Drug Delivery® Technology

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

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Shaukat Ali, PhD
HMW Povidone Polymer-Based Films for Fast-Dissolving Drug Delivery

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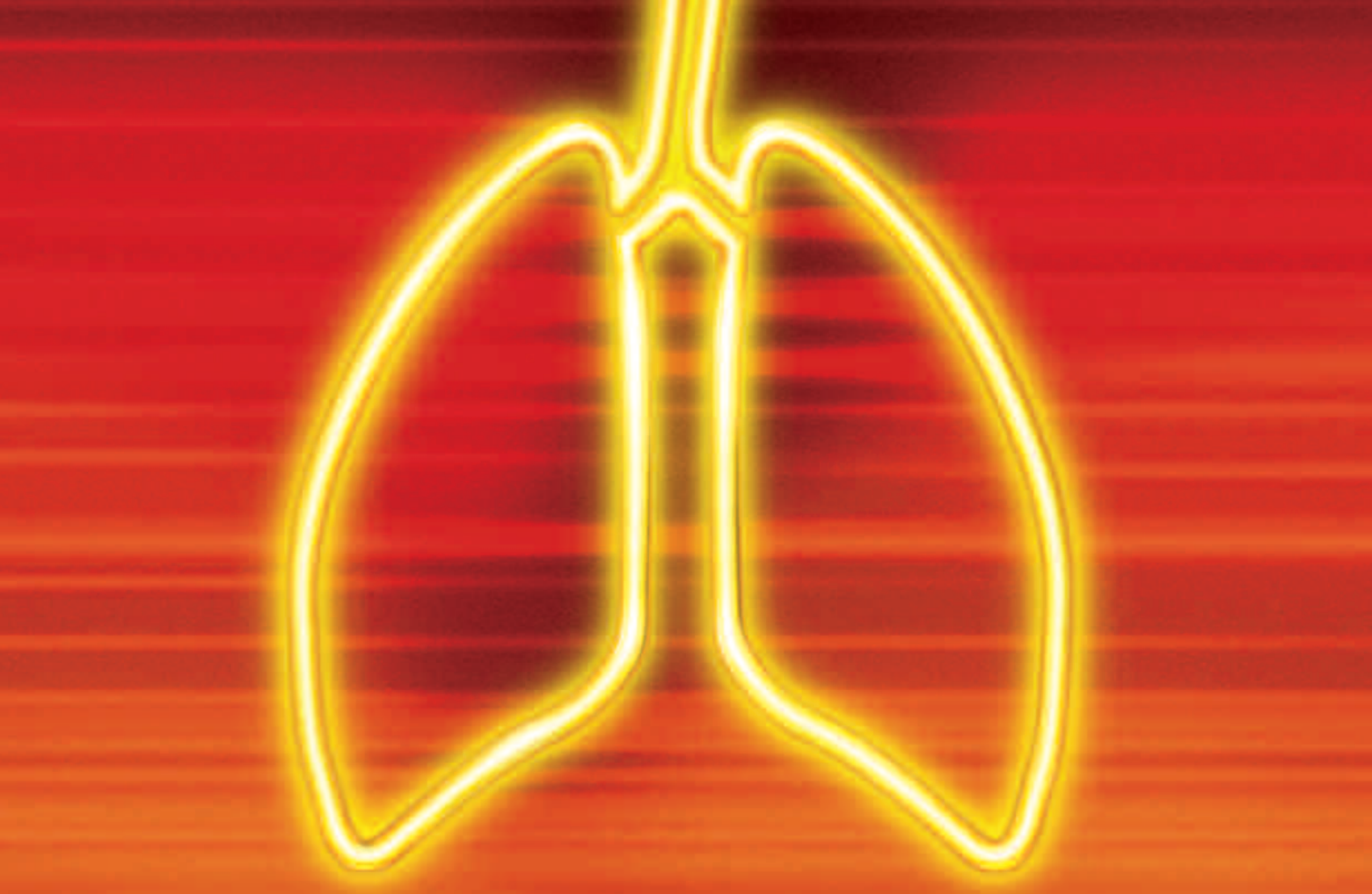

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"In this study, high molecular weight povidone (PVP), for example, Kollidon 90, was used as a carrier in fast-dissolving films, demonstrating strong hydrophilicity and compatibility with a wide array of polymers and copolymers."

p.36

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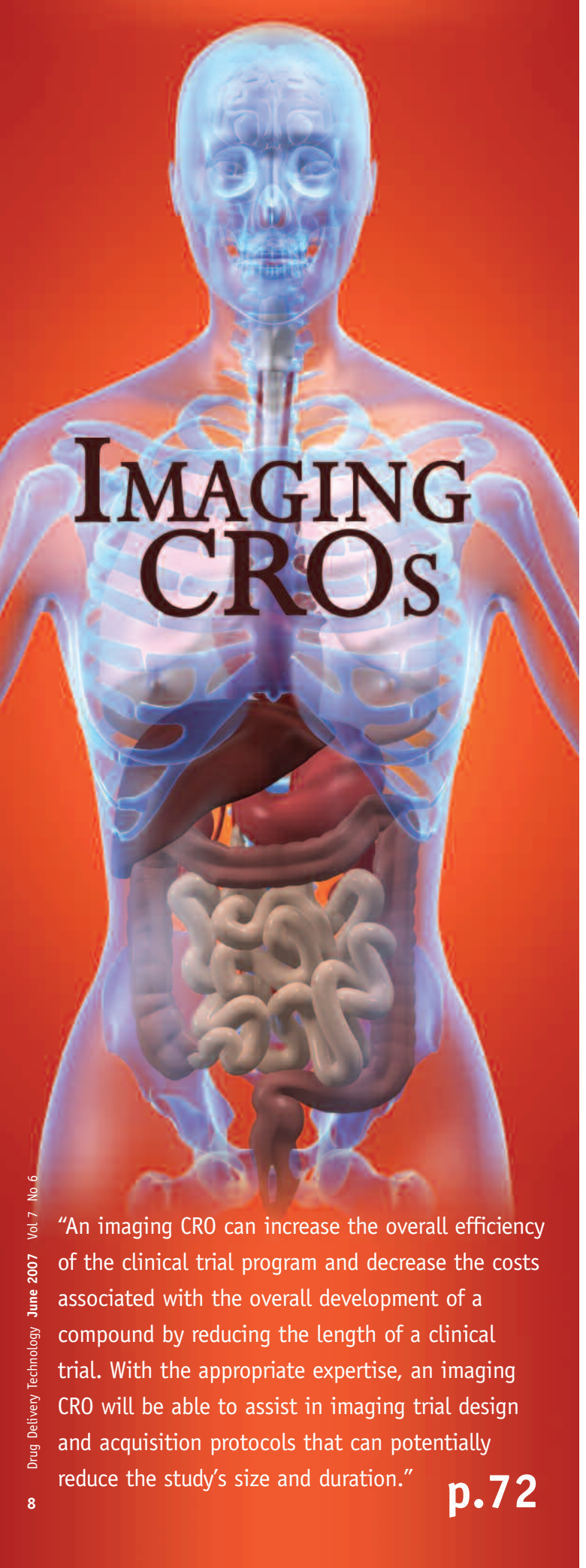

"An imaging CRO can increase the overall efficiency of the clinical trial program and decrease the costs associated with the overall development of a compound by reducing the length of a clinical trial. With the appropriate expertise, an imaging CRO will be able to assist in imaging trial design and acquisition protocols that can potentially reduce the study's size and duration." p.72

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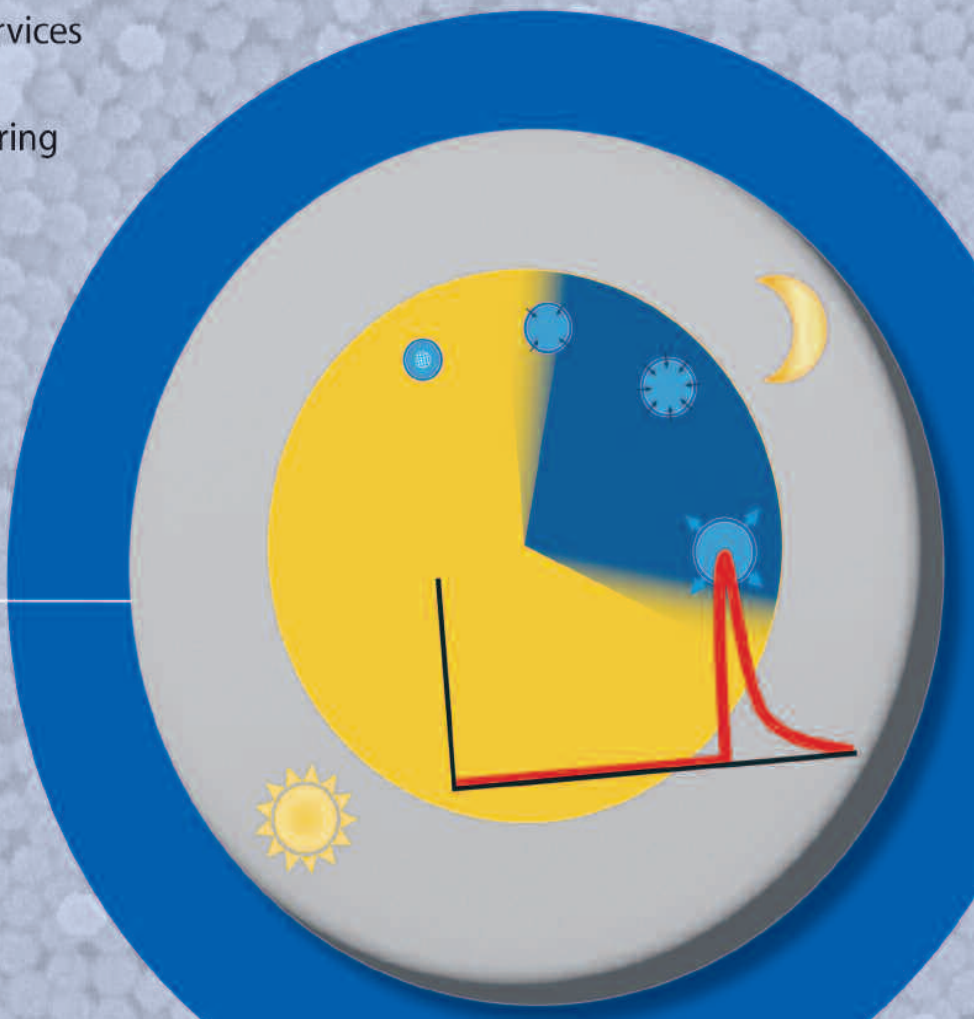

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Market News and Trends

Brookwood Pharmaceuticals, Targeted Technology Ventures Form New Company Aeon Bioscience to Improve Cardiac Stents

Brookwood Pharmaceuticals, Inc. and Targeted Technology Ventures, LLC recently announced the creation of a collaborative joint venture to form Aeon Bioscience, Inc., a company that will work to develop a new drug-eluting stent to overcome the current concerns of late stent thrombosis (LST) or blood clot formation at or near the site of the stent and vessel closure due to formation of scar tissue, known as restenosis.

"The drug-eluting stent (DES) market suffered a setback in September 2006 when, during the World Congress of Cardiology meeting held in Barcelona, Spain, data was presented identifying a concern over the long-term safety of DES, specifically LST," said Christopher E. Banas, Principal, Targeted Technology, who will serve as CEO of Aeon. "This safety issue provides an immediate need to develop a solution to the LST problem. As a result, Aeon will focus on the development of a more effective polymeric coating in order to improve the safety profile of DES. This will ultimately result in an improvement in the quality of life for patients suffering from cardiovascular disease."

Mr. Banas added that the creation of Aeon will spur economic development, job creation, and increased visibility in the medical device industry for Birmingham.

Brookwood Pharmaceuticals is a Birmingham-based drug delivery company. Targeted Technology is a San Antonio-based biotechnology and medical device company. Series A funding was secured through the Birmingham Technology Fund, managed by Greer Capital Advisors, LLC of Birmingham. Aeon Bioscience will be headquartered in Birmingham. The combined strengths of the two parent companies give Aeon a strong development team with a proven track record in biodegradable materials, drug delivery, vascular stent engineering, clinical testing, and regulatory registrations. Brookwood and Targeted Technology also bring strong skills in management of intellectual property portfolios and access to recognized scientific and medical leaders. Additional collaborators will be added as Aeon's technology platforms make progress.

"Aeon Bioscience is uniquely positioned in the race to develop new drug-eluting polymers with the biocompatibility and biological performance necessary to meet the stringent demands of the next generation of coronary stents and cardiovascular implants," said Dr. Paul Castella, Principal, Targeted Technology, who will serve as Aeon's Chief Business Officer.

"We are thrilled to be working with such a strong team with specific focus on stent developing and testing," said Dr. Arthur J. Tipton, President and CEO of Brookwood Pharmaceuticals, who will also serve as President of Aeon. "In addition to the funding from Larry Greer and his team, we are particularly appreciative of Alan Dean (Greer Capital) who was the first to recognize the synergy of putting these teams together."

Alan Dean, Managing Partner, Fund Operations at Greer Capital, who will serve as Aeon's Chairman of the Board said, "It is a rare privilege to be associated with groups of such talent and experience as Brookwood and TTV, working as a team toward an ambitious goal. Brookwood, under Dr. Tipton's leadership, has emerged as our technology crown jewel, and will ultimately prove to be the catalyst for capitalizing on the immense, mostly untapped technology resources residing in Birmingham. The leadership of TTV, Principals Christopher E. Banas and Dr. Paul Castella, bring to this collaboration uncommon experience in developing a range of diagnostic, pharmaceutical, and medical device products, with a particular emphasis on launching new innovative devices for cardiovascular diseases. I appreciate the strong commitment and enthusiasm of everyone involved with this important joint venture."

KV Pharmaceutical Completes Acquisition of US Rights to EvaMist for $150 Million

KV Pharmaceutical Company recently reported it has completed its previously announced transaction with Vivus, Inc. for the sublicense of exclusive rights and purchase of assets related to EvaMist. Under the terms of the all-cash transaction, KV agreed to pay $10 million at closing and to make an additional payment of approximately $140 million at the time of final approval from the US FDA. There are also two, one-time milestone payments tied to the net sales of the product. Ten million will be paid if the product achieves $100 million in net sales in a market year, and up to $20 million will be paid if the product achieves $200 million in net sales in a market year.

EvaMist, which has completed Phase III clinical trials, is a patented estradiol transdermal spray that offers a novel approach to the treatment of vasomotor symptoms associated with menopause. Upon approval, EvaMist is expected to significantly augment the women's health offerings of KV's branded subsidiary, Ther-Rx Corporation. With a PDUFA action date of July 29, 2007, from the FDA, KV currently expects that the product may be approved and launched during the second half of its fiscal 2008, which began April 1, 2007.

The product targets an annual $1.3-billion estrogen replacement market in which physicians and patients are seeking an effective and safe, low-dose estrogen product. The company estimates EvaMist's US market potential to be approximately $125 million in peak, annual net sales with gross margins consistent with those currently being achieved by Ther-Rx Corporation. KV believes EvaMist will offer therapeutic effectiveness with estradiol dosing that is among the lowest available for this indication in a manner that is also cosmetically appealing for women.

KV Pharmaceutical Company is a fully integrated specialty pharmaceutical company that develops, manufactures, and markets and acquires technology-distinguished branded and generic/non-branded prescription pharmaceutical products. The company markets its technology-distinguished products through Ethex Corporation, a national leader in pharmaceuticals that compete with branded products, and Ther-Rx Corporation, its emerging branded drug subsidiary.

Vivus, Inc. is a pharmaceutical company dedicated to the development and commercialization of next-generation therapeutic products addressing obesity and sexual health. Vivus has three products that are positioned to enter Phase III clinical trials, and one product currently under NDA review by the FDA. The investigational pipeline includes Qnexa, for which a Phase II study has been completed for the treatment of obesity; Testosterone MDTS, for which a Phase II study has been completed for the treatment of Hypoactive Sexual Desire Disorder (HSDD); EvaMist, for which a Phase III study has been completed and an NDA submitted for the treatment of menopausal symptoms; and avanafil, for which a Phase II study has been completed for the treatment of erectile dysfunction (ED). MUSE is approved and currently on the market for the treatment of ED.

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Market News and Trends

Dowpharma Licenses Pfinex Expression Technology to VGX Pharmaceuticals

Dowpharma contract manufacturing services, a business unit of The Dow Chemical Company, recently announced that it has licensed its Pfinex Expression Technology to leading biopharmaceutical company VGX Pharmaceuticals. Under this non-exclusive global license, Dow's technology will be used to produce a proprietary VGX therapeutic protein indicated for cancer therapy.

Compared to traditional microbial fermentation techniques, the Pseudomonas fluorescens-based Pfinex Expression Technology produces increased yields of soluble, correctly folded therapeutic proteins. Dowpharma is able to screen hundreds of expression strains, enabling rapid identification of a strain capable of producing high yields of properly folded, active protein. The soluble protein expressed is easier to handle, enables a clearer path through the purification process, and avoids a refold step that significantly reduces the overall cost of goods. This makes Pfinex Expression Technology an obvious choice for the growing number of drug candidates that require complex folding.

"The adoption of the Pfinex Expression Technology has been accelerating rapidly in the past several months, driven by biopharmaceutical developers looking for a more extensive range of proteins, faster results, and better economics," said Nick Hyde, Global Business Director, Dowpharma. "Our collaboration with VGX quickly resulted in the delivery of a very robust Pfinex production strain for its VGX-100 protein, and we are confident that our technology will help advance the development of the therapeutic currently in the works."

Dr. J. Joseph Kim, Co-Founder, President, and CEO, VGX Pharmaceuticals, added, "We have turned to Dowpharma because the Pfinex Expression Technology consistently outperforms other commercially available microbial expression systems. Viral protein R has been difficult to produce in high yields, and we were pleased with the results obtained with the Pseudomonas fluorescens-based technology. The production strain and process for manufacturing VGX-100, our lead protein therapeutic candidate for lymphoma and other cancers, has already been transferred to our contract manufacturer, Diosynth Biotechnology, and further process development and scale-up is underway. The expertise and knowledge that come with the technology and the support we have so far received from Dowpharma have made it an excellent choice for us."

Using a natural isolate of Pseudomonas fluorescens, an abundant and non-infectious component of the microbial flora of soil, water, and plants, many high-performance production strains have been developed. Proteins are expressed in high yields with correct disulfide bond formation, reduced proteolytic degradation, and enhanced solubility/activity, making the process of strain development faster and more efficient than in traditional microbial expression host strain development. Dozens of host strains are tested in parallel to identify expression strategy/host cell combinations that result in improved target protein accumulation and/or stability. The technology is easily employed in traditional fermentation, recovery, and purification settings with no need for additional, unique equipment.

VGX Pharmaceuticals is a biopharmaceutical company with small molecules and biologics product candidates for the treatment of infectious diseases, cancer, and inflammatory diseases.

Dowpharma contract manufacturing services provides the pharmaceutical and biopharmaceutical industries with innovative technologies, products, and services for clients in drug discovery, development, manufacturing, and delivery. Dowpharma offers process development, route selection, methods development, chiral capabilities, and associated analytical services as well as manufacturing and scale-up from feasibility through clinical trials to commercial launch.

AlphaRx & Proprius Pharmaceuticals Announce Top Line Results From Indaflex Phase II Study in Canada

AlphaRx Inc. and Proprius Pharmaceuticals, Inc. recently announced top line results from the Indaflex 2.5% Topical Indomethacin Cream exploratory Phase II clinical trial in osteoarthritis (OA) of the knee (INDF-200). The proof-of-concept study was initiated in September 2005 by AlphaRx and was performed in Canada.

The randomized double-blind placebo and vehicle-controlled trial, which included a 6-week treatment period, was conducted in 233 patients with OA of the knee. The primary endpoints used in the trial were the change from baseline to week 6 in the global Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and the subject's global assessment of efficacy. While the trial did not meet its primary endpoints, subgroup analyses of patients with moderate-to-severe pain and more impaired physical function at baseline showed positive trends in patients treated with Indaflex as compared to patients treated with either placebo or vehicle. Indaflex was demonstrated to be safe and well tolerated.

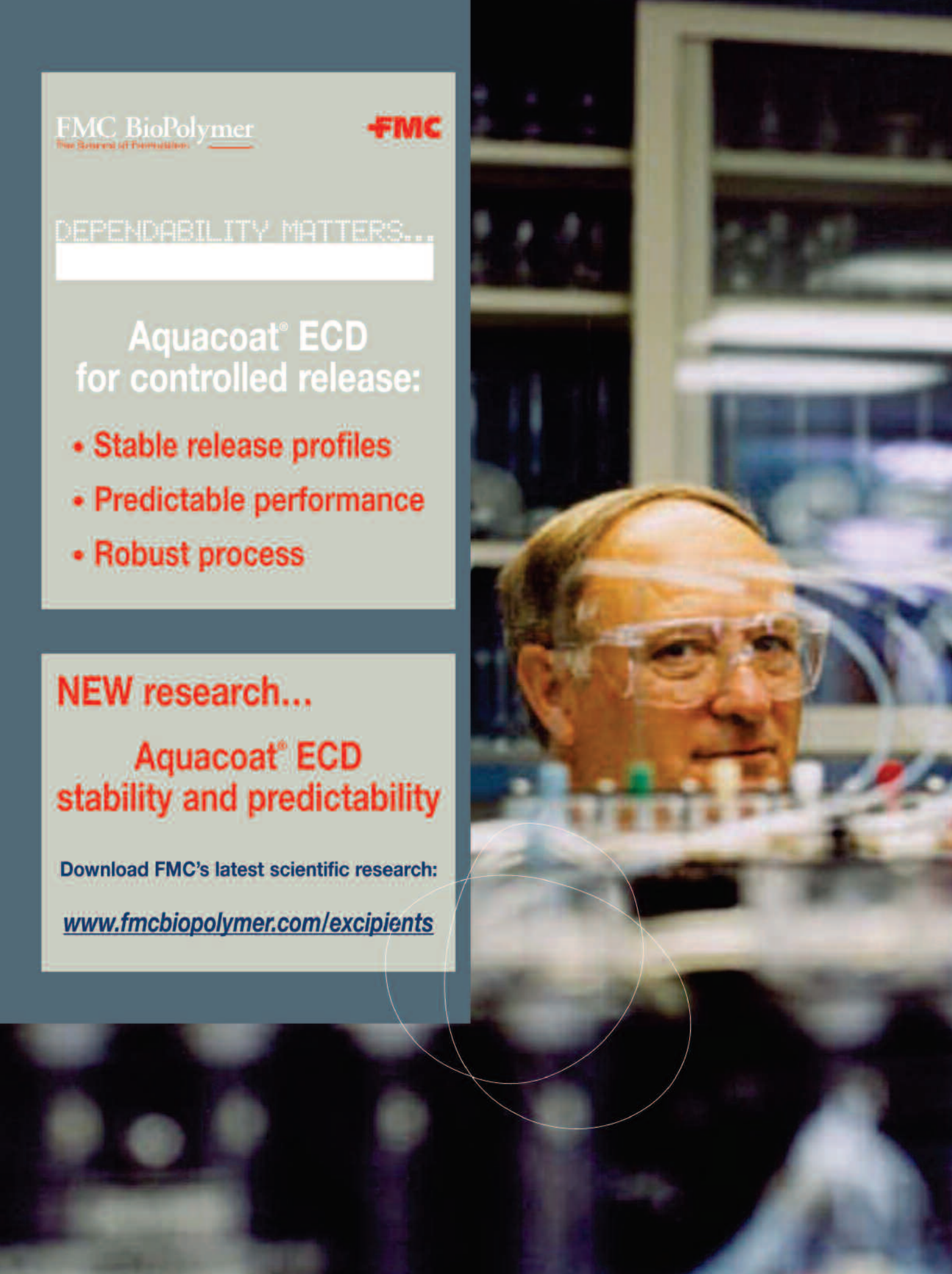
"We are encouraged by the results of this first human efficacy trial comparing Indaflex to both placebo and vehicle," said Michael J. Walsh, President and CEO of Proprius Pharmaceuticals. "The data point to the promise of Indaflex as a very well tolerated and safe topical NSAID product candidate, with potential for efficacy in treating moderate-to-severe pain and improving function for patients suffering from osteoarthritis of the knee. The knowledge gained from this proof-of-concept study has provided important insights on appropriate pivotal trial design. We are eager to discuss our findings with the Food and Drug Administration, and advance Indaflex into registration trials."

Dr. Lee S. Simon, a Rheumatologist and former Director of the Food and Drug Administration's Analgesic, Anti-Inflammatory, and Ophthalmic Drug Products Division, and a consultant to the companies, commented, "The results of this initial clinical trial provide supportive evidence for the efficacy and safety of Indaflex. This therapeutic product candidate has the potential to fulfill the need for an effective, tolerable, and safer alternative to either oral non-selective NSAIDs or COX-2 selective inhibitors for the treatment of osteoarthritis of the knee, as well as other diseases and disorders that are associated with localized pain and inflammation."

Indaflex is a topical NSAID formulation in clinical development for the reduction of signs and symptoms associated with OA of the knee. Arthritis is the most common chronic disease in North America and afflicts an estimated 10% of the world's population. The active ingredient in Indaflex, indomethacin, has a long-standing and proven clinical treatment record. Delivered through the skin using a proprietary nanoparticle technology developed by AlphaRx, the companies believe Indaflex will have an attractive efficacy, safety, and tolerability profile in comparison to oral treatments and other topical preparations. Proprius Pharmaceuticals acquired the exclusive global rights to Indaflex (with the exception of Asia and Mexico) in April 2006.

AlphaRx is a clinical stage pharmaceutical company utilizing proprietary drug delivery technology to develop novel formulations of drugs that are insoluble or poorly soluble in water or have yet to be administrable to the human body with an acceptable delivery method. The company's product candidates address various pharmaceutical markets, including arthritis, tuberculosis, ocular infection, and inflammation, pneumonia, and sepsis.

Proprius Pharmaceuticals is a specialty pharmaceutical company that develops and markets personalized medicine solutions in rheumatology and autoimmune diseases. This novel combination of proprietary pharmaceuticals and diagnostic services provides a strategic and differentiated approach to commercialization. Proprius is a privately held, venture-backed company.



Market News and Trends

IOMED Agrees to be Acquired by ReAble Therapeutics for $22 Million

IOMED, Inc. and ReAble Therapeutics, Inc. (formerly known as Encore Medical Corporation) recently announced the signing of a definitive agreement whereby ReAble will acquire all the outstanding shares of IOMED in an all-cash merger for $2.75 per share, subject to adjustment. The total transaction consideration will be approximately $22 million. The all-cash merger represents a premium of approximately 38% over the average closing price over the last 30 trading days.

IOMED is a leading manufacturer of drug delivery devices used primarily for the management of pain. ReAble Therapeutics is a privately held, leading medical device company in the rehabilitation and orthopedics markets. The acquisition, which has been unanimously approved by IOMED's Board of Directors, is subject to the satisfaction of certain customary closing conditions and is also subject to the approval of IOMED shareholders.

Following the acquisition, IOMED will be a wholly owned subsidiary of ReAble, operating under ReAble's Empi division. Empi is a leading manufacturer and marketer of pain management and rehabilitation devices. As part of the Empi division, IOMED is expected to continue its manufacturing, customer support, and product development functions at its Salt Lake City facility. In addition, IOMED will maintain its field-sales support, and will continue to distribute its core iontophoresis product lines through its existing network of independent sales agents and specialty distributors.

Commenting on the transaction, Kenneth W. Davidson, ReAble's CEO, said, "IOMED has developed an outstanding line of innovative drug delivery devices and technologies, and has built an excellent third-party distribution network. We are very pleased to incorporate IOMED's strong portfolio of products and its excellent product development capabilities into our Empi division. We view IOMED's products and extensive distribution network as important strategic assets. We believe IOMED is an excellent strategic fit with Empi, and that this acquisition represents an important step forward in ReAble's overall growth strategy."

Robert J. Lollini, IOMED's CEO, commented, "Empi is a world-class pain management company. We are very pleased to join together with Empi to continue to offer world-class products and to know that our core capabilities, our products, and our technologies will continue to be utilized effectively and commercialized broadly. IOMED and Empi share a strategic vision of growing and developing the iontophoresis drug delivery category, and this combination makes great strategic sense for both companies."

The definitive merger agreement and the closing of the transaction is subject to certain terms and conditions customary for transactions of this type, including approval by IOMED shareholders in a special meeting yet to be announced. Pending such shareholder approval, the transaction is expected to close in July 2007. Seven Hills Partners LLC acted as exclusive financial advisor to IOMED in this transaction.

ReAble is a diversified rehabilitation and orthopedic device company that develops, manufactures, and distributes a comprehensive range of high-quality medical devices used by physicians, therapists, athletic trainers, orthopedic surgeons, and other healthcare professionals to treat patients with musculoskeletal conditions resulting from degenerative diseases, deformities, traumatic events, and sports-related injuries. Through its Orthopedic Rehabilitation Division, ReAble is a leading distributor of electrical stimulation and other orthopedic products used for pain management, orthopedic rehabilitation, physical therapy, fitness, and sport performance enhancement. ReAble's Surgical Implant Division offers a comprehensive suite of reconstructive joint products. ReAble was acquired by The Blackstone Group, the private equity firm, in a go private transaction in November 2006.

IOMED is a diversified drug delivery product and technology company focused primarily on iontophoresis. Iontophoresis is a technology that delivers pharmaceuticals transdermally using electric current to ionize drug molecules and propel them through the skin. Iontophoresis is used to deliver medication both locally and systemically. IOMED is publicly traded on the American Stock Exchange under the symbol IOX.

Phosphagenics Limited to Commence Phase Ib Transdermal Insulin Clinical Trial in Second Quarter

Phosphagenics Limited recently announced that the company intends to initiate a Phase Ib clinical trial to demonstrate the efficacy and safety of the improved formulation of its transdermal insulin product, TPM-02/Insulin, containing long-acting insulin. The trial is expected to commence in the second quarter of 2007.

TPM-02/Insulin gel is being developed as a novel "needle-free" way of administering insulin to patients with diabetes. Following the successful completion of a Phase Ia study utilizing short-acting insulin, this trial will assess an optimized formulation of long-acting insulin. Recent advancements in Phosphagenics' patented TPM-02 delivery system have enabled the formulation of long-acting insulin, which is significantly less expensive than short-acting insulin, provides appropriate levels of insulin in humans, and is commercially attractive.

"In August 2006, our Phase Ia study demonstrated that a single application of TPM-02/Insulin gel rapidly delivered insulin across the skin and into the bloodstream without any adverse reactions," said Dr. Esra Ogru, Executive Vice President at Phosphagenics. "Additionally, it significantly lowered blood glucose, insulin and c-peptide levels."

"The Phase Ib study is intended to provide additional supporting data for an Investigational New Drug application to the US Food and Drug Administration," continued Dr. Ogru. "The trial will be conducted by CMAX at the Royal Adelaide Hospital, South Australia, will include up to 45 healthy volunteers, and is expected to lead directly into the start of a large multi-site Phase II trial that is likely to include up to several hundred patients."

"This is an important step for the development and commercialization of TPM-02/Insulin," said Harry Rosen, President and CEO of Phosphagenics. "This technology has the potential to provide diabetics with a non-invasive and effective treatment, and we look forward to its continued development."

