Drug Delivery Technology®

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

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3M Drug Delivery Systems

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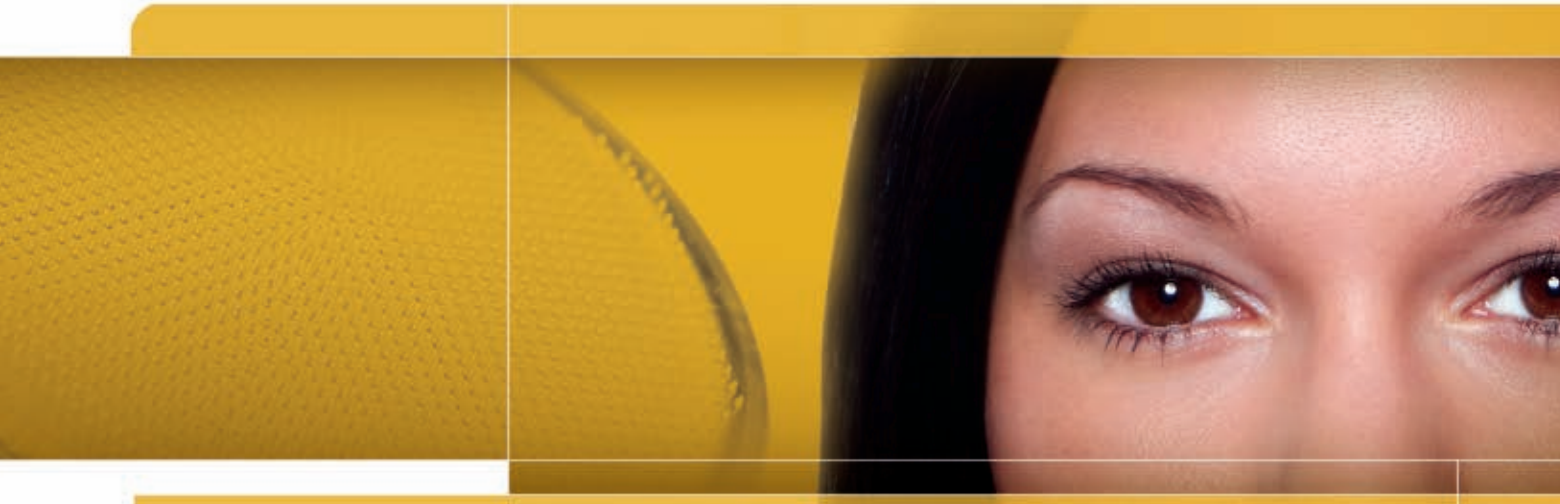

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"Hydrophilic matrix systems have been widely studied and accepted as an ER approach for oral drug delivery, with numerous products in the marketplace. However, there are still some challenges associated with hydrophilic matrix systems, such as potential burst release with high-solubility APIs, size limitations for high dose APIs, potential food effect, and obtaining pH-independent release profiles for drugs that show pH-dependent solubility."

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TRANSDERMAL TRANSCENDENCE

That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

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Outsourcing Outlook

"The total pharmaceutical CMO market, which includes solid dosage and sterile and non-sterile semi-solids and liquids, is forecast to grow from $9.29 billion in 2009 to $15.02 billion by 2014 at a compound annual growth rate (CAGR) of 10.1% In the short-term (2009-2010), we expect the slowdown to affect the expansion activities of small-to-medium CMOs."

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Market News and Trends

Penwest & Endo Grant Valeant Pharmaceuticals Exclusive License to Market Opana ER in Canada, Australia & New Zealand

Penwest Pharmaceuticals Co., Endo Pharmaceuticals, and Valeant Pharmaceuticals recently announced that Endo has signed an exclusive license with Valeant allowing it to market Opana ER in Canada, Australia, and New Zealand. Opana ER, the extended-release formulation of oxymorphone, was jointly developed by Penwest and Endo.

This agreement is the first one resulting from the collaborative work Penwest and Endo began late last year to license Opana ER in territories outside the US. Under the terms of the collaboration agreement between Penwest and Endo, the two companies have agreed to share equally in the proceeds received from Valeant for Opana under the terms of the licensing agreement. The agreement with Valeant also includes rights to Opana, the immediate-release formulation of oxymorphone developed by Endo.

The terms of the licensing agreement call for a payment of C$2 million up-front and payments totaling up to C$1 million when certain sales milestones are reached in Canada and A$1.1 million when certain regulatory and sales milestones are met in Australia. In addition, Valeant has agreed to pay royalties ranging from 10% to 20% of net sales of the Opana products in each of the three countries, subject to royalty reductions upon patent expiry or generic entry.

"We are very pleased with the agreement with Valeant to license Opana ER in Canada, Australia, and New Zealand, all of which are regions where Valeant has a strong regulatory and commercial presence," said Jennifer L. Good, President and Chief Executive Officer of Penwest. "As the first licensing agreement for Opana ER outside the US, this deal represents the achievement of one of the deliverables we committed to our shareholders in optimizing the value of this important asset for them. We continue to work toward achieving additional licensing deals for Opana ER in other territories outside the US."

"We are pleased to be able to add a successful product such as Opana ER to our current product portfolios," added J. Michael Pearson, Chairman and Chief Executive Officer of Valeant. "The addition of this product will extend our successful pain franchise in Canada, while providing Valeant with an opportunity to broaden our therapeutic scope in Australia and New Zealand."

Demand for analgesic narcotics in Canada, a market that includes long-acting opioids, such as versions of oxycodone, morphine, fentanyl, and hydromorphone, has been growing at double-digit rates annually over the past several years. In 2008, analgesic narcotics in Canada represented approximately a C$400 million market.

Opana ER received FDA approval in June 2006 and is currently marketed by Endo as a treatment for moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

As recently reported by Endo, combined net sales for the Opana franchise increased 31% to $52.8 million for the first quarter 2009, compared with $40.3 million in the same period a year ago, while prescription volume for Opana ER and Opana increased 58% in the first quarter 2009, compared with the first quarter of 2008.

Endo Pharmaceuticals is a specialty pharmaceutical company engaged in the research, development, sale, and marketing of branded and generic prescription pharmaceuticals used to treat and manage pain, overactive bladder, prostate cancer, and the early onset of puberty in children, or central precocious puberty (CPP).

Penwest is a drug development company focused on identifying and developing products that address unmet medical needs, primarily for rare disorders of the nervous system. Penwest is currently developing A0001, a coenzyme Q analog drug candidate for inherited mitochondrial respiratory chain diseases. Penwest is also applying its drug delivery technologies and drug formulation expertise to the formulation of product candidates under licensing collaborations with partners.

Valeant Pharmaceuticals International is a multinational specialty pharmaceutical company that develops, manufactures, and markets a broad range of pharmaceutical products primarily in the areas of neurology and dermatology.

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InCube Labs Adds Pharmaceutical Expertise, Creates Drug Delivery Group

InCube Labs, a medical innovation centers, recently announced it has broadened its focus to include pharmaceuticals and cell biology, and created an interdisciplinary team focused on tissue engineering and innovative drug delivery platforms. The company has added deep pharmaceutical expertise with key personnel to support this aggressive research agenda.

"Other companies have dabbled in cross-functional research, but InCube is the first company to pursue drug-device combinations with a team equally expert in drugs and devices," said Mir Imran, Founder and CEO of InCube. "Too much of today's research is focused on trying to adapt existing technologies and therapies to tackle new clinical problems. At InCube, we are creating innovative platforms to address specific medical challenges. The best way to do this is with an interdisciplinary team, and the breadth and depth of expertise that we now have under one roof is unprecedented."

Founded by Mr. Imran in 1995, InCube has a successful track-record that includes groundbreaking innovations and 14 successful medical device companies. One of America's most prolific medical innovators and inventors, Mr. Imran has more than 200 patents and more than 20 successful companies to his name, and he is best known for the invention of the first implantable cardiac defibrillator.

InCube is now applying its trademark approach of fostering groundbreaking innovation in medical devices to novel site-specific drug delivery platforms and tissue engineering. With the addition of high-level employees along with Mr. Imran's own multidisciplinary background, InCube is creating a true merger of device and drug expertise. The revolutionary approach overcomes chronic deficiencies that have long plagued traditional pharmaceutical and device companies.

Unlike other companies that develop new technologies and then seek to apply them to a problem, InCube's research and innovation is driven by clinical needs. InCube's drug-device combination team is already tackling such ills as migraine, atrial fibrillation, epilepsy, anemia, diabetes, obesity, renal disease, depression, anxiety, and Alzheimer's with an array of novel drug delivery platforms and drug formulations, including intrapulmonary, transdermal, intranasal, gastrointestinal, and intramuscular. In addition to pharmaceuticals delivery, the group will focus on the delivery of biotherapeutics, including proteins, peptides, and vaccines.

InCube Labs' mission is to develop high-growth companies that solve major clinical problems by transforming the promise of science and technology into practical medical therapies that restore health and function. With expertise spanning pharmaceuticals, material sciences, software, electrical, mechanical, and tissue engineering, InCube's interdisciplinary teams are currently creating groundbreaking developments in a wide array of therapeutic areas, including central nervous system, metabolic diseases, gastrointestinal ailments, cardiovascular disease, and hematology.

Elan & Transition Therapeutics Receive Key Patent for Alzheimer's Disease Treatment With ELND005

Elan Corporation, plc and Transition Therapeutics Inc. recently announced the United States Patent and Trademark Office issued US patent No. 7,521,481 on April 21, 2009. The patent is titled Methods of Preventing, Treating and Diagnosing Disorders of Protein Aggregation and generally claims methods for treating Alzheimer's disease comprising administering scyllo-inositol (ELND005). The patent will expire in the year 2025 or later due to any patent term extensions.

"The issuance of this patent is an important milestone in the development of ELND005, a unique oral compound with a favorable safety profile that crosses the blood-brain barrier and targets the disaggregation of amyloid beta in the brain," said Dr. Tony Cruz, Chairman and Chief Executive Officer of Transition.

In 2006, Elan and Transition entered into an exclusive, worldwide collaboration agreement for the joint development and commercialization of ELND005 for the treatment of Alzheimer's disease and other indications.

ELND005 is an orally administered therapeutic agent that has received fast-track designation from the US FDA for the treatment of mild-to-moderate Alzheimer's disease. Fast-track designation facilitates development and may expedite regulatory review of drugs that the FDA recognizes as potentially addressing an unmet medical need for serious or life-threatening conditions.

ELND005 is currently in a Phase II clinical study. The study is a randomized, double-blind, placebo-controlled, dose-ranging, safety and efficacy study in approximately 340 patients with mild-to-moderate Alzheimer's disease.

It is currently estimated that more than 5 million Americans have Alzheimer's disease and more than 24 million people worldwide over the age of 60 have some form of dementia, according to the Alzheimer's Association and Alzheimer's Disease International.

Elan Corporation, plc is a neuroscience-based biotechnology company committed to making a difference in the lives of patients and their families by dedicating itself to bringing innovations in science to fill significant unmet medical needs that continue to exist around the world.

Transition is a biopharmaceutical company, developing novel therapeutics for disease indications with large markets. Transition's lead products include ELND005 (AZD-103) for the treatment of Alzheimer's disease and TT-223 for the treatment of diabetes. Transition has an emerging pipeline of preclinical drug candidates acquired externally and developed internally using its proprietary drug discovery engine.

3M Introduces New Dry Powder Inhalers

3M Drug Delivery Systems introduces the 3M™ Taper Dry Powder Inhaler and the 3M Conix™ Dry Powder Inhaler, new technologies that expand its inhalation platform. The 3M Taper DPI was introduced with a workshop at the Respiratory Drug Delivery Conference in Lisbon, Portugal in May, where presenters explained its unique design, which stores APIs on a microstructured carrier tape, enabling it to provide up to 120 pre-metered doses.

The Taper DPI uses 3M microreplication and extrusion technology to create a "dimpled" tape upon which one or more APIs are coated. This unique dimple design allows the use of API only, virtually eliminating the need for lactose or complex powder formulations. The device works via a simple mechanical process: upon opening the mouthpiece, a dose is ready for use. The air flow of the patient's inhalation releases an impactor that strikes the tape and releases API into the airstream. API particles are further deagglomerated as they pass through the device, helping to ensure effective delivery.

A number of features help make the device patient friendly and accurate. A ready indicator provides a visual cue to patients that the device is ready to use. An audible click sounds when the dose has been delivered, and a dose counter displays the number of doses remaining. Its breath-actuated delivery helps ensure effectiveness, and the device works in an easy three-step process - patients simply open the inhaler, inhale, and close. With an API dose range of up to 1 milligram and protection against moisture ingress, the Taper DPI brings important new functionalities to DPI systems.

In addition to the Taper DPI, the Conix DPI further expands the 3M inhalation portfolio. The Conix DPI uses an innovative reverse-flow cyclone design to offer effective drug delivery and simple operation. The inhaler's design allows formulation flexibility and protection from moisture ingress, and is engineered to increase the effectiveness of energy transfer from the patient's inhalation to the drug formulation. Available in single-unit disposable and reloadable dose designs as well as multi-unit dose designs, the Conix DPI is suitable for a variety of applications, including mass immunizations and vaccinations, and treatment of asthma, COPD, and hay fever.

"Companies turn to 3M for its quality portfolio of drug delivery options, especially when it comes to inhalation systems," said Jim Vaughan, Division Vice President, 3M Drug Delivery Systems. "We are the leader in MDI delivery systems, and now we're advancing full-steam into DPI drug delivery with several significant offerings."

Bausch & Lomb Receives FDA Approval of New Topical Ophthalmic Antibacterial for Bacterial Conjunctivitis

Bausch & Lomb, a world leader in eye health, recently announced the US FDA approved Besivance (besifloxacin ophthalmic suspension) 0.6% for the treatment of bacterial conjunctivitis, commonly referred to as pink eye. Besivance is a new topical ophthalmic antibacterial, administered via sterile ophthalmic drops, that treats a wide range of eye pathogens, including those that most commonly cause bacterial conjunctivitis. Bacterial conjunctivitis is one of the most common ocular conditions worldwide.

In December 2008, an FDA Advisory Committee voted unanimously to recommend approval of Besivance.

Besivance is the first fluoroquinolone specifically developed for ophthalmic use and is the first and only ophthalmic fluoroquinolone with no previous systemic use. It offers broad-spectrum antibacterial activity, including activity against the strains that are the most common causes of bacterial conjunctivitis.

"Topical ophthalmic besifloxacin offers physicians the opportunity to provide patients with an anti-infective that treats a broad range of bacterial ocular pathogens," said Marguerite McDonald, MD, FACS, Clinical Professor of Ophthalmology at NYU School of Medicine, New York, New York.

The FDA approval of Besivance was based on a series of eight clinical trials. These studies were designed to test the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics with the topical antibacterial. Its efficacy was evaluated in three multi-center, randomized, double-masked trials involving nearly 2,400 patients with a clinical diagnosis of bacterial conjunctivitis. In clinical trials, investigators found that Besivance treatment resulted in a greater proportion of patients experiencing clinical resolution and microbial eradication, when compared to its vehicle.

"Today's FDA approval of Besivance provides patients with an advanced therapy that can eradicate bacterial conjunctivitis at its source both safely and effectively," said Flemming Ornskov, MD, MPH, corporate Vice President and Global President, Pharmaceuticals, Bausch & Lomb. “At Bausch & Lomb, we are committed to developing innovative eye health products that help enhance patients’ overall quality of life, and we are pleased to offer the medical community a new treatment option for this exceedingly common condition.”

Besivance will be available by prescription in US pharmacies in the second quarter of 2009. Besivance will be promoted by both the Bausch & Lomb and Pfizer, Inc. sales forces.

Exelixis Boosts Cancer Pipeline with Deal; Exelixis Could Get Over $1 Billion in Milestones, Royalties

Sanofi-aventis and Exelixis, Inc. recently announced a global license agreement for XL147 and XL765 and a broad collaboration for the discovery of inhibitors of phosphoinositide-3 kinase (PI3K) for the treatment of cancer. Activation of the PI3K pathway is a frequent event in human tumors, promoting cell proliferation, survival, and resistance to chemotherapy and radiotherapy. Under the license, sanofi-aventis will have a worldwide exclusive license to XL147 and XL765, which are currently in Phase I and Phase Ib/II clinical trials, and will have sole responsibility for all subsequent clinical, regulatory, commercial, and manufacturing activities. Exelixis will participate in conducting ongoing and potential future clinical trials and manufacturing activities.

Under the discovery collaboration, Exelixis and sanofi-aventis will combine efforts in establishing several preclinical PI3K programs and jointly share responsibility for research and preclinical activities related to isoform-selective inhibitors of PI3K. Sanofi-aventis will have sole responsibility for all subsequent clinical, regulatory, commercial, and manufacturing activities of any products arising from the collaboration; however, Exelixis may be responsible for conducting certain clinical trials.

Sanofi-aventis will pay Exelixis aggregate up-front cash payments of $140 million under the license and collaboration. Exelixis will also receive guaranteed research funding of $21 million over a 3-year research term under the collaboration. For the license and the collaboration, Exelixis will be eligible to receive development, regulatory, and commercial milestones of over $1 billion in the aggregate, as well as royalties on sales of any products commercialized under the license or collaboration.

“Sanofi-aventis has a track-record of success in commercializing innovative cancer therapies and is deeply committed to advancing the care of cancer patients,” said George A. Scangos, PhD, President and CEO of Exelixis. “We believe that their expertise and resources will enable us to move aggressively in advancing the development of XL147 and XL765 and other potential PI3K inhibitors. The data generated to date in the XL147 and XL765 clinical programs suggest that these compounds may have utility in treating diverse cancers. Sanofi-aventis and Exelixis are committed to realizing the full potential of these compounds and other PI3K inhibitors to provide cancer patients with new treatment options.”

The effectiveness of the license and collaboration is subject to antitrust clearance under the Hart-Scott-Rodino Antitrust Improvements Act and other customary regulatory approvals.

Exelixis, Inc. is a development-stage biotechnology company dedicated to the discovery and development of novel small molecule therapeutics for the treatment of cancer and other serious diseases. The company is leveraging its fully integrated drug discovery platform to fuel the growth of its development pipeline, which is primarily focused on cancer. Currently, Exelixis’ broad product pipeline includes investigational compounds in Phase III, Phase II, and Phase I clinical development. Exelixis has established strategic corporate alliances with major pharmaceutical and biotechnology companies, including Bristol-Myers Squibb, GlaxoSmithKline, Genentech, Boehringer Ingelheim, Wyeth Pharmaceuticals, and Daiichi-Sankyo.

InSite Vision Announces FDA Approval of New Ophthalmic Product Enabled by InSite's DuraSite Technology

InSite Vision Incorporated recently announced that Bausch & Lomb has received approval of Besivance (besifloxacin ophthalmic suspension) 0.6% for the treatment of bacterial conjunctivitis (pink eye) in patients 1 year and older from the US FDA. Besivance is formulated with InSite Vision's DuraSite technology, a synthetic polymer delivery vehicle that enhances the retention time of the drug on the surface of the eye.

Bausch & Lomb licensed the besifloxacin DuraSite formulation from InSite Vision in 2003 following Phase I clinical studies and continued development of this broad-spectrum, anti-infective drop specifically for ophthalmic use. Based on the terms of the agreement, InSite will receive competitive single-digit royalties on global net sales of the product. Besivance is being launched in the US in the second quarter of 2009. The product will be promoted by the sales forces of both Bausch & Lomb and Pfizer, Inc. under a co-promotion agreement involving both companies' prescription ophthalmic pharmaceuticals.

"We expect this product to offer patients a valuable therapeutic option for one of the most common ocular conditions worldwide," said Louis Drapeau, InSite's Chief Executive Officer. "The launch of Besivance represents the second commercially available product incorporating InSite's DuraSite platform, in addition to AzaSite. This is an exciting milestone that further demonstrates the clinical value of the technology. We continue to look for new opportunities to utilize DuraSite to develop valuable products that treat unmet eye care needs."

DuraSite is a synthetic polymer of cross-linked polyacrylic acid that stabilizes small molecules in an aqueous matrix, allowing for targeted and sustained administration. By increasing the time that a therapeutic level of medication remains on the eye's surface, DuraSite enables a less-frequent dosing schedule, increases patient compliance, and increases the therapeutic efficacy.

InSite Vision is committed to advancing new and superior ophthalmologic products for unmet eye care needs. InSite Vision is recognized for the discovery and development of novel ocular pharmaceutical products based on its DuraSite bioadhesive polymer core technology, an innovative platform that extends the duration of drug delivery on the eye's surface, thereby reducing frequency of treatment and improving the efficacy of topically delivered drugs. By formulating the well-established antibiotic azithromycin in DuraSite, InSite Vision developed the lowest-dosing ocular antibiotic for the treatment of bacterial conjunctivitis available to the US ophthalmic market, AzaSite (azithromycin ophthalmic solution) 1%. AzaSite is marketed by Inspire Pharmaceuticals in the US and Canada and will be marketed by international partners in Japan, South Korea, four countries in South America, Turkey, and China upon approval in those countries.

InSite Vision's ophthalmic product development portfolio also includes ISV-502, which is currently in Phase III pivotal trials for the treatment of eye and eyelid infection and inflammation, and additional product candidates leveraging the company's core technologies.

EyeGate Pharma: EGP-437 Improved Signs & Symptoms of Dry Eye Syndrome in Phase II Study

Based on the top-level analysis of a Phase II study, EyeGate Pharma recently announced that EGP-437, a corticosteroid solution administered by a non-invasive ocular drug delivery system, improved signs and symptoms in patients with dry eye syndrome (DES). For the dry eye clinical trial, EyeGate worked with Ora, Inc., a leading global clinical research and development organization located in Andover, MA.

The Phase II single-center, randomized (105 patients), double-masked, placebo-controlled patient study evaluated the safety and efficacy of a corticosteroid solution (EGP-437) administered by the EyeGate II Delivery System (at two dose levels) twice over a 3-week period. Ora's Controlled Adverse Environment (CAE) clinical research system, which simulates the acute environmental challenges regularly faced by DES patients, was used for this study.

In the top-level analysis, investigators observed that EGP-437 significantly ($p < 0.05$) improved signs and symptoms of DES during the 3-week environmental component, which included three CAE exposures and two doses. EGP-437 also improved signs and symptoms when studied as a treatment and preventative in conjunction with the CAE.

