times for collection origins to each central lab location. We suggest the appropriate courier selection for each country based on specific study parameters. We interact with sponsors on import/export licensing requirements and develop creative solutions for specific country or region requirements. Our goal is to minimize associated transport costs while meeting service requirements to ensure stability of study samples. We have relationships with major national and international courier services to provide global time-sensitive delivery solutions for our clients. These negotiated services and pricing programs are specific to our business needs and allow us to use the most cost-effective solutions based on specific delivery and study requirements. ■

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Generic Medicine

Specialty Generics – The Next Wave of Generics Growth

By: Barath S. Shankar, Industry Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

Introduction

The US generics market has been at the forefront of the pharmaceutical industry, continuing to outpace volume growth of the branded pharmaceuticals market due to lower cost, larger reach, patent expiry of major blockbuster products, and a fast-aging population. However, the generic market has been witnessing a slow-down in revenue growth in recent years (2004-2006) because of increasing competition and pricing pressure. The market is facing intense competition from low-cost foreign manufacturers, forcing domestic companies to expand into international markets to gain access to lower-cost manufacturing locations and markets with potential for growth.

Generic pharmaceutical companies are now also looking at areas within the market that offer a significant growth potential (both volume and revenue) while limiting competition. Specialty Generics is a market segment that has emerged as a potential answer to many of the problems faced by generic companies in the Commodity Generics segment.

Similar to the Specialty Pharmaceuticals space within the mainstream branded pharmaceuticals industry, Specialty Generics is emerging as a high-growth potential area targeted by companies.

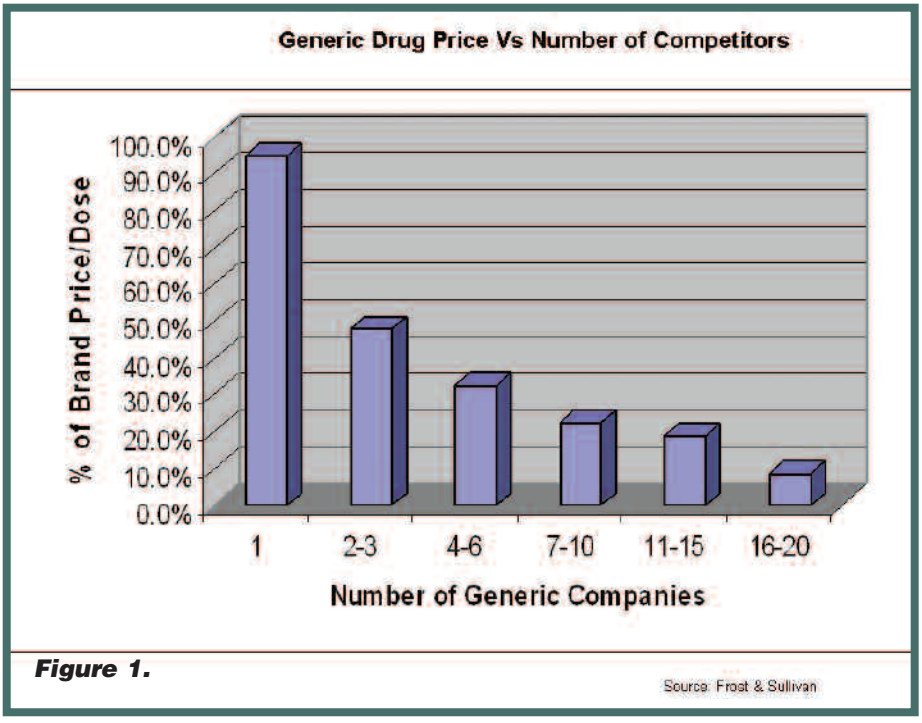

Figure 1.

Source: Frost & Sullivan

What Does Specialty Generics Include?

Specialty Generics are generics with high barriers to competition. These may include modified-release formulations, scheduled drugs, and biogenerics. Companies that have had success with this business model include Endo Pharmaceuticals (pain management) and Barr Laboratories (oral contraceptives). Specialty Generics is usually a part of a broader portfolio of drugs that include Commodity Generics and branded pharmaceuticals, and is often a diversification strategy that seeks to position these products at a niche between Commodity Generics and branded pharmaceuticals, thus providing companies with a more stable revenue stream.