Phosphagenics is a Melbourne-based, globally driven biotechnology company focused on the discovery of new and cost-effective ways to enhance the bioavailability, activity, safety, and delivery of proven pharmaceutical and nutraceutical products. The company's core technology is built around the science and application of phosphorylation, a process in which the addition of a phosphate group has been found to enhance the bioavailability, activity, and safety of existing pharmaceuticals and nutraceuticals, as well as to assist in the production of drug delivery platforms.

Phosphagenics' shares are listed on the Australian Stock Exchange (POH) and the London Stock Exchange's Alternative Investment Market (PSG). An ADR - Level 1 program has been established in the US with the Bank of New York (PPGNY) for US investors to trade in Phosphagenics' stock on the over-the-counter market.

CyDex Licenses Captisol to Sunesis Pharmaceuticals for Oncology Drug Candidate

CyDex, Inc., a specialty pharmaceutical company developing improved products through innovative drug delivery, recently announced an agreement licensing its Captisol enabling technology to Sunesis Pharmaceuticals, Inc. for formulation of a selective Aurora kinase inhibitor with potent anti-tumor activity across a number of nonclinical human cancer models.

CyDex's patented Captisol technology improves water solubility, bioavailability, and complexation characteristics of insoluble and/or unstable drugs. The CyDex pipeline of licensed and proprietary Captisol-enabled formulations targets a range of market segments, including injectables, oral solutions and capsules, ophthalmic solutions, oral solids, and inhalation.

CyDex granted Sunesis global rights to Captisol for a formulation of SNS-314 – a selective small molecule inhibitor of Aurora kinases that potently inhibits proliferation of a wide panel of human cancer cell lines. Aurora kinases are over-expressed in several types of cancer, including colon, breast, ovarian, bladder, esophageal, gastric, and pancreatic.

As demonstrated in multiple nonclinical models, the combination of potency, selectivity and robust in vivo activity, coupled with tumor growth inhibition through intermittent dosing, suggests that SNS-314 may be a best-in-class Aurora kinase inhibitor for the treatment of diverse human malignancies. An Investigational New Drug Application has been submitted for SNS-314, and a Phase I clinical trial for the treatment of patients with solid tumors is planned to begin in the second quarter of 2007. Sunesis Pharmaceuticals is a clinical-stage biopharmaceutical company focused on the discovery, development, and commercialization of novel small molecule therapeutics for oncology and other serious diseases.

"Adding Sunesis to our roster of technology licensing partners is an important advance for CyDex," said John M. Siebert, PhD, Chief Executive Officer of CyDex. "We are pleased to be participating in the process of developing SNS-314 and potentially creating a significant new therapeutic alternative for oncology. Including SNS-314, our partners have a total of 23 licensed Captisol formulations involved in clinical trials around the world. We look forward to further expanding CyDex's technology licensing activity in the months and years ahead. At the same time, we expect to continue making progress on our proprietary products strategy. Our current proprietary pipeline includes eight hospital acute care and four other Captisol-enabled drugs that have the potential to provide unique therapeutic benefits and satisfy unmet medical needs."

CyDex is a specialty pharmaceutical company developing proprietary products and licensing its Captisol enabling technology. CyDex is bringing important new medications to patients by developing its own pipeline of proprietary products with advanced drug delivery solutions, and by partnering with the world's leading pharmaceutical and biotechnology companies. Four Captisol-enabled drugs are currently being commercially marketed. These include Bristol Myers Squibb's Abilify IM, Pfizer Animal Health's Cerenia and Geodon for Injection and Vfend IV, both marketed globally by Pfizer Inc.

In addition, CyDex has development agreements with Allergan, Inc.; Bristol-Myers Squibb; Daiichi Asubio Pharma Co., Ltd., of Japan; Merck & Co., Inc.; Kanisa Pharmaceuticals; Mitsubishi Corporation; OSI Pharmaceuticals, Inc.; PTC Pharma AG; TargeGen, Inc.; Taisho Pharmaceuticals; and Teva Pharmaceutical Industries Ltd. CyDex also has clinical use agreements with major pharma and biotech companies. CyDex is a privately held company located in suburban Kansas City.

Market News and Trends

BioProgress Announces Rocgel Acquisition & Out-Licensing of Two Products

BioProgress plc, the specialty pharma and healthcare company, recently announced the acquisition of Rocgel, an antacid used in the treatment of pain associated with gastro-intestinal conditions. The product will add to the portfolio of the company's sales and marketing division in France, Dexo S.A.

Rocgel is a growth brand and will be distributed by the company in France and in French-speaking African countries. The product is currently prescription-only but has the potential, and registration approvals, for sales into the over-the-counter healthcare market. The Rocgel brand has high recognition in French-speaking markets, making it suitable for line extensions through the company's suite of enabling drug delivery technologies, in particular Solupol.

As the result of a regular review of its product portfolio to ensure that the company's resources are focussed on growth opportunities, the company has out-licensed two low-growth brands in the Dexo S.A. portfolio, Dimegan and Mucipulgite. These brands were unlikely to benefit from enhancement via the company's drug delivery technologies, one of the key elements in the company's growth strategy.

Richard Trevillion, Chief Executive Officer, BioProgress, said "We are delighted by the addition of Rocgel to our portfolio of products in Dexo S.A. Rocgel is a highly recognized brand that brings the potential of both line extensions using our drug delivery technologies and of launching the brand in the over-the-counter market. "The company expects to announce further accretive organic product acquisitions during the course of 2007 as we execute our strategy of marketing high-growth, differentiated and XGEL-enhanced products in both the prescription-only and OTC markets."

BioProgress plc is an innovative specialty pharmaceutical and healthcare business based around its platform technologies in polymer and film systems. Listed on London's AIM in May 2003 and on US NASDAQ in October 2004, the company has over 80 patents granted or in application within 24 patent families and has product development agreements and strategic alliances with several global companies. As a virtually integrated business, BioProgress has acquired sales and marketing resources within Europe and the US as a launch mechanism for its own pharmaceutical products. The business continues to develop innovative delivery mechanisms using its XGEL polymer technology, replacing the need to use animal-derived gelatine in pharmaceutical and healthcare products.

Cipher Pharmaceuticals Receives Approvable Letter From the FDA for CIP-TRAMADOL ER

Cipher Pharmaceuticals Inc. recently announced it has received an approvable letter from the US Food and Drug Administration (FDA) pertaining to its New Drug Application (NDA) for CIP-TRAMADOL ER, the company's once-daily formulation of tramadol.

In its letter, the FDA indicated that Cipher's application is approvable subject to the resolution of certain issues, including chemistry, manufacturing, and controls (CMC) and a request for an additional adequate clinical trial to provide further efficacy data. While Cipher believes its submission includes sufficient data to support regulatory approval, the company requires clarification from the FDA on the issues raised in the action letter before determining the path forward. Cipher anticipates meeting with the FDA shortly to discuss these matters.

Cipher submitted its NDA for CIP-TRAMADOL ER in June 2006, and the NDA was accepted for review during the third quarter of 2006. The NDA contains data from six pharmacokinetic studies and five Phase III studies (three of these providing pivotal efficacy data and two providing long-term safety data).

Cipher Pharmaceuticals is a drug development company focused on commercializing novel formulations of successful, currently marketed molecules using advanced drug delivery technologies. Cipher's strategy is to in-license products that incorporate proven drug delivery technologies and advance them through the clinical development and regulatory approval stages, after which the products are out-licensed to international partners. Because Cipher's products are based on proven technology platforms applied to currently marketed drugs, they are expected to have lower approval risk, shorter development timelines, and significantly lower development costs.

Cipher currently has three late-stage drugs in its pipeline. The company's lead compound, CIP-FENOFIBRATE, received final approval from the US Food and Drug Administration and Health Canada in the first quarter of 2006. In addition, Cipher is developing formulations of the pain reliever tramadol (currently under regulatory review by the FDA) and the acne treatment isotretinoin (currently under regulatory review by the FDA). Cipher is listed on the Toronto Stock Exchange under the symbol DND and has approximately 24 million shares outstanding.

Azopharma Broadens Contract Product Development Services With Additional Acquisitions

US based Azopharma recently announce newly established relationships with iQ Synthesis and Cyanta Drug Development. Phil Meeks, CEO of the Azopharma Product Development Group of companies, said, "These two additions, combined with our four current companies, will round out our service offering portfolio and enhance our position as a major resource in the global contract product development arena. We are now poised to capitalize on the emerging trends transforming the pharmaceutical industry. Our entire network now consists of a family of six companies with capabilities ranging from preclinical to manufacturing. Working either individually or in conjunction, these companies offer tailored choices to the pharmaceutical and medical device industries of North America, Europe, and Asia."

He added, "Clients seeking contract research services and support can turn to the Azopharma Product Development Group of companies for complete solutions. This unique group of companies includes Azopharma Contract Services – Integrated product development and CTM manufacturing; IQ Synthesis – Synthetic chemistry services from discovery to clinical materials; ApiCross Drug Delivery – Proprietary drug delivery platforms for insoluble compounds; Aniclin Preclinical Services – Preclinical services in support of early product development; and Cyanta Drug Development – Analytical chemistry services from development to QC testing, and AvivoClin Clinical Services – Human clinical pharmacology services for Phase I clinical trials.

"Some of our clients prefer one company managing their entire pipeline across several scientific disciplines and prefer a service provider, such as Azopharma Contract Services, while others prefer to outsource a single aspect of their developmental program. The latter can now turn to our other five companies depending upon their scientific needs."

All companies in the Azopharma product development group of companies are wholly owned subsidiaries of Azopharma Contract Services, Inc. The group collectively consists of over 200 scientists providing contract research services both domestically and internationally. All companies are owned by a holding company, Chemir, Inc., based in St. Louis, Missouri. Chemir, Inc. is owned by Dr. Shri Thanedar, who serves as Chairman of all of the companies in the Azopharma product development group of companies.

Endo Pharmaceuticals & Project Sunshine Partner to Brighten the Day of Pediatric Patients

Endo Pharmaceuticals Inc. and Project Sunshine recetly announced a Project Sunshine Patches Day program partnership designed to help brighten the day of pediatric patients at children's hospitals in select cities nationwide. Endo Pharmaceuticals will sponsor 10 Project Sunshine events with pediatric hospital patients to facilitate quality playtime and craft activities, and distribute stuffed animals to all participants.

Despite increasing efforts to assuage fear in hospitalized children, healthcare providers continue to face challenges managing procedure-related pain and the anxiety that can be associated with it. In a recent survey of 200 pediatric healthcare professionals conducted by Roper Public Affairs & Media in partnership with Endo Pharmaceuticals, 75% of respondents said their patients demonstrated anxiety prior to venous access and other superficial procedures. Children who experience pain or anxiety-related discomfort are at risk for developing subsequent, long-term aversions to treatment experiences.

"For pediatric patients, hospital stays can be frightening and even traumatic, which is why we feel it is so important to try to improve the quality of life for these children," said Amy Saperstein, Executive Director, Project Sunshine. "We are delighted to bring our volunteers and arts and crafts activities to hospitals around the country, and thank Endo Pharmaceuticals for their generous support to make these events possible."

"Endo Pharmaceuticals is committed to improving the lives of patients and meeting the needs of healthcare professionals," said Peter A. Lankau, Chief Executive Officer of Endo Pharmaceuticals. "We are pleased to partner with Project Sunshine in an effort to brighten the day of pediatric patients and raise awareness about issues essential to their care."

Endo Pharmaceuticals and Project Sunshine will conduct the Project Sunshine Patches Day events at 10 hospitals across the country during the summer of 2007. Project Sunshine is a nondenominational, nonprofit organization that provides free programs and services to children and families who are affected by serious medical challenges. Project Sunshine sends volunteers to visit hospitalized children and their families to provide arts and crafts, tutoring, entertainment, and special events. Project Sunshine volunteers are corporate executives, lawyers, artists, students, and people of all ages and backgrounds who donate their time and resources to improving the lives of children and families in need. Project Sunshine has 180 chapters throughout the United States, Canada, and in Kenya. In the past year, 10,000 volunteers served 100,000 children and families.

Endo Pharmaceuticals Holdings Inc. is a fully integrated specialty pharmaceutical company with market leadership in pain management products. Through its wholly owned Endo Pharmaceuticals Inc. subsidiary, the company researches, develops, produces, and markets a broad product offering of both branded and generic pharmaceuticals, meeting the needs of healthcare professionals and consumers alike.

Watson Pharmaceuticals Agrees to Permit Sandoz Pharmaceuticals to Launch Metoprolol Succinate Extended-Release 50-mg Tablets

Watson Pharmaceuticals, Inc., a leading specialty pharmaceutical company, recently announced that pursuant to an agreement with Sandoz, a subsidiary of Novartis AG, Watson has relinquished its rights to a 180-day period of marketing exclusivity for its 50-mg strength of metoprolol succinate extended-release tablets (the generic equivalent to AstraZeneca PLC's Toprol XL 50-mg product). Watson was awarded market exclusivity as the first generic applicant to submit an Abbreviated New Drug Application (ANDA) for metoprolol succinate extended-release 50-mg tablets.

As a result of Watson's agreement to relinquish its marketing exclusivity, Sandoz has obtained final approval of its ANDA for metoprolol succinate extended-release 50-mg tablets. Watson will be entitled to a share of Sandoz's profits on the sale of the product. Other terms of the agreement were not disclosed. According to IMS Sales data, Toprol XL extended-release 50 mg had 2006 US brand sales in excess of $600 million.

Watson continues to pursue approval of its own pending ANDA for metoprolol succinate extended-release tablets, but does not anticipate obtaining final approval before AstraZeneca's pediatric study market exclusivity commences. Watson believes that under current US Food and Drug Administration (FDA) policy, applicants that do not obtain final approval before AstraZeneca's pediatric study market exclusivity commences would be barred from obtaining final approval until March 18, 2008, when AstraZeneca's pediatric study market exclusivity expires.

Watson Pharmaceuticals, Inc. is a leading specialty pharmaceutical company that uses innovative science and market insight to develop responsive products for a changing world. Since its founding in 1984, Watson has pursued a growth strategy combining internal product development, strategic alliances and collaborations, and synergistic acquisitions of products and businesses. Watson is uniquely positioned with its infrastructure and internal research and development capabilities to support its three divisions: U.S. Generic, Brand, and Anda Distribution.

Watson has adhered to a three-pronged strategy for growth: internal product development, strategic alliances, and select product acquisitions. The company will continue to grow through the understanding and capitalization of key market trends. As it expands its branded and generic businesses, successful business development deals will continue to be a key component of its success and strategy.

Who Needs Motivation? The New Obviousness Standard in Patents

By: Clifford M. Davidson, Esq. (Davidson, Davidson & Kappel, LLC)

Most individuals reading this publication are well-versed in at least the basic concepts of the standard for patentability in the US. Very basically, in order to obtain a patent, the claimed invention must be considered new, useful, and unobvious. The consideration as to whether something is new (novelty) involves, eg, whether there is one piece of prior art, be it an earlier patent, earlier publication, or earlier use that discloses all of the claimed features of the invention in question. This article addresses the standards for determining obviousness, and how those standards may have been affected by a recent Supreme Court decision.

THE BASICS

Obviousness is a legal conclusion based on the factual inquiries set forth in *Graham v. John Deere Co.*, 383 US 1, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966): (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, if any, of nonobviousness. See *McNeil-PPC, Inc., v. L. Perrigo Company*, 337 F.3d 1362 (Fed. Cir. 2003). A court must also consider any secondary indicators of non-obviousness that are asserted by the applicants, including (1) commercial success; (2) unexpected results; (3) long felt but unsolved need; and (4) failure of others. See *Graham v. John Deere Co. of Kansas City*, 303 US 1, 17-18 (1966).

Typically, a determination of obviousness by a patent examiner or a court is not based on one piece of prior art. Rather, such a determination is based on a combination of prior art (eg, two or more earlier patents/publications). One of the classic arguments that patent practitioners have used to argue in favor of patentability when faced with a combination of two or more prior art references concerns a lack of motivation to combine: that is, a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person having ordinary skill in the art reveals some motivation or suggestion to combine the prior art teachings. Thus, an argument for patentability based on "a lack of motivation to combine the teachings of these references" is found quite often in the file histories of US patents. The argument follows that without such motivation to combine the teachings of those references, a person having ordinary skill in the art would simply not recognize the benefits of combining such teachings. For example, if the prior art references that are to be combined are directed at solving different problems, it is often argued that one of ordinary skill in the art seeking to solve the problem addressed by the claimed invention would not be motivated to prior art directed at solving a *different problem*. Or, if each reference solves the problem addressed in the claimed invention in a *different way*, there might be no motivation to combine such disparate work to solve the problem. As another example, it is often argued that the two references that the examiner seeks to combine are in entirely *different scientific fields*; and so there would be a lack of motivation for the person having ordinary skill in the art to look outside that art for a solution to the problem.

Until now, the law was reasonably clear: "[i]t is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion in the prior art, to combine the elements." See *Ruiz v. AB Chance Co.*, 234 F.3d 654 (Fed. Cir. 2000) quoting *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953 (Fed. Cir. 1997). This rule has sometimes been referred to as the "TSM" test (teaching, suggestion, or motivation). The suggestion or motivation could be explicit or implicit. See *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120 (Fed. Cir. 2000) "the suggestion to combine need not be express, and may come from the prior art, as filtered through the knowledge of one skilled in the art." In other words, the suggestion to combine the disclosures of two or more prior art references in order to establish prima facie obviousness required some suggestion for doing so, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Jones, 958

F.2d 347, 351 (Fed., Cir. 1992).

Have these seemingly well-settled rules for determinations of obviousness/nonobviousness now been eliminated by the Supreme Court? In its recent decision in *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727 (April 30, 2007), the Supreme Court sent shockwaves throughout the patent community, and indeed throughout the scientific community with its holding that the Federal Circuit (which hears all appeals from patent litigations) had been applying a flawed analysis with respect to the obviousness inquiry. The Supreme Court, in reversing a Federal Circuit decision which employed the TSM test to uphold a patent, held that the Federal Circuit "addressed the obviousness question in a narrow, rigid manner that is inconsistent with §103 and this Court's precedents."

THE KSR DECISION

In *KSR*, Teleflex sued KSR for infringement of its US Patent No. 6,236,565 entitled "Adjustable Pedal Assembly With Electronic Throttle Control." The patent litigation involved an adjustable mechanical pedal that KSR developed for Ford, for which KSR added a modular sensor. Teleflex, a rival to KSR in the design and manufacture of adjustable pedals, asserted the '565 patent against KSR. Claim 4 of the '565 patent, which was at issue, claimed a vehicle-controlled pedal apparatus. It includes a pivot for pivotally supporting an adjustable pedal assembly, and an electronic sensor responsive to the pivot for providing a signal that corresponds to pedal arm position. The position of the pivot remains constant. The electronic sensor transmits the position of the pedal to a computer that controls the engine throttle.

There was a robust amount of prior art involved in the obviousness consideration. The prior art included an accelerator pedal that interacts with the throttle via a mechanical link; computer-controlled throttles that open and close valves in response to electronic signals rather than through movement of the pedal; pedals that could be adjusted to change their location in the footwell (for different-size drivers); a patent (Asano) that described a support structure that housed the pedal such that even when the pedal is adjusted relative to the driver, one of the pedal's pivot point stays fixed; a patent (Redding) that describes a different, sliding mechanism where both the pedal and the pivot point are adjusted; a patent that taught that it was preferable to detect the pedal's position in the pedal assembly, not in the engine (and described a pedal with an electronic sensor on a pivot point in the electronic assembly); and finally a patent (Smith) that taught that the sensor should be put on a fixed part of the pedal assembly. In addition, the prior art included patents for self-contained modular sensors to be taken off the shelf and attached to mechanical pedals, and patents that describe placement of sensors on adjustable pedals.

The District Court granted summary judgment in KSR's favor. Following *Graham's* direction, the Court found that the Asano patent taught everything contained in Claim 4 except the use of a sensor to detect the pedal's position, which the Court recognized was taught in patents describing self-contained modular sensors. The District Court determined that the level of ordinary skill in pedal design was an undergraduate degree in mechanical engineering or equivalent experience. The District Court then applied the TSM test and reasoned that the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals; that the prior art patents regarding the placement of sensors on adjustable pedals provided the basis for such developments; and finally that the Smith patent taught locating the sensors on the fixed structure of the pedal. The District Court was further swayed by the fact that the USPTO had not had the opportunity to consider the Asano patent in its patentability determination.

Relying mainly on the TSM test, the Federal Circuit reversed the District Court's decision. It held that unless the "prior art references address[ed] the precise problem that the patentee was trying to solve" the problem would not motivate an inventor to look at these other references (119 Fed. Appx. at 288). The Federal Circuit found that the Asano pedal was designed to solve a "constant ratio problem" whereas the asserted '565 patent sought to provide a simpler adjustable electronic pedal. In similar fashion, the Federal Circuit found that the other prior art patents did not necessarily go to the issue of motivation to attach electronic control on the support bracket of a pedal assembly. When viewed in this manner, the Federal Circuit determined that such prior art would not have led a person of ordinary skill to put a sensor on the sort of pedal described in Asano, and therefore did not render the '565 patent obvious.

The case was appealed to the Supreme Court, which began by rejecting the "rigid" approach of the Federal Circuit. The Decision addressed the Supreme Court's prior decisions concerning obviousness, including *Graham:*

"The principles underlying these cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her

skill…Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue …As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."

While noting that the TSM test is not necessarily inconsistent with the Graham analysis, the Supreme Court wrote a fairly scathing opinion concerning errors in the nonobviousness analysis made by the Federal Circuit. It stated that the Federal Circuit was in error by holding that courts and patent examiners should look only to the problem the patentee was trying to solve in order to determine whether there was motivation to combine. Under the correct analysis, any problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

Second, the Supreme Court found error in the Federal Circuit's assumption that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem.

The Supreme Court then found error with respect to the Federal Circuit's hindsight analysis. It determined that the Federal Circuit found, in error, that a patent claim cannot be proved obvious by merely showing that the combination of elements was "obvious to try." It reasoned that when there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under §103. Thus, while noting that the fact-finders should be aware of the improper use of hindsight, the Supreme Court determined that the "obvious to try" standard nonobviousness was not always correct.

Finally, the Supreme Court noted that after it had made its incorrect decision in KSR, the Federal Circuit had made further decisions that appeared to be more consistent with the Supreme Court's earlier precedents. Those cases required the use of "common knowledge and common sense" in the TSM test, and found that motivation could be found implicitly in the prior art.

WHERE DO WE GO FROM HERE?

There are many messages that might be taken from the Supreme Court's decision in KSR. It is impossible to predict how this decision will affect the future. Does the KSR Decision mean that all previously granted patents in which the combination of prior art was overcome by an argument/determination that there was a lack of motivation (to combine the references) should now be considered invalid? Certainly, given the popularity of the TSM test, that would throw a huge amount of uncertainty into the marketplace. Nevertheless, the KSR Decision does indeed make suspect all patent claims granted by virtue of a "rigid" TSM consideration.

The underlying theme throughout the KSR Decision is the invocation of terms "common knowledge" and "common sense." The Supreme Court was clearly annoyed at the application a rigid test that would not take into account a common sense analysis of combining elements used in the same field, albeit for overcoming different problems.

Another disturbing feature of KSR to future cases is the Supreme Court's statements concerning the "obvious to try" standard. It now appears that the obvious to try standard is indeed permissible as long as it would be obvious to one of ordinary skill in the art using their common knowledge or common sense.

How does this effect pharma? There are important differences between the inventiveness considered in KSR as opposed to pharma. First, mechanical inventions, such as that in KSR, are predictable. It is often the case that inventions in the world of pharma are much less predictable. Likewise, the level of skill of the person of ordinary skill in the art in KSR is well below that typically found in pharma. But does a higher-educated formulator have "more" common knowledge or common sense? Can that higher-educated person apply solutions from more fields than his counterpart in the mechanical arts? Will litigants now have to provide evidence not only directed at what level of education/experience one skilled in the art of the invention is, but also what their common knowledge is? How does one determine what the level of common sense in the art is?

While the long-term effects are not yet known, we can at least speak to the present. Already, the Federal Circuit has quoted the KSR mantra of a lack of a rigid formula for determining obviousness, and the use of common sense of those skilled in the art to demonstrate why some combinations would have been obvious where others would not. See, eg, *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc. and Mattel, Inc.*, ---F.3d--- (Fed. Cir. 2007). ◆

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

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FORMULATION FORUM

Discussing Gastro Retentive Drug Delivery Systems

By: Cindy H. Dubin, Contributor

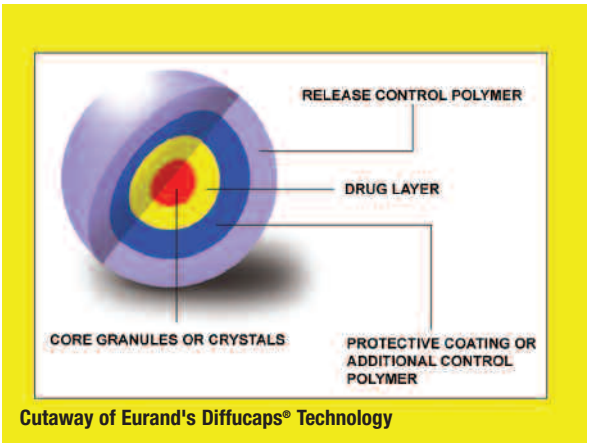
Despite advances made in sustained delivery drug delivery technologies in recent years, a problem still persists in trying to obtain controlled release of a wide variety of medications that have only a narrow absorption window in the upper part of the intestines. That is, these drugs are absorbed rather quickly after being swallowed, negating the beneficial effects of once-a-day medication.

Although oral delivery remains the preferred route of administration of therapeutic agents because of low cost of therapy and ease of administration that leads to high levels of patient compliance, the issue of bioavailability of orally administered drugs is challenging. According to research conducted by Ms. Julan U. Desai, Lecturer, Department of Pharmaceutics, at Anand Pharmacy College, conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. The *de novo* design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability (BA) of drugs.

A major constraint in oral CRDD is that not all drug candidates are absorbed uniformly throughout the gastrointestinal (GI) tract. Some drugs are absorbed in a particular portion of the GI tract only or are absorbed to a different extent in various segments of the GI tract. Such drugs are said to have an "absorption window," thus, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released drug goes to waste with negligible or no absorption, which significantly decreases the time available for drug absorption and limits the success of the delivery system. This has led to the development of gastric retention.

In her research, Ms. Desai writes that one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT) using gastroretentive dosage forms (GRDFs), which offer a new and better option for drug therapy. Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS) and may improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability.

FIGURE 1



Cutaway of Eurand's Diffucaps® Technology

APPROACHES TO GRDDS

To achieve gastro retention, the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying, and once the purpose has been served, it should be removed from the stomach with ease. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems, high-density systems, floating systems, and modified systems.

Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric-emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the residual system is emptied from the stomach. FDDS must comply with the following criteria:

- Have a sufficient structure to form a cohesive gel barrier.
- Maintain an overall specific gravity lower than that of gastric contents.
- Dissolve slowly enough to serve as a drug reservoir.
- Based on the mechanism of buoyancy, two technologies have been utilized in the development of FDDS: noneffervescent and effervescent systems.

One of the approaches to the noneffervescent formulation floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density within the outer gelatinous barrier, explains Ms. Desai. The air trapped by the swollen

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polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release because the drug is slowly released by a controlled diffusion through the gelatinous barrier.

Effervescent FDDS utilize matrices prepared with swellable polymers, such as Methocel® or polysaccharides (eg, Chitosan) and effervescent components (eg, sodium bicarbonate and citric or tartaric acid), or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form to float on the chyme.

FDDS require a sufficiently high level of fluids in the stomach for the drug delivery buoyancy, to float and to work efficiently. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluid. Also, there are limitations to the applicability of FDDS for drugs that irritate the gastric mucosa.

Drug Layering

Eurand's Diffucaps® technology is a multiparticulate system that provides optimum release profiles for single or combination drugs. Drug-release profiles are created by layering active drug onto a neutral core, such as sugar spheres, crystals, or granules followed by a rate-controlling, functional membrane. The Diffucaps system allow for the combination of different types of release profiles into one dosage form. According to Troy Harmon, Vice President of Business Development at Eurand, his company can customize any combination of sustained-release, pulsatile-release, and immediate-release profiles, depending on the specific needs of the product. Mr. Harmon points out that Diffucaps is not a true GRDDS, but it does accomplish what such delivery systems set out to do: address the issue of solubility by allowing the drug to be absorbed in the lower GI tract.

Eurand recently developed a sustained-release formulation of the decongestant Pseudoephedrine using Diffucaps. The sustained-release profile used in this product allows for 12-hour decongestant relief, which eliminates the need for multiple doses throughout the day. Additionally, this product can be combined with once-a-day antihistamine products for more complete treatment of allergy symptoms. Eurand's Diffucaps Pseudoephedrine is currently being marketed by partners throughout the world as a decongestant and in combination with various antihistamines, including in UCB's Cirrus® in combination with Citrizine and in Almirall's Rinoebastel® in combination with Ebastine.

Polymeric Systems

According to Dr. Michel Afargan, Chief Scientific Officer at IntecPharma, the main challenges with GR (Gastric Retention) are related to the following:

- The extent of gastric retention. An effective GR system should exhibit a retention of at least 6 hours in the stomach. This system must be able to overcome the physiological gastric emptying of the stomach.

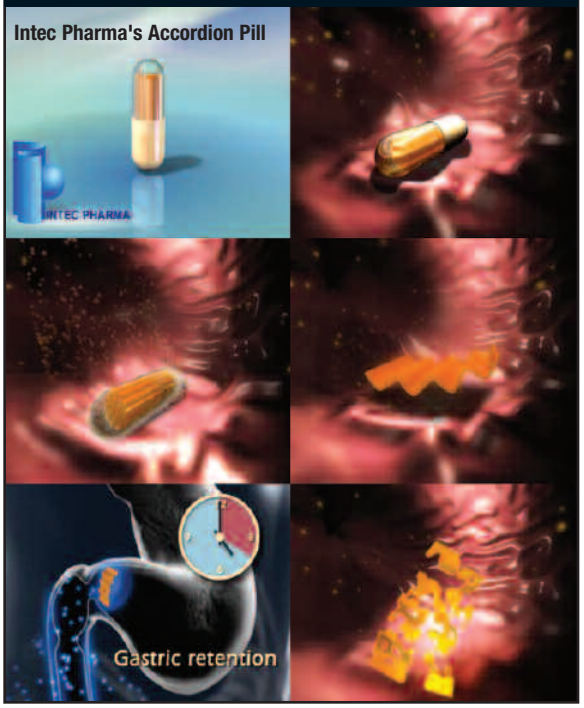
- Food effects. Obtaining the aforementioned GR profile even with or after low calorie meal. One should remember that food increases gastric retention while under fast conditions, the GR is poor due to the "housekeeping wave." Safety issues are a concern. The GR dosage form should not interfere with the physiological gastric emptying of food.

- GR control. The duration of GR (the aforementioned 6 hours) should be controlled in an optimized manner, for each drug, in order to obtain synchronized drug release during GR. Some specific challenges, all related to the GR control, include the following:

  - Gastric pH. A GR dosage form should be robust (intact and stable) to pH fluctuations. The gastric pH under fast condition is about 1 to 2, while under fed conditions, is about 3 to 4 (following the meal).