"This exploratory Phase II study demonstrated significant improvements in signs and symptoms of dry eye during and after CAE exposure following EGP-437 dosing. These effects were observed within hours of dosing, suggesting a rapid onset of action. In addition, EGP-437 significantly improved the post-CAE recovery for patients in the active treatment groups. The impact on signs and symptoms was also observed during the study's 3-week environmental component, further supporting the potential benefits of EGP-437 for these patients," said George Ousler, Director of Dry Eye Department at Ora.

"Ora's CAE clinical research system, which provides a unique ability to screen and qualify patients, played an integral role in minimizing the study's patient numbers while still delivering highly relevant biostatistics," added Stephen From, President and CEO of EyeGate Pharma. "We are excited about the prospect that EGP-437 may prove to be a useful therapy for the moderate-to-severe dry eye patients who are currently underserved by available treatments. This non-invasive drug delivery technology has the potential to help patients with a broad range of eye diseases, and we are encouraged by these results."

DES is the most prevalent form of ocular discomfort and irritation, accounting for 1 in 4 patient visits to a general ophthalmologist. It is estimated that as many as 20 to 40 million Americans suffer from DES, including a significant number of patients who suffer from DES after Lasik surgery. Symptoms such as pain, light sensitivity, blurred vision, and irritation decrease the quality of life for patients and can ultimately lead to loss of function and blindness. The incidence of DES is increasing due to environmental factors, the aging population, and the increasing prevalence of co-morbid diseases, such as diabetes. There is no cure for DES, and the few treatment options currently available primarily provide temporary symptomatic relief.

Ora is a leading independent ophthalmic drug and device development firm, providing technology-based concept-to-market services and solutions that accelerate development timelines and improve the scientific quality of clinical research. Over the past 30 years, Ora has played a central role in the development and FDA approval of more than 30 ophthalmic products.

Eyegate Pharmaceuticals, Inc., was founded in 1998 with technology licensed from Bascom Palmer Eye Institute at the University of Miami. EyeGate's transscleral iontophoresis delivery platform, the EyeGate II Delivery System, was developed to safely deliver a wide range of therapeutics to both the anterior and posterior chambers of the eye.

OctoPlus Wins New Drug Delivery Evaluation Contract for Two Compounds

As part of the company's strategic focus on developing controlled-release formulations for clients, OctoPlus N.V. recently announced it has signed a new drug delivery technology evaluation contract for two compounds with a European biotech company. This is the eighth client for which OctoPlus will work on a controlled-release formulation.

In October 2008, OctoPlus announced a strategic focus on developing controlled-release versions of existing or new drugs for clients, in addition to providing general formulation development and clinical material manufacturing. Under this contract, OctoPlus will evaluate the feasibility of two controlled-release formulations that combine the active ingredients of the client with OctoPlus' proprietary drug delivery technology. If the evaluations are successful, the contract may progress to a full process development, manufacturing, and licensing agreement.

OctoPlus is a product-oriented biopharmaceutical company committed to the creation of improved pharmaceutical products that are based on OctoPlus' proprietary drug delivery technologies and have fewer side effects, improved patient convenience, and a better efficacy/safety balance than existing therapies. Rather than seeking to discover novel drug candidates through early stage research activities, OctoPlus focuses on the development of longer-acting, controlled-release versions of known protein therapeutics, other drugs, and vaccines on behalf of its clients.

The clinically most advanced product incorporating its technology is Biolex Therapeutics' lead product Locteron, a controlled-release formulation of interferon alpha for the treatment of chronic hepatitis C. Locteron is being manufactured for Biolex by OctoPlus and is currently in Phase IIb clinical studies.

In addition, OctoPlus is a leading European provider of advanced drug formulation and clinical-scale manufacturing services to the pharmaceutical and biotechnology industries, with a focus on difficult-to-formulate active pharmaceutical ingredients.

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

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EXCIPIENT UPDATE

Applications of Complementary Polymers in HPMC Hydrophilic Extended Release Matrices

By: Sandip B. Tiwari, PhD, and Ali R. Rajabi-Siahboomi, PhD

ABSTRACT

In the post Hatch-Waxman Act 1984 era, developing an extended release (ER) formulation of a new chemical entity with extended patent life has become very crucial to innovator companies. Patent, market share protection, and extension of a product's life cycle are of utmost importance. While multiple ER technology platforms are being developed, an important area that has not experienced significant change throughout the years is new pharmaceutical excipients for ER applications. This has been attributed mainly to the regulatory and safety framework, which hinders approval of new excipients outside the context of a new drug application (NDA) or abbreviated new drug application (ANDA). The net result is the very slow pace of global development and commercialization of ER excipients. Using blends of approved polymers may be a powerful strategy to overcome this regulatory barrier, but still brings resolution to current challenges (size limitations for high dose APIs, once-daily dose, burst effect with high solubility APIs, and potential food effect) in ER formulations. The following specifically examines the application of co-formulation of polymers in developing ER hydrophilic matrix systems to overcome these challenges and discusses its advantages in drug release modulation from matrices.

INTRODUCTION

For many drugs and therapeutic indications, conventional multiple dosing of immediate release formulations provides satisfactory therapeutic response with an appropriate balance of efficacy and safety. The rationale for development of an ER formulation of a drug is to enhance its therapeutic benefits and minimize its side effects, while improving the management of the disease condition. In addition to its clinical advantages, an innovative ER formulation provides an opportunity for a pharmaceutical company to manage product life cycles.

The prototypes of orally administered hydrophilic matrices were first described more than 4 decades ago, and since then, a number of ER technologies have been developed and registered.[1] From a commercial persepctive, hydrophilic matrices are economical to develop and manufacture due to the use of available equipment without further investment, stable formulations, and broad regulatory acceptance. In most instances, hydrophilic matrices use polymers with flexible chemistry that offer an opportunity to formulate an ER dosage form for a wide range of APIs with varying solubility and doses.

Various high molecular weight water-soluble or water-swellable polymers have been used in hydrophilic matrices, such as hypromellose [hydroxypropyl methylcellulose (Hypromelose, HPMC)], hydroxypropylcellulose, sodium carboxymethylcellulose, sodium alginate, carbomer, and polyethylene oxide. Table 1 shows FDA-registered oral ER formulations containing these commonly used hydrophilic or water-insoluble polymers along with their approved maximum potency levels.[2] HPMC, by far, is the most popular polymer in matrix applications because of its ability to obtain desired release profiles for a wide range of drugs, provide robust formulation, global availability, cost-effective manufacture, broad regulatory acceptance, and extensive history on its use.[3-7]

Although the use of HPMC as a rate-controlling hydrophilic polymer in ER formulations is well-documented, the following are still some unmet needs and challenges associated with ER hydrophilic matrices:

1. HPMC is a nonionic polymer and hence the matrices exhibit pH-independent drug release profiles when drug solubility is pH-independent. However, when drug solubility is pH-dependent, eg, for acidic or basic drugs, the release profile may be affected by the pH of the media.[8-11] In some cases, a pH-independent ER performance in the gastrointestinal tract may lead to consistent bioavailability of the drug.

2. HPMC matrices may exhibit an initial burst release for very soluble drugs.[6,12-14] This behavior has been attributed to the rapid dissolution of the drug from the surface and near the surface of the matrix, while the polymer undergoes hydration to form a protective gel layer.

3. Developing an ER hydrophilic matrix formulation of high dose APIs (eg 500 to 1000 mg) is challenging because of overall restrictions on size of the tablets for ease of swallowing.[5]

4. ER hydrophilic matrix formulations of very slightly soluble or practically insoluble drugs may exhibit food effects, ie, variable bioavailability, depending on administration during fasting or fed state.[15,16] This has been thought

to be attributed to the difference in the hydrodynamic activity of the gastrointestinal tract following postprandial dosing.

There has been a keen interest amongst formulation scientists to develop new polymeric excipients to overcome some or all of the aforementioned challenges. However, due to regulatory constraints, high costs, and time requirements for the development of a new polymeric substance, establishing its safety profile, and gaining market acceptance, there has been very few, if any, new polymeric excipients that have been introduced in the pharmaceutical market in recent years.[17-19] Therefore, efforts have been focused on combining approved polymers of different viscosities and/or chemistries to circumvent and resolve the aforementioned issues and achieve optimized drug release characteristics and product performance. HPMC is typically used as the primary polymer, and other approved polymer(s) have been added to enhance functionality and as a tool to modulate the drug release profile. Here, blends of HPMC with other polymers, including ionic, nonionic, and water-insoluble polymers, are discussed.

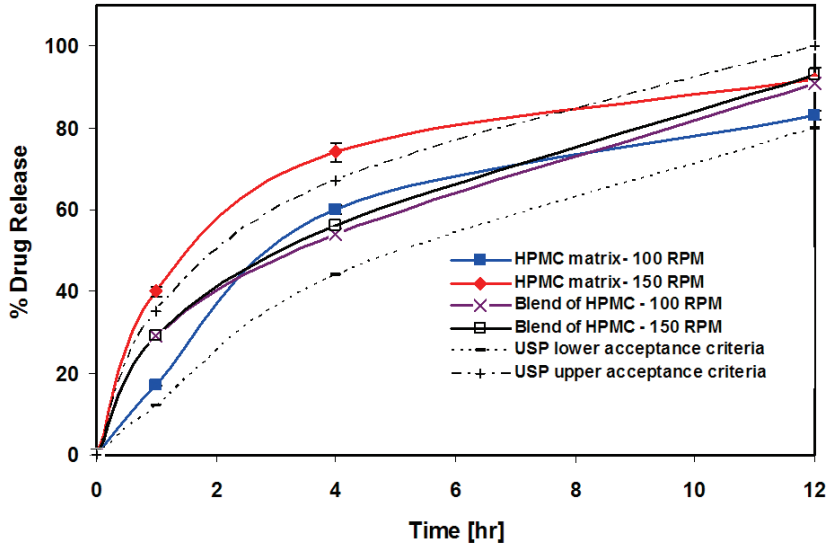
COMBINATIONS OF DIFFERENT HPMC POLYMERS

HPMC is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropoxyl as substituent groups on the cellulose backbone. HPMC is a nonionic water-soluble polymer, and hence, the possibility of chemical interaction or complexation with other formulation components is greatly reduced, and the hydration and gel formation of its matrices are pH-independent. HPMC is available commercially from Dow Chemical Company under the trade name METHOCEL™, premium cellulose ethers.[3-5] High molecular weight METHOCEL Premium K (hypromellose 2208, USP) and E (hypromellose 2910 USP) chemistries are the most widely used in ER matrix formulations and are represented worldwide by Colorcon, Inc.

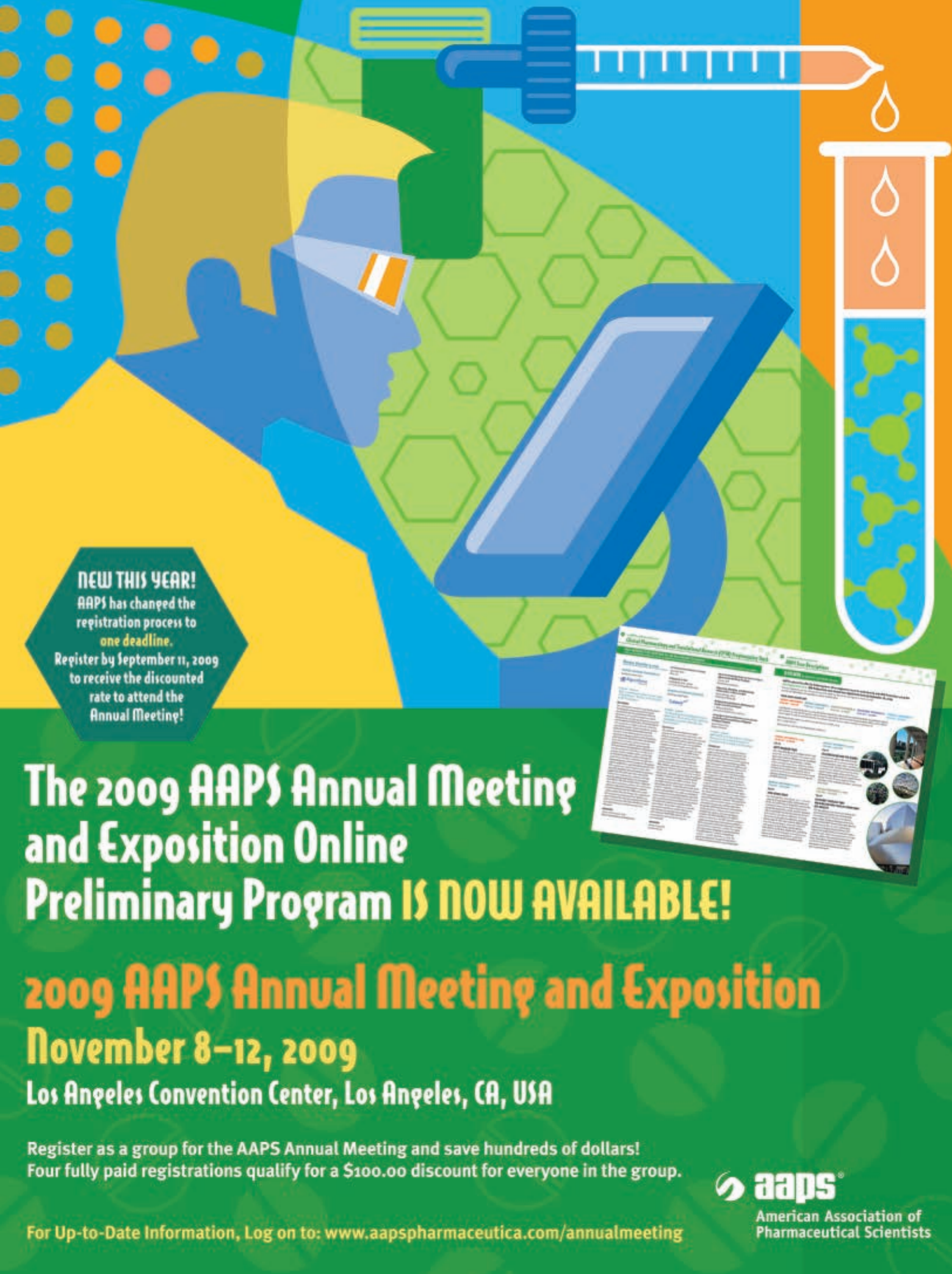
Drug solubility and dose are the most important factors to consider in the design of HPMC ER matrices. In general, ER formulation of extreme drug solubilities coupled with a high dose is challenging. Drug solubility is an important factor determining the mechanism of drug release from HPMC hydrophilic matrices, influencing the choice of polymer viscosity, chemistry, and other excipients.[20-23] Use of an appropriate viscosity grade will enable a formulation scientist to design matrices based on diffusion, diffusion and erosion, or via erosion mechanisms. Practically insoluble drugs (eg, solubility < 0.01 mg/mL) may dissolve slowly and have slow diffusion through the gel layer of a hydrophilic matrix.[5] Therefore, the main mechanism of release would be through surface erosion of the hydrated matrix. In these cases, the control over matrix erosion to achieve consistent ER throughout the GI tract is critical, hence, low viscosity grades of HPMC (eg, METHOCEL Premium K100LV or E50LV) that provide adequate erosion are recommended. For drugs with very high water solubility, the drug dissolves within the gel layer (even with small amounts of free water) and diffuses out into the media. Therefore, it is important to ensure integrity of the gel layer after the drug has been dissolved and released from the gel layer. In this case, it is critical to have a strong gel layer through which diffusion can occur and hence, high viscosity grades of HPMC (METHOCEL Premium K4M, K15M, or K100M) are recommended in their formulations.[24] For successful ER of drugs, either soluble or insoluble, it is essential that polymer hydration and surface gel layer formation is quick and consistent in order to prevent immediate tablet disintegration and premature drug release. For this reason, polymers for hydrophilic matrices can be supplied with a small particle size range (eg, METHOCEL CR or Controlled Release grades) for rapid polymer hydration and consistent formation of the gel layer on the surface of the tablet.[5,25]

Depending on drug solubility, it may be necessary to blend different viscosity polymers to obtain intermediate viscosity grades of HPMC and achieve desired release kinetics. METHOCEL Premium products of the same substitution type, but of different viscosity grades, can be blended to obtain an intermediate viscosity grade. The following mathematical relationship (Equation 1), which is based on the Phillipof equation, can be used

FIGURE 1



Drug release profile of nifedipine from matrices containing 10% drug, 30% METHOCEL™ K100 LV CR, or combination of METHOCEL™ K15M CR + E15LV, 59% (Fast-flo lactose or Starch 1500®, partially pregelantinized maize starch) and 0.5% w/w of Cab-O-Sil and magnesium stearate. Dissolution study was performed using USP apparatus II at 100 (or 150) rpm and 900 ml of simulated gastric fluid without enzymes containing 0.5% w/v sodium lauryl sulfate.



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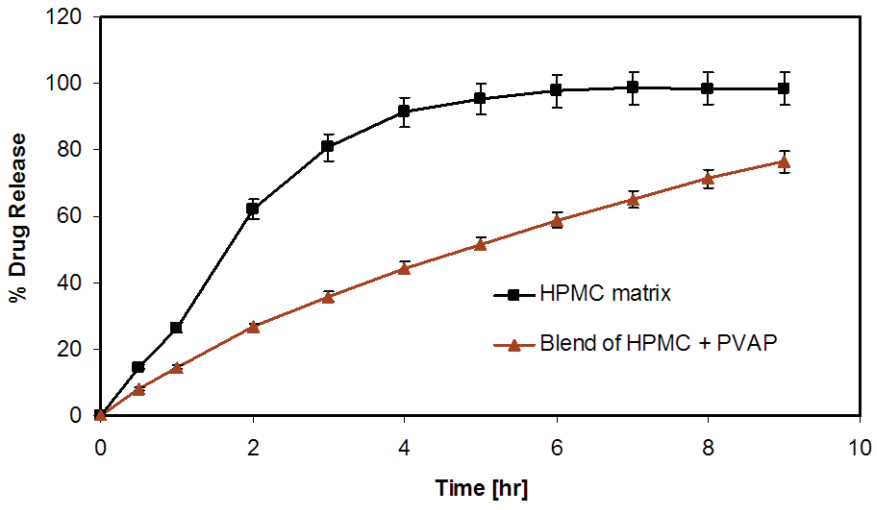


Verapamil hydrochloride release from matrices containing 48% drug, 20% METHOCEL™ K100 LV CR, or combination of 20% K100 LV CR + 8% PVAP, qs% Fast-flo lactose and 0.5% w/w each of Cab-O-Sil and magnesium stearate. Dissolution study was performed using USP apparatus II at 50 RPM, 900 ml of simulated gastric fluid (0 to 1 hrs) and intestinal fluid (2 to 8 hrs) without enzymes.

for calculating the viscosity of the blend product.[25]

Equation 1.

$$\eta_B^{\frac{1}{8}} = X_1 \cdot \eta_1^{\frac{1}{8}} + X_2 \cdot \eta_2^{\frac{1}{8}}$$

Where η_B, η_1, and η_2 are the solution viscosity in mPas for polymer blend, polymer one, and polymer two respectively, and X_1 and X_2 are the weight fractions of polymer one and two, respectively. The influence of blending different polymer viscosity grades on an eroding HPMC matrix of a practically insoluble drug, nifedipine is shown in Figure 1.[26] Erosion is the principal mechanism of drug release for this formulation, containing a very slightly soluble drug and therefore, a low viscosity grade of polymer (ie, METHOCEL K100 Premium LV CR) was used. It was observed that although the dissolution profile of the formulation was within the USP requirement, it showed dependency on hydrodynamic conditions, ie, a faster dissolution rate resulted when the paddle speed was increased from 100 to 150 rpm (Figure 1). Such in vitro behavior may indicate a variable in vivo release rate and possibly food effect.[16,27,28] The study showed that a blend of high-viscosity grade HPMC (METHOCEL K15M Premium CR) to increase the gel strength, and a low-viscosity grade HPMC (METHOCEL E15 Premium LV) to allow for consistent erosion can be used to achieve the desired release profile and meet the USP requirements. Blending of these two viscosity-grade polymers produced matrices with improved release characteristics that exhibited similar dissolution profiles at agitation speeds of 100 and 150 rpm, respectively.

The strategy of blending high- and low-viscosity grades of HPMC has also been reported for achieving the zero-order release profile from matrix formulations and for reducing the drug release variability (low % Relative Standard Deviation, % RSD), thereby providing more uniform clinical levels of the drug.[29,30]

HPMC & IONIC HYDROPHILIC POLYMERS

Combination of HPMC and polymethacrylates, most notably anionic polymers (Eudragit L100 55) in hydrophilic matrices, has been reported for developing pH-independent release profiles for weakly basic drugs.[9,10] The incorporation of anionic polymers in the matrix can influence drug release in basic media by lowering the micro-environmental pH and also retard the drug release in acidic media by forming an insoluble mass, which acts as a barrier to drug diffusion. Moreover, because these enteric polymers have comparatively high molecular weights, they show longer residence time within the matrix gel layer, possibly facilitating their pH modulation effect to last longer compared to "smaller molecular weight" acids, such as citric acid.[9,31] In addition to the control of micro-environmental pH, anionic polymers may also alter the gel strength and erosion rate of the matrix and therefore, release rate of the drug. Similar to the development of pH-independent matrices for basic drugs, incorporation of cationic polymethycrylate polymers in HPMC matrices has been reported for developing pH-independent ER matrices for weakly acidic drugs. Combining of Eudragit E 100 with HPMC matrices has been shown to result in pH-independent release for acidic drugs, such as divalproex sodium.[31] This effect has been attributed to the enhanced solubility and hence, release of the drug in acidic media and retardation of the drug release in basic media.

Polyvinyl acetate phthalate (Phthalavin®, Colorcon) is another enteric polymer used in combination with HPMC to control the micro-enviornmental pH and enhance matrix properties, such as gel strength and erosion. Combining PVAP with HPMC to formulate matrices containing verapamil hydrochloride (HCl) has been reported.[32] When the formulation was subjected to dissolution according to USP 28 (Method 1) in simulated gastric fluid (0 to 1 hours) followed by intestinal fluid (2 to 8 hours), slower drug release was observed for blends of HPMC and PVAP compositions as compared to the single HPMC polymer matrix (Figure 2). Similar to polymethacrylates, PVAP is soluble in

simulated intestinal fluid as it is expected to behave like a soluble filler and result in a faster drug release rate. It has been proposed that the retardation of drug release is attributable to the synergistic interaction between PVAP and HPMC, resulting in the formation of a stronger gel layer and consequent slower diffusion and erosion rates.