The inherent problems associated with Commodity Generics (lack of product visibility, lower margins, and unstable base business) are almost non-existent in the Specialty Generics business. The Commodity Generics business is witnessing significant growth, and major generic pharmaceutical companies like Teva are well poised to take advantage of the rapidly expanding market. However, there is significant pricing pressure that is forcing them to explore other more lucrative segments like Specialty Generics.

The Essentials of Running a Successful Specialty Generics Business

The key to a successful Specialty Generics business is a strong proprietary drug delivery platform or partnerships. Because most Specialty Generic products involve

technology platforms with a high barrier to entry, it is critical to have a strong drug delivery backing to ensure consistent success.

Generic pharmaceutical companies either in-license drug delivery technology platforms or have their own in-house drug delivery arm with proprietary platforms. While the former could benefit emerging companies, it limits margins owing to the revenue-sharing nature of partnerships.

Acquisition of a drug delivery platform/company was not a financially feasible option for several cash-strapped generic pharmaceutical companies, while internal development takes several years. However, generic pharmaceutical companies recently have been able to generate cash to aggressively pursue mergers and acquisitions of other Specialty Generics-focused companies, giving them access to the rapidly expanding market segment. However, this wave of mergers and acquisitions has driven up valuations of companies, products, and technologies.

Why Specialty Generics?

Generic pharmaceutical revenue is a direct function of supply and is determined by the number of companies operating within the space. Commodity generic products often undergo generic erosion rates between 60% and 95% of the branded drug, depending on the number of competitors.

Specialty Generics try to operate within the "sweet spot" range of about 40% to 50% (generic equivalent price as % of branded drug) with 2 to 4 competing products. Figure 1 compares generic drug prices as percent of brand price versus number of competitors. It is very clear that an increase in competition results in a significant reduction in generic drug prices, resulting in squeezing of margins. The higher margins and revenues from Specialty Generics, which operate in the limited competition range, eliminates the risk from rapid erosion of revenues and margins from increasing competition and counter many of the inherent risks associated with Commodity Generics.

Business Strategies of Specialty Generic Companies

Endo Pharmaceuticals develops and markets Specialty Generics used for the treatment of pain. These are products that involve high barriers to entry, complex formulations, regulatory or legal challenges, and/or difficulty in processing of API. Endo has successfully partnered with drug delivery companies to develop and incorporate their drug delivery platform into its products. Endo differentiates itself from other Specialty Generic companies by focusing on a specific therapeutic line (pain management) and not having a broad portfolio that includes other Commodity Generics.

Barr Laboratories develops and markets Specialty Generic oral contraceptives apart from a broad portfolio of branded pharmaceuticals that complement its generic portfolio. Its oral contraceptive portfolio is one of the largest in the US market and competes primarily with Watson Pharmaceuticals. Barr develops it own drug delivery platforms in house.

Despite adopting contrasting business models, both of these companies have experienced significant success in the Specialty Generics market. Innovation and niche positioning are common characteristics to both of these companies. We are likely to see other generic pharmaceutical companies moving into the Specialty Generics market through innovative approaches and adoption of a combination of business models that are better suited to their business strategy.

What Next for Specialty Generics?

The next phase of growth in the Specialty Generics market is likely to be driven by biogenerics. Europe is leading the way in the development of a regulatory pathway toward the entry of biogenerics, and the US is expected to follow suit. Several leading generic pharmaceutical companies are readying themselves for the next wave of growth through biogenerics.

There has also been a wave of consolidation amongst generic pharmaceutical companies worldwide to ramp up capacity and vertically integrate with API manufacturers to achieve cost efficiencies. We are therefore likely to witness several generic pharmaceutical companies adding a Specialty Generics portfolio to their existing product lines.

Overall, Specialty Generics are likely to lead the next phase of growth within the generic pharmaceuticals market driven by the adoption of innovation and unique positioning strategies. Traditional generic pharmaceutical companies are gearing up to take advantage of the growth potential offered by Specialty Generics, which could further enable them to gain an early foothold into the biogenerics market as it evolves. The area of Specialty Generics is likely to emerge as a crucial market segment that is expected to drive the long-term growth of the overall generics market. ◆

Mr. Barath S. Shankar

Industry Analyst, Frost & Sullivan North American Healthcare Practice

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

Specialty Pharma Marketing: Why Are Some Companies More Successful Than Others?