  - Physical properties. The mechanical properties and integrity of the dosage form should enable prolonged stability in the stomach during GR.

FIGURE 2



  - Elimination. The dosage form should be eliminated following its retention in the stomach, ie, biodegradability in the intestines.

- The incorporated API. Because the drug should be stable under acidic pH, some modifications of the drug are sometimes required. The GR should enable a significant increase in absolute bioavailability of narrow absorption drugs. The prolonged drug release should be well controlled in order to prevent possible dose dumping. A combination of immediate- and slow-release profiles may be sometimes crucial, especially for most CNS drugs. Drugs that may affect gastric emptying, such as prokinetics, may reduce the GR of the dosage form.

Dr. Afargan says that the company's Accordion Pill addresses all of the aforementioned. For instance, the Pill exhibits (using different imaging methods in humans) gastric retention of more than 6 hours. It has exhibited prolonged GR even with a low calorie meal, and Intec has demonstrated that following a single dose of the Accordion Pill under fed conditions, there was no interference with the physiological gastric emptying of food.

The Accordion Pill action/deployment in the stomach is not affected by pH. The planar geometry and mechanical properties of the Accordion Pill enable its stability under stomach conditions, and the Pill undergoes a complete biodegradation in the intestine following its gastric emptying.

Finally, the Accordion Pill enables a significant increase of absolute bioavailability. The company has conducted a trial with healthy volunteers, demonstrating that the Accordion Pill doubled the absolute bioavailability of Riboflavin, a known marker for narrow absorption window. To date, Intec has developed a combined-release profile of IR followed by SR with a CNS drug – an ongoing clinical development project.

The Accordion Pill is a polymeric system composed of pharmaceutical synthetic and biodegradable polymers. The polymeric system possesses a unique planar geometry that unfolds like an "accordion" into a standard capsule. When the capsule reaches the stomach, it dissolves, and the Accordion Pill then deploys. The drug is then released in a controlled manner from its reservoir, ie, an inner membrane of the Accordion Pill.

Following the gastric retention period (that may be controlled), the system undergoes a complete biodegradation that mainly occurs throughout the intestines.

Dr. Afargan says, "The Accordion Pill is the only known GR system based on a planar and not spherical geometry. Other dosage forms are mainly spherical and are positioned most of the time near the antrum pylori (the gastric-intestinal sphincter). By using gamma imaging and MRI, it was demonstrated that the Accordion Pill moves within the stomach and does not sit in a specific location.

Moreover, the unique mechanical properties of the Accordion Pill enable its elasticity to overcome the contraction stress imposed by the stomach."

Multiparticulate Dosing

Eurand's proprietary Diffucaps technology can be applied to enable formulation of insoluble drugs and to improve the rate and extent of absorption of drugs from oral dosage forms.

Drug insolubility poses significant challenges throughout drug development owing to its impact on the extent and rate of drug absorption into the body, says Mr. Harmon. It can prevent the absorption of therapeutic levels of drug, delay a drug's onset of action, and decrease its therapeutic benefit. These problems can result in patients being given higher and more frequent drug doses, which can result in increased therapy costs, greater likelihood of side effects, and complicated dosing regimens.

Customized drug release profiles are created by first layering active drug onto a neutral core (such as cellulose spheres) followed by the application of one or more rate-controlling, functional membranes. The drug-layering process can be conducted either from aqueous- or solvent-based drug solutions. Eurand has also developed formulation technology that combines the customized drug release offered by Diffucaps with technologies that enhance the solubility of insoluble drugs in the GI tract. Eurand is using this technology to provide a degree of delivery control that goes beyond that of single technology systems.

Diffucaps beads are small in size, approximately 1mm in diameter, and are filled into a capsule to create the final dosage form. Beads of differing drug release profiles can be easily combined in a single capsule providing high levels of control over release profiles. Diffucaps beads of different drugs can be combined to make convenient single dose units for combination therapies.

Thus, the Diffucaps system offers significant flexibility by enabling the combination of different types of release profiles into one dosage form. As a result, Eurand can combine sustained release, pulsatile release and immediate release profiles depending on the specific needs of the product. Also, different dose-proportional strengths of a product can be easily manufactured by filling capsules with varying amounts of the Diffucaps beads.

SUMMARY

Dosage forms with a prolonged GRT will bring about new and important therapeutic options, says Ms. Desai. They will significantly extend the period of time over which drugs may be released and thus prolong dosing intervals and increase patient compliance beyond the level of existing controlled-release dosage forms. "Many of the "once-a-day" formulations will be replaced by products with release and absorption phases of approximately 24 hours," says Ms. Desai. "GRDFs will be used as carriers of drugs with the "absorption window."

According to Intec's Zeev Weiss, Executive Vice President, Commercial Operations, the GR market is going to face a significant progression within the next years. "We have to remember that GR, under a low calorie meal, was considered as an unmet need, which many pharma and drug delivery companies have tried to address, for many years. Yet, those many failures with this respect have blocked a wide use of GR, and pharma companies were forced to find other solutions that were not always sufficient. Now that GR under a low calorie meal is possible, we witness, through our wide interactions with pharma companies, that GR is considered not only for the traditional drugs known to suffer from a narrow absorption window, but for completely new directions. I truly believe that within a few years, GR will be heavily used as an enhancement technology for the treatment of various GI disorders, such as obesity, IBS, and GERD. Moreover, GR will be widely used to overcome ADR of current drugs and as an enablement technology to obtain new indications for existing drugs." ◆

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.

A Novel Electronic Nebulizer for AAT Patients

By: Shabtai Bauer, PhD, and Markus Tservistas, PhD

Inhaling Alpha-1 Antitrypsin (AAT) using an optimized configuration of the eFlow® Electronic Nebulizer may result in significantly shorter treatment times and the potential to reduce drug dose. As sufficient AAT permeation to the lung tissue can be ensured and biological activity maintained, inhalation may become a new, efficient, cost-effective, and patient-friendly therapeutic alternative for treating patients with AAT deficiency who are currently being treated by the intravenous route on a weekly basis.

ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 Antitrypsin deficiency is a hereditary condition that increases the risk of chronic obstructive pulmonary disease (COPD), mainly emphysema and chronic bronchitis. AAT deficient adults suffering from these indications face progressive loss of lung function that can significantly impact everyday quality of life and life expectancy. AAT deficiency is mostly caused by inheritance of two pairs of the so-called Z allele. Based on the gene frequency of the Z allele, it is estimated that there are at least 100,000 Z allele homozygote individuals in the US. Currently, only about 6,000 of these individuals have been identified.

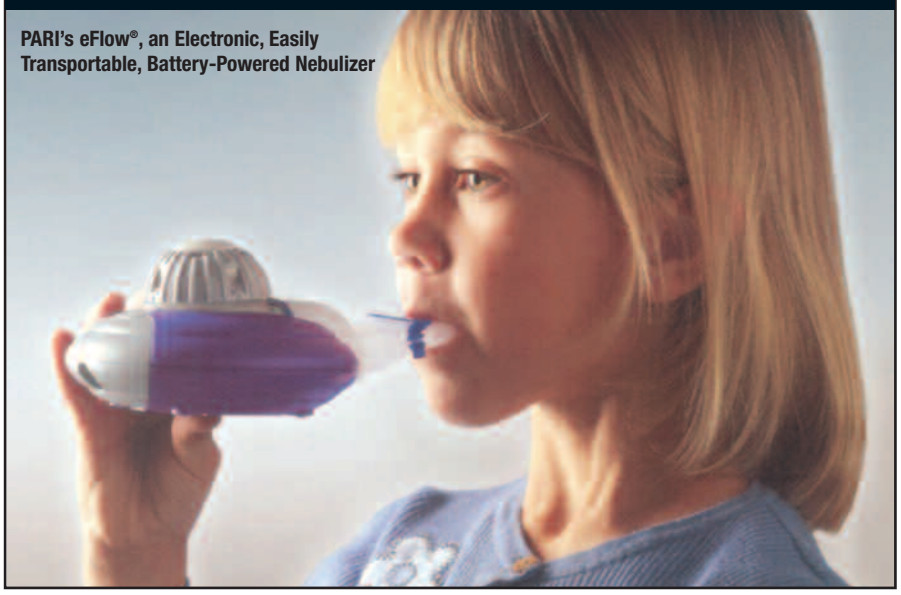
Emphysema is a lung disease caused by the destruction of the delicate walls of small air sacs (alveoli). With this destruction, air sacs lose their elasticity and form larger, inefficient sacs that cannot function properly. Eventually, it becomes more difficult to breathe because each breath inflates the lungs, but the lungs do not return to normal with the exhaled breath. This causes air to become trapped in the air sacs, leading to hyperinflation of the lungs. Emphysema caused by AAT deficiency is a progressive disease. The destructive action continues until the lungs can no longer exchange oxygen and carbon dioxide with the bloodstream. Recent studies indicate that patients with AAT deficiency also suffer from chronic bronchial inflammation that further aggravates their condition by leading to frequent exacerbations resulting in sharp deterioration in the patient's lung function, hospitalization, and in some cases, death.

Symptoms of AAT deficiency include shortness of breath on exertion, wheezing, and cough. Because wheezing and shortness of breath are common symptoms, AAT deficiency is often misdiagnosed as other chronic pulmonary diseases, such as COPD or asthma.

Alpha-1 antitrypsin is a protein that protects the delicate tissues of the lungs by inhibiting the destructive action of an enzyme called neutrophil elastase. Neutrophil elastase is released by white blood cells, and its primary function is to digest bacteria and other foreign objects in the lungs. When a person who is deficient of AAT inhales irritants or contracts a lung infection, the neutrophil elastase released in the lungs continues acting without control, leading to destruction of healthy lung tissue. The eventual result of the damage of healthy lung tissue by neutrophil elastase is emphysema severity, which progresses the disease if not treated.

Emphysema caused by Alpha-1 Antitrypsin deficiency (also known as "genetic" or "inherited" emphysema) is different from emphysema caused by smoking ("acquired" emphysema). In emphysema caused by smoking, the damage usually affects the upper portion of the lungs while in the AAT deficient patient, the lower regions of the lungs are first affected. Nonetheless, emphysema develops eventually throughout the entire lung surface. In either case, the lungs are hyperinflated due to air trapping caused by the destruction of the lung tissue, and the diaphragm is flattened due to the

FIGURE 1



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hyperinflation of the lungs.

Emphysema caused by AAT deficiency usually causes symptoms in people while they are in their 30s or 40s. As discussed, many of these patients also have chronic bronchitis. With this, the lung lining becomes swollen and congested with mucus, restricting air flow. The bronchi often go into bronchospasm in which muscles contract, further reducing air flow. This often results in a chronic cough.

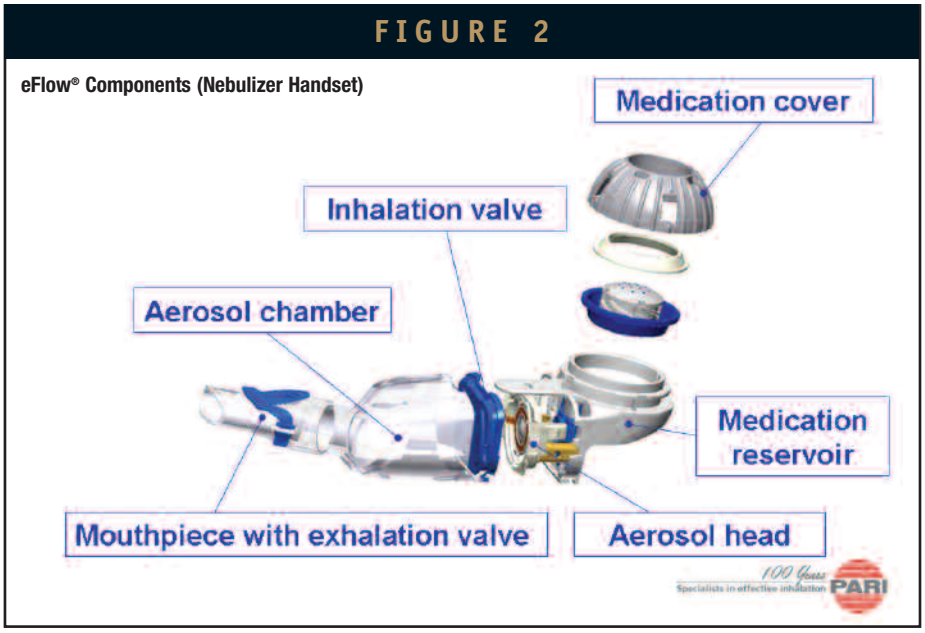
TESTING FOR AAT DEFICIENCY

The guidelines of the American Thoracic Society and the European Respiratory Society strongly recommend testing for AAT deficiency in individuals with chronic airway obstruction. They also recommend testing of family members of AAT-deficient individuals. Although it is simple and painless to detect alpha-1 deficiency, it is unfortunate to say that testing for AAT deficiency is rarely performed, despite the fact that it is a major known genetic risk factor and the fourth leading cause of death in the US, and intervention may substantially improve the lives of many patients and families. This is due to healthcare providers not following testing guidelines for this common genetic condition.

One reason for this may be the fact that recommendations that advocate Z allele identification over AAT concentration assays have been slow in forthcoming. There are likely more general reasons for not following the recommendation of these societies, including the lack of training in genetic diseases, leading to lack of disease awareness.

These deficiencies in training are currently being addressed by training oversight committees. Additionally, new online resources, such as GeneReviews funded by the NIH, are now available to healthcare providers. As these tools find their way into medical practice, there should be a more rapid incorporation of genetics in general clinical medicine.

FIGURE 2



DELIVERING AAT VIA eFLOW®

AAT is currently used for replacement therapy in the form of weekly intravenous infusion that distributes the medication throughout the bloodstream in order to supply AAT to the lungs. An inhaled treatment would offer a more targeted therapy by delivering medication directly to the lungs and avert patient discomfort by avoiding the weekly and time-consuming intravenous infusion of the drug.

eFlow, an electronic, easily transportable, battery-powered nebulizer weighing less than 300 g (9.3 oz), enables extremely efficient aerosolization of liquid medications via a vibrating, perforated membrane. Compared to other nebulizer systems, eFlow can produce aerosols with a very high density of active drug, a precisely defined droplet size, and a high proportion of respirable droplets delivered in the shortest possible period of time. Combined with its silent mode of operation, small size (it fits in the palm of your hand), light weight, and battery use, eFlow helps reduce the burden of daily inhalation treatments.

This past January, PARI's eFlow was awarded the 2006 Good Design Award for medical equipment by The Chicago Athenaeum: Museum of Architecture and Design. This was the second design award eFlow has won to date, following the Medical Design Excellence Award granted in April 2006.

ADAPTING THE eFLOW® NEBULIZER

Emphysema patients show a specific breathing pattern characterized by a relatively short inhalation cycle followed by a prolonged exhalation. A typical breathing pattern consists of, for example, a tidal volume of 450 ml, 17 breaths/min, and an inspiration/expiration ratio of 1:2.5.

Current augmentation therapy uses intravenous AAT application in doses of about 60 to 90 mg/kg body weight (about 4 to 7 g total dose) given once weekly. This treatment regime is burdensome, lasts for a long time, and only about 2% of the dose is estimated to reach the target tissue of the lungs.[1] Because availability of AAT derived from pooled

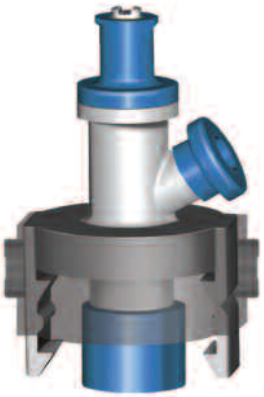


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FIGURE 3

Kamada's AAT IV Drug

human serum is limited and purification is expensive, resulting in high drug costs, administration via inhalation using a nebulizer is regarded as a more economic and less-burdensome alternative.

MATERIALS & METHODS

An eFlow electronic nebulizer in different configurations (PARI Pharma GmbH, Munich, Germany) was used to nebulize a highly purified 2% human, liquid, ready-to-use AAT preparation (Kamada Ltd, Ness Ziona, Israel). Geometric aerosol droplet size distribution was determined by laser diffraction (LD) utilizing a Malvern MasterSizerX device (Malvern, Herrenberg, Germany).

Aerosol delivery efficiency was determined by breath simulation using the emphysema breathing pattern (tidal volume 450 ml, 17 breaths/min, and an inhalation/exhalation ratio of 1:2.5) generated by a PARI Compas™ breath simulator. As a reference, a standardized regular breathing pattern (tidal volume 500 ml, 15 breaths/min, inhalation/exhalation ratio of 1:1) was also investigated. Samples were analyzed for protein content by UV analysis at 280 nm. Nebulization time was determined by an electronic shut-off of the eFlow upon nebulization of the contents of the medication cup.

The drug remaining in the eFlow device is reflected by the Drug Residue. The in vitro Delivered Dose (DD) and Aerosol Losses correspond to the drug collected on and assayed from inhalation and exhalation filters, respectively. The in vitro Respirable Dose (RD) was calculated by multiplying DD with the Respirable Fraction (% mass in droplets < 5 µm) obtained from LD data. The in vitro data shows high delivered doses, even when breathing patterns of patients with impaired breathing capabilities are mimicked.[1]

In a previous study, it has been shown that no degradation of the AAT occurs, and activity is retained at higher than 90% using the eFlow vibrating membrane technology.[2]

The inhaled AAT was designated, both in Europe and in the US, as an orphan drug for the treatment of congenital emphysema and cystic fibrosis. Therefore, should PARI and Kamada be the first to successfully complete the clinical trials and obtain the regulatory authorities' approval, they will be entitled to the rights and enjoy the benefits ancillary to the orphan drug status, including exclusive marketing rights (7 years in the US and 10 years in Europe, as the case may be), research funds support, tax benefits for research purposes, and reduced fees to the FDA and the EMEA. Phases II to III of clinical development of the inhaled API with PARI's eFlow are planned to start during 2008. ◆

REFERENCES

1. Hubbard RC, Crystal RG. Strategies for aerosol therapy of alpha-1 antitrypsin deficiency by the aerosol route. Lung. 1990;168(Suppl):565-578.
2. Keller M, Tservistas M, Bitterle E, Bauer S. Aerosol characterization of alpha-1 antitrypsin after nebulization with the eFlow, a novel vibrating perforated membrane nebulizer. Proceedings Respiratory Drug Delivery X, Boca Raton, Florida;2006:729-732.

BIOGRAPHIES

Dr. Shabtai Bauer earned his MSc in Biochemistry and his PhD in Enzymology from the Hebrew University of Jerusalem. He was a Senior Researcher in the Department of Biological Chemistry, and Chief of the Biotechnology Unit, both at the Hebrew University of Jerusalem. In addition, he was a visiting scientist in the Department of Biology of the Brookhaven National Laboratory, New York. He has been with Kamada, formerly RAD Chemicals, since 1985. Dr. Bauer's activities encompass over 35 years of professional research and consultancy activities, and he authored more than 40 publications in Israel and abroad.

Dr. Markus Tservistas studied chemistry at the University of Hanover, Germany, where he also completed his PhD on the subject of enzymatic reactions in supercritical fluids. From 1997 to 2000, he worked as a Post-doctoral Research Fellow at the University College in London, UK, on a project studying the application of supercritical fluids for the production of drug powders for inhalation. Following this, he took up an R&D position at Vectura Ltd. in Bath, developing powder formulations for pulmonary drug delivery by dry powder inhalers. He returned to Germany in 2003, where he is now working with PARI Pharma, Munich, in the field of nebulization of liquid formulations for inhalation.

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High Molecular Weight Povidone Polymer-Based Films for Fast-Dissolving Drug Delivery Applications

By: Shaukat Ali, PhD, and Anisul Quadir, PhD, MBA

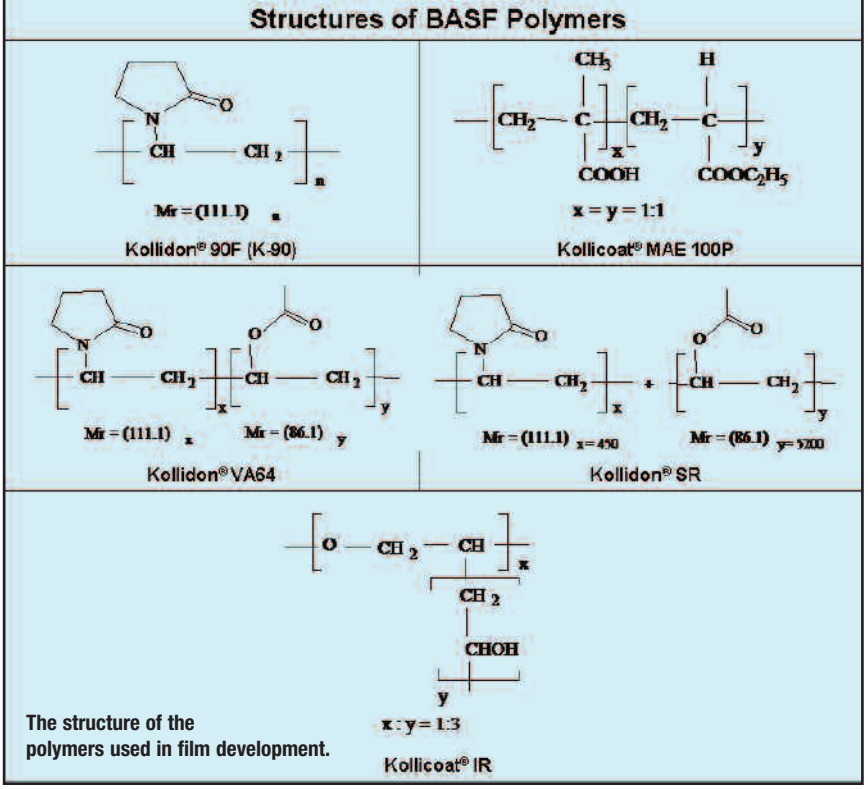
The purpose of this study was to examine high molecular weight povidone K-90 (Kollidon® 90F) polymer as a film-forming excipient for use in the development of a fast-dissolved intraoral drug delivery system. K-90 was evaluated in combination with Copovidone (Kollidon VA64), povidone K-30 polymer (Kollidon 30), polyvinyl acetate-based Kollidon SR polymer, polyvinyl alcohol polyethylene-grafted Kollicoat® IR copolymer, and acrylate-based Kollicoat MAE 100P copolymer for its ability to form flexible, elongated, fast-dissolving films suitable for delivery of highly potent drugs and vitamins.

INTRODUCTION

Life-cycle management has been a subject of continued interest as pharmaceutical companies endeavor to find new and innovative drug delivery systems that are convenient for patients and compliant with various regulations.[1-3] As a result, fast-dissolving film technology has gained attention for efficient delivery of poorly water-soluble and permeable drugs.[4]

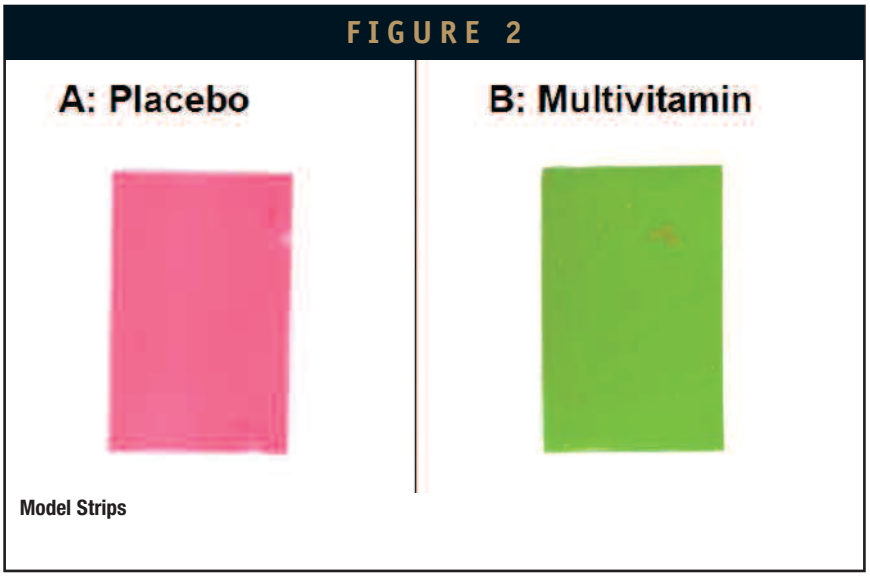
Intraoral films have been a continued focus for delivery devices, such as sublingual fast-dissolving systems, because they have the ability to deliver potent drugs effectively, and with taste-masking effects. Fast-

FIGURE 1



The structure of the polymers used in film development.

FIGURE 2



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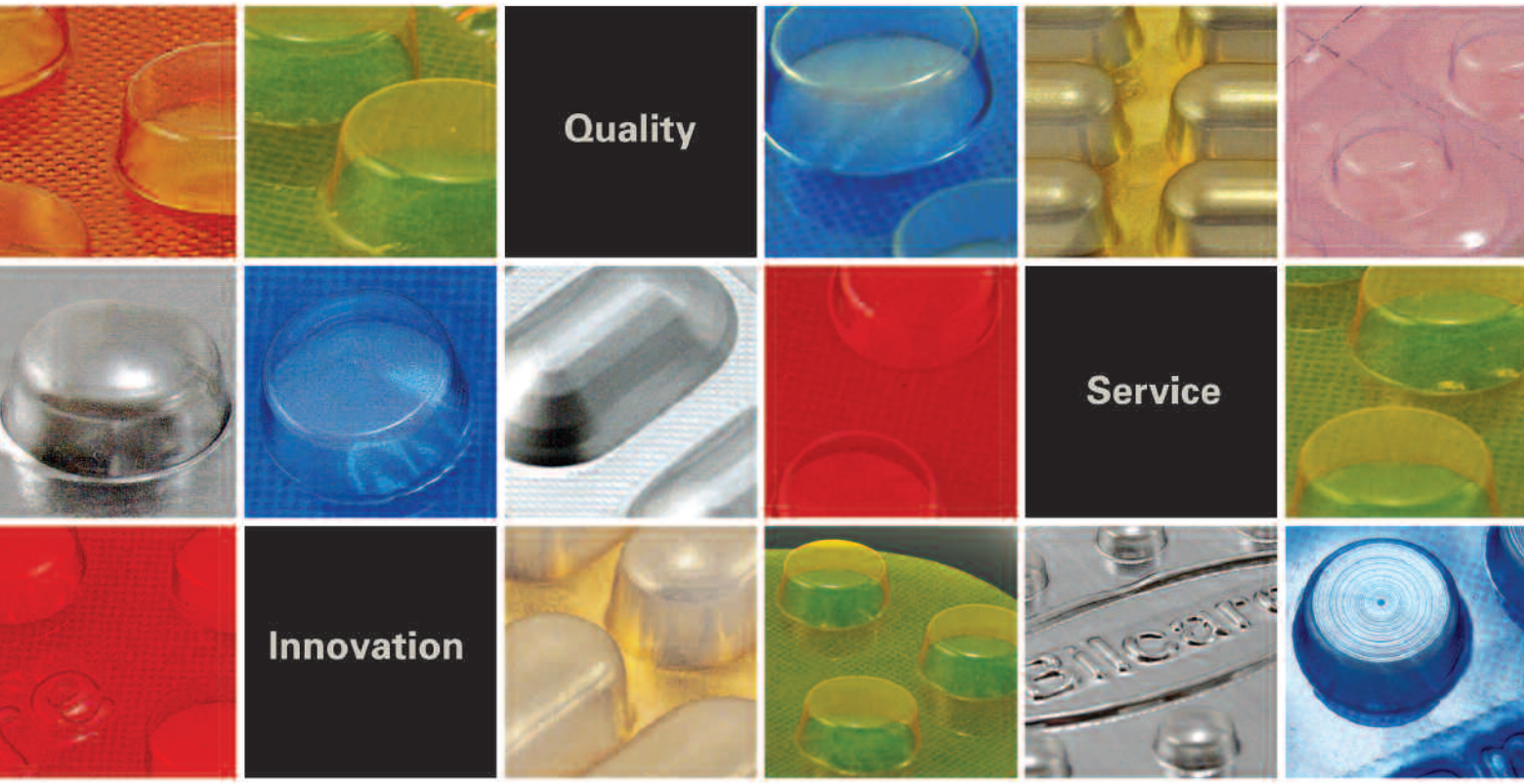

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dissolving strips of Listerine®, Chloraseptic®, Triaminic®, and several other drugs have been launched to alleviate or avoid the dosage-related compliances.

Vitamins and multivitamins have been a subject of recent interest in the development of intraoral strips for children. A number of the multivitamins strips have been launched recently in multiple flavors, including Barbie®, Arthur®, and other brand name flavored strips. Thus, a continued interest in multivitamin and other kinds of strips has extended opportunities to find carriers for safe and effective delivery of the actives.

Cellulose-based polymers have often been used as the carriers in the films. In this paper, we demonstrate that high molecular weight povidone (PVP), for example, Kollidon 90, can be used as a carrier in fast-dissolving films because of its strong hydrophilicity and compatibility with a wide array of polymers and copolymers. Kollidon VA64 in K-90 has been evaluated to demonstrate that the copovidone can be used as an auxiliary excipient in the development of fast-dissolving multivitamin strips.

MATERIALS

Water-soluble and fat-soluble vitamins were obtained from BASF's Human Nutrition business. Kollidon 90F, Kollidon VA64, Kollidon SR, Kollicoat IR, and Kollicoat MAE 100P polymers, and Cremophor® RH 40 are products of BASF Pharma Solutions business. Sucralose was obtained from McNeil Nutrinals (McIntosh, AL). Absolute ethanol (technical grade) and diphenhydramine hydrochloride were obtained from Sigma Aldrich (St. Louis, MO). Viscosity measurements were made at room temperature with a Brookfield DV-II viscometer (Middleboro, MA). The applicator edged with 5 to 50 ml for casting the films was obtained from Gardco, Inc. (Pompano Beach, FL). A Propeller IKA mixer (VWR Scientific; Bridgeport, NJ) and SRT1 roller mixer (Jenkins; Bridgeville, PA) were used to prepare the formulations.