Sodium alginate has also been used within HPMC matrices to obtain a pH-independent release profile for basic drugs.[33,34] It has been reported that at low pH (in gastric environment), sodium alginate precipitates in the hydrated gel layer as alginic acid. This alginic acid then provides a firm structure to the gel and retards rate of erosion. Solubility of basic drugs at this pH is high, hence diffusion through the matrix gel layer predominates as a mechanism of drug release. At higher pH values, the alginate remains as the soluble salt, thus providing less resistance to erosion. Erosion of the matrix facilitates release of the drug substance at these pH values, where drug solubility is reduced due to higher environmental pH. The balance of erosive and diffusive mechanisms at the pH extremes may explain the pH-independent drug release. This balance is required to be optimized for each new drug candidate to be incorporated, principally ensuring an adequate erosion rate at higher pH values compensate for the fall-off in driving force for diffusion/dissolution-mediated release as drug solubility decreases. There are commercially available ER matrices using the combination of HPMC and sodium alginate.[35]

Sodium carboxymethylcellulose (Na CMC) has been reported to have synergistic hydrogen-bonding interactions with HPMC.[36-38] Baveja et al reported combining HPMC with Na CMC may result into zero-order release profiles for the drugs propranolol hydrochloride, metoprolol tartrate, oxprenolol hydrochloride, and alprenolol hydrochloride.[39] The authors postulated that the polymers showed a synergistic increase in viscosity, which allowed erosion to occur at a rate equating to the movement of the front between the glassy and the rubbery polymer. However, it was later confirmed that enhancement in viscosity was not solely responsible for modulating the drug release profile, but that the complex formation between the anionic polymer and cationic drug also played an important role.[40] Freely soluble cationic drugs have been reported to be released slower from combinations of HPMC and Na CMC matrices than when formulated with HPMC alone, an effect attributed to drug/polymer interaction. However, for less-soluble drugs, which are released principally by erosion, this effect has been reported to be reversed. There are commercially available ER matrices using combinations of HPMC and Na CMC.[41]

Combination of HPMC with xanthan gum has been reported to result in greater retardation in drug release profile compared to single polymer systems.[12,42] Rapid hydration of xanthan gum combined with firm gel strength of HPMC have been attributed to slower drug release of high-solubility APIs. In this system, the initial burst release, which is typical of highly soluble drugs, was controlled by rapid hydration of xanthan gum, whereas subsequent drug release and matrix integrity were maintained by the firm gel of HPMC.[12] The rapid gel formation property of xanthan gum has also been exploited in gas-generating gastro-retentive matrices of ciprofloxacin formulated with HPMC.[43]

Combination of HPMC with carbomers has been studied for achieving ER characteristics for various drugs.[44,45] The reported advantages with the use of this blend composition were the use of low levels of the total polymer in the matrix, flexibility in drug release modulation, and ability to extend the release of some cationic drugs.

Recently, the work of our research group has shown that combining HPMC with carbomer and polyvinyl acetate phthalate (PVAP) in a matrix system resulted in slower drug release as compared to matrices comprising single or binary polymer systems.[46] This has been related to a synergistic increase in the viscosity, and therefore gel strength, of the matrix, possibly due to stronger hydrogen bonding between -OH groups of HPMC and the carboxylic groups of the carbomer or PVAP. This stronger hydrogen-bonding between the polymers resulted in a more rigid structure through which drug diffusion can occur. The influence of combination of carbomer, PVAP, and HPMC blend in a matrix formulation of a

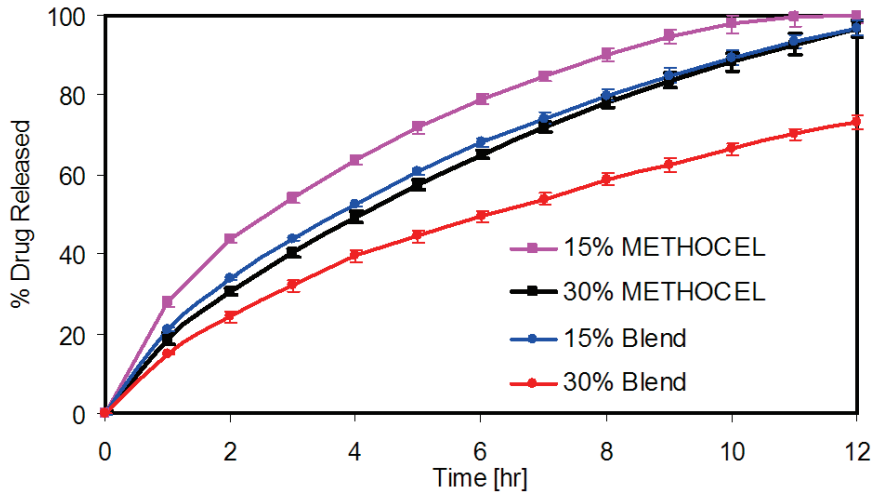
TABLE 1

FDA Registered Oral ER Formulations Containing Commonly Used Hydrophilic or Water-Insoluble Polymers[#]

Polymer/ Material	No of Hits on FDA Web Page*	Maximum Potency Listed for Oral ER Formulations (mg)**
Hydrophilic polymers		
Methylcellulose	15	96[§]
Hypromellose (Hydroxypropylmethylcellulose, HPMC)	91	670.04[¶]
Hydroxypropylcellulose (HPC)	34	240
Sodium carboxymethylcellulose (Na-CMC)	21	155
Sodium alginate	09	350
Xanthan gum	21	109.52
Polyethylene oxide	07	543.90
Carbomers	14	195[§]
Water-insoluble and hydrophobic polymers		
Ethylcellulose	20	308.80
Polymethacrylates (Methycrylic acid copolymers)	54	70.90[@]
Polyvinyl acetate phthalate	02	NA
Fatty acids/alcohols/waxes		
Carnauba wax	21	300
Cetyl alcohol	05	59
Stearyl alcohol	04	244
Glyceryl behenate	09	50.60
Glyceryl monosterate	12	264.30
Hydrogenated cottonseed oil	08	402
Hydrogenated castor oil	11	410.82
Hydrogenated vegetable oil	11	226.5[Δ]

*Listings on FDA web page for use in oral dosage forms.
**Listed potency is for generic material; refer to FDA web page for specific grade listing. Also the maximum potency number value may be higher if the current status of some listings is "pending" or not listed at the time of writing this article.
§A potency of 183.6 mg is also listed for oral tablets however the dosage form i.e. IR or ER is not listed. ¶Listing under carboxypolymethylene
@Listing for enteric product 430.8 mg. ΔThis listing for oral capsule sustained action (Hypromellose 2208 listing is at 480 mg).
NA: not available. ΔListing for oral capsule hard gelatin is at 261 mg
#Inactive ingredient search for approved drug products. http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm [accessed May 31, 2009]

FIGURE 3



Drug-release profile of guaifenesin from matrices containing 69% drug, 15% or 30% METHOCEL™ K4M CR, or combination of METHOCEL™ K4M CR + carbomer and polyvinyl acetate phthalate, qs% Fast-flo lactose and 0.5% w/w Cab-O-Sil and magnesium stearate. Dissolution study was performed using USP apparatus II at 100 rpm and 900 ml of deionized water.

soluble drug, Guaifenesin, is shown in Figure 3.[47] It was observed that the dissolution profile of the matrix blend formulation was significantly slower than the HPMC formulation when a similar level of total polymer was used.

The results showed that 15% of the total polymer blend resulted in a drug release profile that was similar to 30% HPMC alone. This may indicate that one can achieve a drug release profile in vitro similar to HPMC matrices at overall lower polymer inclusion in the matrix. Such polymer or excipient-sparing phenomenon can improve processing, allow larger dose to be accommodated or lower tablet weights to be achieved, and can reduce the overall cost of the final dosage form. The use of this blend also resulted in lower micro-environmental pH (3.5 to 4.5) within the gel layer (micro-environmental pH of HPMC alone matrix: 7.4 to 8.2), which may be beneficial for improving the solubility or stability of some basic drugs. Moreover, as the matrices containing the blends (carbomer, PVAP, and HPMC) produced higher gel strength compared to HPMC matrices, they exhibited less sensitivity to hydrodynamic conditions.[48]

HPMC & FATTY ACIDS, ALCOHOLS, OR WAXES

Combinations of HPMC and fatty acids, alcohols, or waxes have been reported with varied degrees of success.[49,50] Low-melting lipophilic materials blended at low concentrations (≤ 7.5% w/w) with HPMC have shown potential in achieving the ER of metformin, a highly solubile active, suggesting the possibility of niche applications for such matrix blends.[49] However, combinations of HPMC with lipophilic materials at higher concentrations have produced mixed results. While one researcher suggested levels of 20% w/w or more to tailor the drug release profile, other sources have shown the failure of such systems to provide ER.[6,50] When used at high concentrations, because of their low melting points, fatty acids or waxes may enable processing of HPMC formulations by melt granulation.[51]

HPMC & NONIONIC HYDROPHILIC POLYMERS

HPMC and poly (ethylene oxide) [PEO] has been used for modulating drug release and to prevent the burst release of highly soluble APIs.[52,53] In addition, the high-swelling capacity of PEO has been used in HPMC matrices to achieve expanded swelling, resulting in enhanced gastro-retention of the dosage form.[53] There are commercially available products using the combination of HPMC and PEO to achieve enhanced gastro-retention and selective delivery of the drug to the upper part of gastrointestinal tract.[53,54]

Combination of HPMC and HPC in the matrix system has been reported to provide retardation in the drug release profiles compared to single polymer systems.[55-57] This retardation has been attributed to a stronger gel layer of the resultant matrix, reducing diffusion and erosion rate characteristics of the gel layer.

CONCLUSIONS

Hydrophilic matrix systems have been widely studied and accepted as an ER approach for oral drug delivery, with numerous products in the marketplace. However, there are still some challenges associated with hydrophilic matrix systems, such as potential burst release with high-solubility APIs, size limitations for high dose APIs, potential food effect, and obtaining pH-independent release profiles for drugs that show pH-dependent solubility. Developing new polymeric excipients to overcome these challenges remains limited due to the regulatory constraints, cost, and establishing safety and market acceptability. It was shown that blends of pharmaceutically approved polymeric excipients have been a powerful strategy to achieve and optimize desired drug release characteristics and product performance. Combinations of HPMC with ionic and nonionic polymers have been used in hydrophilic matrices to modulate the release profile and overcome some or all of the challenges observed with hydrophilic matrices. The addition of ionic polymers has

been shown to not only modify the drug release profile, but also allow micro-environmental pH control of the gel layer, which may enhance solubility or stability of drugs.

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BIOGRAPHIES

Dr. Sandip B. Tiwari is Senior Manager, Product Development at Colorcon Inc. in West Point, PA. Prior to joining Colorcon, he was a post-doctoral fellow at Northeastern University, Boston, MA, where he investigated the application of nanotechnology in drug delivery and diagnostics. Dr. Tiwari also worked at the Zydus Research Center, Ahmedabad, India, as an Associate Research Scientist and then as a Senior Scientist and Head of the Department of Novel Drug Delivery Systems. He has over 10 years experience in the pharmaceutical field and has participated in various stages of drug development throughout his career. Dr. Tiwari earned his PhD Pharmaceutical Sciences from Mangalore University, India. He has written three book chapters and contributed to over 75 research publications and conference presentations in the areas of controlled-release technology, non-invasive drug delivery, and nanotechnology.

Dr. Ali Rajabi-Siahboomi is Senior Director of Scientific Affairs at Colorcon. He earned his BPharm and PhD in Pharmacy from University of Nottingham (UK). Dr. Rajabi-Siahboomi has held various academic positions (7 years) in Nottingham and Liverpool JM Universities before joining Colorcon as Technical Director (Europe, Middle East, and Africa). His main research interests are in the area of solid dosage form pharmaceutics and pharmaceutical technology with emphasis on oral drug delivery systems. He has published over 150 articles, book chapters, abstracts, and patents.

A Proactive Approach to Developing the Cartridge Pump System (CPS) in a Pressurized Market Environment

By: Degenhard Marx, PhD

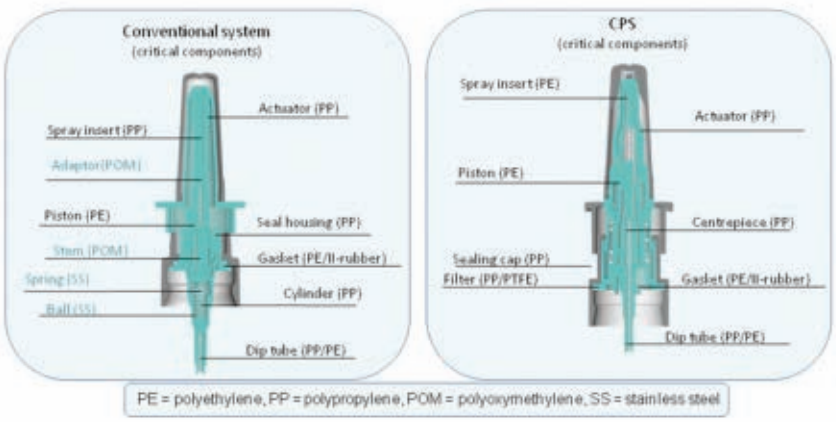
The process of drug development and the subsequent approval procedure has become a tough and time-consuming business in recent years. Worldwide, agencies responsible for new drug approvals have introduced new guidelines to increase safety and efficacy. The pharmaceutical industry now has to spend much more time and money to meet these requirements. Compared with oral formulations, drugs delivered by special devices, such as spray pumps, present additional challenges, as the container closure system (CCS) and the drug delivery system are integral to the drug product. Due to this complexity, anything that can be done to smooth the development process and shorten the time to market is desirable. Manufacturers of CCS and administration devices can contribute by providing high-performing, well-characterized, and reliable devices.

The Cartridge Pump System (CPS) is a newly developed multi-dose pump system, characterized by a metal-free formulation flow path and a consistent spray pattern. The construction of the CCS ensures microbial integrity without the use of oligodynamic compounds and allows its use as a preservative-free system.

COMPATIBILITY BETWEEN THE FORMULATION & THE SYSTEM

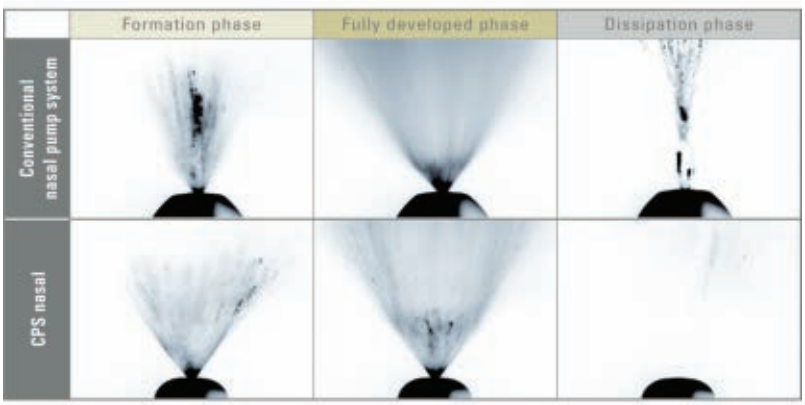
Developing a formulation with one or more active ingredients is a lengthy and challenging process. Rarely is a formulation just a simple water-based solution. Auxiliary compounds often have to be added, for example, to enhance solubility and stability, to increase viscosity, or to prevent microbial contamination. When the final formulation is available, the next step is to ensure the

FIGURE 1



Comparison of materials used in the conventional pump and the CPS.

FIGURE 2



High-speed camera pictures of the three phases following the actuation of a conventional nasal pump and a CPS nasal, using deionized water as medium.

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ingredients do not affect the function and integrity of the CCS. According to EU and FDA guidelines, relevant information should be provided on the characteristics of each of the critical components of the CCS.[1,2] Critical components are defined as: (1) those that come into contact with the patient's mouth or nose or with the formulation, (2) those that affect the overall performance of the device, and (3) any additional protective packaging.[1] Parts with metal balls and springs are prone to cause problems. Even if they are made of non-corrosive material, the surface can rust or discolor the formulation due to impurities or contamination with lower grade material during the manufacturing process.

A unique property of the CPS is that there are no metal parts in the fluid path. All other components of the pump are made solely of medical- or pharmaceutical-grade polyolefines. The materials used in the conventional pump and the CPS are compared in Figure 1.

OPTIMUM SPRAY PERFORMANCE

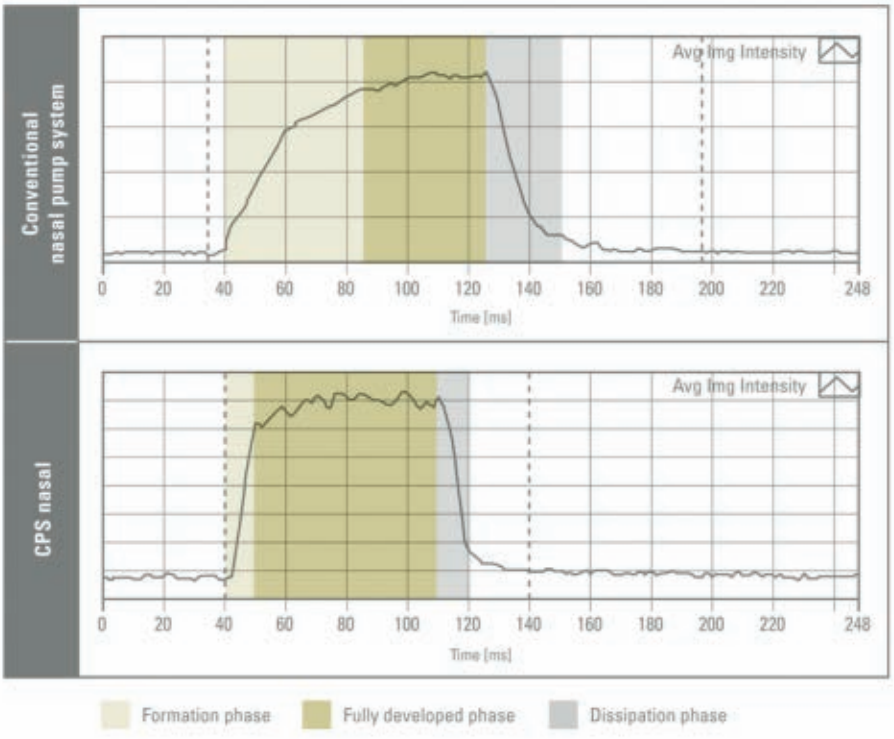
Technical performance of the device is very important for sprays intended to deliver the drug substance into the lungs or to the nasal mucosa. For multi-dose systems, dose uniformity during the lifetime of the device is mandatory. To ensure safety and efficacy, authorities request a detailed description of the spray. The events that follow the pump actuation can be described as the spray formation phase, fully developed phase, and dissipation phase.[1] The fully developed phase is the most important because the formulation will be delivered with the optimum droplet size. During the formation and dissipation phases, larger droplets are formed. Figure 2 compares the three phases in a conventional nasal

TABLE 1

	Test System	n	Short Test Description	Results
Venting System	Artificial dust contaminated with *B. subtilis*	20	Repeated actuations until half the bottle volume was dispensed	No bacterial contamination
Tip Seal	Suspension containing *P. aeruginosa*	20	Repeated actuation of the primed pump with the tip dipped into the contaminated suspension over 5 days	No bacterial contamination

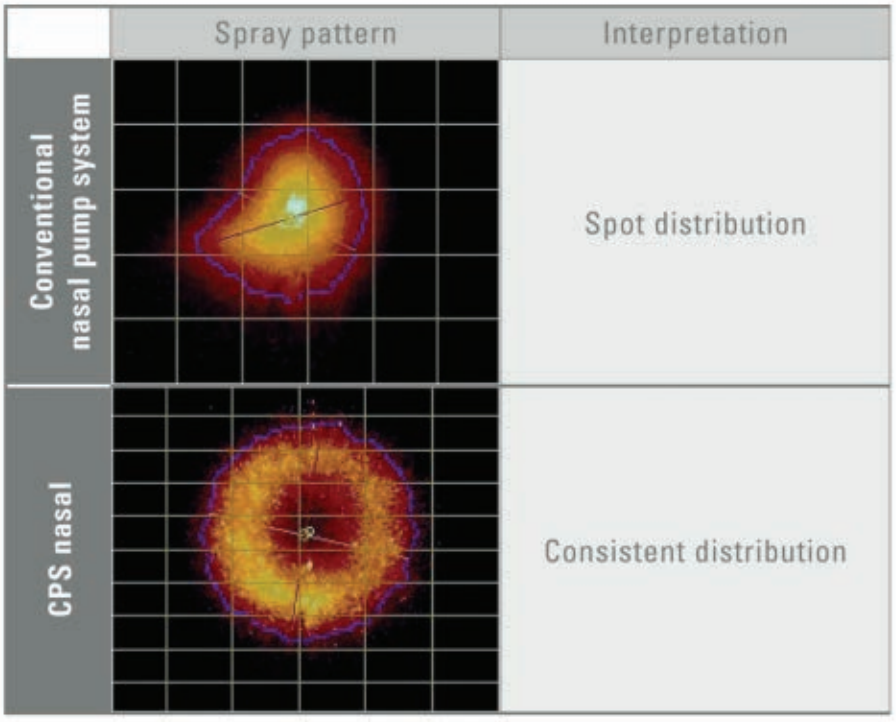
Summarized Results From Microbial-Integrity Testing

FIGURE 3



Delivered dose following actuation of a conventional nasal pump and a CPS nasal, using deionized water as medium. Spray intensity versus time was assessed 30 mm away from the orifice using Proveris' SprayVIEW NSP equipment.

FIGURE 4



Spray pattern of a conventional nasal pump compared with a CPS nasal, using deionized water as medium. Spray geometry was assessed 30 mm away from the orifice using Proveris' SprayVIEW NSP equipment.

pump and a CPS nasal.