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

Introduction

Why are so many pharmaceutical executives comfortable blending into the crowd? Maybe it is a childhood tendency that they have not yet outgrown. As children, it is much easier to blend into the crowd than it is to be a leader. This might explain the lack of innovation in the industry today. Fewer new products are in the pipeline, stocks are lagging behind other industries, and marketing efforts are going unnoticed — all due to a lack of innovation. In the pharmaceutical industry, one cannot afford to blend in. Change is necessary; more of the same won't work.

It's time to change it up; time to stick out; time to bring marketing to a new level. The careless spending of marketing dollars is one of the biggest factors as to why companies fail in their attempts at delivering a message. Just sticking your name on a bulleted list of services and products simply won't cut it. You have to go further; you must really understand your customers. You need to know what excites them, what motivates them, what moves them to make the purchase. This isn't done through speculation and snap decisions. Research is the only way to explore customers' feelings and motivating factors. Once you complete the research and identify your customers' Unique Buying Advantages, you're ready to develop the right message to the right demographic. The following are five cornerstones that will get your company to a higher level.

Cornerstone 1: Determining Your Organization's Unique Selling Advantages

Pull together 6 to 10 people in your organization (not just management) for an intense soul-searching session. You'll need a good cross-section of positions in this endeavor; you need to get beyond management and in the trenches of the organization. List all the relevant facts about your organization, products, and/or services and then distill this list to a shorter one of possible selling advantages. Continue distilling down to a specific list (4 to 8) of the most unique facts about your organization. This half-day session will surprise you.

Cornerstone 2: Research to the Core & Solidify Your Customers' Unique Buying Advantages

Plan out your channel of distribution on a dry-erase board and then transfer it to paper. This should include everything from revenue-stream channels and competitor issues to opportunities and industry details. How will you talk to each audience segment? Create the right questions to produce an inquiry for each segmented group. After careful analysis of the data, your customers' preferences will be clear. This process will produce Unique Buying Advantages, which will craft your messaging and marketing direction.

Cornerstone 3: Crafting Your Big Idea to Speak to Prospects

Every brand and every marketing program needs a big idea. Your customers' Unique Buying Advantages will guide you in crafting a message that will stop your audience in its tracks. You will be tempted to put in the usual bulleted list of stuff you do; fight this urge. This message speaks to the Buying Advantages, not the Selling Advantages. Discipline yourself to ignore the clutter and avoid meaningless messaging.

Cornerstone 4: Holding Everyone Accountable Through Intra-gration

Involve all touch-points of your business by understanding, espousing, and living your brand. It's a good idea to survey your internal customers and get a sense of their interpretation of the brand. This information will aide you in bridging the internal and external communications. Additionally, have each employee establish a goal that will assist the organization in achieving their broader goals. Each employee is responsible for carrying out the message and protecting the brand every day. There is no bigger task than servicing customers.

Cornerstone 5: Marketing Integration is Essential in 2008

This is where you will want to pull your brightest and most unusual thinkers together in a strategy session that will propel the big idea and the organization to another level. The key to getting your message out there in the most compelling and cost-effective way is directly tied to integrating your marketing. Choosing the right communications methods, timing, and venues to deploy precise, evocative marketing will get you there.

Summary

Once these five cornerstones create the foundation for your marketing execution, a lasting, effective, and truly valuable brand of stature will emerge. A brand is not a product or service specifically, but the attitude and perception that back it up. Attitude and perception are things that you can impact. Many organizations fall short, however. They spend a great deal of money on advertising and have beautiful graphics that look impressive. If you go back in history, you'll find some of the most significant brands were made from advertising and great creative only. Over the duration of time, they fell short and eventually paid the price for this limited thinking. Those that executed every detail, exercised meticulous marketing, and insisted that their employees perform at a higher level have become great brands.

The term "integrated marketing" became a buzzword in the 90s. However, it's a great deal more than just a fancy term for multiple marketing methods. Your future customers will need to see your message in as many mediums as your budget will afford. This will remind them of your capabilities and creativity when their need arises. They may not have a need right at that moment, but when the time comes, they will remember your message, provided you keep that message out in the marketplace. Too many companies are coerced into running an ad because they like the rep or the price is extra low at the moment. They take out an ad and then complain that they're not getting a return. I've seen companies run an ad in a publication for several months and then pull it out because they didn't receive any calls. The typical complaint is that the magazine didn't work in the first place, as no customers referred specifically to that one print ad.

Marketing is a commitment, one that needs to be taken seriously. It's not a part-time gig, and it's not something you can turn on and off as you see fit. Marketing is a discipline that can and will determine your progress and profitability. If you stay committed in both good and lean times, you're sure to get a return on investment that will pay dividends.