METHODS

The drawdowns of the wet films were made by casting on the release liner, Scotchpak® 1022 (3M, St. Paul, MN). The wet films with 10-, 20-, 30-,

TABLE 1

(A) Kollidon® 90F & Kollidon® SR

Composition	Formulation A		
	I	II	III
	% (w/w)	% (w/w)	% (w/w)
Kollidon® 90F	13.8	12.5	10.8
Kollidon® SR	0.8	1.7	2.8
Ethanol	82.5	80.4	77.6
DI Water	2.4	5.0	8.5
Lutrol® E400	0.5	0.4	0.4
FD&C Red #40	q.s.	q.s.	q.s.
Total	100	100	100

(B) Kollidon® 90F & Kollicoat® IR

Composition	Formulation B		
	I	II	III
	% (w/w)	% (w/w)	% (w/w)
Kollidon® 90F	13.8	12.6	10.8
Kollicoat® IR	0.9	1.6	2.8
Ethanol	80.0	76.7	69.1
DI Water	4.8	8.7	17.0
Lutrol® E400	0.5	0.4	0.4
FD&C Red #40	q.s.	q.s.	q.s.
Total	100	100	100

(C) Kollidon® 90F & Kollicoat® MAE 100P

Composition	Formulation C		
	I	II	III
	% (w/w)	% (w/w)	% (w/w)
Kollidon® 90F	13.6	12.6	10.7
Kollicoat® MAE 100P	0.9	1.6	2.9
Ethanol	82.3	80.5	77.5
DI Water	2.7	4.9	8.6
Lutrol® E400	0.5	0.4	0.4
FD&C Red #40	q.s.	q.s.	q.s.
Total	100	100	100

(D) Kollidon® 90F & Kollidon® VA64

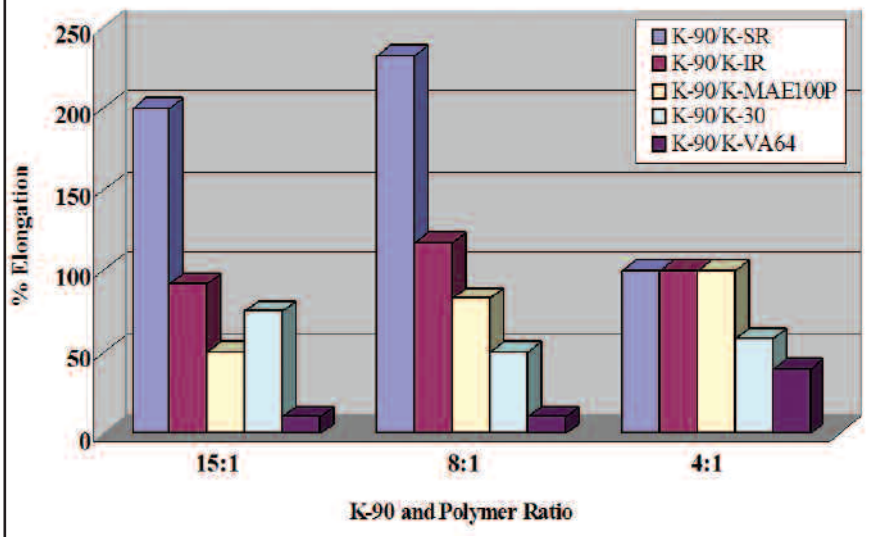
Composition	Formulation D		
	I	II	III
	% (w/w)	% (w/w)	% (w/w)
Kollidon® 90F	13.6	12.5	14.4
Kollidon® VA64	0.9	1.7	4.2
Ethanol	85.0	85.4	81.0
DI Water	0	0	0
Lutrol® E400	0.5	0.4	0.5
FD&C Red #40	q.s.	q.s.	q.s.
Total	100	100	100

(E) Kollidon® 90F & Kollidon® 30

Composition	Formulation E		
	I	II	III
	% (w/w)	% (w/w)	% (w/w)
Kollidon® 90F	13.6	12.5	14.4
Kollidon® 30	0.9	1.7	4.2
Ethanol	85.0	85.4	80.9
DI Water	0	0	0
Lutrol® E400	0.5	0.4	0.5
FD&C Red #40	q.s.	q.s.	q.s.
Total	100	100	100

Formulations (A-E) containing K-90 and other auxiliary polymers.

FIGURE 3



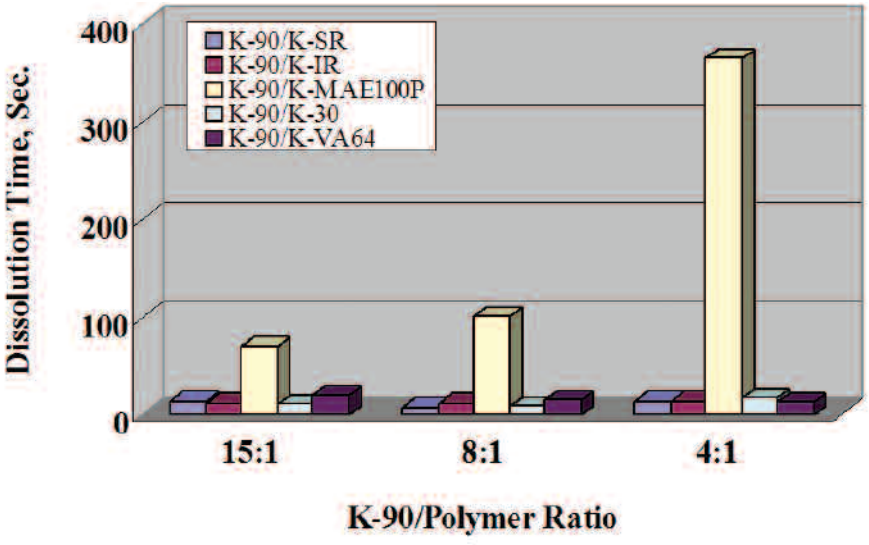
Elongation as a function of polymer composition.

TABLE 2

Vitamin	Amount (wt%)	Target % Daily Value	Amount Per Serving
Vitamin A	0.9	1	50 IU
Vitamin K	0.6	15	12 µg
Vitamin E	5.6	2	0.5 IU
Ascorbic acid (Vit. C)	28.5	10	6 mg
Thiamine HCl (Vit. B1)	3.7	40	0.6 mg
Riboflavin 100 (Vit. B2)	2.9	35	0.6 mg
Niacinamide (Vit. B3)	38.0	40	8 mg
Calcium Pantothenate (Vit. B5)	15.8	30	3 mg
Pyridoxine HCl (Vit. B6)	3.5	30	0.6 mg
Cyanocobalamin (Vit. B12)	0.6	20	1.2 µg
Total	100.0		**23 mg**

Blend of multivitamins prepared based on target % daily dose and required amount per serving.

FIGURE 4



Film dissolution as a function of binary polymer composition.

TABLE 3

Material	Amount Total (g)	Amount Solid (g)	% Solid
Kollidon® 90F	13.7	15.1	67.5
Kollidon® VA64	3.6	4	17.9
Ethanol	76.6	0	0
DI Water	3.2	0	0
Multivitamin	2.1	2.3	10.4
Lutrol E 400	0.5	0.5	2.3
Sucralose	0.2	0.2	0.9
Cremophor® RH40	0.2	0.2	0.9
FD&C Yellow #5	0.02	0.02	0.1
FD&C Blue #1	0.02	0.02	0.1
Total	100	22.4	100

Formulation of multivitamins for strips.

40-, and 50-ml thickness were dried in Blue M (Bluefield, IL) oven at 50°C for 10, 15, 20, 25, and 30 mins, respectively. The dried films were cut with the help of a die board prepared by Bomar Die Co. (Millville, NJ) on a Carver Press (Wabash, IN) to yield strips. The thickness was measured on a Mitutoyo digitmatic indicator (Kawasaki, Japan). The disintegration was carried out in 100-ml aqueous media (DI water) at 25°C to 30°C with a stirring rate of 100 rpm at room temperature. The physical characteristics of the strips such as weight, flexibility, elongation, thickness, and dissolution properties were evaluated as described previously.[5]

FORMULATION PREPARATIONS

Kollidon 90 is a brittle polymer, and to assess the suitability of the excipients in film development, a series of binary formulations were prepared. Each binary formulation (Table 1) contained the high molecular weight povidone (K-90) with approximately 5%, 10%, and 20% (w/w) of an auxiliary polymer component. Lutrol® E 400 was used as plasticizing agent, at 3% (wt/wt) in all formulations. The formulations (A-E) in Table 1 were prepared in ethanol, and unless stated otherwise, the amount of water was kept at the minimum required to dissolve the polymers.

A typical composition of the blend is shown in Table 2. To prepare the blend of 100 g of multivitamins stock, each of the vitamins weighed in at the appropriate amount as required by the target % daily value and were then mixed thoroughly.

The multivitamin formulation was prepared in an 80:20 ratio of K-90 and Kollidon VA64 (Table 3). The multivitamin content was about 10% of the formulation. In addition, the formulation also contained sucralose as a sweetening agent, Cremophor RH40 as a

taste-masking agent, and Lutrol E400 as a plasticizing agent. Table 4 exhibits the viscosity measurement of the placebo (A-E) and the multivitamin formulations.

RESULTS

Formulation Assessment

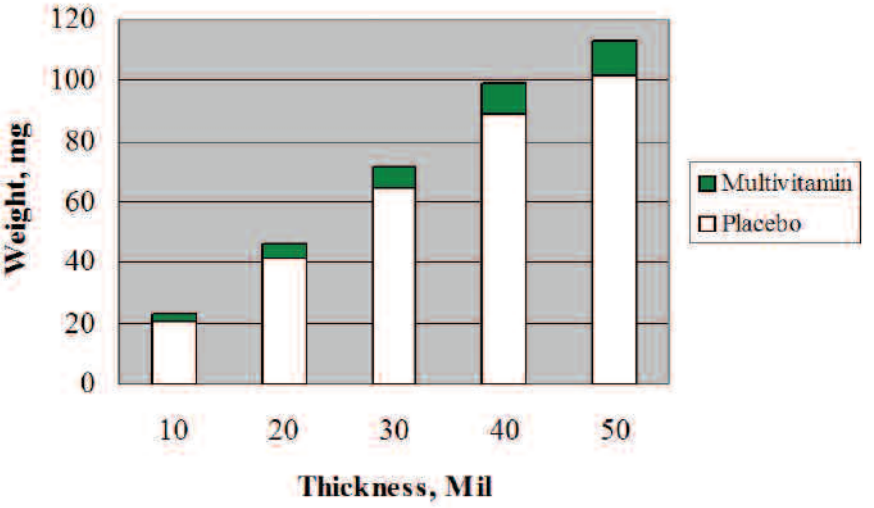
The elongation property of the films composed of K-90 and auxiliary polymers in the approximate ratios of 15:1, 8:1, and 4:1 (A-E) was assessed by stretching the films from both ends as described previously[5] The elongation was estimated (in percentage) from the original distance marked on the films. Figure 3 illustrates the elongation of the films. The data suggests that the films were elongated to approximately 200% with about 5 wt% (15:1) and 10 wt% (8:1) of Kollidon SR in K-90, and were less elongated (around 100%) with about 20 wt% (4:1). This change in elongation was due, in part, to the nature of Kollidon SR, which presumably had a stronger interaction with K-90 at higher composition (4:1). The elongation was significant with Kollicoat IR and Kollicoat MAE 100P, but was not as pronounced as Kollidon SR, and was less pronounced with Kollidon 30 or with Kollidon VA64 at all ratios examined. The K-90 films containing Kollidon VA64 showed relatively less elongation than Kollidon 30 at all compositions investigated.

Figure 4 shows the dissolution profile of the films composed of K-90 and auxiliary polymers. The data suggests that the K-90 film containing Kollicoat MAE 100P showed the maximum dissolution time compared to those containing Kollicoat IR, Kollidon SR, Kollidon 30, or Kollidon VA64. By increasing the amount of Kollicoat MAE100 to 20% (4:1), the dissolution time increased significantly to approximately 6 to 7 mins, presumably attributed due to the acrylic nature of the polymer. It further suggests that lack of pH > 5.5 required for dissolution of methacrylic acid:ethylacrylate copolymer contributed to longer dissolution time. In contrast, K-90 films with Kollicoat IR, Kollidon SR, Kollidon 30, or Kollidon VA64, dissolved in 60 seconds or less at all ratios under the similar conditions.

Kollidon VA64 was selected for its ability to form flexible and elegant films with limited elongation and fast dissolution characteristics. For a prototype formulation, 18 wt% copovidone was used as an auxiliary carrier with K-90 for the delivery of a multivitamin. Figure 5 shows the plot of loading of the multivitamin as a function of thickness. Increasing the weight of the film increased the multivitamin weight gain per strip from the formulation containing 10 wt% of multivitamin.

Figure 6 illustrates that the increase in weight gain was nearly linear with increasing the thickness of the films. For

FIGURE 5



Weight gain as a function of multivitamin and placebo films thickness.

TABLE 4

Formulation	Viscosity (mPas)*		
	I	II	III
A	1250	1130	950
B	1900	2150	2090
C	>5000	>5000	>5000
D	1310	1000	1490
E	1290	1010	1660
Multivitamin (Table 3)	2082		
* Spindle SV4, speed 100 RPM and temp. 23°C			

Viscosity Measurement

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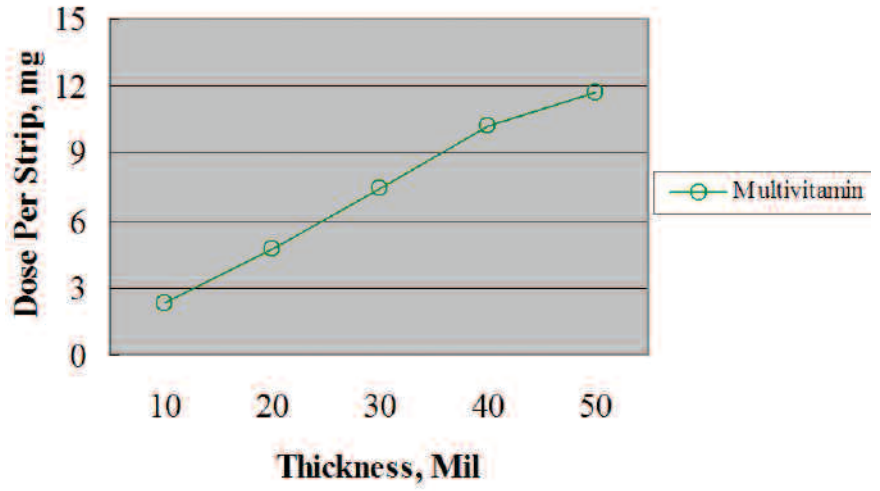
a weight gain of about 12 mg of the multivitamin per strip, the thickness was 50 wet mils (112 microns) from the formulation that contained 10 wt% of multivitamin.

Dissolution properties of the Kollidon 90/Kollidon VA64 films of varied thickness were evaluated, and the results are shown in Figure 7. It is obvious that increasing the film thickness increased the dissolution time. Interestingly, the films dissolved within 60 seconds, suggesting the suitability of the two hydrophilic excipients significantly contributes to the quick dissolution of the multivitamin strips.

DISCUSSION

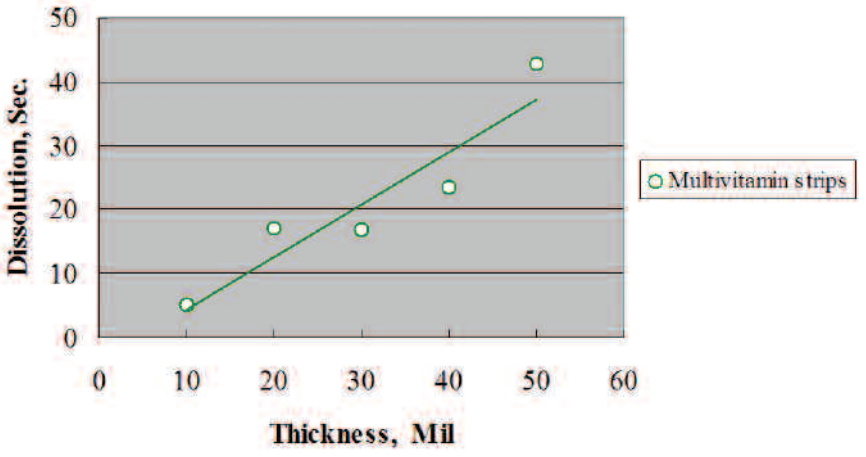
The use of polyvinylpyrrolidone, hydroxyethyl cellulose, and carrageenan as a an auxiliary polymer in combination with microcrystalline cellulose for fast-dissolving consumable films has been reported.[6] Laruelle et al also reported the use of combination of polyvinylpyrrolidone (PVP) and polyvinyl acetate (PVAc) polymers in the development of fast-disintegrating galenic formulations.[7] Other studies also suggest the use of PVP in combination with Eudragit, ethyl cellulose, and/or cellulose acetate in transdermal applications.[8-10]

FIGURE 6



Loading of multivitamin per strip as a function of film thickness.

FIGURE 7



Dissolution of strips as a function of thickness.

The work described in this article demonstrates that high molecular weight povidone can be used in combination with other auxiliary polymers to form fast-dissolving films. The results demonstrate that K-90 films with increasing amounts of polyvinyl acetate and acrylic acid based Kollidon SR and Kollicoat MAE 100P, respectively, showed significant flexibility and elongation. On the other hand, increasing amounts of K-30 or Kollidon VA64 showed good flexibility but limited elongation. This was more pronounced with Kollidon VA64 than K-30. Furthermore, the elongation of K-90 film was nearly two-fold greater with Kollicoat IR than Kollidon VA64 or K-30 at all compositions (Figure 3). Interestingly, all the films were highly hydrophilic and dissolved relatively quickly in 60 seconds or less with the exception of K-90/Kollicoat MAE 100P, which dissolved in 6 to 7 mins (Figure 4). This suggests that an acrylic-based polymer could require a much longer time to dissolve than a hydrophilic polymer.

Multivitamin strips weighing approximately 23 to 113 mg based on a formulation carrier comprising K-90 and Kollidon VA64 (80 wt% to 20 wt%) were flexible, non-tacky, and fast-dissolving. The strips with lower weight dissolved relatively faster than those with heavier weight under the same conditions. But irrespective of the weight and thickness, all the strips dissolved within 60 seconds. (Figure 7). For a strip 6.9 cm^2, the maximum dose limit was about 20 mg/strip at 50-ml and 2.5 mg/strip at 10 ml of thickness. In both the cases, the strips were flexible and non-tacky. The loading of the multivitamin was dependent on the film thickness (Figure 6); however, higher loading may result in tacky films.

Hydrogenated polyoxyl castor oil 40 (Cremophor RH 40) can be used as a taste-masking agent.[11] The mechanism is

not clear, but it is speculated that the solubilizer works by coating the taste bud receptors and delays the response time. The multivitamin strips of K-90/Kollidon VA64 were evaluated for the taste-masking effect and compared to commercially available Barbie brand strips. Preliminary data suggests that these strips were sweet and that the Cremophor RH40 had helped masked to the bitter taste of multivitamins (data not shown). Further work is needed to fully evaluate the taste-masking effect.

CONCLUSIONS

Higher molecular weight K-90 can be used as a carrier for delivery of vitamins and multivitamins. Other polymers and copolymers, such as Kollidon 30, Kollicoat IR, Kollidon VA64, Kollicoat MAE100P, or Kollidon SR, can be used in combination with K-90 as an auxiliary polymer for providing the strength to the films. The hydrophilic nature of the polymers provides added advantage to fast dissolution of the films. The study further suggests that Kollidon VA64 and K-90 formed elegant and flexible films with limited elongation and significantly low tackiness, and might be suitable as a binary carrier mixture for delivery of multivitamin in strips. Furthermore, K-90 in combination with Kollicoat MAE 100P can be used for actives requiring longer dissolution time. The solubilizers, such as Cremophors (Cremophor RH40) and/or poloxamers, can be used to mask the bitter taste of actives. ◆

REFERENCES

1. Slowson M, Slowson S. What to do when patients can't swallow their medications. Pharmacy Times. 1985(Aug):90-96.
2. Lindgren S, Janzon L. Prevalence of swallowing complaints and clinical findings among 50- to 79-year old men and women in an urban population. Dysphagia. 1991;6:187-192.
3. Doheny K. You really expect me to swallow those horse pills? Am Druggist. 1993;208:34-35.
4. (a) Borsadia S, O'Halloran D, Osborne JL. Quick-dissolving films - a novel approach to drug delivery. Drug Delivery Tech. 2003;3(3):63-66. (b) Corniello, CM. Quick-dissolve strips: from concept to commercialization. Drug Delivery Tech. 2006;6(2):68-71.
5. Ali S, Quadir A. BASF polymers in film development technology for drug delivery application. Paper presented at the CRC Annual Meeting, Miami Beach, FL, 2005, Poster # 501.
6. (a) Augello M et al. US Patent No. 6723342. (b) Leung S, S-hS, Leon, RS, Kumar LD, Kulkarni N, Sorg AF. US Patent No. 42443000.
7. Laruelle C. Edible coating composition. US Patent No. 6669957 (2001).
8. Rao PR, Diwan PV. Drug diffusion from cellulose acetate-polyvinyl pyrrolidone free films for transdermal administration. Indian J Pharm Sci. 1996;58:246-250.
9. Mukherjee B, Mahapatra S, Gupta R, Patra B, Tiwari A, Arora P. A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on in vitro skin permeation. Eur J Pharm Biopharm. 2005;59:475-483.
10. Cilurzo F. Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing Ibuprofen. Eur J Pharm Biopharm. 2005;60:61-66.
11. Stier RE, Zanone J. Oral hygiene compositions which mask the burn sensation and the astringency of eucalyptol and zinc. US Patent No. 6306372 B1 (2001).

BIOGRAPHIES

Dr. Shaukat Ali is the Product Development Manager at BASF Pharma Solutions and has over 13 years of experience in the pharmaceutical and biotech industries. He has worked in the areas of drug design, formulations, and drug delivery, and has 25 publications in peer-reviewed journals and 12 US patents to his credit. He joined the Pharma Solutions team over 3 years ago and has worked since with the companies in NAFTA to promote excipients, actives, and dietary supplements by positioning the BASF products to innovative pharmaceutical drug development applications. Dr. Ali earned his BSc from Gorakhpur University (India), his MSc from Laurentian University (Canada), and his PhD from the City University of New York, all in Chemistry. His current research interest includes the polymer evaluation for film development technology, floating drug delivery systems, coatings, and solubilization technology.

Dr. Anisul Quadir is the Technical Development Manager of BASF Corporation in Roxbury, New Jersey. He earned his PhD in Pharmaceutics from the University of Rhode Island and his MBA from Rutgers University at New Jersey. In his current position, he leads the BASF Pharma Solutions, North America development group for new applications of pharmaceutical excipients and to provide technical support to the pharmaceutical industry. The group developed various technologies, such as taste- masking, intraoral film, soft gelatin coating, floating technology, and drug solubilization, which can be used in different drug delivery systems. Before joining BASF, he worked at American Cyanamid and Catalytica Pharmaceutical as a Development Scientist. He has been invited by the FDA to speak about the development of high functionality excipients. He has authored 7 publications in peer-reviewed journals and holds 5 patents.

ADHESIVES

Beyond Sticky to Sophisticated: The Many Dimensions of Adhesives

By: Richard Sitz, MBA

INTRODUCTION

3M's long history with adhesive materials has made its name virtually synonymous with things that stick (sometimes tenaciously) to bond the heaviest of metal parts; other times gently, so that objects can easily be repositioned or removed without leaving a trace. Seemingly mundane in purpose to join materials, adhesives actually comprise one of 3M's broadest and most sophisticated technology platforms. This platform has generated thousands of innovative products that span the full spectrum of adhesive properties, with applications in countless markets. In each of the diverse markets 3M serves, the company's in-house development of adhesives has been a key advantage, allowing it to develop solutions that address unique market issues. Today, 3M combines its adhesives with dozens of other technologies to attach, hold, seal, protect, communicate (think Post-it® Notes, telecommunications) and of course, to deliver drugs.

AN ENABLING TECHNOLOGY FOR TRANSDERMAL DELIVERY

3M's long-standing expertise in adhesives brought to market the world's first stand-alone, 7-day transdermal system, leveraging its proprietary drug-in-adhesive technology. Two of its recent innovations (discussed further) in adhesives are creating additional opportunities to advance the performance of transdermal drug delivery (TDD) systems.

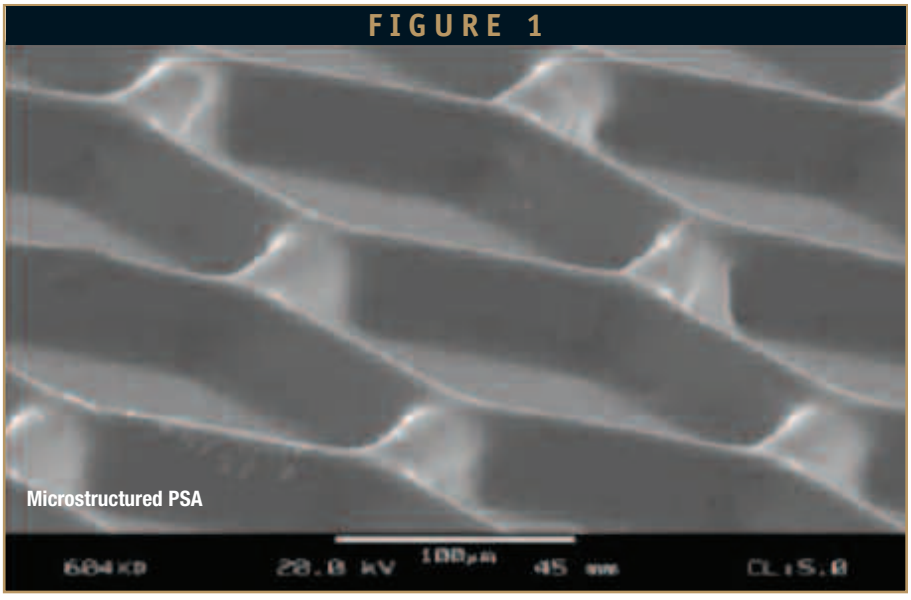
Microstructured Adhesives for Greater Control in Drug Delivery

3M's patented microstructured adhesives involve manipulating pressure-sensitive adhesives (PSAs) to create patterns of micro-wells, which form discrete reservoirs or channels when combined with a cap layer. Performance properties of TDD systems can be tailored by independently varying the rheological properties of the adhesive and the structures formed in the adhesive layer.

The shapes and structures formed in the adhesive can be compartmentalized, channeled, or overlapped to suit applications. Channels, for example, can create unrestricted or less-restricted movement of the substances within the adhesive layer.

Combinations of shapes, sizes, and orientations allow highly regulated placements of

FIGURE 1



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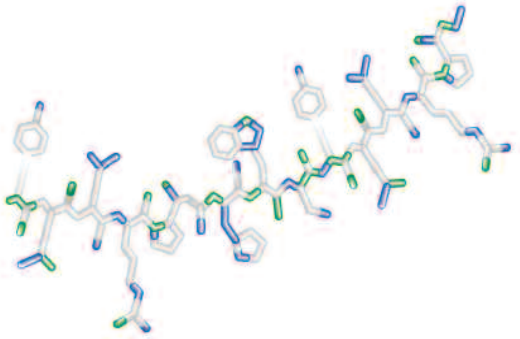

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reservoirs/channels for greater control in drug delivery. Furthermore, additional medicinal ingredients can be introduced in a second adhesive layer or matrix to enable even more sophisticated drug delivery performance.

Creating defined void volumes within a TDD device has a number of benefits. Among these is the ability to contain a medicinal ingredient within the void volume, which can temporarily alter the thermodynamic driving force in the skin-contacting layer by replenishing the layer with drug, penetration enhancers, or other excipients.[1]

As such, the invention provides the advantages of a reservoir-type device, such as the maintenance of a constant thermodynamic driving force and steady delivery rates, without the increased patch thickness and discomfort that are associated with reservoir devices.

Enhanced Adhesive Compositions for Greater Solubility

An acrylic copolymer suitable for PSAs needs to contain a significant fraction of monomers with a low glass transition temperature (T_g) to give the adhesive its soft, tacky properties. It also needs a means to provide reinforcement (using high-T_g functional monomers, for example) to maintain sufficient mechanical strength and to prevent excessive adhesive flow. Unfortunately, the amount of functional monomers that can be incorporated typically is limited because excessive reinforcement will cause a loss of the soft, tacky properties necessary in a PSA.

Using functional monomers with specific chemical structures, 3M has developed adhesives with an optimal level of functional monomers, enabling increased drug solubility in the adhesive without causing excessive reinforcement or loss of PSA properties.[2]

These patented PSAs allow drug-in-adhesive formulations with relatively heavy excipient loadings, while still maintaining important adhesive properties, such as good skin contact and clean removal.[3] Depending on drug properties, this invention may help pharmaceutical companies address vexing issues of patch creep or excessive tackiness. Furthermore, a higher excipient loading can enable potentially higher drug loading and corresponding increases in delivery rate and duration.

These aforementioned technologies represent promising new advances in adhesive technology that help to facilitate improved TDD system performance.

3M & TRANSDERMAL DRUG DELIVERY

Beyond adhesives technologies, 3M Drug Delivery Systems draws on the full array of its 40+ technology platforms (both material and process technologies) to expand the limits of transdermal drug

FIGURE 2

A 3M PSA Helps Secure a Label to the Delicate, Powdery Surface of a Monarch Butterfly's Wing

SIDEBAR 1

PRESSURE-SENSITIVE ADHESIVES

3M pioneered pressure-sensitive adhesives (PSAs) more than 80 years ago with the introduction of Scotch brand masking tape and later, transparent tapes. Since then, the company has engineered countless PSAs that form permanent or temporary bonds with surfaces simply with the application of light pressure. The magic of PSAs is in their viscoelastic nature. That is, they exhibit liquid-like properties at low rates of strain application and solid-like properties at high rates of strain application. Tack and holding power (also known as resistance to creep under load) are the properties most associated with PSAs. Holding power is controlled by the molecular weight of the base elastomer in the PSA and also by the level of crosslinking (connections between polymer chains). Higher levels of crosslinking help to hold the adhesive together for clean removal.

delivery. The company employs different material technologies, components, excipients, and patch designs to solve unique formulation challenges posed by specific drugs.

Backed by 3M technologies and corporate resources, the division has generated more than 150 issued and pending US patents pertaining to transdermal drug delivery, as well as their foreign equivalents.

3M's 30-year track record includes the first stand-alone, 7-day transdermal system, specialty adhesives (including proprietary drug-in-adhesive technology), and a series of exceptional components. In fact, today, more than 80% of TDD products in the US contain a 3M transdermal component, such as backing, liner, membrane, and foam tape.

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REFERENCES

1. Flanigan et al. US Patent No. 6,893,655 B2; 2005.
2. Schaberg et al. US Patent No. 6,902,740 B2; 2005.
3. Garbe et al. US Patent 7,097,853 B1; 2006.

BIOGRAPHY

Mr. Richard Sitz is Technical Manager for the Transdermal Drug Delivery Department in the Drug Delivery Systems Division at 3M. During his 22 years with 3M, he has served in various roles, including R&D, process development and scale-up, commercial manufacturing, business development, and program management, all related to the pharmaceutical industry. Mr. Sitz earned his BS in Mechanical Engineering from Iowa State University and his MBA from California Lutheran University. He can be reached at rgsitz@mmm.com or (651) 736-8567.

PULMONARY DELIVERY

Efficient Pulmonary Delivery of Biological Molecules as PROMAXX Microspheres

By: Julia Rashba-Step, PhD

INTRODUCTION

Since they first emerged as therapeutic products, the delivery of proteins, peptides, nucleotides, antibodies, and other biologics has been almost exclusively the preserve of the injectable route. However, in recent years, developments in the pulmonary administration of biologics have gathered pace. Today, local delivery to the lung and systemic delivery through the lung both represent viable, proven delivery options for biological therapeutics.