To improve the spray performance of a device, technical measures should be taken to keep the formation and dissipation phases as short as possible. The majority of the dose should be delivered during the fully developed phase, which is reached when the pump mechanism secures a certain pressure within the system. In the CPS, a spring-loaded tip seal keeps the system closed until a predefined pressure is reached, at which point the formulation is forced through the orifice with a well-controlled pressure. When the pressure drops at the end of the process, the tip seal immediately closes the orifice. Figure 3 illustrates the amount of delivered dose during the three phases of the actuation of a nasal spray pump. In a conventional system, only 30% to 40% of a dose is delivered during the fully developed phase, compared with 80% in the CPS nasal.

The technical measures already mentioned and the design of the swirling chamber have a positive effect on spray-pattern geometry (Figure 4). As a result, the CPS delivers a very consistent and regular spray pattern.

THE ROLE OF PARTICLE SIZE DISTRIBUTION

Two important features of spray pumps are the size range and distribution of the delivered droplet. The size of the particles or droplets depends on the intended use. If the spray is for oral inhalation of beta-agonists, for example, the majority of droplets should be from 1.5 to 6 microns in order to reach the middle and lower airways. Larger particles will be deposited in the pharynx. For nasal sprays, much larger droplets are required to get a good distribution and deposition in the nasal cavity. During the formation and dissipation phases, very large droplets (> 300 microns) can be formed, which may irritate the nasal mucosa and induce discomfort. At the other end of the size range, particles with less than a 10-micron median aerodynamic diameter can reach the lower airways during nasal breathing.[4] The authorities therefore consider that droplets less than 10 microns in diameter in the spray should be characterized.[1] Depending on the active ingredient, any auxiliary compounds, and the total amount delivered, this fine particle fraction may cause side effects.

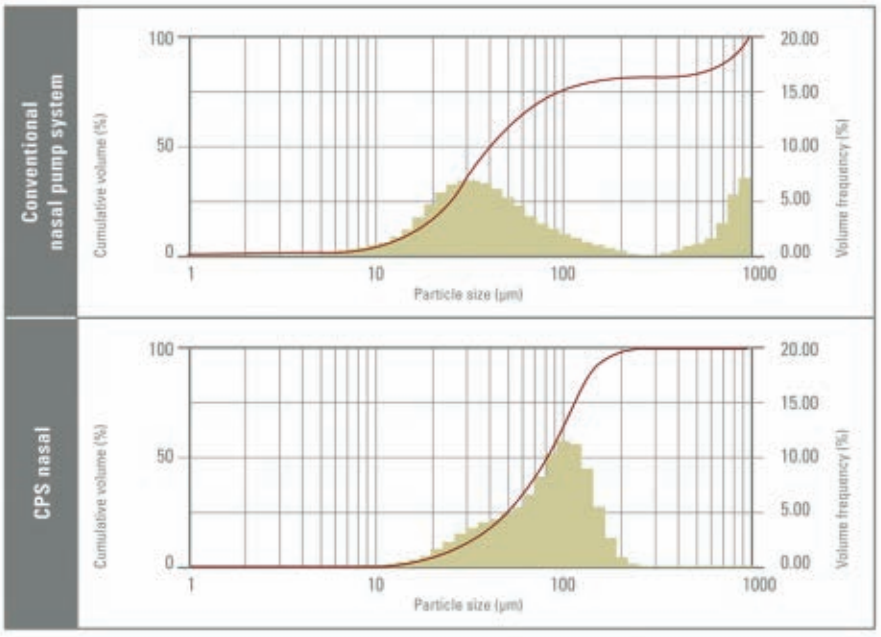
When using deionized water, the number of droplets less than 10 microns in diameter is significantly lower in the CPS nasal, compared with a conventional pump, and no droplets larger than 300 microns are created (Figure 5), so it is less likely to cause problems.

MICROBIAL INTEGRITY

During the manufacturing process, microbial contamination of the formulation will affect the product's quality and shelf-life. Depending on the product's intended use, microorganisms should be absent (products for inhalation) or as low in number as possible. Depending on the drug, the formulation may be manufactured under sterile conditions or treated using autoclaving or radiation to ensure inactivation of microbial contamination. These approaches are not always viable, however, and preservatives such as benzalkonium chloride may need to be added. The use of preservatives is controversial and has to be justified to the authorities.[1,2,5] For multiple-dose systems, preservatives may also be used to control microbial contamination during the regular use of the product. Microorganisms can enter the system via the venting air or through the orifice. In preserved formulations, the added preservative just controls microbial growth, and no measures need to be taken to prevent the microbial occupation in a conventional system. If the formulation cannot contain preservatives, the pump must be able to keep microorganisms out of the system.

The CPS uses a sterile filter in the venting system (0.2 micron nominal pore size) to prevent microorganisms from entering. The principle of sterile filtration is well recognized and widely used. To prevent contamination via the orifice, a pure mechanical approach is applied. The CPS' spring-loaded tip seal keeps the system closed until a defined pressure is reached, then the formulation is forced through the orifice. When the pressure drops at the end of the process, the tip seal immediately closes the orifice and no back-flow of contaminated particles is possible. This mechanism should therefore provide sufficient protection from microbial occupation.

FIGURE 5



Droplet size distribution of the full spray of a conventional nasal pump compared with a CPS nasal, using deionized water as medium. Droplet size distribution was assessed 30 mm away from the orifice using Malvern's Spraytec RTsizer.

To support this claim and to provide data on the microbial integrity of the CPS, challenging test procedures for the venting system and the tip seal were developed and used.[6] The tests were carried out at Qualis Laboratorium in Constance, Germany, using sterilized (gamma-radiated) pumps and glass bottles.

MICROBIAL INTEGRITY TESTS ON THE CPS

For both test series, glass bottles were filled with sterile bacterial culture medium, and the CPS nasal was mounted under sterile conditions.

VENTING SYSTEM: The pumps were wrapped in a rubber sealing, and the space between the pump and the sealing was filled with artificial dust containing spores of Bacillus subtilis (10^8 to 10^9 dry bacillus spores per gram). The primed pumps were then vortexed twice (topside up and upside down) for 3 seconds at 2500 rpm and actuated several times. This procedure was repeated until the bottle was emptied to half its filling volume. Next, the systems were incubated for 7 days at 30°C. At the end of the experiment, the culture medium in the bottle was analyzed for the presence of microbial growth. Even under these harsh test conditions, all spores were kept out of the system, and no bacteria could be detected inside the system.

TIP SEAL: A culture medium containing 10^7 colony-forming units (CFU) per ml Pseudomonas aeruginosa was prepared. The nasal actuator of a primed system was dipped into this suspension, then the pump was actuated and released in an upside-down position. The systems were then challenged twice a day for 5 days, and the tips were not wiped. Between the challenge procedures, the systems were incubated at 35°C. At the end of the experiment, the culture medium in the bottle was analyzed for the presence of microbial growth. The tip seal prevented the entrance of CFU into the system, and no bacteria could be found inside the system after 5 days.

CONCLUSION

It is likely that regulatory challenges and the ensuing pressure on pharmaceutical manufacturers to minimize the time to market for new products will only increase in the years to come. If manufacturers of dispensing systems are highly proactive in their development activity, they can significantly reduce the financial and human resources needed. Based on its experience with the development of the CPS, Pfeiffer is committed to applying this proven approach to future systems, continuing to provide measurable benefits to customers and patients.

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BIOGRAPHY

Following the study of veterinary medicine and the successful completion of his thesis at the University of Leipzig, **Dr. Degenhard Marx** joined the Arzneimittelwerke Dresden/Asta Medica co-operate research in 1992. In 2001, he took over a Senior Research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardiovascular drugs. In 2008, he was appointed Business Development Manager at Ing. E. Pfeiffer, Pharma Division.

Molecular Responsibility

David Versus Goliath: Why the Little Guys Have All the Advantages

Part IV of a Six-Part Series

By: Derek G. Hennecke, MBA

When you're in the mood for a burger, there are probably several megachains you know you can go to for a reasonably good, reliably consistent burger. But what if you're in the mood for a really juicy, hedonistic kind of burger? I mean the kind of burger that changes lives - that stimulates and invigorates all of your senses, and makes you believe that man truly is a spiritual being. Is that megachain where you go?

My favorite burger is from a little local restaurant called Catch 23. Unpredictably, Catch 23 is a latin-infused seafood restaurant in Tampa, Florida, and its seafood really is quite exquisite. But everyone around here knows it also makes a breathtakingly fabulous burger. On $2.99 burger night, you'll be hard-pressed to get a seat after 5 PM.

If Catch 23 were a megachain, do you believe they would have a burger night? Not a chance. It wouldn't fit their strategic mandate as a latin-infused seafood chain. But Catch 23 knows its market. The little guys generally do.

In the Canadian town I grew up in, there is a fast-food restaurant (I won't name it because it's still in business) that always sold soft ice cream and made a killing on it all summer long. We kids headed over there on a regular basis because there was no other soft ice cream in town. We often had a burger or two as well while we were there.

One day, I was in the shop when the manager flew out of his office, unplugged the soft ice cream machine, and raced it into the backroom. He threw a bunch of oil-soaked cloths over it, and rushed back out, ordering us to down our cones. Apparently the franchise owner was coming by, and because the ice cream wasn't "officially" part of the franchise formula, he wasn't allowed to sell it. Once the owner left, the manager returned the much-loved machine to its regular spot, plugged it back in, cleaned it out, and was back in business.

I returned to the restaurant many years later and noticed the machine was no longer there. The story is that the manager got caught off-guard one time, and our beloved ice cream machine was history. So, coincidentally, was the restaurant's status as a youth hangout, and the place has never truly prospered since.

When David challenged Goliath, many people assumed that David's win was kind of an exception to the rule. I mean really, the odds were in Goliath's favor, right? Malcolm Gladwell wrote an article in the May New Yorker called, *How David Beats Goliath* that throws things into a completely different light.

Mr. Gladwell points to research by political scientist Arreguín-Toft. Apparently, in every war fought in the past 200 years between strong and weak combatants, the David's won almost one-third of the time. This is particularly exceptional when you consider that he only looked at those wars where one side was at least 10 times more powerful than the other in terms of weaponry and population.

When David walked out to meet Goliath, he wore a coat of mail, a brass helmet, and a sword. This was the conventional means of meeting an opponent on the field of battle. But then he returned, claiming he couldn't walk wearing all that gear because he wasn't used to it. So he dropped the gear and chose to fight Goliath on his own terms. He picked up five smooth stones, and the rest is history.

This gave Arreguín-Toft pause. He re-analyzed those same battles looking for those cases in which the underdogs chose, like David, to follow an unconventional strategy. Under those circumstances, the underdog's winning percentage went from 28.5% to 63.6%! When the little guys break the conventional rules, they win, Arreguín-Toft summarized, "even when everything we believe we know about power indicates they shouldn't."

Even in a wildly uneven battle, if you're willing to go beyond the conventional wisdom and find a new way of doing things, the odds of winning are in your favor.

This changes everything. It might be argued that in business, we've always known this truth. Small business drives innovation. David is our source of innovation. It's not the megachains that will turn on a dime to keep/earn a customer. And it's rarely Goliath who will take the time to figure out what a local market needs or wants, and make it happen.

I would put it this way. In the drug development industry, CROs are the Davids. We are the change masters, the innovation leaders. We're by far the most likely to pick up those rocks and define a new way to win the battle. Let me tell you about five smooth rocks a good CRO should have in its pocket. Your CRO should be:

QUICKER TO ADOPT STATE-OF-THE-ART TECHNOLOGY: Small organizational size combined with the right attitude means that we can take on the latest innovations without months of testing or persuading levels of management. Because our clients wanted faster drug development, we were able to become the first North American CRO to invest in Capsugel's Xcelodose® precision powder micro-dosing system. Now, we've built up industry-leading expertise having processed more than 30 APIs and 100 batches, and our instruments are in steady demand. We continue to push the envelope by expanding our expertise with Xcelodose into more challenging technical areas, such as low-weight fills or high-potency compounds, while at the same time looking ahead to new markets that address unmet customer needs. Adopting liquid-in-capsule technology is an example of this. Still, we will never be defined solely by the equipment we own.

PROVIDE PERSONALIZED, DEDICATED, PROJECT MANAGEMENT: At school, you want to know not just your child's teacher, but also his/her special teachers and principal. You want access to them all. Isn't that easier the smaller the school? So it is with project management, when it works the way it really should. At Xcelience, project management is central to project success. What this means is that you have a single, dedicated advocate within our organization who cares about your project as much as you do, and who also facilitates (not blocks!) your access to all our other scientific or technical resources. We have been told by many clients that we set the standard for this approach in our industry.

ROUTINELY FIND OUT-OF-THE-BOX SOLUTIONS: Ever heard about a giant cargo ship turning on a dime? Not happening. But sometimes we need scientific solutions to do just that. One of the really cool things about being small is that we cannot only find but also implement those solutions on a dime. And I am talking about low-cost as well as creative solutions. At Xcelience, we offer customized business solutions like an FTE program or dedicated equipment that make Xcelience feel like a small, flexible, dedicated extension of the client facility. This approach allows us to serve both virtual and large pharmaceutical companies equally well. We are willing to take an unconventional approach if needed – once, when a customer needed a tablet splitter for a comparator product blinding study and a suitable machine wasn't available, we made one out of plexiglass and piano wire. How's that for thinking outside the box?

OFFER SPEED & EASE OF COMMUNICATION: All departments at Xcelience reside under one roof, which allows for quick and regular communication. Our "team assignment" approach to projects involves a dedicated project manager and weekly client meetings that address project status. This also has been cited by numerous clients as a "best-in-industry" strength.

FACILITATE FASTER, MORE FLEXIBLE OPERATIONAL DESIGN: When you are a small company with fewer dedicated rooms, you have to get creative. We turned this disadvantage into an advantage by adopting a flexible operational design, scheduling model, and even keeping equipment on wheels. Because we're not a commercial-scale provider, our projects tend to be smaller. We move projects through our systems much more quickly and then move on to the next project – capacity is never tied up for long periods of time. So, for example, we could complete an API-into-capsule project enabling speed to first-in-human studies, and then move very quickly into traditional formulation development for the same compound even within the same year.

I'm not saying Xcelience is the only David amongst CROs. There are other worthy Davids out there. I'm just saying that we little guys have all the advantages. Seems kind of unfair, doesn't it? ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

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

SOLID DISPERSION TECHNOLOGY

Oral Delivery With Novel Solid Dispersions: Stable Self-Assembled Formulations of Lipophilic Drugs With Improved Bioperformance

By: Galia Temtsin Krayz, PhD; Maryana Averbuch, PhD; Anna Berman, MSc; Amir Zalcenstein, PhD, MBA; and Irene Jaffe, PhD

INTRODUCTION

Overcoming solubility limitations remains one of the most challenging aspects of pharmaceutical formulation development. Traditional solutions to this problem, such as pro-drug synthesis, salt formation, and use of co-solvents have been augmented by more recent approaches. These methodologies include: (1) improvement of water miscibility by employing self-emulsification, lipid-based techniques, solubilization into micellar cores, or alternatively complexation with cyclodextrins; (2) reduction of particle size to nano-scale via mechanical milling or high-pressure homogenization accompanied by particle stabilization; and (3) impacting crystal lattice energy using polymorphs or co-crystals, or through the creation of solid dispersions of drug in inert carriers or matrices.[1-10]

Solid dispersions have inherent advantages over other approaches. Presence of an active compound as a molecular or nano-particle dispersion combines the benefits of decreasing crystal lattice energy and surface area maximization, thus facilitating better contact with dissolution media. Advantageously, many of the carriers that can be employed for the production of solid dispersions are already extensively used as excipients, easing the regulatory process.

In spite of these advantages, only very few solid dispersions have reached the market to date. This is due to a number of reasons, including the absence of sufficient in vivo validation, laborious preparation, lack of reproducibility of physico-chemical analytics, cumbersome incorporation into suitable dosage forms, unsuccessful manufacturing scale-up, and instability of the drugs and their vehicles.[11-12] Thus, technologies that can effectively overcome these challenges are highly desirable.

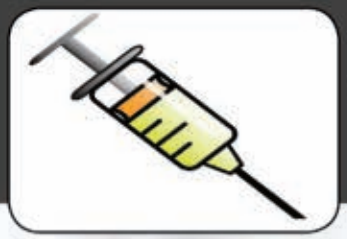
SoluBest has developed a unique solid dispersion technology for significantly improving the bioperformance of poorly soluble drugs. This robust and versatile technological platform, referred to as Solumer™, can be applied toward a wide range of marketed drugs and molecules in development.

TECHNOLOGICAL CONCEPT & METHODOLOGY

Solumerization is based on the self-assembly of selected components, enabling the design of new polymer-drug constructs with well-defined physical-chemical properties. Leveraging the thermodynamic behavior of amphiphilic and hydrophilic polymers in mixed solvents, SoluBest has developed a proprietary platform for the creation of drug-polymer solid dispersions in which the lipophilic drug is homogeneously interwoven within a multi-polymer matrix. Moreover, due to interaction with the amphiphilic polymer, Solumerized drugs exhibit modified physico-chemical properties (eg, decreased enthalpy and temperature of melting) compared to the crystalline lipophilic APIs.

Solubility parameters can be used as a semi-empirical tool for the prediction of component interactions, facilitating their selection.[13] Specific amphiphilic and hydrophilic polymers at optimal ratios yield solid dispersions with a unique built-in hydrophobic-hydrophilic gradient. This gradient enables the rapid disintegration of the powder in aqueous media, generating easily measurable colloidal nano-dispersions.

In the context of the Solumer technology, amphiphilic polymers are defined as soluble both in organic solvents and in water. Examples of



Drug Delivery Summit

2 - 4 September 2009 London, England

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Tudor Arvinte, Professor, Department of Pharmaceutics & Biopharmaceutics, University of Geneva
Justin Hanes, Professor, Advanced Drug & Gene Delivery Group, John Hopkins University
Jean Cuine, Principle Scientist, Pharmaceutical and Analytical R&D, Novartis Pharma AG
David Brayden, Associate Professor, University College Dublin
Cheryl Barton, Managing Director, Pharmavision
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amphiphilic polymers suitable for use with Solumer include but are not limited to polyethylene oxides (PEO, also commonly referred to as polyethylene glycol or PEG), PEO derivatives, PEO copolymers such as PEO/polypropylene glycol (PPG) copolymers, PEG-modified starches, poloxamers, poloxamines, polyvinylpyrrolidones, hydroxypropyl cellulose, hypromellose and esters thereof, vinyl acetate/vinylpyrrolidone random copolymers, polyacrylic acid, and polyacrylates. Hydrophilic polymers are defined as those soluble in water or in a mixture of organic solvent and water, but not soluble in organic solvent alone. Examples of hydrophilic polymers include but are not limited to starch, sodium carboxymethylcellulose, hydroxyethylcellulose, polyvinyl alcohol, sodium alginate, chitosan, and carrageenan. Notably, SoluBest formulations utilize only FDA-approved polymers.

The use of hydrophilic polymers that ionize at different pH allows for the design of formulations targeted either to the stomach or the intestine. For example, chitosan, which is ionized at low pH, promotes drug release in the stomach, while sodium carboxymethyl cellulose and sodium alginate, ionized at neutral conditions, facilitate release in the small intestine.

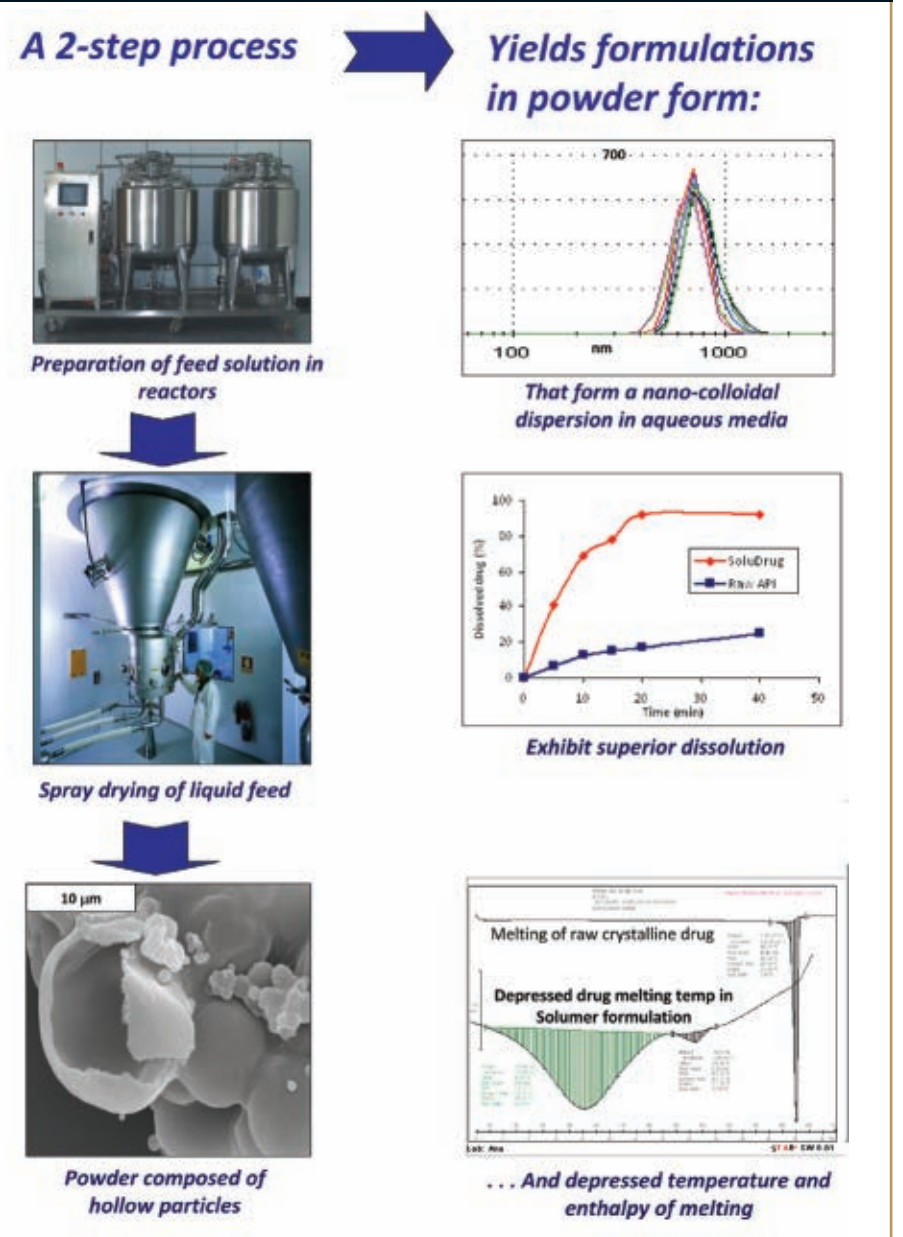
The Solumer process is an easily scalable two-step preparation. The first step involves the preparation of a liquid feed, which is a homogeneous solution of the lipophilic drug and at least two polymers in a mixed solvent (organic/water). The second step involves spray-drying of the solution to obtain a well-characterized powder. In contrast with other technologies, there are no intermediate steps including formation and separation of nano-particles in the liquid media. Thus, drawbacks inherent to other nano-technologies (eg, milling, homogenization), such as the agglomeration of nanoparticles or chemical degradation upon application of shear force, are not relevant to the Solumer platform.[14]

Solumer feed solution amenability to spray-drying results in an attractive industrial process. Spray-drying allows for flexible capacity and continuous and automatic production. The widespread availability of spray-drying equipment enables the process to be easily implemented without an increase in the manufacturing footprint. Furthermore, the Solumer platform is applicable to a wide range of products, including those that are toxic, aseptic and heat sensitive. An illustration of a typical SoluDrug preparation and its physico-chemical characterization is demonstrated in Figure 1.