To create a truly successful brand, everyone in the company, from the CEO to the receptionist, should understand and live the core values of the company; know that the business and its products/services are there to serve the consumer; and understand that the brand is alive in the sense that it augments the loyal consumer's life, hopefully for a very long time. ◆

Malcolm A. Teasdale

Big Idea Catalyst
Teasdale Worldwide

Mr. Malcolm A. Teasdale leads the creative force and is the marketing expert behind Teasdale Worldwide, the Agency of Innovation that's creating edgy, effectual messaging while continuously applying his Marketing of Distinction™ — a revolutionary process that goes beyond the flawed nature of advertising. For more than 20 years, Mr. Teasdale has elevated the core practice of research combined with vivid imagination, resulting in client revenues that have increased from $48 million to $100 million over a 2-year period. As a sought-after speaker, his energetic style invigorates and brings a creative and motivational excitement to conferences, seminars, and results-driven workshops. He shares his expertise based on his extreme aversion to the fact that billions of dollars are wasted annually on advertising messaging that is completely ineffective. Methods to break through and overcome these pitfalls have become the foundation for creating BRANDFiltration™, ChannelNSIGHTS™, and Intragrate-M™. He is the author of insightful articles and white papers and is currently completing his first book, Your Opinion Really Doesn't Matter (Your Customer's Does)™.

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

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Why Don't More Business Executives Run For President? – Part II

By: John A. Bermingham

I was talking with our publisher Ralph Vitaro a few weeks ago, and he believed that in fairness, I should write about a business executive actually becoming President of the United States since I "trashed" the politician becoming a business CEO in the last issue. Yes boss!

So here we go. A corporate CEO eeks out a narrow win in the Presidential election, something no one thought possible. He is a member of the male gender. In a speech to the American public immediately after being sworn in, he tells the people that he is now an Independent rather than remaining with the major political party that helped him get elected. He explains that his management and leadership style is such that everyone in Congress is important, and therefore, he does not want to align himself with either side of the aisle. He is the "Man of the People!"

The next day he calls his first Cabinet meeting and explains to the attendees that this group will no longer be referred to as a Cabinet. They will be called the Executive Management Team. His rationale is that people store things in cabinets and EMT should not be stored away but out in the open at all times. Next, he tells all assembled that no one will be called secretary of anything going forward. The term secretary is demeaning and sexist so those with that word in their title will now be called Admins. Admin of the Interior, Admin of Defense, Admin of State, etc.

The following week he holds his first Town Hall Meeting for all members of the EMT (formerly the Cabinet), all members of Congress, White House Staff Members, and several outside advisors. He explains his management style and the need for a sense of urgency, hard work, and extra hours from all elected officials. There will be no more filibusters. He also announces that all members of Congress will now be called "Team Members," defined as a House Team Member and a Senate Team Member. After all, he is the Man of the People and the "President of Change" and will turn this country around within 2 years.

There will be no more budget deficits or a trade imbalance that is negative to the US. There will be sustained economic growth, and all illegal residents will be shipped out of the US after giving them 2 weeks severance pay. A new "US Country Handbook of Policies and Procedures" will be distributed. Any violation of these policies and procedures will result in immediate termination from elected office for cause, and a new election will be held for that vacancy. This will be enforced by the newly established Human Resources Department.

He institutes a vacation policy that allows 1 week of vacation for the first-time elected, rising over time to 4 weeks for those who have been re-elected for more than 20 years. He also allows everyone three religious holidays and two personal days. Everyone is to fly discounted coach, particularly when on foreign travel. No exceptions! Frequent Flyer miles will be turned into the Travel Office. No exceptions! Air Force I, II, III, and IV will be mothballed. However, the President will be allowed first-class air travel on commercial flights due to his need to work on flights and the need for "spread-out room" for his papers.

Finally, as a Man of the People, he announces that his wife will no longer be referred to as the First Lady. This term is sexist and elitist, so she will therefore be referred to as the Presidential Significant Other (behind his back, Congress refers to her as the Pres' First Main Squeeze).

Ninety days after assuming office, the President is visited by the newly appointed Senate Majority Leader/Team Member from Chicago who makes the President an offer he cannot refuse. This immediately results in the newly elected President's resignation in order to pursue other interests, spend more time with his family, and for other personal reasons. It is rumored that he is now living quietly in a villa in Europe. ◆

BIOGRAPHY

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

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