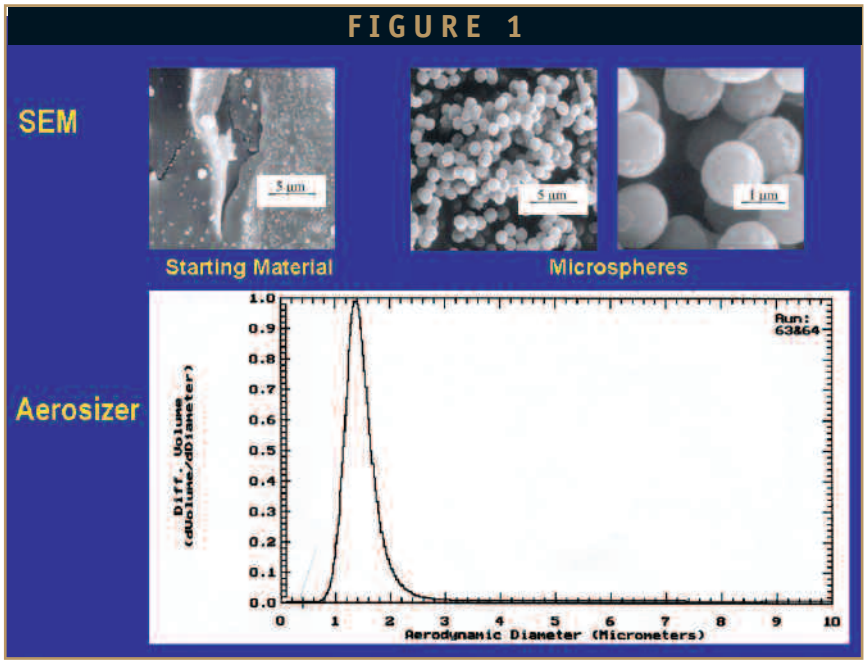
Technologically speaking, the key to delivering biological molecules to and through the lung successfully is the ability to produce a suitable dry powder formulation that meets precise specifications using a simple, robust, and cost-effective process. In terms of delivering the successful commercial product, it is equally important that the company developing and carrying out that formulation process has the right credentials to affect an efficient, mutually rewarding, and long-lasting working relationship with its drug partner.

In this article, we present robust scientific data combined with a candid account of some of our internal procedures and company culture, as evidence that when it comes to the development of inhalable biologics, the PROMAXX microsphere delivery technology is capable of yielding a suitable inhalable formulation, and that Epic Therapeutics (a wholly owned subsidiary of Baxter Healthcare Corporation) is a company with the necessary credentials to deliver a commercial product.

FORMULATION CHARACTERISTICS

PROMAXX microspheres are produced via a controlled phase-separation process, most commonly involving cooling a super saturated solution of aqueous protein and aqueous polymer under controlled conditions. The conditions, including ionic strength, pH, polymer concentration, protein concentration, and rate of cooling (among others), may all affect formation of PROMAXX microspheres and can be varied to produce precisely the required results. PROMAXX microsphere formation takes place in an aqueous system and at mild temperatures, yet it is highly versatile, meaning that in addition to proteins and peptides, it is also applicable to other classes of biological therapeutic molecules, including nucleic acids, siRNA, and small molecules.

FIGURE 1



SEM Images of AAT Starting Material & PROMAXX Particles & Aerosizer Particle-Size Range Data

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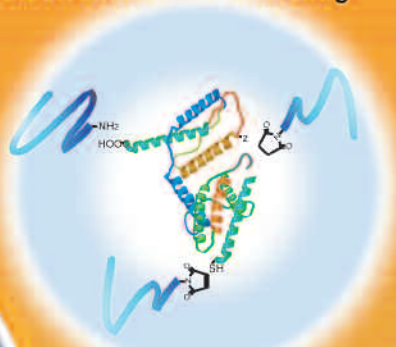
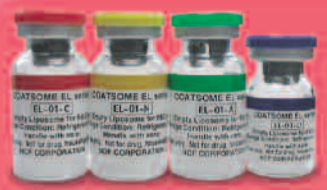


PEG-DRUG



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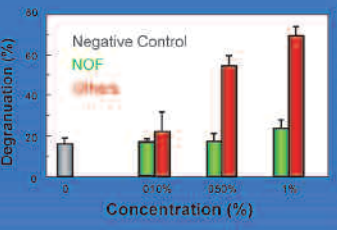

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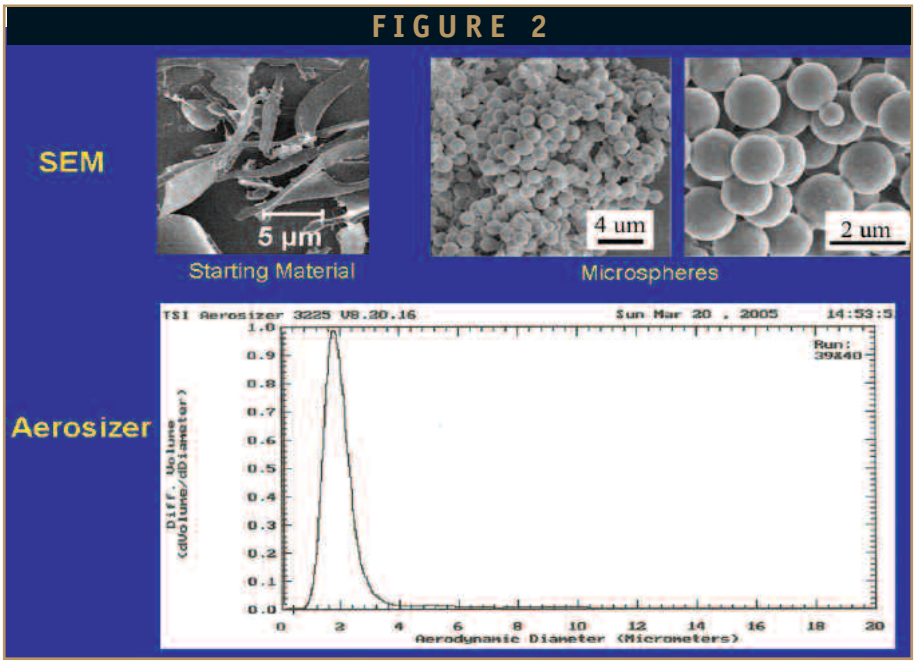
The attributes that differentiate the PROMAXX process from other pulmonary powder production techniques, such as spray drying, include the following:

- The process yields homogenous particles within tightly specified size ranges, so no sieving is required.
- Although it is possible to incorporate excipients into PROMAXX formulations, there is not a requirement for excipients, meaning that microspheres consisting of essentially only active molecule can be produced. High-dose loading (comfortably above 90%) means that less powder mass need be delivered to achieve the desired pharmacological effect.



SEM Images of hGH Starting Material & PROMAXX Particles & Aerosizer Particle-Size Range Data

Epic Therapeutics has produced and characterized multiple PROMAXX microsphere formulations for pulmonary delivery. Here, we discuss in detail two examples of PROMAXX formulations of human growth hormone (hGH), alpha-1 anti-trypsin (AAT), and insulin. The results demonstrate how PROMAXX microspheres measure up against the criteria that a successful inhalable dry powder formulation must meet.

ALPHA-1 ANTI-TRYPSIN (AAT)

The physiological function of AAT is to control the levels of the neutrophil elastase enzyme. In patients with AAT deficiency, a serious hereditary disorder, inadequate levels of the protein can cause liver damage and destruction of the alveolar tissue. The condition is traditionally treated with intravenous AAT augmentation, but a pulmonary formulation allows administration directly to the site of action. Also, delivery to the lung can solve the challenge of limited availability of AAT.

Particles within the target size range of 1 to 3 microns are essential if AAT is to be delivered to its site of action in the deep lung. Time-of-flight measurements made using a TSI Aerosizer and scanning electron microscopy showed that the PROMAXX process generated AAT microspheres within the required size range and very narrow particle size distribution (Figure 1).

Andersen Cascade Impactor (ACI) studies showed that high respirable fraction (73%) of AAT protein particles were delivered to stages 2 to F, with an emitted dose of 86% from a Cyclohaler™, a simple, pocket-size dry powder inhaler developed by Pharmachemie, The Netherlands. These excellent aerodynamic properties were reproducible across different lots of microspheres.

Another critical test of a pulmonary dry powder production process is the retention of activity after the process, compared with activity before the process. AAT is a labile protein prone to aggregation and oxidation. An in vitro AAT activity assay quantifying the level of elastase inhibition showed that PROMAXX AAT retained at least 95% of its activity compared with the starting material.

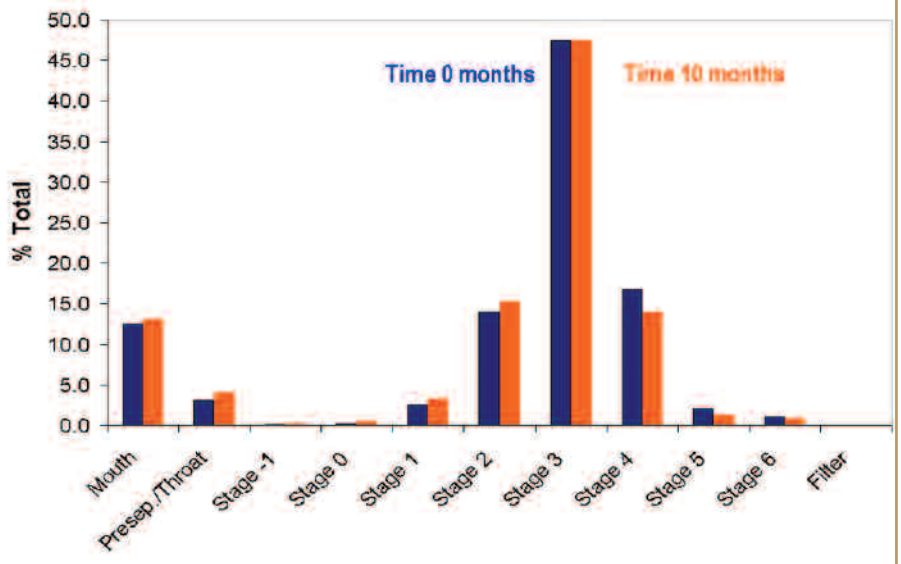
Finally, shelf stability studies carried out at 4°C and at room temperature for 12 months showed no difference in activity loss between PROMAXX AAT microspheres and a lyophilized control drug.

HUMAN GROWTH HORMONE (HGH)

Human growth hormone (hGH), currently administered by daily subcutaneous injection to children with growth hormone deficiency, is a promising candidate for formulation for inhalable delivery. Not only would convenience and comfort be significantly enhanced compared with

FIGURE 3

USP Andersen Cascade Impactor
Aerodynamic Stability of PROMAXX Insulin



USP Andersen Cascade Impactor Aerodynamic Stability of PROMAXX Insulin

injection, but therapeutic efficacy is also likely to be improved. The protein is relatively small at 22 kDa, meaning that high bioavailability in the lungs is likely. Furthermore, using inhalation, it may be possible to mimic the pulsatile nature of endogenous release.

The PROMAXX microsphere formulation of hGH yields particle sizes in the range 1 to 5 microns with an MMAD of 3 microns. As with AAT, the microspheres consisted essentially wholly of active protein because no excipients are needed, and there was a narrow particle size distribution (Figure 2). Andersen Cascade Impactor analysis showed the emitted dose from the Cyclohaler was 62.8%, and the respirable fraction was 67.4%. SEC and RP-HPLC showed that compared with starting material, after the PROMAXX formulation process, at least 95% of hGH activity was retained.

Systemic delivery of hGH PROMAXX microspheres to dogs via pulmonary administration resulted in very high serum concentrations of hGH and bioavailabilities of 30% to 50% relative to subcutaneous injections. Pulmonary administration of hGH resulted in a considerably lengthened pharmacodynamic response relative to that of subcutaneous administration as measured by IGF-1 serum concentrations versus time post administration.

INSULIN

Inhalable insulin has perhaps the highest profile amongst all of the biological molecules under development for pulmonary administration, with one pulmonary insulin product having reached the market last year.

Similar to AAT and hGH, the PROMAXX formulation process has yielded positive results when applied to insulin. Particle size distribution studies have revealed that 95% of particles fall within the range 0.95 to 2.1 microns, and greater than 80% of the emitted dose of the formulation was delivered to stages 2 to F of the Andersen Cascade Impactor. Figure 3 shows that PROMAXX insulin powder retained its aerodynamic stability over 10 months, with little variation in Andersen Cascade Impactor data over the time period. One investigator commented, "The deposition of the radiolabeled insulin into the peripheral lung was superior to any aerosolized product this investigator has seen."

Preclinical studies in dogs have revealed pharmacokinetic and pharmacodynamic profiles of PROMAXX insulin comparable with subcutaneous injection. Specifically, serum insulin levels following inhalation of 0.44 mg of PROMAXX insulin were comparable with levels obtained following 0.12 mg delivered SC. Figure 4 shows that the effect on serum glucose levels following 0.44 mg of PROMAXX pulmonary insulin mirrored that of the subcutaneous dose very closely.

A Phase I clinical trial of PROMAXX insulin delivered using a simple DPI was recently completed. A total of 30 subjects participated in the randomized, two-way crossover study conducted in Germany. The trial showed the product to be safe and well tolerated in healthy volunteers. The bioavailability relative to SC was more than 12%. No coughing or shortness of breath was observed following inhalation. PROMAXX insulin has performed very well thus far through its development. Baxter recently presented the Phase I data at the Respiratory Drug Delivery Europe 2007 Conference in Paris.

FROM SAMPLE API TO CGMP FORMULATION SCALE-UP

The following is intended to give an account of the various stages a biological molecule from the partner might go through on

its journey toward full-scale manufacture as an inhalable PROMAXX formulation.

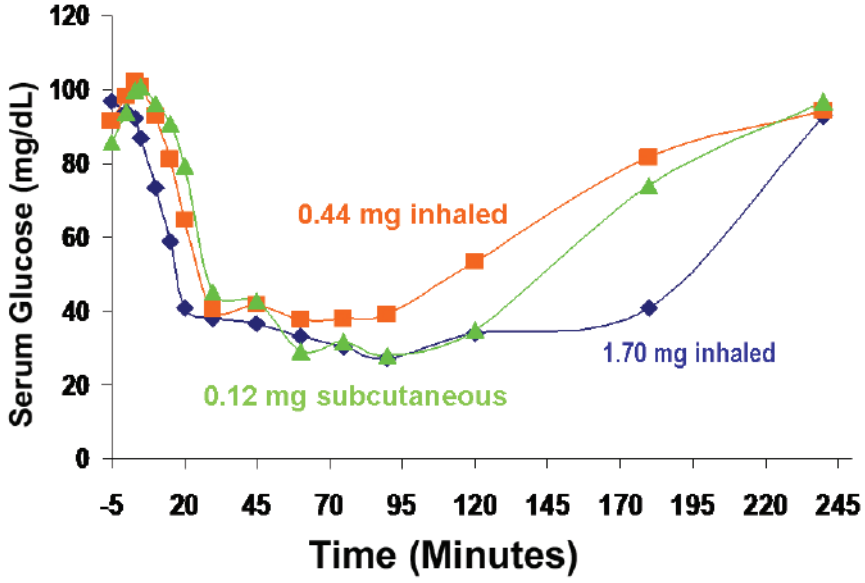
The process usually begins with Epic being supplied with a small quantity of the molecule by a company interested in finding out whether it is suitable for formulation using PROMAXX technology. A go/no-go decision is usually reached within 8 weeks following rapid screening studies at the > 1 mL scale. These investigations will include solubility profiling, generating phase diagrams for the formation of solid precipitate, and identification of process boundaries.

There are two important points to note at this initial stage. Firstly, due to the complex and expensive nature of producing many biological molecules, it is common that only a very small amount of the candidate molecule is made available for Epic to assess. This presents no problem because only a tiny quantity is required for initial studies to assess whether the PROMAXX technology can be effectively applied to a molecule of interest; a far smaller amount than would be required for a similar initial assessment for a spray dried formulation, for example.

The second point to note is about the context and the likely events leading up to the initiation of studies to explore the potential of the molecule with PROMAXX technology for pulmonary delivery. In many cases, companies will approach Epic because they have a problem formulating their molecule in-house using their own approaches. Thus for Epic, the starting point, as it first takes delivery of the test quantity of API, is often to resolve an existing problem. Epic's team of problem-solvers work diligently to create a viable formulation.

After the initial go/no-go decision is made, preliminary formulation work can begin in 1- to 40-mL reactors. A biophysical characterization of the formulation, molecular integrity, microparticle morphology, and yield analyses are often conducted. Informal PK studies can be conducted at this stage before fine tuning the formulation, after which the project moves to process development for scale-up.

FIGURE 4



PROMAXX Insulin Pharmacodynamics (n = 5 dogs at each time point)

Figure 5 outlines the complex web of relationships between the key process parameters. An empirical approach for formulation development is possible, but it is time and labor intensive. A high throughput screening approach using DOE rapidly increases efficiency of formulation process and identifies optimal formulation conditions.

The final formulation is developed and produced in 50- to 500-mL reactors. Process characterization and control is carried out at this stage using online monitoring and data collection. Molecular integrity, microparticle morphology, and yield analysis are conducted as well as in vitro and in vivo aerodynamic performance studies.

The last stage is manufacturing scale-up, conducted in 1- to 10-liter reactors under "clean" conditions.

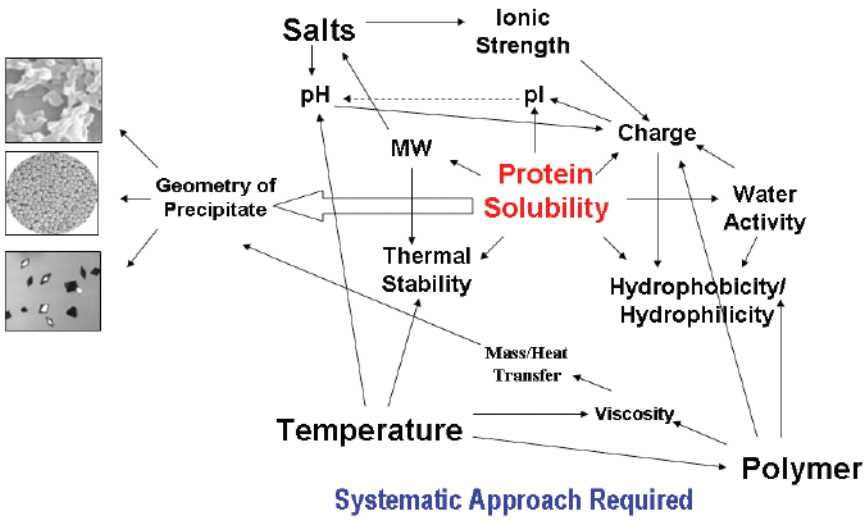
Epic is keen to stress that although it benefits from experience, and there are precedents to use as guides, there is no rigid, standard procedure to follow as a project progresses. The project design is highly versatile and succeeds because it is readily tailored to the particular needs of each individual formulation and, crucially, to each individual partner's requirements and specifications.

For example, two key factors shaping the design of the project are the amount of test substance made available to Epic, and the partner's time requirements. Indeed, planning the timing of the project carefully and meeting the specified timelines are paramount.

STEPS OF A TYPICAL PARTNERSHIP

In the same way the structure and timing of the various practical/technical development stages of each project are unique to that project, the commercial and legal structure of every individual project is tailored to that

FIGURE 5



Process Parameters: Interrelation of the Key Factors

particular project's needs.

Typically, a partner comes to Epic needing to enable or enhance the continued development of their molecule. An initial non-confidential discussion reveals a likely fit and then, under a Confidential Disclosure Agreement, Epic and its partner may share data on the molecule, the project, the objectives, and the PROMAXX technology.

It is important to note that while Epic might be approached by a company with PROMAXX technology in mind, it could be that one of Baxter's many other drug delivery technologies are appropriate. Partners approaching Epic will have all of Baxter's technologies and services available to them as potential solutions. If the initial assessments indicate that the PROMAXX technology can address the project requirements, a work plan is generated outlining the scope of the project, the metrics to judge progress, and the API requirements to complete the work. Additionally, an estimate of the time and resources required to conduct the study is prepared.

When the work plan has been agreed upon, a feasibility study agreement is signed, and the study is conducted. Throughout the study, Epic communicates with the partner constantly. There is typically a face-to-face project "kick-off" meeting, and face-to-face meetings are arranged whenever needed. In between, a continual exchange of information and feedback is maintained. Stages of the project are defined in the agreement, each stage normally culminating in at least one report summarizing results. When the necessary data are available and the results support further development, the parties may execute a license and supply agreement. A broad patent estate surrounds the PROMAXX technology, and Epic's partners can therefore benefit from the enhanced value this strong IP protection provides.

SUMMARY

Multiple biological molecules, including AAT, hGH, and insulin, have been successfully formulated using the PROMAXX microsphere delivery technology as viable products with excellent characteristics for pulmonary drug delivery using a simple dry powder inhaler. In addition to proteins and peptides, the technology is being developed for nucleic acids pulmonary delivery.

Epic's team consists of problem-solvers who can use the PROMAXX technology to create innovative solutions for its partners' problems. Epic benefits from the creativity and attention to detail that it can give to projects through its innovative, dedicated, and agile team, and from its ability to draw on the infrastructure and resources of its parent organization, Baxter Healthcare Corporation.

BIOGRAPHY

Dr. Julia Rashba-Step is the Director of Formulation Research at Epic Therapeutics, Inc., a wholly owned subsidiary of Baxter Healthcare Corporation, located in Norwood, MA. Dr. Rashba-Step manages a team of 15 scientists who conduct the formulation research work on feasibility studies on behalf of partners' proprietary molecules. Her team is also enhancing the breadth and depth of the portfolio of technologies that Baxter can apply to solve challenging drug delivery problems. She is a speaker at a number of professional drug delivery conferences, has published in peer reviewed journals, and authored many patents. Previous to joining the company in 1997, she was engaged in academic research at Mount Sinai Medical School, Columbia University, and the University of Southern California. She earned her PhD in Biophysics from the Academy of Sciences of Russia, in Moscow. Dr. Rashba-Step's expertise is in the field of protein and peptide formulations for the pulmonary and injectable routes of administration, particle engineering, coating, and microencapsulation technologies.

BIOADHESIVE MICROSPHERES

Bioadhesive Microspheres & Their Pharmaceutical Applications

By: Jayvadan Patel, PhD

ABSTRACT

Bioadhesion is a topic of current interest in the design of controlled or targeted drug delivery systems. Recent advances in polymer science and drug carrier technologies have promulgated the development of novel drug carriers, such as bioadhesive microspheres that have boosted the use of bioadhesion in drug delivery. Bioadhesive microspheres exhibit a prolonged residence time at the site of application or absorption and facilitate an intimate contact with underlying absorption surface and thus contribute to improved and/or better therapeutic performance of drugs. In recent years, such bioadhesive microspheres have been developed for oral, buccal, ocular, rectal, nasal, and vaginal routes for systemic or local effects. This article presents an introduction to and the advanced pharmaceutical applications of bioadhesive microspheres.

INTRODUCTION

The term bioadhesion describes materials that bind to biological substractes, such as mucosal members. Adhesion of bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption, and in combination with controlled release of a drug, can also improve patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle, such as microspheres, nanospheres, liposomes, nanoparticles, etc, which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity. However, the success of these microspheres is limited due to their short residence time at the site of absorption. It would therefore be advantageous to have a means for providing intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres.[1-5] Bioadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1 to 1000 microns in diameter and consist entirely of a bioadhesive polymer or an outer coating of it, respectively.[6] Microspheres, in general, have the potential to be used for targeted and controlled-release drug delivery, but coupling of bioadhesive properties to microspheres has additional advantages, eg, efficient absorption and enhanced bioavailability of the drugs due to a high surface-to-volume ratio; a much more intimate contact with the mucus layer; and specific targeting of drugs to the absorption site achieved by anchoring plant lectins, bacterial adhesins, and antibodies on the surface of the microspheres.

Bioadhesive microspheres can be tailored to adhere to any mucosal tissue, including those found in the eye, nasal cavity, urinary tract, colon, and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs. Bioadhesive microspheres can be prepared using different techniques. Application of bioadhesive microspheres to the mucosal tissues of the ocular cavity and gastric and colonic epithelium is used for administration of drugs for localized action. Prolonged release of drugs and a reduction in frequency of drug administration to the ocular cavity can highly improve patient compliance.[7] The latter advantage can also be obtained for the drugs administered intranasally due to the reduction in mucociliary clearance of drugs adhering to the nasal mucosa. Microspheres prepared with bioadhesive and bioerodible polymers undergo selective uptake by the M cells of Peyer patches in gastrointestinal (GI) mucosa. This uptake mechanism has been used for the delivery of protein and peptide drugs, antigens for vaccination, and plasmid DNA for gene therapy. Moreover, by keeping the drugs in close proximity to their absorption window in the GI mucosa, the bioadhesive microspheres improve the absorption and oral bioavailability of drugs like furosemide and riboflavin.[7]

PREPARATION OF BIOADHESIVE MIRCROPSHERES[7]

Solvent Evaporation Technique

The solvent evaporation technique is the most extensively used method of microencapsulation. A buffered or plain aqueous solution of the drug (which may contain a viscosity-building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water-in-oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsion (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The microspheres can then be washed, centrifuged, and lyophilized to obtain the free-flowing and dried microspheres.

Hot-Melt Microencapsulation

In this technique, the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 microns. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5°C above the melting point of the polymer. When the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed via decantation with petroleum ether. The only disadvantage of this method is the moderate temperature to which the drug is exposed.

Solvent Removal

In this technique, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent such as methylene chloride. This mixture is then suspended in silicone oil containing Span 85 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until the solvent is extracted into the oil solution. The resulting microspheres can then be dried in a vacuum.

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TABLE 1

METHOD	DESCRIPTION
Wilhelmy Plate Technique	The measurement of dynamic contact angles, and involves the use of a microtensiometer or a microbalance.
Novel Electromagnetic Force Transducer (EMFT)	The EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the bioadhesive force.
Shear Stress Measurement	The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact.
Adhesion Number	Determined as the ratio of the number of particles attached to the substrate to the total number of applied particles, expressed as a percentage.
Falling Liquid Film Method	Quantitative in situ method, wherein an excised intestinal segment cut lengthwise, is spread on a plastic flute and positioned at an incline, and suspension of microspheres is allowed to flow down the intestinal strip. Particle concentrations entering the segment from the dilute suspension reservoir and leaving the intestinal segment can be determined with the help of Coulter counter.
Everted Sac Technique	A passive test for bioadhesion involving polymeric microspheres and a section of the everted intestinal tissue.
Novel Rheological Approach	The rheological properties of the mucoadhesive interface (ie, of the hydrated gel) are influenced by the occurrence of the interpenetration step in the process of bioadhesion.

Measurement of Adhesive Strength / In Vitro Tests [7]

Hydrogel Microspheres

Gel-type polymers, such as alginates, are used for preparation of microspheres and are produced by dissolving the polymer in an aqueous solution, suspending the active ingredient in the mixture and extruding through a precision device, producing microdroplets that fall into a hardening bath that is slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer forming gelled microspheres. The method involves an "all-aqueous" system and avoids residual solvents in microspheres. The particle size of microspheres can be controlled by using various size extruders or by varying the polymer solution flow rates.

Spray Drying

The drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray-dried microspheres can be improved by the addition of plasticizers, which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of microspheres can be controlled by the rate of spraying, the feed rate of polymer drug solution, nozzle size, and the drying temperature.

Phase Inversion Microencapsulation

The process involves addition of drug to a dilute solution of the polymer. The mixture is poured into an unstirred bath of a strong non-solvent (petroleum ether) in a solvent-to-non-solvent ratio of 1:100, resulting in the spontaneous production of microspheres through phase inversion. The microspheres are then filtered, washed with petroleum ether, and dried at room temperature. This simple and fast process of microencapsulation involves relatively little loss of polymer and drug.

CHARACTERIZATION OF BIOADHESIVE MICROSPHERES

Morphological Examination

The morphology of bioadhesive microspheres were examined by scanning electron microscopy. The samples of microspheres were dusted onto double-sided tape on an aluminum stub and coated with gold using a cold sputter coater to a thickness of 100 to 400°A.

Production Yield

The percentage of production yield (wt/wt) was calculated from the weight of dried microspheres (W_1) recovered from each of the batches and the sum of the initial dry weight of starting materials (W_2) using the following equation:

Percentage of Production Yield = W 1 W 2 x 100

Drug Content & Loading Efficiency

Bioadhesive microspheres of each formulation were extracted in dissolution medium and assayed by suitable analytical methods. The actual amount of drug loaded relative to the theoretical amount in the microspheres was calculated as a percentage and expressed as the loading efficiency.

Particle Size Measurement

The prepared bioadhesive microspheres were suspended in suitable solvents and sized by using a laser particle size distribution analyzer or the microscopic method.

Determination of Bulk Density

Accurate weights of microspheres (Wm) were transfer into a 100-mL graduated cylinder to obtain the apparent volumes (V) between 50 and 100 mL. The bulk density was calculated in grams per milliliter using the following formula:

Bulk Density = W m/V

Angle of Repose

The angle of repose can be measured by the heap carefully built up by dropping the microsphere samples through a glass funnel to the horizontal plate of a powder characteristic tester.

Zeta Potential Study

The zeta potential of bioadhesive microspheres dispersed in dissolution medium can be determined using a zeta meter. The directional movement of 200 microspheres from each formulation were observed and averaged from three determinations.

Swelling Property

The swelling of bioadhesive microspheres were conducted in dissolution medium. Their diameters were periodically measured using a laser particle size distribution analyzer or microscopic method until they were decrease by erosion and dissolution. The percentage of swelling is determined at different time intervals by the difference between diameter of microspheres at time t (D_t) and initial time (t = 0 [D_0]) as calculated from the following equation:

Percentage of Swelling = D t - D 0/D 0 x 100

Would you like to convert your drugs from IV to subcutaneous (SC) delivery or enhance the dispersion of your existing SC compounds? With Enhanze™ Technology, microgram quantities of a fully human recombinant enzyme act as a "molecular machete" to clear the subcutaneous "jungle." Based upon this mechanism of action, co-delivery with Enhanze is anticipated to permit the SC administration of large volumes of antibody drugs, speed onset of action relative to SC delivery without Enhanze, and improve patient comfort. Backed by a robust IP portfolio, Enhanze may extend a compound's patent life and potentially reduce COGS for products that are expensive to manufacture.

Enhanze Technology employs the first and only human recombinant enzyme for injectable drug dispersion. The enzyme in Enhanze has been used in two FDA-approved formulations. Enhanze is being developed to deliver an optimized pharmacokinetic profile and thus offers a potential competitive advantage for partners' products. Potential benefits of this technology include:

- Enhancing the dispersion and absorption of other injected drugs
- Allowing SC injection of up to 10 mL in a single push or a mean infusion rate of ~500 mL/hour
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Halozyme
THERAPEUTICS

Infrared Absorption Study

The IR spectra of drug and additives in the bioadhesive microspheres were examined via the potassium bromide disc method using an infrared spectrophotometer in the require range.

In Vitro/In Vivo Bioadhesion Study

To evaluate bioadhesive microspheres is to evaluate the effectiveness of bioadhesive polymers to prolong the residence time of drug at the site of absorption, thereby increasing absorption and bioavailability of the drug. The methods used to evaluate bioadhesive microspheres are listed in Tables 1 and 2.

In Vitro Drug Release Study

The in vitro drug release test of the bioadhesive microspheres were performed using a Franz diffusion cell with dialysis membrane or a USP dissolution test apparatus.

Drug Permeation Study

Cell cultures techniques were mostly used for the drug permeation study.

Pharmaceutical Applications

Bioadhesive microspheres have been extensively studied for a number of applications. The ajority of these can be understood by classifying these applications on the basis of route of administration. All these applications have been reviewed in the subsequent sections and listed in Table 3.