The resultant spray-dried powder is well-defined and exhibits the following collective unique "fingerprints" of a Solumer solid dispersion:

- Solubilized drug homogeneously interwoven into a polymer matrix,
- Modified thermal behavior demonstrating depressed melting temperature and enthalpy of melting of the drug,
- Spontaneous formation of nano-colloidal dispersions upon contact with aqueous media,

FIGURE 1



Overview of Solumer™ process and product characterization

TABLES 1 & 2

TABLE 1

Formulation	Fenofibric Acid		
	C_{max} (μg/ml)	AUC_t (μg·hr/ml)	T_{max} (hrs)
SoluFeno	7.06 ± 1.16	109.20 ± 37.45	3.0 ± 0.8
TriCor 145	8.10 ± 1.63	113.9 ± 38.70	2.0 ± 0.8
Test / Reference	0.87	0.98	-
90 % Confidence Intervals	0.76 – 1.01	0.91 – 1.01	-

Pharmacokinetics of fenofibric acid in the plasma of volunteers (n=12) following oral administration of SoluFenofibrate versus Tricor 145.

TABLE 2

Formulation	Resveratrol			Resveratrol Total Metabolites			
	Mean AUC_t (ng·hr/ml)	Mean C_{max} (ng/ml)	Median T_{max} (hrs)	Mean AUC_{inf} (ng·hr/ml)	Mean AUC_t (ng·hr/ml)	Mean C_{max} (ng/ml)	Median T_{max} (hrs)
SoluResveratrol	504	330	0.50	28410	27600	8820	1.00
Raw Resveratrol	331	111	2.00	23960	22430	4160	1.50
Test/Reference	1.52	2.97	-	1.19	1.23	2.12	-
90% Confidence Intervals	0.90-2.58	1.95-4.54	-	0.95-1.48	0.97-1.56	1.58-2.83	-
Statistical Significance	NS*	<0.00009	<0.0013	NS*	NS*	<0.0009	<0.003
*** NS – No statistically significant difference**							

Pharmacokinetics of resveratrol and metabolites in the plasma of volunteers (n=12) following oral administration of SoluResveratrol versus raw resveratrol.

- Enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and

- GI site-targeted release of the drug.

The Solumer platform was validated for a number of marketed compounds. Collectively, these formulations have repeatedly demonstrated the platform's key properties: stability (measured up to 2 years), batch-to-batch consistency, commercial scalability, and clinically proven increased bioavailability compared to API (or bioequivalence to marketed nano-pharmaceuticals). Clinical and preclinical studies on Solumerized molecules demonstrate a direct correlation between their increased solubility and bioperformance (Figures 2 through 4 and Tables 1 and 2).

Lastly, the Solumer platform has distinct advantages in the context of the pharmaceutical development process, due to the rapid screening times possible for determination of candidate suitability (up to 4 weeks) as well as the short time required for product formulation. SoluBest can proceed from feasibility studies to clinical studies in less than 6 months.

ALBENDAZOLE

Albendazole is an anti-helmintic or anti-worm medication that prevents newly hatched insect larvae from growing and multiplying in the body. Albendazole is insoluble in water with MW = 265 Daltons; log P = 3.0; T_{melt} = 215°C, and ΔH_{melt} = 210 J/g. The Solumer formulation of this drug with poloxamer 407 and sodium carboxymethyl cellulose yields a composition with decreased albendazole melting temperature and enthalpy (161°C and 31 J/g, respectively, according to DSC analysis). As evidenced by X-ray analysis, the effective crystallite size of formulated albendazole is 33 nm.[15] Laser Diffraction and Dynamic Light Scattering analysis show that disintegration of formulated powder in water results in colloidal dispersion with a mean particle size of 419 nm. All these properties lead to a high dissolution rate for solubilized albendazole (SoluAlbendazole or SoluABZ) versus raw bulk material in a sodium lauryl sulfate, a surfactant that is a typical medium for dissolution of insoluble drugs (Figure 2A). Supersaturation is shown in physiological media, exemplified by fast state simulating intestinal fluid (FaSSIF) (Figure 2B).

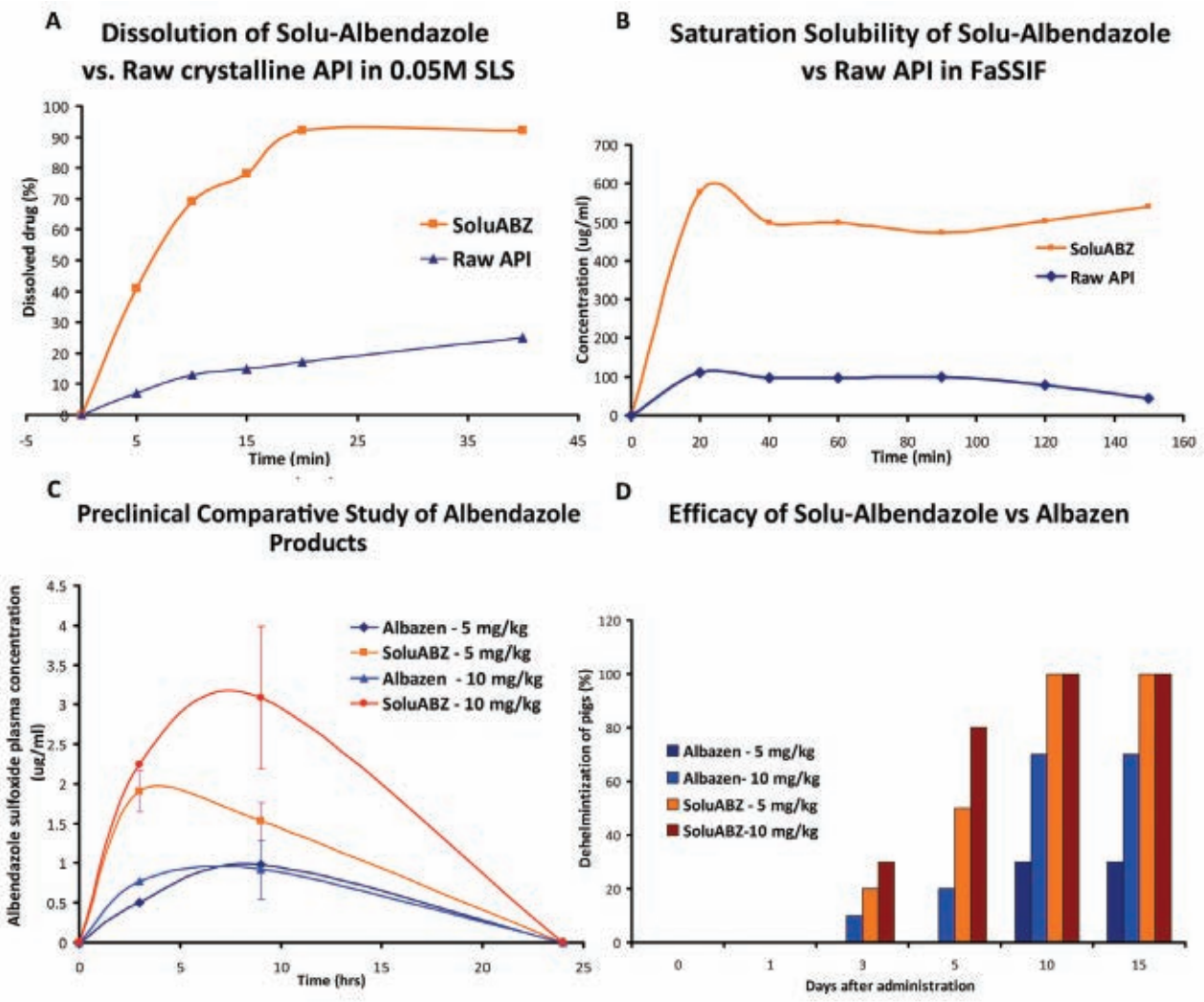
The correlation between physico-chemical properties, demonstrated through in vitro tests, and bioavailability was studied using a pig model. A comparative evaluation of the bioavailability and therapeutic efficacy of an orally administered Solu-Albendazole (test) formulation and a commercial formulation of Albazen (reference) was carried out at Rubikon Ltd. under supervision of its Chief Pharmacologist, Prof. Vasil Piatrou. Albazen, which is manufactured by Rubikon, is the generic version of Pfizer's Valbazen. A total of 40 pigs (aged 75 days) spontaneously infected by nematodes were treated with water suspensions of the test and reference formulations at doses of 5 and 10 mg/kg. Both formulations were administered orally through a pig-dozator under fasted conditions with free access to water.

For pharmacokinetic studies, blood samples were collected at 0, 3, 9, and 24 hours after oral administration. Concentrations of the therapeutically active metabolite of Albendazole, Albendazole sulfoxide (ABZSO), in pig plasma were determined using an HPLC method with UV detection.

In order to estimate therapeutic efficacy of the test and reference formulations, feces samples were collected for coproscopy on days 0, 1, 3, 5, 10, and 15 following administration. Hematological and biochemical blood tests were carried out to identify the safety of the formulation. Pharmacokinetic study results are presented in Figure 2C.

As is evident from the PK data, oral absorption of Albendazole from Solu-

FIGURES 2A-2D



Correlation between in-vitro release profiles and bioperformance for SoluAlbendazole vs Albazene

Albendazole is significantly higher (two- to three-fold) than the absorption from a commercial Albazen suspension. Solu-Albendazole exhibits a clear dose dependence, while Albazen does not. Evaluation of hematological and biochemical data demonstrate that increased drug absorption observed subsequent to Solu-Albendazole administration does not cause abnormal changes in blood parameters; the formulation can therefore be considered safe.

A comparison of anti-helminitic activity of the reference and the test formulations (Figure 2D) clearly favors Solu-Albendazole. Solu-Albendazole exhibits higher efficacy at a lower dose. Complete dehelmintization is achieved in ten days after administration of 5 mg/kg of SoluABZ while Albazene does not result in complete dehelmintization even at a higher dose.

Thus, this study demonstrated a good correlation between the in vitro and in vivo behavior of Solumerized Albendazole. Furthermore, the increased bioavailability exhibited by this product resulted in increased efficacy.

FENOFIBRATE

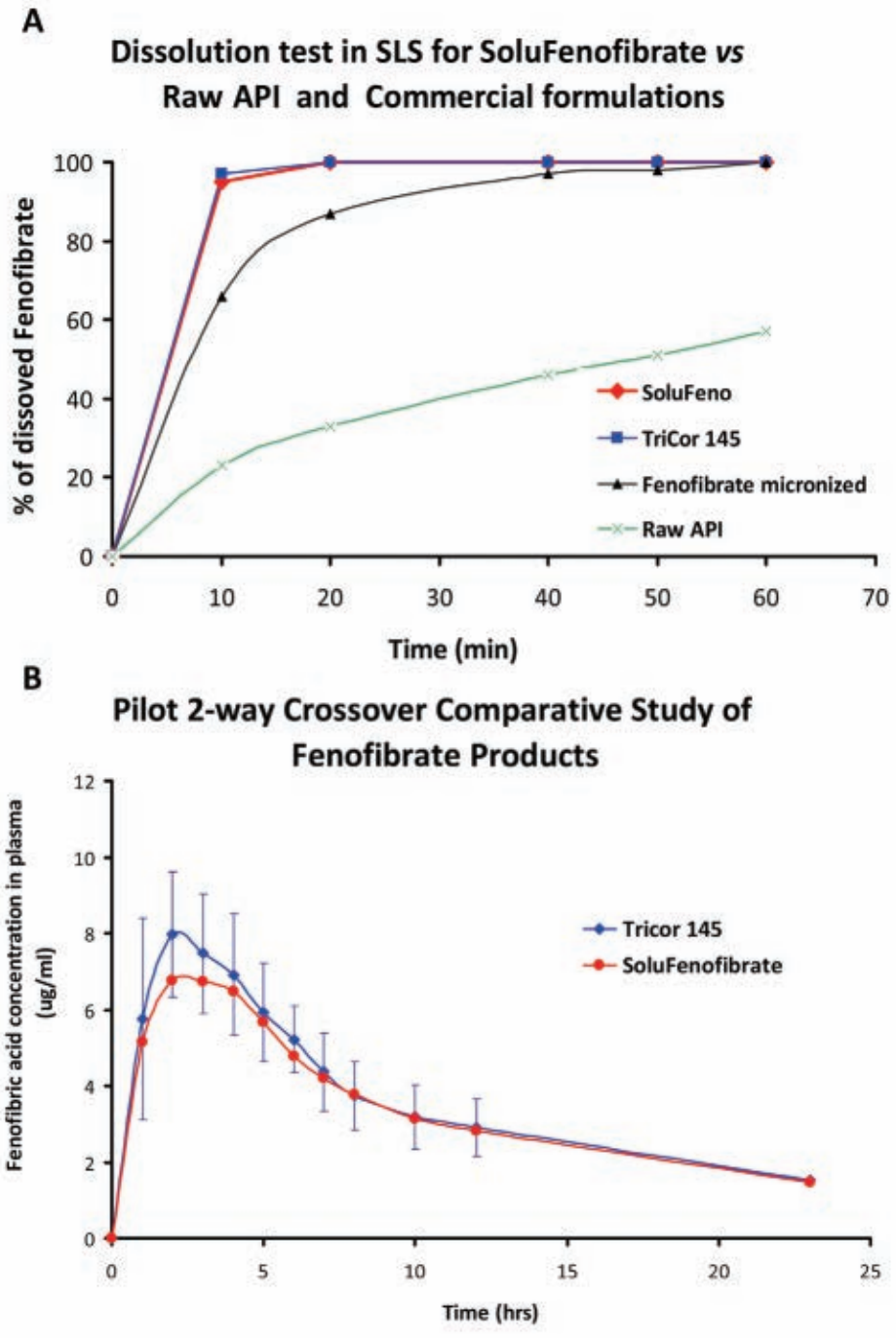
Fenofibrate, a cardiovascular drug used to lower triglycerides and cholesterol, is practically insoluble in water. It is a lipophilic, crystalline substance with MW = 360.8 D; log P = 4.8; T_{melt} = 82°C, and ΔH_{melt} = 74.3 J/g. The Solumerized formulation of this drug with poloxamer 407 and sodium carboxymethyl cellulose yields a composition with decreased temperature and enthalpy of fenofibrate melting (64.4°C and 9.3 J/g, respectively, according to a DSC analysis). As exhibited by X-ray analysis, the effective crystallite size of formulated fenofibrate is about 40 nm. Disintegration of formulated powder in water results in a colloidal dispersion with a mean particle size of 774 nm as measured by Dynamic Light Scattering. These collective properties result in a higher dissolution rate of solubilized fenofibrate as compared to raw API and commercial micronized fenofibrate. The dissolution profile of SoluFenofibrate appears to be similar to that of the leading market nano-formulation TriCor 145, which is manufactured by Abbott using Elan's NanoCrystal milling technology (Figure 3A).

To determine SoluFenofibrate bioavailability in comparison to a reference product (TriCor 145 tablet), a randomized cross-over study was conducted in 12 healthy volunteers. A single oral fenofibrate dose of 145 mg was administered under

fasted conditions. Plasma concentrations of fenofibrate active metabolite, fenofibric acid, were analyzed using HPLC-UV. Monitoring of adverse effects, clinical chemistry, hematology, and urine analysis was performed for all subjects prior to and upon study termination.

The results of these pharmacokinetic studies are presented in Figure 3B and Table 1. As shown in Table 1, the geometric mean test/reference ratios for AUC values fall well within the accepted limits for bioequivalence. The geometric mean test/reference ratio for C_{max} also meets bioequivalence requirements; however, it must be noted that some test/reference C_{max} values for individual volunteers fell outside these requirements. As the pilot study involved a relatively small number of volunteers, it is anticipated that these values would be found within the required limits in a formal bioequivalence study having a greater number of volunteers. Administration of the SoluFenofibrate formulation did not result in any adverse effects or abnormal changes of the blood and urine parameters.

FIGURES 3A & 3B



Correlation between in-vitro release profiles and bioperformance for SoluFenofibrate vs Tricor 145

RESVERATROL

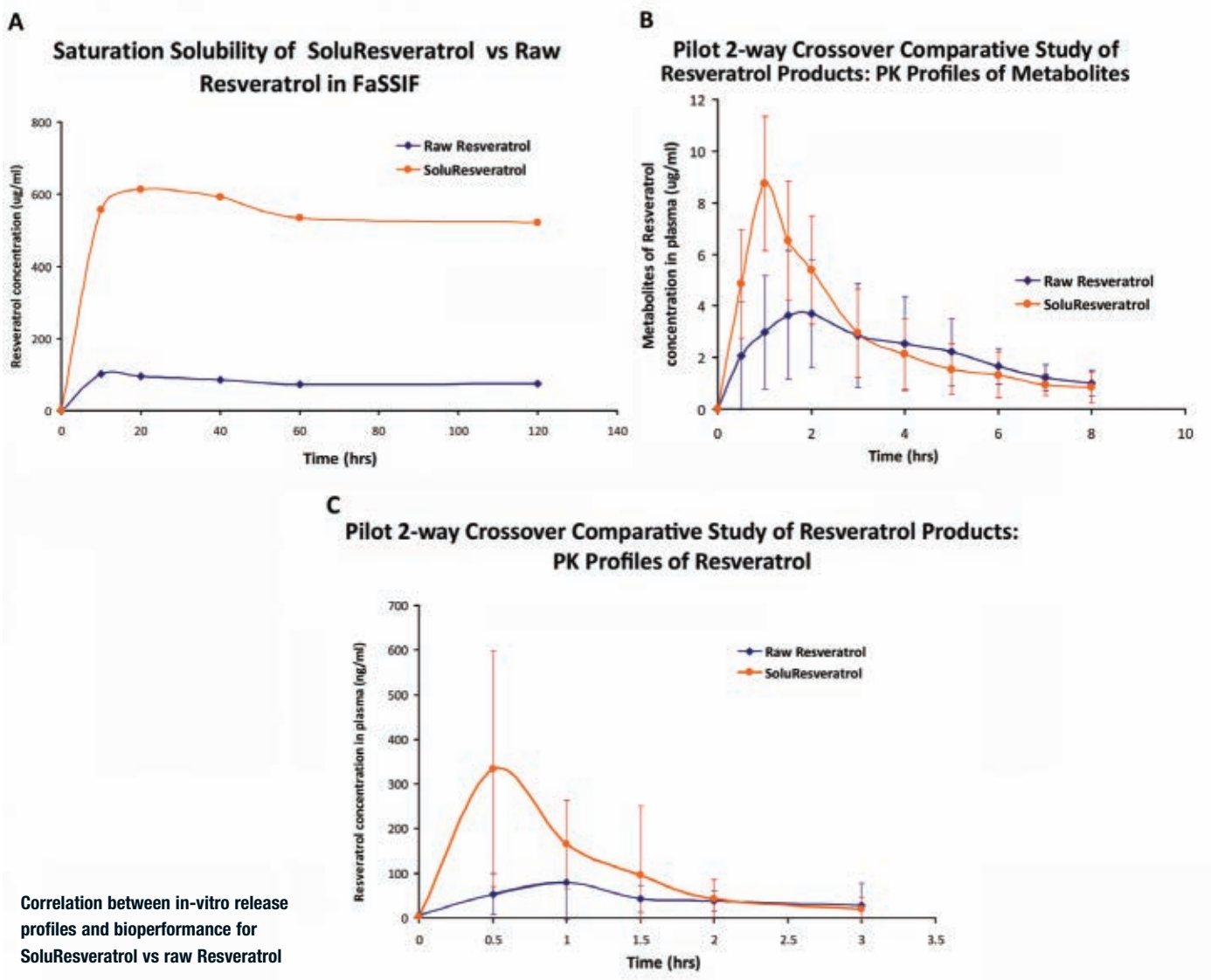
Resveratrol is a small molecule activator of sirtuin enzymes, which may control age-related disorders in various organisms and in humans. These disorders include the aging process, obesity, metabolic syndrome, type II diabetes mellitus, etc.[16] Resveratrol was also found to be an effective agent in reversing arterial damage, in increasing nitric oxide concentration, in neurodegenerative protection and as an anti-cancer drug.[17-20]

Resveratrol exists as two geometric isomers: cis-resveratol and trans-resveratrol; however; only the trans-resveratrol was found to be biologically active. Trans-resveratrol is degraded or converted to the inactive cis-isomer when exposed to light, heat, or oxygen.[21] Resveratrol is practically insoluble in aqueous media, demonstrates very low bioavailability, and rapid, extensive metabolism resulting in only trace amounts of unchanged resveratrol in the systemic circulation.[22]

Resveratrol is currently marketed as an oral nutritional supplement. However, its therapeutic effects are being extensively tested in the clinic. If successful, these trials may potentially elevate resveratrol to drug status in a number of therapeutic fields.

The physico-chemical characteristics of resveratrol are similar to other lipophilic small molecules, which are typical candidates for Solumerization. Its molecular weight is 228 D; log P = 3.1; T_{melt} = 267.4°C, and ΔH_{melt} = 253.6 J/g. The Solumer formulation of this compound with poloxamer 407 and sodium alginate comprises only the active trans-resveratrol isomer. This formulation possesses decreased temperature and enthalpy of resveratrol melting (199.1°C and 14 J/g, respectively, according to DSC analysis). As exhibited by X-ray analysis, the effective crystallite size of formulated resveratrol is 45 nm, and it shows a 55% decrease in the amount of crystallinity compared to the raw material.

FIGURES 4A-4C



Correlation between in-vitro release profiles and bioperformance for SoluResveratrol vs raw Resveratrol

Disintegration of the formulated powder in water results in a colloidal dispersion with a mean particle size of 1244 nm as shown by Laser Diffraction Analysis. These collective properties impact a significantly increased saturation solubility for Solumerized resveratrol versus raw API in a fast state simulated intestinal fluid (Figure 4A).

The in vitro data correlates well with the enhanced bioavailability of Solu-Resveratrol compared to raw resveratrol as was shown in an exploratory clinical study. In a two-way crossover randomized trial in 12 healthy volunteers with a single oral administration of 500 mg of resveratrol, under fasting conditions, test and reference formulations were administered as a powder dispersed in water. The plasma concentrations of resveratrol and its metabolites were analyzed by HPLC-UV with complementary LC-MS analysis. The results of these pharmacokinetic studies are presented in Figures 4B and 4C and Table 2.

As can be clearly seen from the data presented, a significantly higher bioavailability was demonstrated not only for the total resveratrol metabolites but also for resveratrol itself subsequent to oral administration of Solu-Resveratrol.

SUMMARY

Solumer is a novel technology improving the solubility of lipophilic drugs, hence enhancing their bioavailabilities. The technology is based on vastly improved solid dispersions possessing a unique collection of "fingerprint" features, exemplified by modified thermal behavior, nano-colloidal dispersions formation upon contact with aqueous media, and GI site-specific release. Investigations involving the insoluble drugs, albendazole, fenofibrate, and reseveratrol have shown that an excellent correlation was obtained between physico-chemical characteristics, dissolution profiles, and oral bioavailability. Furthermore, Solumer lends itself easily to industrial scale-up, employing spray-drying processing. The Solumer platform allows for rapid candidate screening as well as formulation development.

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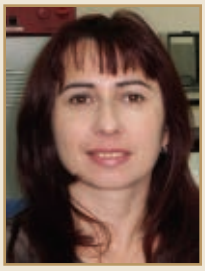
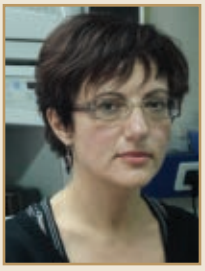


Dr. Galia Temstin Krayz, directs SoluBest Formulation R&D, analytical method development, process optimization and scale-up. She earned her PhD in Organic and Material Chemistry from Ben Gurion University in Beer Sheva, Israel. She has both academic and industrial experience in organic synthesis and process development of APIs.

Dr. Maryana Averbuch, SoluBest's Chief Technology Officer is responsible for development and implementaion of polymer enhanced drug solubilization concepts. She has extensive expertise in the physico-chemical properties of polymers and colloidal systems. She brings valuable experience in instituting and evaluating correlation between physico-chemical properties and biological activity of drug delivery systems.



Anna Berman earned her MSc from the Institute of Civil Engineering, St. Petersburg, Russia. She has brought to SoluBest essential experience in the bioanalytical field after having worked previously for two of Israel's leading commercial analytical laboratories.

Dr. Amir Zalcenstein is involved in business development and planning at SoluBest. He earned his PhD in Cancer Genetics, completed his post-doc in Nanotechnology from the Weizmann Institute of Science, and received his MBA from the Technion, Israel Institute of Technology. His experience entails business development and public relations in the life science sector.

Dr. Irene Jaffe has been involved in technological management and evaluation in the biomedical sector, and at SoluBest directs R&D and IP strategy. She earned her PhD in Chemistry from the Weizmann Institute of Science in Israel and completed post doctoral research at MIT's Dept. of Chemistry. Her scientific experience spans organic, organo-metallic, and polymer chemistry as well as materials research.

SPECIAL FEATURE

PENETRATING THE MARKET WITH INNOVATIVE TRANSDERMAL TECHNOLOGIES

By: Cindy H. Dubin, Contributor

Led by innovative market entries of promising new APIs, prescription transdermal patches and gels for pain management are positioned for double-digit growth throughout the next 4 years, according to Applied Data Research (ADR). Responding to the desires for simplified dosing, reduced side effects, and improved safety of transdermal pain patches and gels, drug developers are investing in the clinical development of a range of pain drugs that can be delivered via the skin. Pipeline pain patches that will enter the market within the next 3 years include products based on bupivacaine, desamethasone, ketoprofen, and capsaicin.

Narcotic pain drugs now account for more than half of all transdermal pain products worldwide. Increasing demand in existing markets and greater emphasis on under-developed regional markets will drive the total value of the pain mangement sector beyond $8 billion by 2012. For example, Alpharma's Flector diclofenac patch exceeded analysts' estimates in 2008, its first full year of FDA approval, demonstrating the potential of non-opioid drugs for the treatment of neuropathic pain. In Latin America, Amarin's diclofenac TDS is becoming available in a growing list of countries. Sales of buprenorphine patches are growing 16% annually in Europe; German-based Grunenthal's Versatis is the only approved topical anesthetic patch. And in Australia, a jewelry designer is working on a silver vial necklace that would not only carry a supply of tiny insulin patches but act as an applicator as well.

Fentanyl will remain the drug of choice for breakthrough pain associated with cancer; Teva's fentanyl patch won FDA approval in October. However, there was the recall of the Johnson & Johnson (Alza Corp.) Duragesic Pain Patch in which approximately 32 million of these fentanyl-containing transdermal patches were recalled due to defects that could lead to accidental overdoses.

Issues of patient compliance and safety also permeate delivery methods for CNS drugs, as these patients' cognitive abilities are often compromised by the nature of their diseases. Drug developers are increasingly turning to transdermal formulations of CNS drugs to overcome patient compliance issues. According to ADR, the ability of transdermal CNS therapeutics to respond to the growing unmet need for patient-friendly administration has analysts predicting the total value of transdermal CNS drug products exceeding $1 billion in 2012.

SURVIVING THE ECONOMY

The economic downturn has affected the drug delivery industry. Budgets are tight, and funding is harder to come by. As a result, it is even more important than ever for companies to be focused and control costs, as well as concentrate their efforts on programs that add real value to patients and the healthcare system. Companies are evaluating programs and ensuring they are applying resources to the highest-priority opportunities, says Peter Staple, President and CEO of Corium.

"We are seeing that investors are more careful with their money; therefore, it is wise to plan ahead long enough for financing rounds," says Dr. Christof Boehler, CEO of Pantec Biosolutions.

Planning for some drug delivery firms includes deal-making and partnerships. Consider Altea's partnerships with Lilly/Amylin and Hospira, as well as Intercell's acquisition of Iomai for its transdermal vaccine technology and Lilly's agreement with TransPharma Medical for a transdermal PTH product.

Proper planning and continuous influx of funding should help the $7.1-billion transdermal and topical drug delivery market reach an estimated $8.2 billion by 2010, according to ADR. But, given the current economic climate, 2009 will remain relatively flat. What could help is the emergence of the active marketplace in the coming years. Industry sources estimate the active market will represent 10% of the total transdermal drug delivery market by the end of this year.

"After a decade of basic research and development, active transdermal technologies are now emerging as promising new ways to deliver large molecules through the skin," says Mr. Staple. "There are now

FIGURE 1

real options for the delivery of biotech-based large molecules, such as proteins, peptides, and vaccines without using the traditional syringe and needle."

MARKETPLACE HAPPENINGS

Transdermal delivery systems are based on passive or active transport. Passive patches utilize a one-size-fits-all approach. Drug is preloaded into the adhesive on the patch, and all the patient has to do is peel and stick the patch on the body, and the drug will passively transport across the skin barrier. These patches fill the need for delivery of drugs (ie, nicotine, contraceptives) with small molecular weight that are fairly stable and do not require any customization of delivery.

For drugs with a larger molecular weight, active patches transport the drug through the stratum corneum through a variety of modalities, such as heat, microporation, or iontophoresis. The following highlights what some of the players in the active and passive markets have in their pipelines. Featured companies include Altea Therapeutics, Aveva, Corium, Isis Biopolymer, LTS Lohmann, Pantec Biosolutions, and Transpharma Medical.

ALTEA THERAPEUTICS — PARTNERSHIPS PROPEL PASSPORT® PLATFORM

Altea Therapeutics is a clinical-stage specialty pharmaceutical company with a proprietary platform technology, The PassPort System is broadly applicable to the transdermal delivery of biological drugs (proteins and carbohydrates) that otherwise would be administered by needle injection or infusion. The PassPort Transdermal System (Figure 1) is also suited for delivering highly water-soluble, low-molecular weight drugs that otherwise could not be delivered transdermally. These include ionic salt forms of drugs, eg, fentanyl citrate, that can be delivered more safely and effectively than by the existing transdermal product, and other low molecular weight drugs with potencies too low to be delivered using conventional transdermal patches, says Eric Tomlinson, DSc, PhD, President and CEO of Altea.

"The Altea Therapeutics PassPort Transdermal System can alter the way several diseases are currently managed by enabling the efficient transdermal delivery of biologicals and water-soluble low molecular weight drugs," he adds. "This technology has the potential to grow the current market of transdermal patches by replacing injections, and in some cases, even oral agents."

By enabling transdermal delivery of medications currently administered via injection, the PassPort System offer benefits related to convenient drug administration and compliance.

"Patient compliance is a critical issue for patients on insulin who are uncomfortable with needles or have lifestyle concerns surrounding the need to self-administer one or more injections per day, as is the case with many type 2 diabetes patients," says Dr. Tomlinson. "The unique attributes of our transdermal technology provide substantial benefits, such as improvements in quality of life, greater compliance, better efficacy, and safety, mostly by replacing injections, some conventional patches, and even oral agents."

Altea's business model relies on partnering its products with the pharmaceutical industry. Its current product portfolio includes two partnered products: a transdermal version of exenatide (currently available on the market as Byetta® injection) with Lilly/Amylin and a transdermal product with Hospira. Further, Altea is in clinical development for a Transdermal Basal Insulin Patch that provides continuous delivery of insulin for people with type 1 and type 2 diabetes, and for a Transdermal Fentanyl Citrate Patch that enables rapid and safe management of moderate-to-severe pain. The company is in preclinical development with several product candidates, including a Parathyroid Hormone Transdermal Patch for the prevention and management of osteoporosis.

"Altea's partnerships with Lilly/Amylin and with Hospira were significant events that both validate our transdermal PassPort System technology and provide us with enormous business opportunities," says Dr. Tomlinson. "Both our partnerships and our broadly applicable technology platform have enabled us to insulate ourselves from the travails of capital formation that private and publicly traded companies are currently experiencing. There is no doubt though that a continued weakness in the economy could begin to impact our future ability to raise significant capital to grow the business faster than our corporate deals permit."

AVEVA DRUG DELIVERY SYSTEMS — DELIVERING DRUGS WHEN NEEDED

Despite an economy that is forcing many companies to do more with less, Aveva Drug Delivery Systems is experiencing explosive growth, which is attributable to global expansion, a healthy pipeline, as well as Aveva's new product approvals and commercial launches, explains Robert J. Bloder, Vice President Business Development at Aveva, which is part of the $7 billion Nitto Denko Group. Recent product approvals in the US and Canada include Aveva's Fentanyl patch marketed by Teva and its Nicotine patch marketed by Watson in the US and Perrigo in Canada. Aveva is also manufacturing the 7-day Sancuso Patch for ProStrakan. Sancuso is the first patch indicated for the treatment of chemotherapy-induced nausea and vomiting. Aveva also has many products in various stages of development available for licensing and manufactures the Onsolis product (awaiting FDA approval) for BioDelivery Sciences Incorporated. Onsolis is a bioerodible, mucoadhesive indicated for breakthrough pain associated with cancer pain.

Aveva and Nitto Denko provide patches designed to exceed industry performance standards. Whether the transdermal platform is active or passive, patch comfort and wear are important features. The Gel Matrix adhesive system provides the perfect balance of gentleness and reliability. It is one of the many performance adhesives utilized in our matrix systems that have met or exceeded market expectations over the years. Unlike conventional adhesives, the gel matrix adhesive causes little disruption of the stratum corneum during removal, which greatly diminishes skin irritation. Thusly achieving a desirable patient experience that is mindfully present in all product development projects, says Mr. Bloder.

FIGURE 2

Corium's proprietary MicroCor™ active transdermal technology uses mechanical energy to deliver the active therapeutic agent.

The company's crystal reservoir technology has resulted in the development of smaller patches with a more controlled and sustained drug release. Drug release is based on the oversaturation of an adhesive polymer with API forcing a partial crystallization of the drug. The presence of molecular solute and solid crystal forms allow for a considerably higher concentration and consistent supply of drug in each patch, explains Mr. Bloder. This technology is employed in the commercial production of an Asthma Patch currently sold in China and Japan.

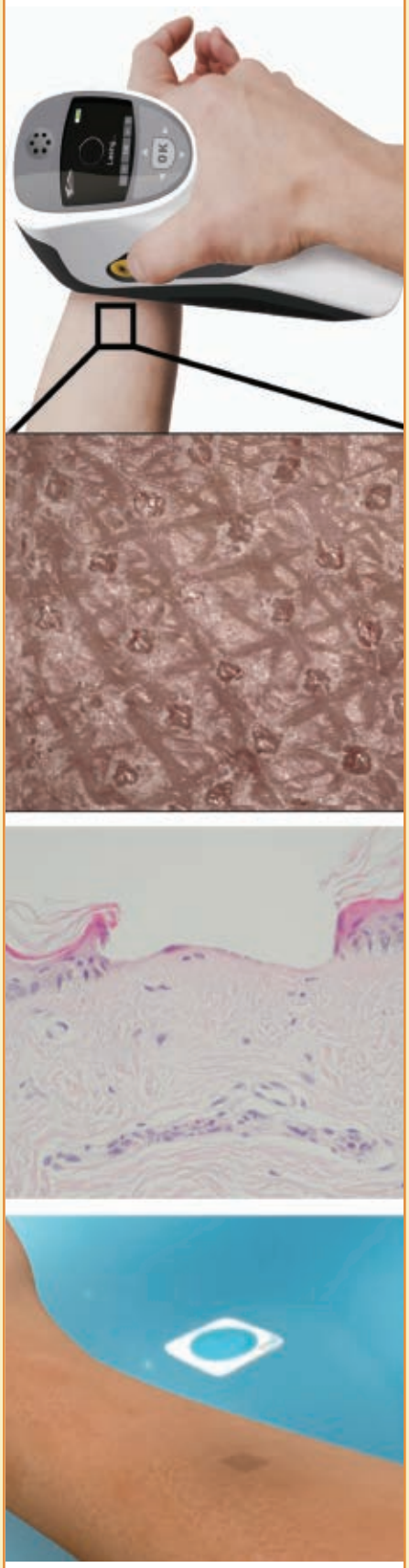
Nitto Denko's asthma patch is the world's first and only asthma patch, also indicated for emphysema as well as acute and chronic bronchitis. The product's delivery profile is designed to peak in the early morning when patients most need the drug to prevent coughing related to broncho-constriction, says Mr. Bloder.

As far as where Aveva and the transdermal industry are headed, Mr. Bloder states, "I believe we will begin to see how passive delivery can be maximized with new and unique enhancers, excipients, and alternative occluding technologies. We may also have the opportunity to assess the receptivity of patients and learned-intermediaries to disruptive skin technologies, including microneedles and other active patch platforms, which through various modalities, alter the stratum corneum to increase drug delivery."

FIGURE 3

Isis Biopolymer's Isis Patch has the ability to transport up to three drugs per patch and is fully programmable for customized delivery.

FIGURE 4



Pantec's P.L.E.A.S.E. hand-held laser device creates aqueous micropores in the epidermis to deliver drugs painlessly.

CORIUM — NIXING THE NEEDLE IN THE NAME OF PATIENT COMPLIANCE

Corium focuses on product opportunities in which a transdermal dosage form can reduce or eliminate side effects, improve efficacy, or access a patient population that has problems with existing dosage forms. For example, in some disease categories and in an elderly population, swallowing difficulties present challenges for oral dosage forms. Additionally, for certain applications, the use of subcutaneous injections for chronically administered therapies can cause patients to discontinue their medication.

With its MicroCor™ active transdermal technology, Corium replaces the needle and syringe and offers improved convenience and compliance for subcutaneous, intramuscular, and intravenous drug delivery (Figure 2).

Corium's proprietary MicroCor active transdermal technology uses mechanical energy to deliver the active therapeutic agent via microstructures that are incorporated into a very small patch. The patch is worn for a very short period of time, and its drug-sparing design enables delivery of nearly 100% of the drug. The biodegradable nature of the microstructures enhances safety by leaving no residual sharps and reduces any abuse potential. This technology also eliminates the need for cold storage, which is common with most large molecules.

In the passive transdermal field, Corium's Corplex™ technology presents opportunities for never-before transdermally delivered drugs, says Mr. Staple of Corium. Corplex is a flexible polymer system that encompasses a new class of biocompatible hydrophilic pressure-sensitive adhesives that can adhere to wet or dry surfaces over a range of wear times. The highlight of this system, says Mr. Staple, is its ability to hold large amounts of drug and enhancers in a small, solid-state matrix patch. This allows for greater flux through the skin and improved adhesion for 7 days or more. There are many opportunities in the CNS arena to exploit the Corplex advantages.

"Whether delivered actively with MicroCor or passively with Corplex, our technologies look to offer the patient a painless and user-friendly way of taking medication and delivering small and large molecules through the skin," says Mr. Staple. For example, Corium is developing a multi-day transdermal system for delivery of Tamsulosin, a drug used for the treatment of benign prostate hyperplasia that has not previously been delivered through the skin.

Corium's partnering efforts are underway as well. Corium is looking at significant growth in demand for products it has already developed for partners. As a result, its revenues are expected to increase two-fold throughout the next year, explains Mr. Staple.

"Like all companies, we have to be thoughtful about product selection and commercialization strategies, and not just follow-the-technology. Transdermal companies must choose products with a market need and a consumer advantage in order to succeed. As we look into the future, we also see opportunities to address the need for a personalized medicine approach by combining aspects of our technologies into a detect-measure-deliver process with integrated feedback to ensure the correct dose for an individual patient's needs."

ISIS BIOPOLYMER — TRANSDERMAL GOES WIRELESS

Isis Biopolymer has developed technology to prevent inadvertent or over delivery that results from changes in the skin, such as temperature, moisture, and movement. Its proprietary single electrode design removes the variability of these changes in the skin, while the selective barrier membrane facilitates transport or complete cessation of drug delivery.

The single-use, band-aid-like active patch controls and monitors transdermal drug delivery, ensuring safe and accurate administration through the skin using iontophoresis. The Isis Patch has the ability to transport up to three drugs per patch and is fully programmable for customized delivery and monitoring via an integrated wireless communication platform (Figure 3).

"The shift to fewer healthcare providers and a stronger focus on home and self-care requires transdermal devices with this technology and is ideal for this trend," says Emma Durand, President and CTO of Isis. "We have the ability to wirelessly program the Isis Patch, which will have important implications in the future."

The Isis Patch is also a biosensor, which can detect skin emanations that may be indications of medical events, such as heart attack, shock, or diabetic reactions. "In addition to being intelligent and highly reliable, the Isis Biopolymer patch is very safe," adds Ms. Durand.

The company's target audience is primarily pharmaceutical companies that have a current unmet patient need for drug delivery. "We are focused on working with organizations that have approved drugs, as well as pipeline products or drugs in development that have challenging delivery issues where active transdermal delivery offers a solution," she says.

Therapeutic areas of interest are both chronic and acute, such as pain management, oncology, neurology, women's health, endocrinology, and cardiovascular.

Founded a little more than 2 years ago, Isis Biopolymer has successfully completed animal trials and has recently initiated its first human clinical trials, as well as filed a 510k for FDA approval. "This year was very busy for us, building our patent protection portfolio as well as fueling our R&D projects. We are also engaged in ongoing discussions with several pharmaceutical and biotech companies," says Ms. Durand.

Isis Biopolymer's business model was originally designed to make it capital efficient and to generate profit within the first 3 years, she explains. "The strategy has been to raise enough funds to get us quickly and successfully through our initial milestones, such as R&D, intellectual property, and commercialization, that will ultimately lead to licensing agreements and manufacturing. In essence, our goal is to do more with less."

LTS LOHMANN — DEVELOPING PATCHES FOR TODAY'S TRANSDERMAL REQUIREMENTS

This past year, LTS launched its first Alzheimer transdermal patch manufactured for one of its customers. This patch is an alternative to the capsules that have been on the market with the same active ingredient. Additionally, the company has developed a Parkinson patch, which is the first patch including an NCE. Smoking cessation, pain management, CNS, contraception, and hormone replacement therapy make up LTS' therapeutic focus areas.

"Our technology relies on state-of-the-art historical techniques of medical product manufacturing," explains Yvonne Müller, Marketing Manager at LTS. "Technologies of coating and drying have been applied by scientists and developers into a unique pharmaceutical technology for all forms of application with thin-film elements."

Transdermal system concepts usually are divided between matrix systems and reservoir/membrane types. This separation is no longer sustainable with today's transdermal products, she says. Multiple types of different system designs exist. The main functionalities (adhesion, reservoir function, driving force, and rate control) can be assigned to different substructures of the patch, but are also influenced by the human skin. LTS supports all different system variations, from both a development and manufacturing capability."

The company's Estradiol Matrix Patches deploy the concept of mono-layered drug matrices, allowing efficient manufacturing, but more comfortable wearing properties to the consumer as well.

"Estradiol is the most important natural estrogen that can be delivered transdermally efficiently and devoid of sudden changes in blood level," Ms. Müller says.