ORAL APPLICATIONS

Buccal

The oral cavity is used for both systemic delivery and local treatment. Systemic delivery of drugs is either sublingual (through the mucosal membranes lining the floor of the mouth) or buccal (through the mucosal membranes lining the cheeks). Furthermore, oral transmucosal drug delivery bypasses the first-pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oro-mucosal cavity a very attractive and feasible site for systemic drug delivery.[24] Composition of the oral epithelium varies depending on the site in the oral cavity. The areas exposed to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids, such as ceramides and acylceramides, which have been associated with the barrier function. It is estimated that the permeability of the buccal mucosa is 4 to 4000 times greater than that of the skin. In general, the permeabilities of the oral mucosa decrease in the order of sublingual greater than buccal and buccal greater than palatal. The daily salivary volume secreted in humans is between 0.5 and 2 L, which is sufficient to hydrate oral mucosal dosage forms. This water-rich environment of the oral cavity is the main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems. Vyas and Jain prepared polymer grafted starch microspheres bearing isosorbide dinitrate and evaluated their potential as a sustained-release buccal bioadhesive system both by in vitro release studies and in vivo absorption studies.[25] Starch microspheres grafted with polymethyl methacrylate (PMMA) exhibited relatively slow drug release as compared to polyacrylate- (PAA) grafted microspheres. Moreover, the C_{max} and AUC recorded for the acrylic acid-grafted starch microspheres were found to be more than that for PMMA- grafted starch microspheres. It has been revealed by the in vivo absorption studies that steady state plasma levels can be maintained above the minimum effective concentration (MEC) over a period of 12 hrs after buccal administration of the grafted microspheres.

TABLE 2

Method	Comment
GI Transit Using Radio-Opaque Microspheres	The use of radio-opaque markers, eg, barium sulfate, encapsulated in bioadhesive microspheres to determine the effects of bioadhesive polymers on GI transit time.
Gamma Scintigraphy Technique	Distribution and retention time of the bioadhesive intravaginal microspheres can be studied using the gamma scintigraphy technique.

Measurement of the Residence Time / In Vivo Techniques [7]

Gastrointestinal (GI)

The development of peroral controlled-release DDS has been hindered by the inability to restrain and localize the drug delivery system in selected regions of the gastrointestinal tract (GIT). Bioadhesive drug delivery systems form an important approach to decrease the GI transit of drugs. Drug properties especially amenable to bioadhesive formulations include a relatively short biological half-life of about 2 to 8 hrs, a specific window for the absorption of drug by an active, saturable absorption process, and small absorption rate constants.[26] The GI epithelium consists of a single layer of simple, columnar epithelium lying above a collection of cells called the lamina propria and supported by a layer of smooth muscle known as the muscularis mucosae. Tight junctions or the zona occludens hold the cells together. A special type of GI epithelium, the Peyer's patches (PP) of the gut-associated lymphoid tissue (GALT), is also present. Polymeric microspheres can also be phagocytized by these microfold cells and hence can be used for vaccination purposes.[27]

Specially engineered polymeric bioadhesive microspheres can traverse both the mucosal absorptive epithelium and follicle-associated epithelium covering the lymphoid tissues of the Peyer's patches, depending on the particle size, polymer composition, and the surface charge of bioadhesive microspheres.[6] Bioerodible bioadhesive microspheres have been reported to increase the peroral bioavailability of dicumarol and insulin and have been investigated for peroral gene delivery.[6] The increased bioactivity of insulin and plasmid DNA can be accounted to the uptake of microspheres by cells lining the GI epithelium. Thus, these uptake pathways can be used as a platform for the systemic delivery of a variety of therapeutic agents showing poor absorption through GI epithelium. Bioadhesive microspheres, by keeping the drug in the region proximal to its absorption window, allow targeting and localization of the drug at a specific site in the GIT. An adhesive micromatrix system (AD-MMS), a novel formulation approach, reported by Akiyama and Nagahara consists of the drug and an adhesive polymer dispersed in a spherical matrix of the PGEFs with a diameter of 177 to 500 microns.[14] This formulation showed strong adherence to the stomach mucosa. Drug release from this system could be regulated by appropriate selection of the HLB value of the PGEFs. Various channeling agents were reported to regulate drug release through the micromatrix systems, eg, mannitol, acrylic acid, and lactose. In experiments using rats, prolongation of GI transit time and improvement in the bioavailability of furosemide (with a narrow absorption window) has been shown. The MRT values after PGEF microspheres and the AD-MMS administration were found to be 6.1 ± 0.6 and 6.7 ± 0.7 hrs, respectively. While the AUC (0 to 24 hrs) after AD-MMS administration (11.57 ± 1.84 µg h/ml) was 1.8 times that of the PGEF microsphere (6.56 ± 0.93 µg/ml). The results could be explained to be due to the adherence of the AD-MMS to a more proximal area of the GIT rather than the absorption window, and furosemide was thereby effectively absorbed from the absorption window.[28] AD-MMS containing amoxicillin have been evaluated against the amoxicillin suspension for *Helicobacter pylori* clearance in vivo using Mongolian gerbils as the animal model. A ten-fold greater anti *H. pylori* activity after oral administration of AD-MMS as compared to the amoxicillin suspension has been reported that could be due to the difference in gastric residence provided by the two dosage forms.[29] Amoxicillin AD-MMS adheres to the infected mucosa and thereby provides a higher *H. pylori* eradication or clearance rate. Patel et al prepared glipizide microspheres containing chitosan using a simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent.[17] In vivo testing of the mucoadhesive microspheres to albino Wistar rats demonstrated significant hypoglycemic effect of glipizide.

TABLE 3

Drug	Route of Administration	Bioadhesive Polymers Used	Comments/Results	References
Acyclovir	Ocular	Chitosan	Slow release rate increased AUC.	8
Methyl Prednisolone	Ocular	Hyaluronic Acid	Slow release rates sustained drug concentration in tear fluids.	9
Gentamicin	Nasal	DSM+LPC	Increased nasal absorption.	10
Insulin	Nasal	DSM+LPC	Efficient delivery of insulin into the systemic circulation via nasal route.	10
Human Growth Hormone (hGH)	Nasal	DSM+LPC	Rapid and increased absorption.	11
Desmopressin	Nasal	Starch	Addition of LPC causes a five-fold increase in Cmax and two-fold increase in bioavailability.	12
Haemagglutinin (HA) obtained from Influenza A virus	Nasal	HYAFF	With mucosal adjuvant serum IgG antibody response as compared to i.m. immunization.	13
Furosemide	GI	AD-MMS (PGEFs)	Increased bioavailability, higher AUC, effective absorption from the absorption window.	14
Amoxicillin	GI	Ethyl Cellulose-Carbopol-934P	Greater anti H. pylori activity.	15
Delapril HCL	GI	AD-MMS (PGEFs)	MRT of drug is increased.	16
Glipizide	GI	Chitosan	Prolonged blood glucose reduction.	17
Glipizide	GI	Chitosan-Alginate	Prolonged blood glucose reduction.	18
Vancomycin	Colonic	PGEF Coated With Eudragit S 100	Well absorbed even without absorption enhancers.	19
Insulin	Colonic	PGEF Coated With Eudragit S 100	Absorbed only in the presence of absorption enhancers, eg, EDTA salts.	19
Nerve Growth factor (nGF)	Vaginal	HYAFF	Increased absorption from HYAFF microspheres as compared to aqueous solution of the drugs.	20
Insulin	Vaginal	HYAFF	Increased absorption for HYAFF microspheres as compared to aqueous solution of the drugs.	21
Salmon Calcitonin	Vaginal	HYAFF	Increased absorption from HYAFF microspheres as compared to aqueous solution of the drugs.	22
Pipedimic Acid	Vesical	CMC as Mucopolysaccharide+ Eduragit RL as Matrix Polymer	-	23

CMC (carboxy methyl cellulose), DSM (degradable starch microspheres), EDTA (ethylenediaminetetraacetic acid), GI (gastrointestinal), HYAFF (hyaluronic acid esters), IgG (immunoglobulin G), LPC (lysophosphatidylcholine), PGEFs (polyglycerol esters of fatty acids)

Applications of Bioadhesive Microspheres

Colon

Colon drug delivery has been used for molecules aimed at local treatment of colonic diseases and for delivery of molecules susceptible to enzymatic degradation, such as peptides. The mucosal surface of the colon resembles that of the small intestine at birth but changes with age, causing the loss of villi leaving a flat mucosa with deep crypt cells. Therefore, the absorptive capacity of the colon is much less compared to the small intestine. The mucus layer provides not only a stable pH environment but also acts as a diffusion barrier for the absorption of drugs. Mucus production is seen more in the elderly as the number of mucous-secreting goblet cells increase with age. Colonic mucosal environment is also effected by the colonic microflora as they degrade the mucins.[7] Bioadhesive microspheres can be used during the early stages of colonic cancer for enhancing the absorption of peptide drugs and vaccines, for the localized action of steroids, and drugs with a high hepatic clearance (eg, budesonide), and for the immunosuppressive agents such as cyclosporine. Colon-specific bioadhesive microspheres can be used for protection of peptide drugs from the enzyme rich part of the GIT and to release the biologically active drug at the desired site for its maximum absorption. Insulin was found to be absorbed well in the colon only in the presence of absorption enhancers, eg, EDTA salts, which cause chelation of calcium ions present in the tight junctions and hence opening of water channels in the cell membranes. Geary et al prepared targeted release formulations of vancomycin and insulin (utilizing Eudragit® S100 enteric coating and a decreased GI transit time), comparing two bioadhesive polymers (chitosan and Carbopol® 934).[19] Salicylate microspheres incorporated in enteric and non-enteric formulations with chitosan or Carbomer (Carbopol 934) were tested for sustained delivery in the lower GIT using rat and dog animal models. Optimized formulations were designed for porcine insulin, which was then tested in the non-diabetic dog model for bioavailability and pharmacological response. Microspheres of triglyceride mixtures and low-melting fat composition were prepared using a spinning disk method and subsequently incorporated in two-part gelatin capsules containing Carbopol 934 or chitosan film prior to placement in two-part gelatin capsules. Improved bioavailability for the enteric-coated oral insulin formulation was observed in the dog model with prolonged decrease in plasma glucose. Recently, Varshosaz et al have developed mesalazine (5-ASA)-chitosan coated microspheres via the emulsion-solvent evaporation technique based on a multiple w/o/w emulsion.[30] The drug is effective in Crohn's disease and ulcerative-colitis but is rapidly absorbed from the small intestine, hence it is necessary to develop a colon-specific delivery system for it.

TOPICAL APPLICATIONS

Nasal

The basic function of the nose, in addition to functioning as a sensory organ, is the pretreatment of inspired air. The air is heated and humidified, and its passage through the nose will help clear particles and bacteria from the air before it reaches the lung. The nasal cavity offers a large, highly vascularized subepithelial layer for efficient absorption. Also, blood is drained directly from nose into the systemic circulation, thereby avoiding first-pass effect.[31] However, nasal delivery of drugs has certain limitations due to the mucociliary clearance of therapeutic agents from the site of deposition, resulting in a short residence time for absorption. Use of bioadhesive drug delivery systems increases the residence time of formulations in the nasal cavity, thereby improving absorption of drugs. It has been shown by gamma scintigraphy studies that radiolabelled microspheres made from diethyl amino ethyl dextran (DEAE–dextran), starch, and albumin are cleared significantly more slowly than solutions after nasal administration in human volunteers.[32] Hence, it was suggested by Illum et al that the intranasal application of bioadhesive microspheres (in powder form) causes them to swell upon coming in contact with the nasal mucosa to form a gel and decrease their rate of clearance from the nasal cavity, thereby providing poorly absorbed drugs a longer time for absorption.[33]

Bioadhesive microspheres have also been investigated as vehicles for peptides and proteins. An increased bioavailability of FITC-dextran was observed in rats when microspheres made from Carbopol were used as a vehicle in comparison with reference lactose microspheres.[34] A significantly greater hypocalcaemic effect was observed after administration of salmon calcitonin in gelatin microspheres in comparison with salmon calcitonin in buffer.[35] The bioavailability of salmon calcitonin was greater when using positively charged spheres than when using negatively charged spheres of the same size. Long-term use of bioadhesive microspheres however may reduce bioavailability. For example, after 8 days of nasal delivery of insulin from microspheres made from starch and Carbopol, a reduced bioavailability and lower decrease of blood glucose levels were noticed.[36]

The excellent absorption-enhancing properties of bioadhesive microspheres are now being used extensively for both low molecular weight as well as macromolecular drugs like proteins. The nasal cavity as a site for systemic drug delivery has been investigated extensively, and many nasal

formulations have already reached commercial status, including leutinizing hormone-releasing hormone (LHRH) and calcitonin.[33]

Chitosan and starch are the two most widely employed bioadhesive polymers for nasal drug delivery. It has been reported that the clearance half-life was 25% greater for chitosan microspheres than for starch microspheres. This may be due to the differences in the surface charge, molecular contact, and flexibility of two polymers. Chitosan exerts a transient inhibitory effect on mucociliary clearance of the bioadhesive formulations. The concept of using a bioadhesive delivery system in the form of degradable starch microspheres (DSM) for nasal delivery of drugs was introduced in 1988. A DSM system, when combined with absorption enhancers, such as lysophosphatidylcholine (LPC), successfully improved the nasal absorption of gentamicin.[3] The bioavailability of gentamicin was increased to 10% with the use of bioadhesive microspheres and was further increased to 57% by the addition of LPC to the microsphere formulation. The DSM/LPC system has also been proposed as an efficient method for delivery of insulin into the systemic circulation via the nasal route.[10] A rapid and much higher absorption of human growth hormone (hGH) has been observed when hGH was administered in the form of a DSM/LPC system of microspheres.[11]

Critchley et al evaluated bioadhesive starch microspheres as a nasal delivery system for desmopressin, and observed significant improvement in the absorption of drug, both in terms of peak plasma levels and bioavailability.[12] A five-fold increase in maximum plasma concentration (C_{max}) and a doubling of bioavailability was observed upon addition of LPC in a concentration of 0.2% to the starch microspheres. Other bioadhesive microspheres used for nasal administration of peptides and proteins include the cross-linked dextran microspheres, which are water insoluble and water absorbable. Sephadex and DEAE-Sephadex were found to improve the nasal absorption of insulin, but to a lesser extent than the starch microspheres.[37] Hyaluronic acid ester microspheres were used for the nasal delivery of insulin in sheep, and the increase in nasal absorption was found to be independent of the dose of microspheres in the range of 0.5 to 2.0 mg/kg.[21]

Preda et al studied in vitro and in vivo experiments in rats showed good adhesive characteristics of the gelatin/poly(acrylic acid) microspheres, which were greater if the poly(acrylic acid) content was greater.[38] A significant retardation in gastric and intestinal emptying time of the beads was observed. This was also suggested by the bioavailability of the model drug after intragastric and intranasal administration of the microspheres. The pharmacokinetic parameters after microsphere administration were more appropriate to a slow-release drug delivery system. Harikarnpakdee et al prepared spray-dried mucoadhesive microspheres for nasal delivery.[39] Microspheres composed of hydroxypropyl methylcellulose (H), chitosan (CS), Carbopol 934P (CP), and various combinations of these mucoadhesive polymers, and maltodextrin (M), colloidal silicon dioxide (A), and propylene glycol (P) as filler and shaper, were prepared using the spray-drying technique. Prepared microspheres were at loadings exceeding 80% and yields between 24% and 74%. Bulky, free-flowing microspheres with a particle size between 15 and 23 microns were obtained.

Ocular

Topical is the route of choice for the treatment of ophthalmic diseases because of the blood-ocular barrier. Achieving therapeutic concentrations in the eye via systemic administration necessitates the usage of such high systemic concentration that, in many cases, systemic side effects and toxicity results. Traditional ophthalmic formulations, such as aqueous solutions and ointments, have low (typically 2% to 10%) bioavailability of drugs due to the small surface area available for penetration, the presence of absorption barriers, and a number of precorneal elimination factors.[40] These elimination factors include drainage of instilled solutions: lacrimation and tear turnover, drug metabolism, tear evaporation, and possible binding to lachrymal proteins. To prolong the residence time of drugs in the pre-ocular area, bioadhesive drug delivery systems have been developed, taking advantage of the presence of a mucin-glycocalyx domain in the external portion of the eye.

Various bioadhesive systems employed for ocular delivery of drugs include the semi-solids, viscous liquids, solids/inserts, and the particulate DDS, including bioadhesive microspheres and liposomes. The advantages of microspheres, ie, increased residence time and decreased frequency of administration, were quite evident with chitosan microspheres of acyclovir and methyl prednisolone-loaded hyaluronic acid microspheres.[8,9] Acyclovir loaded chitosan microparticles showed an increased drug bioavailability in the eye as compared to the drug administered alone. Genta et al reported an approximately a four-fold increase in the aqueous humour concentration of suspension (39.37 µg/ml min) after a single instillation into the rabbit's eyes.[8] Increase in levels and the prolonged release of acyclovir from bioadhesive microspheres can be used to overcome the inconvenience caused by frequently applied ointments. The release of methyl prednisolone from hyaluronic acid ester films and microspheres has been investigated in vitro and in vivo (in tear fluid of rabbits).[8] Methyl prednisolone was either physically dispersed in the polymeric matrix or covalently linked to hyaluronic acid. Microspheres containing methyl prednisolone chemically bonded to the polymeric backbone of hyaluronic acid showed slower release of drug in vitro and produced sustained drug concentrations in the tear fluids of rabbits.

Durrani et al investigated the effect of these parameters on the precorneal clearance of In^{111}-labelled microspheres prepared using Carbopol 907.[41] Clearance of microspheres administered in dry form was faster than in the hydrated form, probably due to incomplete hydration in the tear fluid. The in vivo slow basal phase clearance constants were found to be 0.007 and 0.034 min^{-1} for the suspension of microspheres at a pH of 5.0 and 7.4, respectively. At pH 5, presence of protonated carboxyl groups permits enhanced adhesion due to hydrogen bonding between the polymer and mucin strands resulting in reduced clearance values. Clearance of microspheres that significantly limits their residence time in the ocular cavity is a direct function of the pH and hydration state of microspheres and follows a biphasic process with an initial rapid clearance followed by a much slower basal phase. The initial clearance phase is independent of the pH and hydration state, while the basal phase clearance value varies with these factors. Coating the microspheres with bioadhesive polymers has also been evaluated as a potential way of increasing the bioavailability. Chitosan-coated microspheres, which increased the bioavailability of indomethacin in rabbits and PEG-coated microspheres, resulted in an increased in the bioavailability of acyclovir.[42,43]

Vaginal

Traditionally, this route of administration is used for delivery of therapeutic and contraceptive agents to exert a local effect (antifungal, spermicidal) and for the systemic delivery of drugs.[44] It has been used for the delivery of drugs, which are susceptible to gastrointestinal degradation or hepatic metabolism following peroral delivery, eg, oestrogens and progestogens for the treatment of postmenopausal symptoms and for contraception. This route has also been explored for the delivery of therapeutic peptides, such as calcitonin and for microbicidal agents to help prevent the transmission of human immuno-deficiency virus and other sexually transmitted diseases. Using absorption enhancers, such as surfactants and bile salts, can increase absorption of peptides from the vagina. However, the adverse effects of absorption enhancers on the mucosal integrity can be bypassed by employing bioadhesive microspheres within the vaginal cavity.

The retention of microspheres made from a benzyl ester of hyaluronic acid (HYAFF) was studied using gamma scintigraphy in sheep.[44] The microspheres were either delivered as a dry powder or included in Suppocire BS_2X pessaries. A substantial percentage of the radiolabelled spheres remained in the vagina until the 12th hr after administration. The retention was greater for the dry powder formulation than for the pessary formulation, which the authors suggested might be caused by loss of microspheres on leakage of the molten base.

HYAFF microspheres have been successfully used for the incorporation of peptides, such as nerve growth factor and salmon calcitonin.[20] HYAFF microspheres have demonstrated good bioadhesive properties both in vitro and in vivo. In an unconscious rat model, these microspheres maintained contact with the vaginal epithelium for at least 6 hrs after administration. Hypocalcemic effects in the rat and sheep confirmed that absorption of salmon calcitonin was increased after administration of bioadhesive (HYAFF) microspheres compared with an aqueous solution of calcitonin.[22] HYAFF microspheres, due to their high biocompatibility and controllable degradation rate, have been used for the localized drug delivery of steroids, analgesics, anti-inflammatories, and anti-infectives. This has led to a

great deal of enthusiasm in the development of safe and effective bioadhesive vaginal contraceptive and anti-infective formulations to control pregnancy and help prevent the spread of STDs.[44]

Insulin was administered vaginally to sheep as an aqueous solution and as a lyophilized powder with bioadhesive starch microspheres. The effect of lysophosphatidylcholine (LPC) on the vaginal absorption of insulin from both formulations was studied. While the vaginal absorption of insulin from insulin solution was minimal, the addition of LPC resulted in a rapid rise in plasma insulin and a pronounced fall in plasma glucose levels. The absolute bioavailability of the peptide from the latter solution was 13%. The hypoglycaemic response to vaginally administered insulin was also improved using the microspheres delivery system, compared to insulin solution alone, and was further enhanced by LPC. Vaginal absorption of insulin from each formulation appeared to be influenced by the oestrous cycle and was thought to correlate with changes in vaginal histology.[45]

SUMMARY

Due to the large number of target sites of bioadhesive drug delivery systems, there are many formulations that may be explored for drug delivery purposes. Bioadhesive microspheres offer a unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue, including those found in the eyes, oral cavity, and throughout the respiratory, urinary, and gastrointestinal tract. The bioadhesive microspheres can be used not only for controlled release but also for targeted delivery of the drugs to specific sites in body. Recent advances in medicine have envisaged the development of polymeric drug delivery systems for protein/peptide drugs and gene therapy. Although significant advances have been made in the field of bioadhesives, there are still many challenges ahead in this field. Very important is the development of universally acceptable standard evaluation methods and development of newer site-directed polymers. Polymeric science needs to be explored to find newer bioadhesive polymers with the added attributes of being biodegradable, biocompatible, bioadhesive for specific cells or mucosa, and which could also function as enzyme inhibitors for the successful delivery of proteins and peptides. A multidisciplinary approach will therefore be required to overcome these challenges and to employ bioadhesive microspheres as a cutting-edge technology for site-targeted controlled-release drug delivery of new as well as existing drugs. The future direction of bioadhesive microspheres lies in vaccine formulation that adhere to the mucosal surface and result in mucosal immunity.

REFERENCES

1. Ikeda K, Murata K, Kobayashi M, Noda K. Enhancement of bioavailability of dopamine via nasal route in beagle dogs. Chem Pharm Bull.1992;40:2155-2158.
2. Nagai T, Nishimoto Y, Nambu N, Suzuki Y, Sekine K. Powder dosage form of insulin for nasal administration. J Control Release. 1984;1:15-22.
3. Illum L, Furraj NF, Critcheley H, Davis SS. Nasal administration of gentamycin using a novel microsphere delivery system. Int J Pharm. 1988;46:261-265.
4. Schaefer MJ, Singh J. Effect of isopropyl myristic acid ester on the physical characteristics and in vitro release of etoposide from PLGA microspheres. AAPS Pharm Sci Tech. 2000;1(4):article 32.
5. Hannah B. Novel bioadhesive formulation in drug delivery. In: The Drug Delivery Companies Report. Research and Markets: Dublin, Ireland. Autumn/Winter 2004;16-19.
6. Mathiowitz E, Chickering DE, Jacob JS. US Patent No. 6,197,346; 2001.
7. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. Int J Pharm. 2003;255:13-32.
8. Genta I, Conti B, Perugini P, Pavanetto F, Spadaro A, Puglisi G. Bioadhesive microspheres for ophthalmic administration of acyclovir. J Pharm Pharmacol. 1997;49:737-742.
9. Kyyronen K, Hume L, Benedetti L, Urtti A, Topp E, Stella V. Methylprednisolone esters of hyaluronic acid in ophthalmic drug delivery: in vitro and in vivo release studies. Int J Pharm. 1992;80;161-169.
10. Farraj NF, Johansen BR, Davis SS, Illum L. Nasal administration of insulin using bioadhesive microspheres as a delivery system. J Control Release. 1990;13:253-261.
11. Illum L, Farraj NF, Davis SS, Johansen BR, O'Hagan DT. Investigation of the nasal absorption of biosynthetic human growth hormone in sheep-use of a bioadhesive microsphere delivery system. Int J Pharm. 1990;63:207-211.
12. Critchley H, Davis SS, Farraj NF, Illum L. Nasal absorption of desmopressin in rats and sheep-effect of a bioadhesive microsphere delivery system. J Pharm Pharmacol. 1994;46:651-656.
13. Singh M, Briones M, O'Hagan DT. A novel bioadhesive intranasal delivery system for inactivated influenza vaccines. J Control Release. 2001;70:267-276.
14. Akiyama Y, Nagahara N. Novel formulation approaches to oral mucoadhesive drug delivery system. In: Mathiowitz E, Chickering DE, Lehr CM, eds. Bioadhesive Drug Delivery Systems-Fundamentals, Novel Approaches and Development. Marcel Dekker: New York, NY;1998:477-505.
15. Liu Z, Lu W, Qian L, Zhang X, Zeng P, Pan J. In vitro and in vivo studies on mucoadhesive microspheres of amoxicillin. J Control Release. 2005;102:135-144.
16. Akiyama Y, Yoshioka M, Horibe H, Inada Y, Hirai S, Kitamori N, Toguchi H. Anti-hypertensive effect of oral controlled release microspheres containing an ACE inhibitor (Delapril hydrochloride) in rats. J Pharm Pharmacol. 1994;46:661-665.
17. Patel JK, Patel RP, Amin AF, Patel MM. Formulation and evaluation of mucoadhesive glipizide microspheres. AAPS Pharm Sci Tech. 2005;6:49-55.
18. Patel JK, Amin AF, Patel MM. Formulation optimization and evaluation of controlled release mucoadhesive microspheres of glipizide for oral drug delivery using factorial design. Drug Delivery Technology. 2004;4:48-53.
19. Geary S, Schlameus HW. Vancomycin and insulin used as models for oral delivery of peptides. J Control Release. 1993;23:65-74.
20. Ghezzo E, Benedetti L, Rochira N, Biviano F, Callegaro L. Hyaluronane derivative microsphere as NGF delivery device: preparation methods and in vitro release characterization. Int J Pharm. 1992;87:21-29.
21. Illum L, Farraj NF, Fisher AN, Gill J, Miglietta M, Benedetti LM. Hyaluronic acid ester microsphere as a nasal delivery system for insulin. J Control Release. 1994;29;133-141.
22. Richardson JL, Armstrong TI. Vaginal delivery of calcitonin by hyaluronic acid formulations. In: Mathiowitz E, Chickering, DE, Lehr CM, eds. Bioadhesive Drug Delivery Systems - Fundamentals, Novel Approaches, and Development. Marcel Dekker: New York, NY; 1998:563-599.
23. Bogataj M, Mrhar A, Korosec L. Influence of physicochemical and biological parameters on drug release from microspheres adhered on vesical and intestinal mucosa. Int J Pharm. 1999;177:211-220.
24. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992;81:1-10.
25. Vyas SP, Jain CP. Bioadhesive polymer grafted starch microspheres bearing isosorbide dinitrate for buccal administration. J Microencap. 1992;9:457-464.
26. Longer MA, Ch'ng HS, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery, part III: oral delivery of chlorthiazide using a bioadhesive polymer. J Pharm Sci. 1985;74:406-411.
27. Carino PG, Jacob JS, Chen CJ, Santos CA, Hertzog BA, Mathiowitz E. Bioadhesive, bioerodible polymers for increased intestinal uptake. In: Mathiowitz E, Chickering DE, Lehr CM, eds. Bioadhesive Drug Delivery Systems-Fundamentals, Novel Approaches and Development. Marcel Dekker: New York, NY; 1998:459-475.
28. Akiyama Y, Nagahara N, Nara E, Kitano M, Iwasa S, Yamamoto I, Azuma J, Ogawa Y. Evaluation of oral mucoadhesive microspheres in man on the basis of the pharmacokinetics of furosemide and riboflavin, compounds with limited gastrointestinal absorption sites. J Pharm Pharmacol. 1998;50:159-166.
29. Nagahara N, Akiyama Y, Nako M, Tada M, Kitano M, Ogawa Y. Mucoadhesive microspheres containing amoxicillin for clearance of Helicobacter pylori. Antimicrob Agent Chemother. 1998;42:2492-2494.
30. Varshosaz J, Dehkordi JA. Golafshan S. Colon-specific delivery of mesalazine chitosan microspheres. J Microencap. 2006;23(3):329-339.
31. Soane RJ, Perkins AC, Jones NS, Davis SS, Illum L. Evaluation of the clearance characteristics of bioadhesive systems in humans. Int J Pharm. 1999;178:55-65.
32. Illum L, Jorgensen H, Bisgaard H, Krogsgaard O, Rossing N. Bioadhesive microspheres as a potential nasal drug delivery system. Int J Pharm. 1987;39:189-199.
33. Illum L. Bioadhesive formulations for nasal delivery. In: Mathiowitz E, Chickering DE, Lehr CM, eds. Bioadhesive Drug Delivery Systems-Fundamentals, Novel Approaches and Development. Marcel Dekker: New York, NY: 1998:519-539.
34. El-Shafy AM, Kellaway IW, Taylor G, Dickinson PA. Improved nasal bioavailability of FITC-dextran from mucoadhesive microspheres in rabbits. J Drug Target. 2007:355-361.
35. Morimoto K, Katsumata H, Yabuta T, Iwanaga K, Kakemi M, Tabuta Y, Ikada Y. Evaluation of gelatin microspheres for nasal intramuscular administrations of salmon calcitonin. Eur J Pharm. 2001;124:173-182.
36. Callens C, Ceulemans J, Ludwig A, Foreman P, Remon JP. Infuence of multiple nasal administrations of bioadhesive powder on the insulin bioavailability. Int J Pharm. 2003;250:415-422.
37. Edman P, Bjork E, Ryden L. Microspheres as a nasal delivery system for peptide drugs. J Control Release. 1992;21;165-172.
38. Preda M, Leucuta SE. Oxprenolol-loaded bioadhesive microspheres: preparation and in vitro/in vivo characterization. J Microencap. 2003;20:777-789.
39. Harikarnpakdee S, Lipipun V, Sutanthavibul N, Ritthidej GC. Spray-dried mucoadhesive microspheres: preparation and transport through nasal cell monolayer. AAPS Pharm Sci Tech. 2006;7(1):Article 12.
40. Saettone MF, Burgalassi S, Chetoni P. Ocular bioadhesive drug delivery systems. In: Mathiowitz E, Chickering DE, Lehr CM, eds. Bioadhesive Drug Delivery Systems-Fundamentals, Novel Approaches, and Development. Marcel Dekker: New York, NY; 1998:629-630.
41. Durrani AM, Farr SJ, Kellaway IW. Precorneal clearance of mucoadhesive microspheres from the rabbit eye. J Pharm Pharmacol. 1995;47:581-584.
42. Calvo P, VilaJato JL, Alonso MJ. Evaluation of cationic polymer-coated nanocapsules as ocular drug carriers. Int J Pharm. 1997;153:41-50.
43. Fresta M, Fontana G, Bucolo C, Cavallaro G, Giammona G, Puglisi G. Ocular tolerability and in vivo bioavalability of poly(ethylene gycol) (PEG)-coated polymethyl-2-cyanoacrylate nanospheres-encapsulated acyclovir. J Pharm Sci. 2001;90:288-297.
44. Richardson JL, Whetstone J, Fisher NF, Watts P, Farraj NF, Hinchcliffe M, Benedetti L, Illum L. Gamma scintigraphy as a novel method to study the distribution and retention of a bioadhesive vaginal delivery system in sheep. J Control Release.1996;42:133-142.
45. Richardson JL, Farraj NF, Illum L. Enhanced vaginal absorption of insulin in sheep using lysophosphatidylcholine and a bioadhesive microspheres delivery system. Int J Pharm. 1992;88:319-325.