PANTEC BIOSOLUTIONS — A P.L.E.A.S.E.ING SOLUTION FOR INFERTILITY

Pantec has recently completed major clinical milestones for peptides and proteins with its P.L.E.A.S.E. (Painless Laser Epidermal System) in its key focus area of infertility, which represents a hormone drug market of about $1.5 billion.

"We have chosen infertility as our first target area as it is an ideal market to introduce such a new technology," says Dr. Christof Boehler, CEO of Pantec. "The most widely used method to treat infertility globally is *In Vitro* Fertilization, which forces women to apply 50 hormone injections or more. The industry's current hormone therapy is very complex and complicated for patients as they frequently have to self-inject up to three hormones all coming in different application forms, suvch as syringes, needles, prefilled syringes, and pens. Pantec Biosolutions has already indentified several private infertility clinics confirming strong interest in adopting P.L.E.A.S.E."

And, it's not just the women who benefit from the P.L.E.A.S.E. system. Doctors want to achieve drug serum concentration over a certain period of time, something a patch can do because it releases drug continuously over several hours and days, if it is well designed, he says.

"With our clinical data, we can now work toward pivotal studies and leverage the results in other applications in the biopharmaceuticals market, which has a size of $80 billion and growing at 10%. Several discussions currently held with pharmaceutical companies might lead into partnering deals."

P.L.E.A.S.E. is designed to deliver high molecular weight drugs. The hand-held laser device creates controlled aqueous micropores in the epidermis (Figure 4). The laser procedure lasts only a few seconds, followed by attaching the drug-containing patch over the microporated area on the skin. Due to the special features of the device, the micropores do not reach the dermis where nerves and blood vessels reside. A graphical user interface guarantees simple and safe use by the medical personnel or the patient, who can use the device without supervision.

TRANSPHARMA MEDICAL — SAFELY DELIVERING PROTEIN DRUGS

TransPharma Medical successfully completed a Phase I clinical study that included a 7-day repeated application of its ViaDerm-hPTH (1-34) and subsequently entered into a Phase II trial. In parallel, TransPharma has advanced the development and design of its commercial prototype product and accomplished building scaled-up manufacturing lines for its ViaDerm system, explains Dr. Daphna Heffetz, TransPharma's CEO.

"In the past year, we have demonstrated through advanced clinical trials that our system is offering patients a safe and therapeutically effective method for administering drugs," says Dr. Heffetz. "More than 450 patients have been treated with our ViaDerm system in various clinical trials, and we are seeing not only promising clinical results, but also patients' and caregivers' enthusiasm toward the ViaDerm system."

The ViaDerm transdermal system is intended for patients who require chronic treatment of therapeutic compounds (Figure 5). Transdermal delivery here can improve the compliance, safety, and ease of their administration, adds Dr. Heffetz.

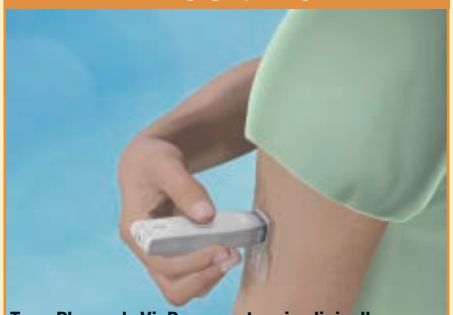
"We have further established that ViaDerm's system is designed for delivering peptides and proteins and that the system's patch component allows for a stable drug product at room temperature, which adds to the convenience of the product supply and handling."

In June 2008, TransPharma Medical and Eli Lilly entered into a licensing agreement for the development and marketing of ViaDerm-hPTH (1-34) for treating osteoporosis.

"This validates the product potential and ViaDerm's clinical and manufacturing process achievements," says Dr. Heffetz.

TransPharma's ViaDerm hPTH (1-34) is intended for osteoporosis patients who require daily painful injections of hPTH (1-34). "Currently, hPTH (1-34) is the only osteoporosis drug with anabolic properties, stimulating new bone growth that results in increased bone strength and a decrease in fracture risk. Anabolic agents are projected to be the fastest growing segment in the US osteoporosis market, which is expected to reach $1.24 billion by 2010. "Our proprietary products in development enable transdermal delivery of large, hydrophilic molecules by creating temporary, shallow aqueous microchannels in the skin," says Dr. Heffetz. "The ability to efficiently deliver protein drugs by methods that are safe and appealing to patients is one of the greatest unmet needs of the drug delivery field."

FIGURE 5



TransPharma's ViaDerm system is clinically proven to deliver peptides and proteins.

SUMMARY

Transdermal drug delivery offers compelling opportunities to address unmet needs in the market for safety, convenience, and compliance. Novel approaches to transdermal drug delivery have significantly expanded the platform of molecules that can be delivered via the skin.

"In 3 to 5 years, we will see more transdermal patches in the market than ever," insists Dr. Boehler of Pantec Biosolutions.

In addition to passive transdermal patches containing small molecular weight drugs, a handful of active transdermal systems that consist of devices that either pretreat the askin to make it temporarily more permeable or patches that force drug molecules to enter the skin mechanically, electrically, or thermodynamically, will also be available. Active systems will offer greater flexibility in dose sizes, frequency, and controlled release. In general, transdermal systems will become more user friendly.

"We cannot ignore the fact that 40% of patients do not follow their prescribed regimen," says Ms. Durand. "The companies that will thrive in the future will provide products and services that help to obtain better compliance."

"The skin is our largest organ, and in addition to performing as a protective barrier, it is also one of the most direct routes to our blood system," adds Isis Biopolymer's Dr. Heffetz. "Passive transdermal delivery has already become a widely acceptable route for delivering small molecules, such as hormone-replacement therapies, pain management therapeutics, anti-emetics, etc. Innovative technologies for transdermal delivery will undoubtedly extend the use of transdermal delivery to a wider variety of drugs, which is why we believe that transdermal delivery will become the leading alternative delivery route." ◆

BUSINESS ANALYSIS

Up, Down, Sideways - A Look at Drug Delivery Strategy

By: Josef Bossart, PhD

ABSTRACT

If you attended drug delivery meetings in the past decade, you surely remember the prescription offered for Drug Delivery company success was to be found in transitioning to the Specialty Pharma model. Margins in the drug delivery business were seen as tight, and Big Pharma seemed to have little respect for technology-only Drug Delivery companies when negotiating deals. In contrast, Specialty Pharma companies were by any measure masters of the universe, capable of launching and selling their own products at high margins and earning consistent profits. This mastery not only provided for high stock prices, it also allowed access to the capital necessary to be successful. And of course, if a Specialty Pharma company were too successful, Big Pharma would acquire it at a very attractive premium. All one needed to do was make the move and soon enough the market would recognize the wisdom of the strategic decision and reward the company with greater market capitalization and funding.

That was the best thinking of industry minds in the middle of this decade, and a number of companies moved in this direction. After all, hadn't Alza, Biovail, and Elan moved their valuations into the stratosphere by adopting the Specialty Pharma model?

It seems a good time to take a look at how this strategy has played out for companies that decided to take this strategic direction, and how it's worked out for companies that stayed on the traditional Drug Delivery track.

A word of caution; this is not a discussion for those who like everything neat and tidy. The analysis is a little messy because many companies keep one foot in Drug Delivery while placing the other in Specialty Pharma. We will handle this by looking at groups of companies, an average effect, rather than focusing on specific companies. The net/net will be insights on how the strategic move from Drug Delivery to Specialty Pharma might play out for companies already on that path or thinking of heading in that direction.

WHAT IS A SPECIALTY PHARMA COMPANY?

We toss around the expression Drug Delivery very casually in our discussions with a sense of confidence about what we mean. But what about Specialty Pharma? What defines a Specialty Pharma company? While open to opinion, my sense is that a Specialty Pharma company is not a company that simply focuses on one or two therapeutic areas. If that were the case, then all Biotech companies developing kinase inhibitors to treat cancer or new agents to treat neurological diseases would be considered Specialty Pharma companies, but they're not. For the purpose of this article, we'll use the following definition:

A Specialty Pharma company is a biopharmaceutical company with no discovery operations primarily focused on developing and commercializing validated actives in a very limited number of therapeutic areas.

WHAT IS A DRUG DELIVERY COMPANY?

This should be pretty obvious to the readers of this magazine, but it's worth defining Drug Delivery companies as will be used in this article:

A Drug Delivery company is a biopharmaceutical company with no discovery operations primarily focused on developing and validating drug delivery technologies and products for commercialization by other companies.

These two definitions provide a reasonably good distinction between the two companies. For a Drug Delivery company to become a Specialty Pharma company, it would need to retain its portfolio products through to commercialization. Simply taking products through approval and then licensing them out does not reclassify a Drug Delivery

company as a Specialty Pharma company based on our definitions.

THE BIONUMBERS INDEXES

The Bionumbers indexes have been presented on occasion in this magazine and track the market capitalization of Drug Delivery and Specialty Pharma companies as defined earlier. Details on these indexes can be found at www.bionumbers.com. In summary:

1. The indexes are based on the market capitalization value of individual companies summed to create a total value. Market capitalization is stock price multiplied by shares outstanding as reported by the companies.

2. Market capitalization is followed month by month for three separate groups of companies:

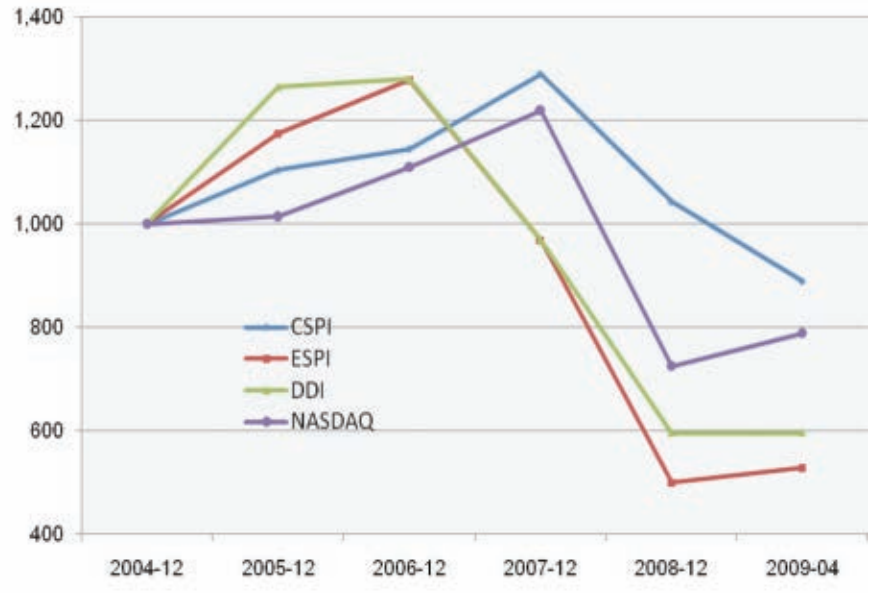
   - Commercial Specialty Pharma Index (CSPI) - includes Specialty Pharma companies as defined earlier that have active commercial operations.

   - Emerging Specialty Pharma Index (ESPI) - includes Specialty Pharma companies that have expressed an intent to market their own products but have not yet reached the stage of commercialization.

   - Drug Delivery Index (DDI) - includes Drug Delivery companies that have expressed no intent to move to product commercialization activities.

3. All indexes are normalized at a value of 1,000 based on the closing market capitalizations on the last day of 2004. The indexes cover the period from the end of 2004 through to the present and are updated monthly.

FIGURE 1



Bionumbers Market Index Summary, December 2004 to April 2009

4. The companies included in each of the indexes are listed at the Bionumbers website. Note that some companies are included in both the ESPI and DDI because, as noted earlier, they have one foot in each business.

MARKET CAPITALIZATION PERFORMANCE

Figure 1 and Table 1 provide a summary of the performance of the three indexes (CSPI, ESPI, and DDI) plus the NASDAQ Composite since the end of 2004, a period of about 4.5 years. Figure 1 summarizes the closing values on the last day of the year for 2004 though 2008, and for the last day of April 2009.

A quick look at Figure 1 reveals a troubling trend. All of the companies in the index have lost market capitalization value over the past 4.5 years. Even NASDAQ performance, which uses other methodology, shows a drop in value of 20% over this same period.

The CSPI has done the best over this period, losing a little over 10% of its value. This is followed by the DDI, which has lost 40% of its capitalization value. The ESPI has done the worst of the bunch, losing a little less than half of its value.

It's worth noting, but not obvious from Figure 1 and Table 1, that there has been considerable acquisition activity in the Commercial Specialty Pharma group. Of the 43 companies initially included in the CSPI, 16 have been acquired in the 4+ year period the index covers. By contrast, the DDI and ESPI have seen almost no merger and acquisition activity in this same period.

All of the indexes have a very similar shape, up in the 2004 to 2006 period (when Specialty Pharma was THE model) followed by a severe dip that started in 2007 and 2008.

For all practical purposes, it seems there is little difference in market capitalization performance between companies that pursued a Drug Delivery strategy and those that went off in search of Specialty Pharma riches. And given the reasonably large sample size, 50 public Drug Delivery and 20 Emerging Specialty Pharma companies, the observations are reasonably robust.

TABLE 1

Index/Companies	End 2004	End 2005	End 2006	End 2007	End 2008	End April 2009
Specialty Pharma						
-Commercial Stage	1,000	1,104	1,145	1,290	1,043	889
- Emerging Stage	1,000	1,174	1,277	968	500	529
Drug Delivery	1,000	1,264	1,279	968	595	596
NASDAQ Index	1,000	1,014	1,110	1,219	725	789

Bionumbers Market Index Summary, December 2004 to April 2009

Ah, but you say the pay-off for an Emerging Specialty Pharma company is still a few years off. It takes time to develop a product and bring it to market. Good point. According to the Bionumbers 2009 Drug Delivery report issued in June, the average time to take a drug delivery product from the start of Phase I trials to approval is 5.8 years. So for those companies that jumped on the Specialty Pharma bandwagon in 2003, 2004, and 2005, the pay-off in terms of commercial rewards is not going to arrive before 2010 if they had nothing already in their clinical pipeline. But just how much and how soon does a marketed product impact the market capitalization of a company?

Auxilium Pharma may be a reasonable success model to consider. The company's capitalization has grown from about $180 million in 2004 to $1.2 billion by the end of 2008. It now sits at around $970 million. This growth has largely paralleled the growth of their first product (Testim), a second-to-market testosterone gel approved in October 2004. But the six-fold increase in valuation has come 3 to 4 years after Testim's approval, which implies the interval between the start of clinicals to real market value creation is perhaps 9 years (6 years for clinicals and approval, and 3 years for substantial market penetration).

A less happy example is Alkermes, one of the model Drug Delivery companies that has taken on a Specialty Pharma identity. Despite the approval of their first internal portfolio product (Vivitrol in April 2006), which they co-promoted with Cephalon, their market capitalization has dropped from about $1.3 billion at the end of 2004 to $1 billion by the end of 2008, and to $720 million by the end of April 2009. Shouldn't its valuation have increased? Having a product on the market doesn't have the same value as having a successful product on the market.

These companies are examples of how the market has treated those that have adopted a Specialty Pharma approach. The Bionumbers indexes average out these extremes by aggregating the performance of multiple companies, and the resulting average is not pretty. As we'll see in the next section, the loss in market capitalization is exceeded by the loss in share price, the factor of most interest to investors.

TABLE 2

Index/Companies	End 2004	End 2005	End 2006	End 2007	End 2008	End April 2009
Specialty Pharma						
- Commercial Stage	$1,000	$1,111	$1,208	$1,220	$865	$785
- Emerging Stage	$1,000	$959	$942	$560	$218	$214
Drug Delivery	$1,000	$1,164	$1,078	$815	$503	$496

Share Price Performance Index, 2004 to Present

SHARE PRICE PERFORMANCE

Another measure of a company's performance and its ability to attract investors, new capital, and employees is the performance of its stock price. A doubling in market capitalization at the expense of a 100% dilution is not very attractive to an investor, although it is better than a loss in market capitalization and a drop in stock price. There are many ways to calculate stock price performance for a group of companies. For our purposes, we'll use the December 30, 2004, closing price as our base, and apportion our price index as a function of each company's market capitalization share of the total index on that date. This means if a company accounted for 10% of a group's capitalization at the end of 2004, it will account for 10% of the index stock price performance. See the Bionumbers website for additional explanation and examples.

If the market capitalization figures were discouraging, the share price performance for all of the groups is even more disappointing (Table 2). These figures represent the ongoing value of a portfolio that invested $1,000 on December 31, 2004, in each of the indexes, and held the shares through to the end of April 2009. This $1,000 base allows us to roughly compare performance with the market capitalization figures presented in Table 1.

The greatest difference between market capitalization and stock price performance is seen with the ESPI. On a stock price basis, the market has hammered Emerging Specialty Pharma companies. The reason of course is that to pursue the Specialty Pharma model, these pre-commercial companies have been forced to go to the market for funds to finance clinical development and premarketing

expenses. This financing has come by diluting existing shareholders with the issuance of additional stock. This effect is largely hidden when looking at market capitalization, but shows up glaringly with stock price.

In contrast, the Commercial Specialty Pharma and Drug Delivery companies seem able to support expenses through income from commercial sales of products, technology, and/or services. Yes, there is some loss of share price consistent with a drop of market capitalization, but much less than those companies with no access to cash except that provided by issuing additional stock.

Oh, and what about Auxilium and Alkermes? How has their stock done? Well Auxilium's share price has almost tripled, from $8.85 to $22.90, much to the delight of investors, option holders, and employees' 401k plans. Alkermes' stock price in stark contrast has sagged from $14.09 to $7.65.

Taking on product development activities requires major planning and provisioning, in this case, provisioning cash for development expenses. And like a major expedition into uncharted territory, you need to be provisioned to handle all situations and delays, or you need to be able to "live off the land" as you go forward. Having supplies airlifted in, if even a possibility, is bound to be horribly expensive.

REFLECTIONS

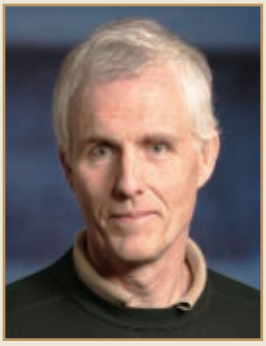
Well, the overall numbers probably won't surprise anyone. The market has been in a deep funk for more than 18 months, and there is no reason why the Biopharma industry should be immune. What is surprising is how poor the return has been for companies starting on the Specialty Pharma trail. One dollar invested in these companies at the end of 2004 is worth a little more than 20¢ today. That's not a great way to win friends and influence people. The performance of Drug Delivery companies is better but not great; that same dollar is worth a little less than 50¢.

With these figures in hand, the question is why would a Drug Delivery company jump onto the Specialty Pharma track? Well, because if you can get to the stage of being a successful Commercial Specialty Pharma company, the outlook is rather good; market capitalization and stock price are sure to jump, and there is the possibility for an acquisition premium. The challenge is getting through the very lean years of being an Emerging Specialty Pharma company, a period that can last on the order of a decade, depending on the product and development strategy chosen. For Emerging Specialty Pharma companies, it seems as important to have a successful financing strategy as it is to choose a winning product and development strategy.

Up, down, sideways. Well it seems that after a short upward trend for the first couple of years, it's been mostly down for Drug Delivery and Specialty Pharma company stocks. This period has seen some strong successes, but they are far outnumbered by companies in distress. Does it make sense for a Drug Delivery company to consider adopting a Specialty Pharma strategy? My sense is yes, but with a few provisos. It's hard to imagine any Drug Delivery company being able to load up enough cash to take it through to early commercialization, so it must be able to survive by leveraging its technology base to bring in service and licensing income. This needs to be complemented by a product candidate selection and development strategy that can get through development and approval in less than the average 6-year development and approval cycle. It's possible but not always obvious.

Up, down, sideways. Let's hope the path is all up from here. But hope is not as important as a good strategic and tactical plan; plus a boatload of cash in the bank and very supportive investors.

BIOGRAPHY



Dr. Josef Bossart is Managing Director of Pharmanumbers, a boutique research group analyzing the parameters and numbers that drive biopharma success and profitability, with a focus on Drug Delivery. In addition to issuing industry reports, such as the recently released Drug Delivery 2009 report, Bionumbers provides emerging companies with as-needed business development resources, including transaction support, product forecasting, and strategy development. Dr. Bossart has held senior sales, marketing, operational, and/or business development positions within the biopharmaceutical industry with Enzon Pharmaceuticals, GeneMedicine, and Rhône-Poulenc Rorer. He regularly publishes articles providing strategic and tactical analyses in the areas of Drug Delivery and Specialty Pharma. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University.

OPPORTUNITY REPORT

Medication Management in the Elderly: Major Opportunity for Advances in Drug Delivery & Formulation Technologies

By: Thomas M. Reilly, PhD, MBA

INTRODUCTION

Geriatrics is a growing area of critical importance in our national healthcare system. The number of American citizens over the age of 65 is already a major segment of the US population and is projected to reach 70 million by 2030.[1] Compared with younger Americans, the elderly population also fills a disproportionate number of drug prescriptions. By age 65, two-thirds of all seniors have two or more chronic conditions requiring prescription medications. Each additional chronic diagnosis adds a medication or two.

Medication mismanagement, including non-compliance, under- and over-medicating, is a serious problem in the elderly population.[2] For example, up to 35% of hospital admissions of the elderly and over 125,000 deaths each year are attributable to medication mismanagement. A myriad of reasons exist why elderly patients are especially vulnerable to incorrect uses of medications. These include cognitive impairment, vision loss, increased adverse drug reactions, dysphagia (difficulty in swallowing), and increased gastric stasis, which impacts drug absorption. These problems are often compounded with traditional oral formulations.

The development of effective solutions for medication management problems in the elderly represents major market opportunities for drug development companies. One important strategy for addressing these issues is the development of user-friendly and effective drug delivery and formulation modes. The following will highlight the significance of this opportunity by reviewing just a few of the leading diseases affecting the geriatric population (Table 1) and identifying specific advances in drug delivery and formulation technologies that have been, or will be applied, to aid this population and their caretakers with medication management.