BIOGRAPHY

Dr. Jayvadan K. Patel is an Assistant Professor in Pharmaceutics at the Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Gujarat, India, with 11 years of teaching and research experience. He has supervised 19 MPharm thesis candidates and has 50 publications in international and national journals of repute. His area of research includes novel drug delivery systems and bioadhesive technology. He has presented research papers and delivered lectures in the UK, US, and Singapore. He can be reached at jayvadan04@yahoo.com.

DRUG DELIVERY Executive

EURAND

EURAND: CREATION OF ADVATAB® - A NEW TECHNOLOGY FOR ORALLY DISINTEGRATING TABLETS

Eurand has successfully established itself as a leading innovator in drug delivery, and a proven developer of specialty pharmaceutical products. An example of Eurand's track-record of innovation in the drug delivery field is the development and commercialization of a new technology platform for orally disintegrating tablets (ODTs). Eurand entered into this area of drug delivery, initially with the development of its Ziplets® technology, then followed with the licensing of certain technologies from the Japanese company Kyowa Hakko Co., Ltd. in early 2003. Eurand created a new brand, AdvaTab®, for the technology and initiated efforts to promote the advantages of the new technology. Four years later, Eurand has multiple AdvaTab products under internal development, and has announced co-development partnerships that are leveraging the technology to create important life-cycle management opportunities for its partners. Drug Delivery Technology recently interviewed Mr. John Fraher, Chief Commercial Officer of Eurand, to discuss the company's successful strategy behind AdvaTab and how Eurand views its co-development programs in light of its specialty pharma growth strategy.

Mr. John Fraher
Chief Commercial Officer
Eurand

"We also signed a very significant co-development agreement with GlaxoSmithKline in 2006 for the development of an ODT formulation for an undisclosed GSK compound. The GSK transaction provides Eurand with attractive commercial terms, and as a big pharma partner, this collaboration provides us with further validation of the AdvaTab platform. The GSK program is progressing toward an NDA filing later this year."

Q: What prompted Eurand to enter into the highly competitive field for ODTs?

A: Our strategy is to develop enhanced pharmaceutical and biopharmaceutical products based upon our drug formulation technologies. To support that strategy, we continue to improve and acquire innovative drug delivery technologies that can contribute to the development of products that can offer therapeutic, market, and patient benefits. We identified the orally disintegrating tablet field in the late 90s as an area in which we wanted to create new technologies to complement our taste-masking platform, Microcaps. We also believed there was a need in the marketplace for an effective dosage form that met the needs of certain patients, such as pediatrics and geriatrics among others, who have difficulties in swallowing standard tablets and capsules. In addition, our customers had consistently expressed interest in combining our market-leading taste-masking, controlled-release, and solubility enhancement technology platforms with the benefits of an ODT. We

saw the opportunity to leverage our broad technology base by coupling it with a superior ODT technology.

Q: What strategy has Eurand employed for its ODT franchise?

A: In 1999, we developed an ODT technology, Ziplets, which was an ODT suitable for certain products and markets. This technology was successfully commercialized by Novartis, which launched a product, Cibalgina DueFast, in certain European countries. This product combined our Ziplets ODT with our Microcaps® ibuprofen product. We obtained a number of issued patents for this technology worldwide.

As is our strategy with a number of our technologies, we wanted to develop a broad platform that would provide us with solutions to the many formulation challenges presented by the wide variety of molecules in the marketplace. This was also true for our ODT platform. We wanted to be able to combine our ODT products with our other technologies, be able to provide high-drug loading even for extremely bitter drugs, and create a product that could be packaged in standard packaging materials, such as bottles and standard blister packs.

We identified an ODT technology that had been developed by Kyowa Hakko in Japan, which we believed would be complementary to our other technology and meet our requirements for the entire ODT platform. Kyowa had successfully commercialized the technology in Japan with two products. We entered into a licensing arrangement with Kyowa that provided us with exclusive rights to the technology worldwide, except for Japan, where we have semi-exclusive rights with Kyowa. This technology has now been trademarked as AdvaTab.

So, we now have two technologies within the ODT platform. Both have been successfully commercialized, and we now have flexibility in applying the appropriate technology to deliver the desired formulation development outcomes. Due to the unique characteristics of AdvaTab, the majority of our ODT product development programs use this technology.

Q: What are the advantages of Eurand's ODT technologies versus other technologies?

A: One of the most important features of an ODT is its taste – Eurand can combine AdvaTab with our Microcaps technology, which is recognized as one of the foremost taste-masking technologies in the industry. For many years, we supplied a range of Microcaps taste-masked products to other ODT companies, and we observed that they generally encountered difficulties in maintaining taste integrity with their products and processes. When we develop a product, we take an integrated development approach in that the ODT and Microcaps are developed as one product, thereby ensuring that we maintain taste integrity while achieving the desired characteristics of an ODT, such as oral disintegration time, physical requirements for the tablet, stability etc. Additionally, AdvaTab can be combined with our Diffucaps® controlled-release technology to develop highly differentiated CR ODT products. Our ODTs differ from

others on the market in that the tablets are less friable, can incorporate high-drug loading, are cost-effective to manufacture and package, and can be applied to actives that are soluble or insoluble. We saw these as key differentiation factors that made entry into this field strategically sound.

Q: How did Eurand go about implementing and creating a new ODT brand, AdvaTab, in a crowded field?

A: There were a number of initiatives we had embarked upon to establish the new technology platform and take advantage of the market opportunity. We formed a cross-functional global integration team to represent the key areas required to make AdvaTab successful – R&D, Intellectual Property (IP), Commercial, and Operations worked closely together on the project. We decided to make Eurand's Vandalia, Ohio, site the "center-of-excellence" for the AdvaTab technology. The R&D team at that site was responsible for the technology transfer to the company and also for establishing a comprehensive development program to expand the application of the technology. The IP team was responsible for continued prosecution of the patent estate we acquired, and continues to pursue patent applications that extend the utility of the technology and integrate it with our other technologies. The commercial team established a worldwide strategy for differentiating the technology in the marketplace and created the AdvaTab brand name, marketing materials, and an advertising campaign. Also, our operations staff began scale-up trials as soon as the technology was transferred so we could demonstrate the capacity and validation goals necessary to attract co-development partners. Finally, the integration team selected several internal programs to work on to demonstrate the capability of the technology.

Q: What product development efforts has Eurand initiated?

A: Once the technology transfer was complete, we initiated a number of product development programs that would expand the boundaries of the technology. We used high-dose active ingredient molecules, molecules with known stability issues, and a variety of Microcaps products to create the specifications for the AdvaTab technology. We also conducted pharmacokinetics studies on one of those products, Cetirizine, to demonstrate that we were able to achieve bioequivalence with immediate-release dosage forms. In parallel, our business development team began promoting the new AdvaTab technology to potential customers worldwide. Our competitive differentiation combined with the continued growth of the ODT marketplace began to pay dividends. To date, we have completed seven co-development agreements for this technology platform in the past 2 years. For confidentiality reasons, a number of these projects have not been made public. Some that have been announced include, EUR-1047, a project with Pfizer Consumer Healthcare, now J&J, for a new ODT formulation of the Benadryl® product line. We are very pleased that this new and improved formulation should be available on US pharmacy

shelves this quarter. We also signed a very significant co-development agreement with GlaxoSmithKline in 2006 for the development of an ODT formulation for an undisclosed GSK compound. The GSK transaction provides Eurand with attractive commercial terms, and as a big pharma partner, this collaboration provides us with further validation of the AdvaTab platform. The GSK program is progressing toward an NDA filing later this year.

In November 2006, Questcor, a US specialty CNS company, announced the filing of an IND for a formulation of Acetaminophen/Hyrocodone product developed using our AdvaTab and Microcaps technologies. We are very pleased to have entered into these co-development partnerships and others, and we consider it as a validation of our technologies, intellectual property, and development capabilities that such companies chose Eurand as their partner for these projects.

It is worth mentioning that in all of our license transactions, Eurand retains manufacturing rights as we have a core competency in this component of our business, and it provides us with more control of our intellectual property. In terms of strategy, we will continue to offer this state-of-the-art technology to our current and future partners, and we will continue to apply it to a select number of our internal pipeline candidates.

Q: Looking forward, how do you see Eurand growing and evolving?

A: Our strategy is to be a leader in the development, manufacturing, and commercialization of innovative specialty pharmaceutical and biopharmaceutical products. We have had three products approved by the FDA since 2000, and we have a pipeline of products in development for ourselves and our co-development partners. Our lead product candidate, EUR-1008, is a new proprietary enzyme replacement product for the treatment of exocrine pancreatic insufficiency (EPI). EPI is a deficiency of digestive enzymes normally produced and secreted by the pancreas, and it can result from a number of diseases, including cystic fibrosis, chronic pancreatitis, and other diseases. The product has completed Phase III clinical trials in the United States. Additionally, we intend to continue to enter into co-development partnerships with other pharmaceutical companies. We believe that we are an attractive partner for larger pharmaceutical companies due to our broad portfolio of proprietary technologies, our development track- record, and our multinational infrastructure and manufacturing capabilities. In 2005, we had revenues of approximately $92 million, primarily from sales of products using our formulation technologies that our co-development and licensing partners commercialize. In 2006, we signed six new co-development agreements with companies located in the United States, Europe, and Japan. We foresee continued growth of our company as these products are commercialized. ◆

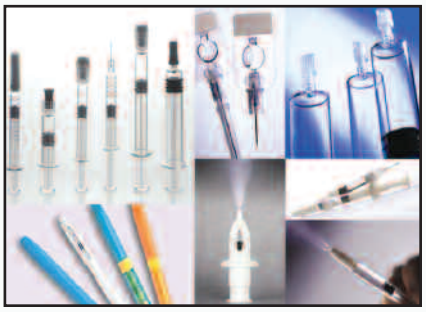
Technology Showcase

Transdermal & Film Delivery

AVEVA Drug Delivery Systems
A Nitto Denko Company

Aveva Drug Delivery Systems owns proprietary transdermal formulation and manufacturing technologies that focus on elegant "matrix" patch designs for the incorporation of drugs into adhesives that attach the patch to the skin. 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 to suit particular drug characteristics and product needs, and rapidly developed from feasibility stage through clinical and commercial production stages. The company provides vertical integration of adhesive, film coating, and transdermal formulation technologies to produce the most efficient and cost-effective products. The company is applying its transdermal delivery system technology to proprietary as well as generic drugs. Patches can be designed to deliver from 1 through 7 days. For more information visit Aveva DDS at **www.avevadds.com**.

Prefillable Delivery Systems

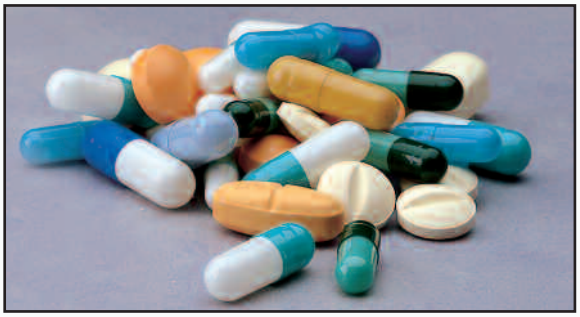


BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. Whether a glass or plastic prefillable syringe, a nasal spray system, a dry drug reconstitution system, an injection or self-injection device, BD Medical - Pharmaceutical Systems provides the expertise and experience required by the pharmaceutical industry in a packaging partner. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. All of its prefillable devices are designed to meet healthcare professionals' demands for safety and convenience and to fulfill patients' needs for comfort. BD's worldwide presence, market awareness, and pharmaceutical packaging know-how allow it to propose suitable solutions for all regional markets and parenteral drug delivery needs. For more information, contact BD Medical - Pharmaceutical Systems at (201) 847-4017 or visit **www.bdpharma.com.**

Micro-Filling System

With the Xcelodose™ system, creating manufacturing batches for clinical trials and small-scale production has never been easier or more precise. This unique technology allows companies to fill capsules with drug substances alone, thereby eliminating the need for excipient compatibility and preformulation activities. By implementing the Xcelodose system, pharmaceutical companies benefit from a shorter drug development process by reducing the need for costly and time-consuming stability studies, not to mention the avoidance of labor costs and possible inaccuracies associated with hand-filling. This in turn reduces the time taken to reach the "first-in-man" clinical trial decision point, which allows for an increase in throughput of candidate compounds for development. For more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com.**

Oral Modified-Release Technologies



The Pharmaceutical Technologies and Services Group of Cardinal Health is the global leader in development, drug delivery technologies, contract manufacturing, and packaging, serving the pharmaceutical and biotechnology industries. We have a range of experience with innovative and traditional controlled-release technologies, such as EnCirc® pellets for higher drug loading and uniformity of dose, which can be used for immediate- and controlled-release capsules and tablets; EnVel® system for taste-masking, which can greatly improve patient acceptance of Rx or OTC chewable tablets; and EnSolv® for improved dissolution, which can provide a formulation solution for new chemical entities as well as extend life cycles of many marketed products. For more information, contact Cardinal Health at (866) 720-3148 or pts@cardinal.com to explore how our advanced delivery technologies can enhance your drug's performance.

Technology Showcase

Polymers & Delivery Technologies

Pharma Polymers is one of the world leaders in the manufacturing and supplying of functional coatings for the pharmaceutical industry. EUDRAGIT® polymers are ideal for Enteric Delivery, Controlled Release, and Protective Coatings. Based on more than 50 years of experience in EUDRAGIT® polymer design and formulation know-how for pharmaceutical applications, Pharma Polymers has developed intellectual property on advanced oral drug delivery technologies. The different brands of EUDRAPULSE™, EUDRACOL™, and EUDRAMODE™ are the achievements of this intensive research and development effort so far. Pharma Polymers' business models for commercialization of these drug delivery technologies range from the development of customer-specific solutions to out-licensing strategies. For more information, contact Degussa Corporation, Rohm America LLC at (877) 764-6872 (Option 4) or visit **www.pharma-polymers.com**

Drug Development Services

DPT Laboratories, Ltd, is a fully integrated contract development and manufacturing organization (CDMO) that specializes in semi-solid and liquid dosage forms. Through innovation, technology, and service, the company delivers drug development and manufacturing solutions to the world's leading pharmaceutical, biotechnology, and consumer healthcare companies. Drug development services range from preformulation, formulation and biopharmaceutical development, analytical development and validation, through process development. Specialized production capabilities include four cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-IV, and complete supply chain management. Packaging services encompass engineering and procurement resources necessary for both conventional and specialized packaging. To get your next product to market fast and with confidence, contact DPT – The Industry Source for Semi-Solids and Liquids.SM For more information, contact DPT at (866) CALL-DPT or visit **www.dptlabs.com**.

Custom Manufacturing Services

DSM Pharmaceuticals, Inc. is a business unit of DSM Pharmaceutical Products, a global provider of custom manufacturing services to the pharmaceutical and biopharmaceutical industries. DSM Pharmaceuticals provides a breadth of manufacturing services in the areas of steriles, orals, and topicals, including dose form manufacturing; scheduled drugs; clinical manufacturing Phase I,II, and III; fill finish manufacturing; and lypholization services. 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 Pharmaceuticals at (973) 257-8011 or visit **www.dsmpharmaceuticals.com**.

Filtration Products

Filtertek, a leading designer and manufacturer of filters, recently launched a new line of 50-mm filtration products. This product line is designed for venting or liquid filtration applications in the biotechnology, pharmaceutical, and food and beverage industries. Filtertek's 50-mm products are offered in either an over-molded or welded version in a wide range of standard inlet/outlet connection options. Whether for sterilization of gasses for medical procedures, microbial filtration of protein solutions, or venting applications, Filtertek can provide membrane alternatives for the customer to qualify and validate for its particular application. For more information, visit the Filtertek at **www.filtertek.com**.

DRUG DELIVERY Executive
Corium

CORIUM: NEW DIMENSIONS IN TRANSDERMAL SOLUTIONS

Gary W. Cleary, PhD
President & CTO
Corium International, Inc.

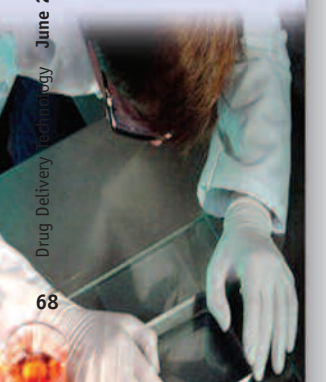
"We have products in several therapeutic areas, including CNS, cardiovascular, and endocrine to name a few. We also have a number of vaccine candidates. The passive products in development have never been delivered transdermally before, and the active products include drug molecules that previously have been administered by injection."

Corium International, Inc. is a privately owned company engaged in the research, development, and manufacture of advanced transdermal drug delivery technologies and therapeutic products. Through the combination of its proprietary delivery technologies and its development and manufacturing expertise, Corium has developed a range of novel transdermal products. Corium also enjoys a strong patent estate with 150 US and international issued and pending patents protecting its drug delivery technologies, processes, and expertise. Drug Delivery Technology recently interviewed Dr. Gary W. Cleary, Co-Founder, President, and Chief Technology Officer of Corium to discuss the exciting opportunities on the forefront of novel drug delivery.

Q: Please give us an overview of Corium and your business model.

A: Corium was established in 1999, and is a privately owned company engaged in the research, development, and manufacture of advanced transdermal drug delivery technologies and products. My business partner and Co-Founder Adrian Faasse and I have been involved in the transdermal medical product field for more than 3 decades. Our experience dates back to the introduction of the first transdermal patch products introduced into the market. We started Corium because we saw a need in the marketplace for a company that could deliver innovative transdermal solutions from concept to commercialization. And hence, the Corium mission was born.

Initially, Corium funded itself by utilizing its proprietary technologies and web-based manufacturing expertise to develop and manufacture non-prescription products on a contract basis. This strategy provided a steady revenue stream that allowed us to further the development of our polymer technology platform called Corplex™, and begin internal development of transdermal Rx products. Today, Corium has



many partner-funded projects for transdermal forms of FDA-approved drugs as a result of this effort.

In 2005, after acquiring a mechanical microporation technology from Procter & Gamble, Corium began to fund development of its own proprietary products. These self-funded products are based on both the Corplex polymer technology as well as the microporation technology we call MicroCor™.

Our business model has evolved from a contract development and manufacturing partner model to a concentrated focus on the development of proprietary self-funded products. Our goal is to develop and fund these products through Phase I or II clinical trials and subsequently seek a commercial marketing partner. We will continue to entertain contract transdermal opportunities and out-license any non-strategic intellectual property with significant market potential, but our mission remains firm: to emerge as the leader of transdermal products in the marketplace.

Q: Can you describe your drug delivery technologies to our readers?

A: As I just mentioned, we have two core proprietary technologies that allow us to deliver both small and large molecules through the skin. MicroCor is the active transdermal technology that we acquired from P&G. Specifically, it is a proprietary mechanical microporation technology, sometimes referred to as "microneedles," that creates temporary micropores in the skin to enable the painless transdermal delivery of larger molecules like therapeutic proteins and vaccines. Since acquiring MicroCor, we have significantly enhanced the technology and now have an impressive patent portfolio consisting of over 65 issued and pending US and international patents.

Our Corplex technology is a versatile polymer technology that can be utilized in many drug delivery and medical product applications — not just a traditional transdermal patch. Corplex consists of a composite blend of non-adhesive hydrophilic polymers that can be processed such that the resulting product can stick to either dry or wet surfaces. Unlike typical pressure-sensitive adhesives that lose "tack" when the surface of the substrate becomes wet, Corplex can maintain its adherence to moistened skin and can even adhere to very hydrated biological tissues, such as the oral mucosa. Corplex can be developed so that it dissolves in a matter of seconds (like an oral dissolving film) or can adhere for several days in a conventional transdermal patch. Corplex is covered by a patent portfolio of more than 80 issued and pending US and international patents.

Q: How does mechanical microporation differ from other "active transdermal" technologies? Does MicroCor have any advantages over the other mechanical microporation technologies in development?

A: Mechanical microporation is one of several "active" transdermal technologies. First, let's take a step

back and compare "passive" to "active" technologies. When a conventional passive patch is adhered to the skin, the drug simply diffuses through the upper layers of the skin into the dermis where it accesses the blood vessels to reach the systemic circulation. In order for this process to happen, the drug must be lipophilic and have a low molecular weight and dose, that's why there are relatively few drugs that are available in conventional patch form. In contrast, "active" transdermal technologies utilize some mechanism to cause a "temporary" disruption of the stratum corneum to create a passage way, like a tunnel, through the skin layers so the drug can more readily reach the systemic circulation. Because you are creating an artificial micropore in the skin, additional types of molecules, such as macromolecules and hydrophilic small molecules, can now traverse the skin. The "active" mechanisms to porate the skin include heat, electricity (iontophoresis), ultrasound, radiofrequency, and mechanical (microneedles). Most mechanical microporation technologies include a microthin array of microstructures that can penetrate the skin when an external force is applied. In my opinion, mechanical microporation offers advantages over other active transdermal technologies in that its simpler format does not require a separate power source, so the regulatory and development risk profiles are lower.

Now, let me explain the advantages that MicroCor offers over other mechanical microporation technologies. As far as we are aware, we are the only company in this space that has a fully integrated device that incorporates the microstructure array, drug, and force applicator. The other mechanical technologies have a separate force applicator device that causes the microstructure array to porate the skin and applies a drug-containing patch to the skin. With our system, the patient would simply apply the patch using a small amount of pressure with the forefinger or thumb, wear it for a predetermined period of time, and remove. It is extremely user-friendly and provides a convenient, painless way to deliver drugs that are normally administered by injection.

In addition to the integrated system design, Corium has a number of proprietary mechanisms to associate the drug with the microstructures to maximize the amount of drug that is delivered to the skin (drug-sparing). We also have the ability to deliver the drug in a controlled fashion after the patch is removed. Finally, we are able to produce this integrated system at a very low cost with an enhanced safety profile, positioning us uniquely in this marketplace.

Q: What types of molecules are most suitable for MicroCor?

A: That's the beauty of MicroCor. The possibility for delivering drug molecules is infinite. As I mentioned earlier, we can deliver large therapeutic proteins and vaccines as well as small, high-dose hydrophilic drugs. We have even demonstrated the ability to deliver particles as large as 1 micron in size into the skin in vitro. MicroCor can also be used broadly across many therapeutic areas from pain, cardiovascular, endocrine, and depression to neurological diseases, autoimmune diseases, and vaccines.

Q: Can you talk about your product pipeline? How do you plan to commercialize your products?

A: Currently, our product pipeline consists of both previously executed partner-funded projects as well as our self-funded proprietary projects. The partner-funded projects are made up of several passive transdermal products and range in clinical status from Phase I to awaiting final FDA approval. For most all of these projects, Corium will also manufacture the commercial product. The proprietary pipeline products utilize our MicroCor and Corplex technologies and offer both active and passive drug delivery. We have products in several therapeutic areas, including CNS, cardiovascular, and endocrine to name a few. We also have a number of vaccine candidates. The passive products in development have never been delivered transdermally before, and the active products include drug molecules that previously have been administered by injection. Corium plans to introduce the first of these products to the marketplace by 2011.

As mentioned previously, Corium plans to take its proprietary pipeline through Phase I or II trials before seeking a commercial marketing partner. This strategy takes significant development risk off the table for our potential partner and in turn provides Corium with increased rewards. Corium is uniquely positioned because we are fully equipped to manufacture both passive and active transdermal products in all regulatory/clinical phases from Phase I through continuous commercial supply. I like to think of us as Films 'R' Us.

Q: Have any products been commercialized with either Corplex or MicroCor?

A: Yes, we initially developed non-prescription products as a means to ensure a faster stream of income in the early days. As such, we have had the opportunity of developing and manufacturing some excellent oral care, foot care, and wound care products based on our Corplex technology for some of the largest marketers in these areas. We also have several prescription transdermal products in various stages of development that utilize Corplex, including some awaiting final FDA approval. Our MicroCor products are in earlier stages of development and have yet to be commercialized.

Q: Where do you see the company in 5 years and beyond?

A: These are very exciting times for the drug delivery industry. In 5 years, Corium will be on the forefront of novel transdermal drug delivery. The combination of our Corplex and MicroCor technologies will yield truly market-disrupting products. The conventional needle will be replaced with a painless, self-administered, easy-to-use patch. Drugs taken by injection will now be as simple as putting on a Band-Aid. Beyond that, you'll see more technologies converging and emerging. Corium's ingenuity will play a role in personalized medicine that will biosample, monitor, and deliver biomolecules, all integrated into a single wearable device. Imagine the advancement of the medical world with such effective, affordable, and available treatments for disease. ◆

SPECIALTY PHARMA
Strategies For Business Development

Clinical Trials

Imaging CROs & Their Impact on Clinical Trials

By: **Richard Taranto,**
President, WorldCare Clinical, LLC

Introduction

As the use of medical imaging in clinical trials increases, imaging biomarkers are more frequently accepted as surrogate endpoints. In many cases, imaging technologies, such as computed tomography (CT) and magnetic resonance imaging (MRI), and functional imaging techniques, such as dynamic contrast enhanced (DCE)-MRI, and nuclear medicine techniques, such as positron emission tomography (PET), can help prove the efficacy and safety of drug therapies and medical devices faster than traditional clinical endpoints.

Medical imaging can help biopharmaceutical and medical device companies meet the demands of the continued market pressure to shorten the therapeutic development process. By changing the way disease progression is measured, medical imaging can assist clinical trial sponsors in increasing their clinical trial efficiency and decreasing their costs.

Clinical trial sponsors turn to organizations variously known as imaging core laboratories, central imaging laboratories, or imaging CROs to manage the medical imaging process for clinical trials. For clarity, this article will use the term imaging CRO to describe these organizations.

A critical component of many successful clinical trials, the imaging CRO helps to secure the collection of consistent, high-quality imaging data and ensure minimal variability through central reading. Imaging CROs guide the sponsor in designing appropriate imaging acquisition protocols and provide the services to implement and manage the imaging portions of trials, including imaging site qualification and coordination, independent radiologist reading services, quality control, regulatory submissions, and other related tasks.

An imaging CRO can increase the overall efficiency of the clinical trial program and decrease the costs associated with the overall development of a compound by reducing the length of a clinical trial. With the appropriate expertise, an imaging CRO will be able to assist in imaging trial design and acquisition protocols that can potentially reduce the study's size and duration.

There are several critical qualities to consider when choosing a central imaging CRO. These qualities, which include knowledge of specific operational procedures, access to therapeutic and modality expertise, adherence to rigid quality control processes, use of technology that improves workflow, and the ability to provide regulatory support, should be evaluated carefully as they can significantly influence the success of a clinical study.

Operational Procedures

Imaging CROs manage physician readers using various operational procedures. An imaging CRO may rely only on in-house radiologists or it may outsource the reading to a number of independent radiology groups, a single "nighthawk" radiology group, or a research-based academic institution or hospital.

Some imaging CROs focus on providing services for specific therapeutic areas, while others are dedicated to specific measurement modalities, tools, or other technologies. Regardless of the modality and therapeutic focus, an imaging CRO must have the necessary reading expertise and technology in place to manage a trial with a specific modality and therapeutic outcome.

Therapeutic & Modality Expertise

Regardless of the operational model the imaging CRO relies upon, its readers should be board-certified radiologists with relevant experience in the therapeutic area and affected anatomical region being studied for a particular protocol. Some imaging CROs may specialize in certain disease states, such as oncology or musculoskeletal diseases.

The imaging CRO must have access to enough seasoned radiologists to efficiently control both small and large volumes of images and data. The capacity to conduct small studies and quickly scale to manage large trials means that trial sponsors are not burdened with additional fixed costs or delays as the imaging CRO works to find additional radiology support.

Imaging CROs that deploy several radiologists from the same hospital, university, or reading services organization have an edge in reducing reading variability because all physicians are similarly trained and have the same "reading culture." When all radiologists belong to the same organization, any issues that arise can be addressed immediately and consistently.

Before each trial, the imaging CRO should require that all study radiologists complete training that ensures a low variability level between image reads, resulting in the generation and submission of consistent data. Variability training should cover intra-variability — the variability in image reads produced by a single reader — and inter-

variability — the variability in image reads among multiple readers.

To ensure low variability, the imaging CRO determines the variability threshold, a certain percentage that variability should not exceed. During variability training, radiologists evaluate representative scans, discuss the review process of the relevant imaging modalities, determine a standardized assessment procedure, and complete an independent assessment of test scans that are compared to confirm that intra- and inter-variability is within the appropriate limits.

The trial must then be monitored continually to make certain that variability stays below the variability threshold. If more than one radiologist is reading cases, a lead radiologist should serve as the gold standard.

In addition to therapeutic knowledge, imaging CROs should have access to major imaging modalities (or its specific expertise) used in clinical trials. Some frequently used and emerging imaging modalities are:

- Magnetic resonance imaging (MRI), a technology that uses magnets and radio waves to produce two- and three-dimensional images and is particularly well-suited for the study of soft or non-calcified tissues.

- Computed tomography (CT), an X-ray-dependent technology that provides two- and three-dimensional images that are ideally used to view bones and detect calcified areas, air, and gas.

- Positron emission tomography (PET), a new technique that is growing in importance because it can provide researchers with metabolic data about disease status.

- Dual energy X-ray absorptiometry (DEXA), a technique used to measure bone mineral density that is considered the gold standard for osteoporosis trials.

- Dynamic contrast enhanced (DCE)-MRI, a specialized MRI technique that can show metabolic changes, such as the rate of blood flow to a tumor.

Quality Control & Data Variability

Imaging for clinical trials is often conducted at multiple global sites, perhaps with substantial differences in equipment, acquisition techniques, or post-processing software tools. Data variability increases with the number of imaging sites in a clinical trial. The imaging CRO is responsible for verifying that the image acquisition was managed according to the acquisition protocol, and must regularly provide feedback to the imaging sites to ensure that consistent, high-quality data is obtained. In addition to having seasoned radiologists who have been trained to read images for each specific trial, a precise and well-documented quality control (QC) process is required to reduce data variability.

A thorough QC process will include a rigorous qualification process for imaging sites, a review of equipment variability at all participating facilities, technical support to imaging sites, and quality control of images. It should extend to all parts of the imaging protocol, from the protocol and imaging charter design through the regulatory submissions process.

Technology & Efficient Workflow

Imaging CROs should have state-of-the-art technology at their disposal, such as:

- Picture archiving and communications systems (PACS), the radiology image, and information management system that stores, retrieves, transmits, and displays digital images and patient information.

- Software applications, preferably customized to meet the needs of each specific study, that provide a complete audit trail, centralized database, and image manager that tracks the image as it moves from the imaging site to the independent review process.

- A secure portal, or intuitive user interface, for administering the receipt and processing of scans, managing queries with the imaging sites, and providing the sponsor with an instant view of the status of a trial.

- Site communication software that notifies the imaging site of

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In addition to guaranteeing high-quality data, advanced technology ensures the most logical and efficient workflow among the imaging sites, the CRO, and the trial sponsor. A smooth and productive operational process enables the imaging CRO to meet the trial sponsor's demand for fast turnaround times, without sacrificing data quality.

Quality Assurance & Regulatory Support

Imaging CROs must develop and execute imaging studies that conform to the Good Clinical Practice guidelines. The imaging CRO is often responsible for compiling, archiving, and submitting imaging data to the regulatory agency once the study is completed. The imaging CRO's quality assurance process — a systematic and independent examination of all trial-related activities and documents — determines whether the imaging process was appropriately conducted and the data was accurately generated, recorded, analyzed, and reported according to the protocol, standard operating procedures, and good clinical practice.

The study methods and analysis must be defined, monitored, and audited, and the resulting data must be verified, archived, and submitted according to regulatory requirements. For example, the FDA emphasizes blind readings with a physician reader that is independent of the sponsor and the clinical site.

In addition to imaging charter development and submitting data for regulatory audit and approval, the imaging CRO should be evaluated on its ability to support the trial sponsor at meetings with regulatory agencies, respond to agency questions about image analysis and management, produce electronic data sets for case report tabulations and reports that meet electronic submissions requirements, and log and track regulatory correspondence.

Summary

An experienced imaging CRO assists the clinical trial sponsor in developing imaging trial design and acquisition protocols that can potentially reduce the study's size and duration. As medical imaging continues to increase overall clinical trial efficiency and decrease development costs by reducing trial length, imaging CROs will continue to play a critical role in managing the clinical trial medical imaging process.

In evaluating the abilities of an imaging CRO, clinical trial sponsors must consider its operational procedures, access to therapeutic and modality expertise, adherence to stringent quality control processes, use of workflow-improving technology, and the ability to provide regulatory support. A proven track-record in managing images from around the globe for different therapeutic indications, combined with access to radiologists with the relevant therapeutic expertise, is the best indicator of an imaging CRO's ability to successfully manage and submit an imaging study. ■

Richard Taranto

President
WorldCare Clinical, LLC

Mr. Taranto has been in the clinical trial imaging industry since 1997 and has experience managing multiple clinical imaging trials for biopharmaceutical and medical device companies. Mr. Taranto has overseen more than 25 Phase II-IV studies in multiple therapeutic areas, including oncology, cardiology, diagnostic imaging, and women's health. He also has extensive experience with multiple imaging modalities, such as MRI, CT, bone scan, echocardiogram, ultrasound, and radiograph imaging studies.

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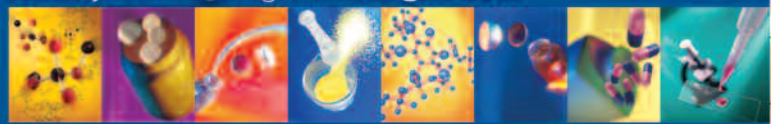


Facts & Figures

Bionumbers: Specialty Pharma Market Indices Through April 30, 2007

Index Trends

Like the Big Market, both of the Specialty Pharma indexes were on a run in April. The Commercial Stage Specialty Pharma Index (CSPI) was up almost 7% for the month and 11% for year-to-date, while the Emerging Specialty Pharma Index (ESPI) was up 5% for the month and 4% for the year. Through the middle of May, the CSPI has held onto its April gains, while the ESPI has slumped to end of 2006 values.

Commercial Stage Index Trends (CSPI)

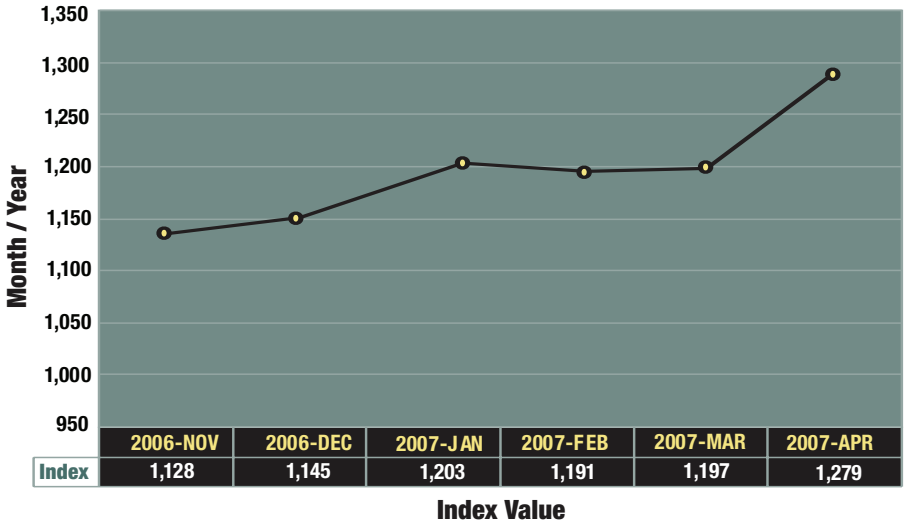
The strong keep getting stronger. Except for Abraxis, the top five companies by market capitalization are all up by 19% or more for the year. The leading gainers for the year on a percentage basis are to be found in the small to mid-cap companies, with Avanir picking itself up off the canvas for a remarkable 80% YTD gain. Even the laggards have either stopped their slide or shown a gain for the month. The index market capitalization increased to $63.9 billion, fueled by overall growth and Shire's acquisition of New River.

Emerging Stage Index Trends (ESPI)

With the engine of growth for this index, New River, acquired by Shire mid-month, other companies picked up the slack for a 5% growth for the month. The index now is positive for the year, up about 4%. The larger part of monthly growth for the index came from the smaller to mid-tier players. Epicept was up 80% for the month, followed by Somaxon at 50%, and Acusphere at 46%. It will be interesting to see who breaks out of the pack to follow New River to the $2-billion market cap level. Index market capitalization (but not the Index Value) will drop next month when New River is removed. ■

Bionumbers Commercial-Stage Specialty Pharma Index

APRIL 2007



Key Figures April 2007
Index Value: 1279
Change YTD: +11.7%
Total Index Capitalization: -$63.9 Billion

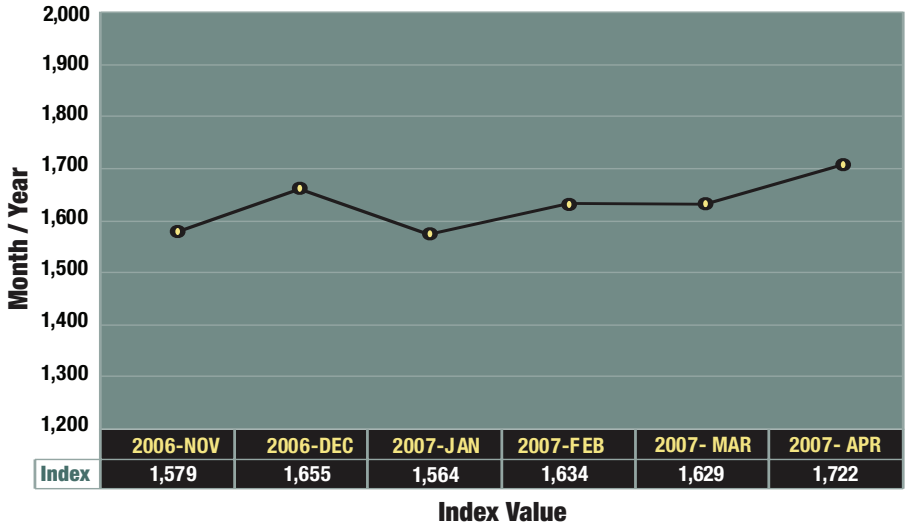
Top 5 Gainers YTD Change	
Avanir	+80%
Vivus	+79%
ISTA	+38%
Indevus	+34%
King	+29%

Top 5 Laggards YTD Change	
Columbia Labs	-50%
Questcor	-38%
Angiotech	-34%
Medicines Co.	-27%
Novavax	-27%

Top 5 Capitalizations YTD Change		
Shire	$12.9 Billion	23%
Hospira	$6.4 Billion	19%
King	$5.0 Billion	29%
Abraxis	$4.6 Billion	4%
Warner	$4.2 Billion	22%

Bionumbers Emerging-Stage Specialty Pharma Index

APRIL 2007



Key Figures April 2007
Index Value: 1722
Change YTD: +4.0%
Total Index Capitalization: $5.7 Billion

Top 5 Gainers YTD Change	
Epiicept	+116%
Acusphere	+65%
Cadence	+37%
Somaxon	+30%
Antares	+28%

Top 5 Laggards YTD Change	
Scolr	-45%
Penwest	-27%
AP Pharma	-27%
Keryx	-23%
NovaDel	-18%

Top 5 Capitalizations YTD Change		
New River	$2375 Million	+21%
Nektar	$1134 Million	-17%
Aspreva	$795 Million	+8%
Cadence	$472 Million	+37%
Keryx	$444 Million	-23%

Revimmune: Delivering a Knockout Punch to Autoimmune Diseases

By: Douglas Kerr, MD, PhD, and Adam Kaplin, MD, PhD

Introduction

Autoimmune diseases are the third most common category of disease in the United States after cancer and heart disease, affecting approximately 5% to 8% of the population or 14 to 22 million people.[1] There are 80 recognized autoimmune diseases, and nearly three-fourths of those affected are women. Among the most prevalent autoimmune diseases are lupus, type I diabetes, scleroderma, multiple sclerosis (MS), Crohn's disease, chronic active hepatitis, rheumatoid arthritis, Graves' disease, myasthenia gravis, myositis, antiphospholipid syndrome (APS), Sjogren's syndrome, uveitis, polymyositis, Raynaud's phenomenon, and demyelinating neuropathies.

Autoimmune diseases occur when the body's immune system no longer differentiates between "self" and "other," meaning the immune system cells begin attacking various organs and tissues. In the case of type I diabetes, the target tissues are insulin-producing islet cells in the pancreas; in lupus, it is connective tissues and sometimes major organs.

Conventional Treatment

In recent years, more than 30 neurologic diseases have been recognized either to be caused primarily by autoimmune mechanisms or to have important autoimmune components. Although many of these diseases can be treated clinically by currently available conventional immunosuppressive regimens, important problems remain. Some patients are refractory to standard immunotherapy, and others respond only partially. In nearly all cases, immunotherapy must be continued indefinitely, maintaining an impaired immune system, and often resulting in cumulative adverse side effects. Despite this, the vast majority of patients on conventional immunomodulatory treatment for MS continue to accrue disability.

Depending on the disease, immune-modulating treatments for autoimmune disease fall far short of the goals of safe, long-term relief and acceptable quality of life for many patients. Therapies must be administered chronically, from several times a day to every few weeks, for life. Many of these treatments are quite expensive, in the range of $30,000 per year.

Potential Treatment

A potential treatment for autoimmune diseases is Revimmune™, which includes high-dose cyclophosphamide. Revimmune, a patent-pending pharmaceutical treatment in late-stage development for a variety of autoimmune diseases, is a potential treatment option for severe, refractory, immune-mediated illnesses, such as MS. Revimmune uses an ultra-high intensity, short-course of an intravenous

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formulation of cyclophosphamide to "reboot" a patient's immune system, thereby eliminating the autoimmunity.

Revimmune temporarily eliminates peripheral immune cells, including the immune cells causing the autoimmunity, while selectively sparing the stem cells in the bone marrow, which are subsequently able to repopulate the body with a nascent immune system. By inducing immunoablation and subsequent immune reconstitution, Revimmune eliminates or reduces dependence on chronic immunosuppressive therapies, which are potentially more toxic, carcinogenic, inadequate, inconvenient, and very expensive, especially in the case of monoclonal antibodies. Revimmune's use would also obviate the risk and expense of allogeneic (donor) stem cell transplantation to treat severe cases of autoimmune diseases.

Accentia Biopharmaceuticals, Inc. has acquired the exclusive worldwide rights for Revimmune. Based on long-term follow-up showing durable remissions, there is substantial evidence that Revimmune has the potential to cure cases of severe refractory autoimmune diseases, such as aplastic anemia and myasthenia gravis. To date, more than 175 patients, mostly those with severe refractory autoimmune diseases, have been treated with Revimmune. The company believes that Revimmune is a "platform" technology that can be used in any autoimmune disease.

Revimmune is administered as an in-patient or outpatient infusion for 4 hours per day for 4 consecutive days. Patients can recover at home while their immune system reconstitutes itself during a 2- to 3-week period. Revimmune includes a risk management program to enhance patient safety by ensuring appropriate patient selection, supportive care, and tracking of outcomes data, which could be critical to reimbursement coverage and malpractice protection for healthcare providers.

"Depending on the disease, immune-modulating treatments for autoimmune disease fall far short of the goals of safe, long-term relief and acceptable quality of life for many patients. Therapies must be administered chronically, from several times a day to every few weeks, for life. Many of these treatments are quite expensive, in the range of $30,000 per year."

Developed by Dr. Richard Jones, Dr. Robert Brodsky, and colleagues at the Johns Hopkins University School of Medicine, Revimmune works by temporarily eliminating peripheral immune cells responsible for autoimmunity, while selectively sparing the stem cells in the bone marrow. Investigators at Hopkins discovered that stem cells possess high levels of a protective enzyme that makes them impervious to Revimmune. Over the course of 2 to 3 weeks after treatment, these stem cells produce a new, improved immune system. Newly reconstituted peripheral immune system cells lack the misdirected immunity to self-antigens, which is characteristic of autoimmune diseases.

The principal investigator for the ongoing Revimmune MS study at the Johns Hopkins University School of Medicine is Douglas Kerr, MD, PhD. In a follow-up of up to 2 years, most patients have shown substantial improvement and many have a complete elimination of signs of the disease. The co-principal investigators on this study are Dr. Daniel Drachman and Dr. Robert Brodsky.

"Revimmune offers the hope of sustained remissions and cures for autoimmune diseases, says Frank E. O'Donnell, Jr., MD, Chairman and CEO of Accentia. "Moreover, it eliminates the dependence on chronic immunosuppressive therapies, which are toxic, carcinogenic, inconvenient, not very effective, and in the case of monoclonal antibodies, quite expensive."

Accentia is preparing an IND application for Revimmune for severe refractory MS, and is proposing to enter a Phase III clinical trial to support licensure under the abbreviated 505(b)(2) regulatory pathway. According to the National Multiple Sclerosis Society (www.nationalmssociety.org), approximately 400,000 people in the US suffer from the disease, 85% of whom are classified within the "relapsing-remitting" category, meaning that

symptoms wax and wane over time, with the overall trend toward worsening symptoms.[2] Two published studies of Revimmune in 20 MS patients found a reduction or elimination of new and enhancing lesions in all patients.[3,4] Furthermore, no patient experienced a clinical exacerbation following treatment, and most showed reductions or stabilization of clinical markers for the disease. In clinical studies, the drug regimen improves function in most patients and stops progression in over 90% of cases refractory to standard therapies.

The Company

Accentia Biopharmaceuticals specializes in development of late-stage under-utilized drug products, in particular, approved medicines in new formulations and/or for new, patentable indications. The company's lead respiratory product candidate, SinuNase™, is currently in clinical development for treating chronic sinusitis (rhinosinusitis). SinuNase, a novel application and formulation of a known anti-fungal compound licensed from the Mayo Foundation for Medical Education and Research, has been fast-tracked by the FDA and is now in Phase III clinical trials. Accentia's other lead product, BiovaxID™, a patient-specific anti-cancer vaccine for treating non-Hodgkin's lymphoma, has also received FDA fast-track status and is in Phase III testing. ■

References

1. Fairweather D, Rose NR. Women and autoimmune diseases. Emerg Infect Dis. 2004 November. Available from http://www.cdc.gov/ncidod/EID/vol10no11/04-0367.htm.
2. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurol. 2007;68:326-337.
3. Krishnan C, Drachman D, McArthur J, Irani D, Nath A, Pardo-Villamizar C, Yousem D, Brodsky R, Calabresi P, Kerr DA, High-dose cyclophosphamide in the treatment of aggressive multiple sclerosis. Baltimore, MD. AAN Abstract (P01.072); April 4, 2006.
4. Gladstone DE, Zamkoff KW, Krupp L, Peyster R, Sibony P, Christodoulou C, Locher E, Coyle PK. High-dose cyclophosphamide for moderate-to-severe refractory multiple sclerosis. Arch Neurol. Vol 63. Published Online August 14, 2006.

Douglas Kerr, MD, PhD

Associate Professor of Neurology, Molecular Microbiology & Immunology
Director, Johns Hopkins Transverse Myelitis Center

Dr. Douglas Kerr earned his MD and PhD from Jefferson Medical College at Thomas Jefferson University in Philadelphia. He then completed an internship in Medicine at The Graduate Hospital, also in Philadelphia. He went on to complete his residency in Neurology at The Johns Hopkins Hospital in Baltimore. Now an Associate Professor of Neurology at Johns Hopkins, Dr. Kerr serves as the Director of the Transverse Myelitis Center, focusing on comprehensive evaluation of TM. His research strives to determine the causes of TM and develop new treatment options. Dr. Kerr further focuses on stem cells as a tool for functional recovery in patients with TM and motor neuron diseases.

Adam Kaplin, MD, PhD

Assistant Professor of Psychiatry
Johns Hopkins University

Dr. Adam Kaplin graduated Magna Cum Laude from Yale University before earning his MD and PhD from The Johns Hopkins School of Medicine, where he was a Medical Science Training Program awardee. He went on to complete an internship in Internal Medicine at Johns Hopkins Bayview Medical Center and a residency in Psychiatry at Johns Hopkins Hospital, where he served as the Chief Resident of Psychiatry. Now an Assistant Professor of Psychiatry at Johns Hopkins, Dr. Kaplin focuses on the psychiatric complications of neurological diseases. He researches the immune-mediated mechanisms of depression and cognitive impairment in transverse myelitis, multiple sclerosis, and related autoimmune neurologic disorders, and the role of cytokines in these processes.

Dr. Kaplin is on the Board of Medical Advisors to the Transverse Myelitis Association (TMA) and the Montel Williams MS Foundation.

Executive Summary

Ron Wooten
President
NovaQuest

NovaQuest: Strategic Partnering to Optimize Portfolio Value, Growth & Profits

By: Cindy H. Dubin, Contributor

Each year, the strategic and financial challenges faced by pharmaceutical and biotech companies grow and change: maximizing investment needed for the future and dealing with the escalating risk and cost of development, all within the context of infrastructure and financial pressures. Strategic investment partnerships are increasingly seen as the best way to break through the logjam of resource constraints. NovaQuest provides alternative growth strategies designed around partners' specific challenges and goals. Ron Wooten, Executive Vice President of NovaQuest, recently shared with Specialty Pharma magazine what the company brings to the table when entering into a partnership. These include: product development and commercialization expertise from Quintiles and Innovex, and access to the investment expertise of TPG-Axon Capital.

Q: ***What makes a company attractive to NovaQuest in terms of partnering or investment?***

A: We want to partner with companies on their most important products and work on their most critical challenges. We're all about helping companies maximize the value of their portfolios, manage financial challenges, and optimize growth and profits. You can't do that by operating on the fringes. One key thing that makes a company attractive is the commitment of its senior management to adopting new ways of doing business. It's not easy to break from traditional models of development and commercialization, especially for pharma companies with huge fixed costs in R&D infrastructures and sales forces. However, with the recent well-publicized examples of blockbuster-category drugs being halted in development or pulled from the market because of safety concerns, we're seeing increasing interest from big and mid-size pharma in risk-based partnering. Rather than bearing all development costs and risks for a product — at $800 million to $1 billion a pop — partnering can mitigate that risk and allow a company to accelerate development of several promising products. It makes sense to spread your bets rather than hoping for one blockbuster. Market pressures are forcing pharma to try to get more and more products through the pipeline — more shots on goal — and therefore, they're interested in partnering on a broader array of their portfolio.

Q: ***What makes NovaQuest unique?***

A: Four things: our intellectual capital, financial resources, management expertise, and Quintiles. We know how to analyze, structure, and manage alliances. We screen 150 to 200 opportunities a year and conduct full due diligence on 15 or so. We've signed more than 60 partnerships since NovaQuest was formed in 2000. In the vast majority of those there was a valuable intellectual exchange about how to improve development or commercialization. So it's not just about money; it's about doing things better,

smarter, and faster. Our financial resources also set us apart. In 7 years, we've committed more than $1.6 billion in either cash or Quintiles' services to customer partnering, and we plan to pick up the pace of our investment. Our alliance with TPG-Axon, an independent investment fund with almost $6 billion in capital, gives us the resources to fund partnerships of virtually any size.

Another characteristic that makes us unique, I believe, is our "managed partnership" approach. Each of our partnerships is overseen by an experienced, well-trained alliance manager. They're responsible for ensuring the partnership works as structured and for developing a collaborative win-win mindset. Finally, we're a part of Quintiles, so we can craft partnering solutions that use Quintiles' global clinical development and commercialization resources in a dedicated, long-term "managed partnership" manner. That is a tremendous advantage.

Q: ***Can you discuss with our readers your business model and why it's working?***

A: We have three main models. First is what we call "strategic resourcing," which helps companies manage their budgets by converting fixed costs to variable costs. Pharma has huge fixed costs associated with development and sales, often on the development side those people are underutilized. We're in conversations with at least the top 20 of the top 50 pharma companies about how we can take over those resources, make them more "virtual," and get full utilization out of those fixed costs. This can significantly improve the efficiency of development and commercialization. We believe there's the potential on the development side to improve efficiency enough to deliver three products to market for the costs now needed to deliver two.

Second is risk-based co-development or co-promotion in which NovaQuest provides money or, more typically, Quintiles' development or sales resources. In exchange, we receive milestone or royalty payments on the products. Therefore, our repayment is based on the clinical, regulatory, and commercial success we achieve. Typically, we invest resources and services and not cash, which combines our intellectual capital and management expertise along with our partners. They like the notion of partnering with someone who has global experience and expertise, so it's more than just money.

Our third model is what we call "eBio," which is tailoring strategic and financial solutions for biotech companies. We provide investment dollars to facilitate their development programs, along with consulting on their drug development and regulatory plans. This approach, combined with co-development and co-promotion partnerships, helps them hold onto their products longer and creates an opportunity for them to realize full value for their innovation excellence.

Q: ***What companies have you partnered with, and on what products?***

A: Our partner companies include Eli Lilly, Solvay Pharmaceuticals, and Astellas UK, plus others that cannot be disclosed for confidentiality reasons. We've partnered with many biotech companies — Scios to help market Natrecor®, its treatment for acute congestive heart failure [J&J later acquired Scios]; Kos Pharmaceuticals to co-promote its Advicor® and Niaspan® treatments for cholesterol disorders; and with Columbia Laboratories to help co-promote several products. These are just a few of our biotech partnerships.

Our largest and most well-known alliance is with Lilly to help develop and promote its Cymbalta® antidepressant. We provided more than $100 million for development and marketing support prior to its approval in the summer of 2004, and since then, we've provided a 550-member NovaQuest sales team to co-promote Cymbalta in the US in return for royalties on Cymbalta sales. That agreement exceeded our expectations and has led to other further partnering opportunities with Lilly.

Our partnership with Astellas UK to help promote VESIcare®, its treatment for overactive bladder, also has been very successful. Using Quintiles' contract sales organization, Innovex, we helped Astellas build an integrated UK sales force that was ready faster and was larger than Astellas could have done on its own. Since launching in January 2005, the VESIcare team has exceeded its sales targets and tripled the product's market share.

Q: ***What does the Solvay partnership mean to NovaQuest and Quintiles?***

A: To me, the Solvay alliance represents the future of product development. It's a great example of how alliances — when executed properly — expand as the partners see the benefits and build trust. Back in 2000, Solvay's challenges were typical of a mid-size pharma company. It didn't have the global clinical structure or resources needed to realize the full value of its pipeline, which was strong — more than 30 compounds — but most stuck in Phase II. Quintiles Clinical Development sat down with Solvay and in 2001 formed a preferred provider alliance that consolidated most of Solvay's outsourced Phase I to III clinical projects to Quintiles.

The results have been fantastic. Since 2001, the alliance has completed three Phase III trial programs, and Solvay has filed two NDA submissions, including one in October for its schizophrenia treatment, bifeprunox. Two compounds moved from Phase II to Phase III a year earlier than expected, and Solvay was awarded a $298 million contract from the US Health and Human Services to develop cell-based influenza vaccines with Quintiles to conduct 9 clinical trials.

That success led to more discussions. In 2004, NovaQuest and Solvay signed a risk-sharing development partnership, with

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NovaQuest providing $25 million in Quintiles' development services for 10 of Solvay's Phase II products. Solvay will make milestone payments to us for each compound that moves onto Phase III. This agreement basically doubled Solvay's early development capacity.

Q: ***NovaQuest has an alliance with the investment fund TPG-Axon. How much easier does this make funding your partnerships?***

A: Much easier. TPG–Axon has almost $6 billion in capital. It has already invested $375 million in strategic partnering opportunities along with us, and it's our first-line partner for major co-development and co-promotion alliances. Until now, most of our investment dollars have come from Quintiles, but I expect that in the future we'll rely more on TPG–Axon and possibly other outside investment groups in part because of the sheer volume and size of the opportunities we're considering.

Q: ***What are your long-term goals or ultimate objectives for NovaQuest?***

A: Our long-term and short-term goals are the same. We want to be the unquestioned partner of choice for pharmaceutical and biotechnology companies. We want to be unsurpassed in terms of adding value to our partner's products. We want to be known for our responsiveness, for our flexibility, innovation, and above all, for delivering on what we promise.

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

A: We must avoid chasing marginal opportunities that are not strategic for our customers. We've been successful mainly because we partner on our customers' most strategic assets. This creates a partnership whose success is critical for both parties. This means we get the best thinking and experience behind the product opportunity and the chances for success go up.

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

A: Mostly the same things that keep pharma executives up. These include worries about the changing regulatory and commercial environments for drug development and product sales. Will these force changes in our development or commercial plans that drive profitability out of our partnerships? Will older, generic technologies dominate prescriptions because of cost alone? A worry unique to NovaQuest is — Will the pharmaceutical industry move slowly in embracing a more effective way to do business? ■

June 2007

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Company	Pg	Phone	Web Site
3M Drug Delivery Systems	5	800-643-8086	www.3m.com/dds
Aveva Drug Delivery Systems	13	954-624-1374	www.avevaDDS.com
Azopharma	4	954-433-7480	www.azopharma.com
Baxter BioPharma Solutions	2	800-422-9837	www.baxterbiopharmasolutions.com
BD	31	800-225-3310	www.bdpharma.com
Bilcare	37	610-935-4300	www.bilcare.com
Bilcare	75	800-310-4445	www.bilcare.com
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Dow Chemical Company	24, 25	1-800-447-4369	www.dowexcipients.com
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Frost & Sullivan	85		www.frost.com
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InnerCap Technologies	3	813-837-0796	www.innercap.com
Iomed	35	801-975-1191	www.iomed.com
Nektar Therapeutics	81		www.nektar.com
NOF Corporation	49	914-6819790	www.nof.co.jp/dds
PharmaCircle	17	847-729-2960	www.pharmacircle.com
PharmaForm	4	512-834-0449 ext 201	www.pharmaform.com
Safety Syringes	55	760-918-9908	www.safetysyringe.com
Scolr Pharma, Inc	9	425-373-0171	www.scolr.com
Zeon	19	1-877-ASK-Zeon	www.zeonchemicals.com/Medical2

Resumes 101

By: John A. Bermingham

At one time or another, almost everyone has had to create a resume, me included of course. That document can be the world's greatest personal sell sheet or the most dangerous document known to man kind.

We all know the basics of a resume: Two pages in length; no typos; no gimmicks, such as your picture or clip art, total honesty; use of power words; printed on high-quality paper and envelopes; great cover letter; etc.

As a CEO, I have the opportunity to read many resumes. The good ones are pretty similar to each other, and the bad ones are all different from each other. The good ones contain bullet points that provide enough information to peak a hiring manager's interest, and the bad ones either don't provide you enough information or have so much information that it is put aside because the reader loses interest. So what is the purpose of a resume you ask?

A resume should have only enough information on it to get you to the interview. It should not be a complete and detailed history of your career. Just a snap shot. A lot of people believe that they only require one resume. That is a mistake.

Every resume you send out should be tailored to the position you are looking to secure. As an example, if you are trying to obtain a position that is for a sales and marketing, then that version of your resume should emphasize your expertise in sales and marketing. If it is for an R&D position, then you should emphasize your resume in that direction.

I have one basic format of my resume that I tailor for the position I am seeking. So, as an example, when a recruiter or a private equity firm calls me to discuss an opportunity, I interview the recruiter or private equity partner to gain as much knowledge as I can on the position and what type of person they are seeking. That accomplished, I then tailor my resume to fit the position. I do not add fluff or false information; I just tailor the resume to fit the opportunity by emphasizing certain key areas.

What continually astounds me is the number of people who falsify their resume and believe they will never get caught. When I was with Sony, I retained a recruiter to help me find a Vice President of Advertising. After many interviews, I finally settled on a candidate and made him an offer contingent on passing our background check. He listed Harvard College for his undergraduate degree. Well, the background check showed that he never attended Harvard, which prompted a call to him from our Human Resources person telling him that the offer was revoked. The following Monday, I arrived at the office and there he was, standing in our lobby waiting for me to try to explain away his falsification on his resume. I told him there was no excuse for submitting false information and that he should leave the building. With that, he broke down into tears and started to follow me to my office. I had to have security remove him from the building. The sad part for him was that I would have offered him the position without Harvard.

Another classic was a resume sent directly to me when I was with AT&T by a person who also listed his education as Harvard College in Boston, Mass. He also listed his most recent position as President of Sony Magnetic Products Group. The following two things were wrong with that:

1. I went to Harvard Business School and recall quite clearly that Harvard is in Cambridge, Mass.

2. His claim to be President of Sony Magnetic Products Group happened to be at the same time that I was President of Sony Magnetic Products Group.

Okay, one more. I recently interviewed a candidate for a senior position here at Lang Holdings, Inc. During the interview, he had to refer to his resume to answer my questions on the companies he had worked for and the detail I was looking for. Do you think that I may have had some concerns about why he had to refer to his resume to answer a question? So there is a huge difference between falsifying your resume and tailoring it in a truthful manner to emphasize your value for the position. And don't forget to review your resume prior to an interview so that you do not have to refer to your resume to answer a question! ◆

BIOGRAPHY

John A. Bermingham is currently the CEO of The Lang Companies, an innovative leader in the social sentiment and home décor industries. He was previously the President, Chairman, and CEO during the successful turnaround and sale of Ampad, a leading manufacturer and distributor of office products. With more than 20 years of experience in guiding enterprises to new levels of performance, Mr. Bermingham also held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Among many career highlights in the role of President and CEO, he also successfully reorganized Smith Corona Corporation and refocused operations and a strategic vision for a dramatic turnaround for Rolodex Corporation. Mr. Bermingham's expertise has also been deployed at industry giants, such as AT&T Consumer Products Group, and by having served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, 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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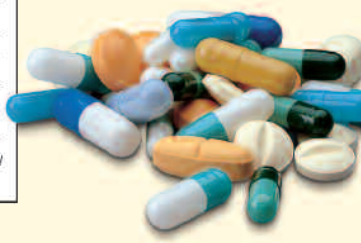

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