ALZHEIMER'S DISEASE

Alzheimer's Disease (AD) is the most common cause of dementia and the fourth leading cause of death after heart disease, cancer, and stroke. Approximately 10% of people over the age of 65 may develop AD.[3] Although currently no treatments can stop the progression of AD, the US FDA has approved two types of medications to treat cognitive symptoms of AD: cholinesterase inhibitors such as Rivastgimine (Exelon), Donepezil (Aricept), and Galantamine (Razadyne), and Memantine (Namenda), which works by regulating the activity of glutamate. These drugs are widely available in oral formulations. However, due to a multitude of risk factors in the AD population, including memory loss and high incidences of dysphagia, compliance to conventional oral formulations has been poor.[4]

Eisai and Pfizer introduced a new formulation of Aricept, Aricept ODT orally disintegrating tablets, in October 2004 for patients with swallowing problems. Aricept ODT

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disintegrates in the mouth within seconds, and dosing is followed by drinking a glass of water. Applied Pharma Research of Switzerland and Labtec Gmbii of Germany are also developing an ODT formulation generic to Aricept ODT using Labtec's proprietary Rapid Film technology. Its potential advantage is that no water intake after dosing is needed. Aricept's base patent expires in 2010.

The many challenges facing caretakers who supervise the dosing of medications to AD patients prompted Novartis to introduce the Exelon Patch in 2007, the first transdermal therapy for AD. Transdermal patches are designed to provide controlled, continuous delivery of drug through the skin. This maintains steady drug levels in the bloodstream, avoiding the peak and trough drug levels often associated with side effects from oral dosing. Transdermal administration also avoids first-pass metabolism of drugs following oral administration. Finally, transdermal delivery overcomes the problem of swallowing oral capsules in patients with dysphagia, common in the AD patient population.

The 6-month IDEAL trial of 1,195 AD patients showed that the Exelon patch provided benefits across a range of symptoms, achieving efficacy comparable to that observed with the highest dose of capsules.[5] The patch was associated with three times fewer reports of nausea and vomiting than the capsules, well-known side effects of cholinesterase inhibitors. Local skin tolerability was good, as was skin adhesion of the patch over a 24-hour period in a range of everyday situations such as bathing. In addition, according to a questionnaire, over 70% of caregivers in the IDEAL study preferred the patch to capsules as a method of drug delivery for reasons including overall ease of use, advantages in keeping to the treatment schedule, and less interference with daily life. The Exelon patch, with its clinical efficacy, patient acceptability, and caretaker preference, represents a significant advance for patients with AD. Eisai was collaborating with Nitto Denko Corporation in developing a transdermal patch for its cholinesterase inhibitor, Aricept. However, this agreement was terminated in early 2009, apparently because of lack of technical progress with the program.

TABLE 1

Indication	US Patient Population (Millions)	Percentage of Patients 65 or Older
Alzheimer's Disease	5.3	94
Parkinson's Disease	1.5	87
Urinary Incontinence	19	50
Macular Degeneration (Wet & Dry)	10	75

Indications With a High Percentage of Geriatric Patients

PARKINSON'S DISEASE

Parkinson's Disease (PD) is the second most common neurodegenerative disorder following Alzheimer's disease. Approximately 60,000 new cases are diagnosed each year in the US, adding to the 1.5 million Americans who already have the disease.[6] The average age of onset is 60, and significant prevalence growth is expected over the next 25 years due to the increase in the elderly population. Currently, there is no cure for PD; however, a number of drugs are available to provide either neuroprotection and/or symptomatic relief. The challenges of medication management in Parkinson's patients, particularly the elderly, have triggered a number of developments in drug delivery and formulation products.

Levodopa, a precursor to dopamine,

and carbidopa, a peripheral dopa decarboxylase inhibitor that prevents levodopa conversion to dopa in the periphery, have long been the mainstay of treatment for PD. However, levodopa/carbidopa, which is available as a generic (brand name Sinemet) has a number of limitations, including inconvenient dosing (4 to 6 times daily), and blood level fluctuations that contribute to the most troubling side effect: involuntary motor fluctuations (on-off phenomena) characterized by tremors, bradykinesia, and freezing episodes. Theoretically, administration of levodopa/carbidopa to patients in a form that provides steady state blood and CSF levels of levodopa for extended periods of time offers a more physiologic exposure of the brain to dopamine with reduced disabling motor fluctuations. This rationale led to the development of Sinemet (CR), which is designed to reduce the variability in plasma levels of levodopa, while reducing the number of daily doses. Catechol-o-methyltransfease (COMT) inhibitors, such as entacopone and tocopone that inhibit the degradation of levodopa in the stomach, have also been used in conjunction or combination (Stalevo) with levodopa-carbidopa to provide more constant dopaminergic stimulation in the brain.

NeoPharma, which was acquired by Solvay, developed a unique delivery system for levodopa/carbidopa termed Duodopa. The system consists of a programmable pump that allows physicians and patients to individually tune the delivery of active ingredients, suspended as a stable gel from a cassette worn outside the body, via a small tube inserted directly into the duodenum. Intraduodenal administration offers more steady levels of levodopa and can result in better control of body movements in many PD patients. However, the invasive administration limits its widespread use in clinical practice. Duodopa was granted Orphan status in the US for treatment of advanced Parkinson's disease and has been approved in all EU countries.

Normal gut motility, called peristalsis, is essential for passage of food and solid dose form drugs (tablets and capsules) through the stomach to the parts of the intestine where absorption into the bloodstream takes place. Because stomach and intestinal motility are often impaired in elderly patients, this can lead to poor levodopa absorption, which occurs in a very specific domain of the upper small intestine. To address this issue, a number of companies are developing controlled-release, gastroretentive dosage forms, such as DepoMed's CR-GRDF. This is based on compounding levodopa within an unfolding polymeric membrane matrix. Studies in beagle dogs showed absorption times were significantly increased with CR-GRDF, maintaining therapeutic levodopa concentration (> 500 ng/ml) over 9 hours, in comparison to non-gastroretentive CR particles and an oral solution. DePoMed has obtained a grant from The Michael J. Fox Foundation to support this project.

Another novel formulation approach for levodopa is an effervescent formulation, termed V1512, from the British biopharmaceutical company, Vernalis. V1512 combines levodopa methylester, an enhanced soluble pro-drug of L-dopa, with carbidopa. Being fully soluble in water, V1512 is administered in liquid form and therefore is less susceptible to impaired gut motility as it quickly passes through to the small intestine assisted only by gravity. V1512 has been shown to work more rapidly than conventional L-dopa in tablet form in patients with motor complications. Vernalis owns the worldwide rights to V1512 outside of Italy and is continuing to develop the product, which is ready to start Phase III trials under protocols agreed with the FDA through the SPA process.

A second class of drugs, dopamine receptor agonists, has been available for years and is a useful symptomatic long-term treatment for PD. Non-ergot dopamine agonists such as ropinirole (Requip) and pramipexole (Mirapex) are generally favored because of better side-effect profiles and longer half-lives. Recent formulation developments with this class of drugs include GlaxoSmithKline's RequipXL, an extended-release, once-daily tablet

formulation that uses SkyePharma PLC's patented Geomatrix technology. This product is designed to provide patients with a simpler titration schedule compared with the recommended titration schedule for immediate-release Requip, which is dosed three times a day. This represents a significant convenience factor for patients, particularly the elderly. RequipXL was launched in the US market in 2008.

Another delivery project that met with initial success was the Neupro® transdermal patch, developed by Schwarz Pharma and designed to deliver a continuous flow of the dopamine agonist, rotigotine, over a 24-hour period through the skin. This product proved very popular with patients in Europe because it avoided the need for multiple daily dosing. However, in 2008, UCB, who had acquired Schwarz Pharma, recalled Neupro from the US market and certain batches in Europe due to problems with solubility of the active component in the patch. Apparently, a new formulation will be required to address this solubility issue, and it is not known if and when Neupro will make it back to the US market.

URINARY INCONTINENCE

Urinary incontinence is a common problem among elderly individuals, with prevalence of patients as high as 15% to 35% in the 65 and over population.[7] Women are twice as likely as men to suffer from the condition. Urinary incontinence is a leading cause of institutionalization among the elderly, with at least 50% of nursing facility admissions listing a diagnosis of incontinence. Because of the high costs of incontinence, estimated between $25 and $35 billion in the US for overactive bladder alone, and the increase in prevalence that will occur as the population ages, there is a growing market need for convenient delivery and formulation modes for drugs to treat this condition.[8]

Anticholinergic agents such as oxybutnin (Ditropan) and tolterodine (Detrol) are used widely to treat urge incontinence. Both are available in extended-release forms that offer the advantage of once-a-day dosing over immediate release. However, these drugs are associated with high rates of side effects, particularly dry mouth and constipation. Orally administered oxybutynin is metabolized by the liver and intestines to N-desmethyloxybutynin (N-DEO), which is active and contributes to the dry mouth. Elderly patients are more sensitive to side effects of these agents, which often lead to discontinuation of therapy.

To address this problem, Watson developed Oxytrol, a transdermal patch designed to deliver oxybutynin continuously and consistently over a 3- to 4-day interval after application to intact skin. Transdermal delivery bypasses the presystemic metabolism of oxybutynin, resulting in reduced plasma levels of N-DEO and reduced side effects. The most common side effect of the skin patch is skin irritation.

Accordingly, Watson also developed, GELNIQUE, a second-generation transdermal delivery system for oxybutynin. GELNIQUE is a quick-drying, clear, colorless, fragrance-free, hydroalcoholic gel containing 100 mg/g of oxybutynin chloride. The gel is applied once daily to the thigh, abdomen, upper arm, or shoulder and delivers a consistent dose of oxybutynin transdermally during a 24-hour period. In addition to reducing the incidence of skin irritation associated with the patch, Watson reports that GELNIQUE may also be associated with a lower incidence rate of dry mouth than Oxytrol. GELNIQUE was approved by the FDA in early 2009. In other developments, Antares Pharma is also developing a topical gel of oxybutynin, ANTUROL, using their proprietary ATD gel technology.

AGE-RELATED MACULAR DEGENERATION

Perhaps in no disease area are the needs and the challenges for drug delivery and formulation greater than those in ocular diseases, such as age-related macular degeneration (AMD).

AMD is caused by the deterioration of the macular, the central portion of the retina, inside the back of the eye. By definition, it is confined to adults aged 50 or older, affects more than 10 million Americans, and is the leading cause of vision loss in the elderly. Currently, there are no approved treatments for the most prevalent from of AMD, dry AMD.[9] Ideally, drug therapy for AMD should be targeted directly to the retina, to limit side effects and low retina uptake associated with systemic delivery of drugs. However topical ocular medications do not reach the back of the eye in any appreciable quantities, and repeated intravitreal injections are quite invasive. Because of the difficulties in delivering drugs to the posterior segment of the eye, many intraocular delivery systems that release therapeutic concentrations of drugs for long periods are being studied, including nanoparticle and microparticle formulations, and nonbiodegradeable and biodegradeable implants.

One such example is Neurotech Pharmaceutical's, NT-501, an intraocular implant that consists of human cells that have been genetically modified to secrete a low and continuous therapeutic dose of ciliary neurotrophic factor (CNTF) into the back of the eye using its Encapsulated Cell Technology (ECT) platform. Neurotech's device is implanted in the vitreous humor, a transparent gel that lies between the lens in front and the retina in back. The capsule is made of a semipermeable plastic, which allows the CNTF protein produced by the genetically engineered cells to diffuse into the retina. CNTF is a growth factor capable of rescuing dying photoreceptors and protecting them from degradation. In March 2009, Neurotech announced a positive proof-of-concept study for NT-501 in a Phase II clinical study in patients with AMD involving geographic atrophy (GA); they plan to start pivotal studies in GA in 2010.

SUMMARY

Recognition of the important medication management problems of the growing geriatric population has led to several drug delivery and formulation products that are driving significant growth in this market segment. Continuous advances in new technologies that enable drugs to be delivered in ways that preserve efficacy, provide convenience, and promote compliance in the geriatric population represent an important business strategy for drug developers as the number of elderly patients continues to increase.

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BIOGRAPHY

Dr. Thomas M. Reilly is Founder of BDHORIZONS, LLC, a firm that provides a full range of business development and licensing services to pharma, drug delivery, and technology companies. He has over 20 years of business development and R&D experience in senior level roles in pharma companies, including BTG and DuPont Pharmaceuticals. His experiences include licensing, managing, and commercializing several drug development programs, including those involving novel formulation and delivery technologies. At DuPont Pharmaceuticals, Dr. Reilly directed the company's Cardiovascular Diseases Discovery Department. He earned his PhD in Microbiology from Rutgers University and his MBA in Finance from the University of Delaware. He is also a Fellow of the American Heart Association, holds four different patents, and has over 80 publications in peer-reviewed journals.

DRUG DELIVERY Executive

Henkel

HENKEL: PROVIDING ADVANCED ADHESIVE SOLUTIONS FOR DRUG DELIVERY SYSTEMS

Michael Trisch
Global Business Director, Transdermal Business
Henkel

"A number of factors contribute to our success. A very important one is our committed and undying focus on the transdermal market and the development of close relationships with our customers, some of whom have been with us for more than 2 decades. Our customers know that we are dedicated to the transdermal business long-term."

Henkel is a leading global supplier of adhesive systems for transdermal drug delivery systems, offering a wide range of innovative products coupled with confidential technical support. With the acquisition of the National Starch and Chemical Adhesives business in 2008, Henkel gained a business unit with over 35 years experience in acrylic copolymers and one that has been an integral part of the transdermal market since its inception more than 25 years ago. Today, Henkel's portfolio includes pressure sensitive adhesives that are approved in over 40 unique commercial patches marketed throughout the world. Under the Henkel umbrella, the Transdermal team continues to offer the same innovative DURO-TAK products, the same level of manufacturing expertise, and the same high level of customer service that transdermal patch developers, manufacturers, and marketers demand. Drug Delivery Technology recently interviewed Michael Trisch, Global Business Director of Henkel's Transdermal Business, to learn more about Henkel's products, innovations, and business strategy.

Q: Can you provide us some insights into Henkel's transdermal adhesives product portfolio?

A: We have three areas of focus, or platforms if you will, within our excipient offerings. They are Henkel's DURO-TAK® transdermal-grade pressure sensitive adhesives, PROLOC™ bioadhesives for transmucosal delivery, and VELOX™ MCS (microcrystalline starch) for multiparticulate delivery.

The cornerstone of our business is the well-recognized DURO-TAK brand, representing dozens of acrylic copolymers with a variety of chemical compositions and performance properties. The DURO-TAK brand also represents our platform of polyisobutylene (PIB) and styrenic rubber adhesives, which offer additional options for transdermal system developers.

Q: Why should patch developers choose DURO-TAK for transdermal patches?

A: We're the number one supplier of acrylic solution pressure sensitive adhesives for transdermal patches. We're confident that

when a transdermal patch project is initiated, DURO-TAK is the first adhesive considered, and we are contacted by the patch developer soon thereafter. Because of our experience and know-how, patch developers trust us to work closely with them on this critical excipient within the transdermal delivery system. Patch developers are assured that we work under strict confidentiality as we support them throughout their patch development and approval process. Our goal is two-fold: to provide the innovative products, prompt, expert technical support, and regulatory expertise that our customers need in order to develop an optimal transdermal formulation for their API and to do all of this as efficiently as possible. To this end, Henkel's staff of experts communicates with our customers throughout the development process.

Additionally, behind the DURO-TAK brand, Henkel provides the requisite manufacturing controls, regulatory support, safety testing, and Drug Master Files.

Q: Can you expand upon that from a technical perspective?

A: DURO-TAK performance has been well demonstrated and well documented throughout the years. DURO-TAK acrylics give ideal solubility for a wide range of drugs, low skin irritation, and good wear properties. DURO-TAK PIB solutions offer higher solubility for lipophillic drugs in a chemistry proven through many years of use in transdermal patches.

Additionally, we have a global team completely dedicated to the transdermal market. So no matter where you are in the world, you can work with Henkel experts supported by local representation. Patch developers know that Henkel is responsive, well prepared to collaborate on projects, and able to identify the right system that helps speed commercialization.

Furthermore, I can't say enough about the resources Henkel has to support our customers. While our direct group is capable of providing everything from wear-testing and rheological analysis to IR and HPLC, we are supported by an on-site analytical services group. This team has specialists in molecular structure identification, compositional analysis, and material characterization. They operate state-of-the-art equipment in such areas as NMR, GPC, and even SEM. The molecular modeling specialists in our analytical group have worked with customers to model drug movement through our DURO-TAK polymers. Working with these molecular modeling specialists and the polymer scientists in our R&D group, we developed Henkel's proprietary Drug-In-Polymer Solubility Calculator. This is a confidential online tool that enables our customers to see the solubility of their API in all of our DURO-TAK acrylic solutions.

Q: Where does Henkel manufacture DURO-TAK products?

A: We manufacture our DURO-TAK transdermal products in Salisbury, NC, or Antwerp, Belgium. These facilities are ISO 9001 certified and follow IPEC-GMP guidelines. In addition, we host a number of customer audits each year, which help us to continually improve. With this manufacturing expertise and precision in mind, the patch developers we serve know Henkel will supply a DURO-TAK adhesive that meets their API delivery goals and that Henkel can provide the support, experience, and expertise they require.

Q: What are some of Henkel's recent adhesive innovations?

A: I can think of several examples. We have developed adhesives that are enabling platforms for highly reactive drugs, acrylic-rubber hybrid adhesives that deliver excellent alcohol resistance with good resistance to cold flow, and

adhesives that enable dispersed-phase drug loading. Another recent development is our acrylic block copolymer platform for transdermal patches that gives good wear on skin, yet provides gentle removal. Also, we're constantly working on adhesive projects that respond to changing regulatory requirements. Additionally, we will continue to offer and develop customized adhesives to meet specific and unique customer needs.

Q: What particular advantages does the Henkel PROLOC Bioadhesive drug delivery system offer?

A: We have recently begun promoting our proprietary PROLOC Bioadhesive platform. This technology stems from our National Starch and Chemical days, when we successfully demonstrated our competencies in polymer science and adhesion science. Our efforts established a proprietary process for the manufacture of the PROLOC Bioadhesive powder material, which incorporates a USP-grade polysaccharide and a USP-grade polycarboxylated polymer into a single phase. PROLOC Bioadhesive is proving to be a superior means to deliver therapeutic agents locally and across mucosal membranes at various absorption sites. The technology provides superior bioadhesive performance with the capacity for higher drug loading while remaining gentle to the mucosa.

Q: Can you provide any details about the types of projects currently in development?

A: What I can tell you is that based on clinical work, PROLOC Bioadhesive is suited for buccal/sublingual, vaginal, intranasal, and ocular delivery. These absorption sites have proven to be ideal for the technology, and rectal delivery is still another possibility that is yet to be studied. Our first commercial product is an over-the-counter buccal tablet incorporating benzocaine for mouth sores, marketed under the Orajel® brand. We have a number of projects covering all these absorption sites, and we're looking to take on additional projects.

Q: With all of these viable absorption sites, the PROLOC Bioadhesive must have flexibility in its commercial form?

A: Yes, indeed. The powder can be direct-compression tableted, and it can also be cast into a thin film or utilized as a powder. The powder form, for example, has generated promising results for applications such as intranasal vaccination, an area that we are very excited about. But no matter what form the PROLOC Bioadhesive material is processed into (tablet, film, or powder), the fact that it completely erodes away is a true benefit.

Q: How long does it take for PROLOC Bioadhesive to erode away?

A: One factor, of course, is the physical form the product takes. For example, a thin film will erode sooner than a tablet. Having said that, there are many variables to consider, but we do have flexibility within the system to manage the rate of erosion. For example, a tablet could be developed to erode from within a matter of hours to several days, depending on the needs of the application.

Q: What about the performance of PROLOC Bioadhesives?

A: In addition to product versatility that provides formulators with a way to deliver therapeutic agents across a variety of absorption sites, PROLOC's platform for muco-adhesion enables the delivery of larger molecules compared to transdermal absorption. Delivery across the mucosa can allow for

lower dosages, resulting in fewer side effects, with rapid, direct system absorption and rapid onset of therapeutic effects.

Q: How has the Henkel PROLOC Bioadhesive been received so far?

A: The technology has been received very well. We have projects underway for both OTC and Rx applications, and we are confirming our original position. Simply stated, that position is: PROLOC Bioadhesive can provide a unique and viable avenue for delivery of new drug molecules and the redirection and reformulation of existing drugs.

Q: What are the benefits of redirecting and reformulating existing drugs?

A: As I see it, the biggest benefit by far is product lifecycle management. By taking advantage of the PROLOC Bioadhesive system, marketers can implement line extensions and extend patent protection, extending the life of a brand. Existing products can be repositioned or developed into new ones for existing compounds. These possibilities represent tremendous financial returns.

Q: What can you tell us about Henkel's new VELOX MCS (microcrystalline starch) excipient?

A: VELOX MCS is another new excipient offering we're very excited about. VELOX MCS is an ideal excipient for extrusion-spheronization, offering the essential physical properties to produce smooth, uniform spheres via the extrusion spheronization process. In contrast to traditional MCC (microcrystalline cellulose), VELOX MCS completely disintegrates in the GI tract, providing rapid and complete release of poorly soluble drugs. In addition, VELOX MCS produces spheres in high yield with low friability, and the resulting spheres are also suited for enteric coating.

Q: What business strategy has contributed most to Henkel's success in your area of drug delivery?

A: A number of factors contribute to our success. A very important one is our committed and undying focus on the transdermal market and the development of close relationships with our customers, some of whom have been with us for more than 2 decades. Our customers know that we are dedicated to the transdermal business long-term. Throughout the years, we have invested in a dedicated global transdermal technical support team, and we have recently invested in a new manufacturing facility. We have invested significantly to meet current regulatory requirements and also to anticipate future requirements. We have invested heavily in R&D, bringing adhesive solutions to our customers for challenging drugs. We have created tools to make our customer's job easier, such as the drug-in-polymer solubility calculator. And we work in close, confidential partnerships to enable our customers to develop their optimum patch as efficiently as possible.

With Henkel, our customers get the best of both worlds. They get a highly skilled, responsive partner with a flexible can-do entrepreneurial approach. At the same time, they get the long-term stability and resources of Henkel behind them. ◆

Technology Showcase

MDI Components

3M Drug Delivery Systems has been a major supplier of metered-dose inhaler valves and canisters for more than 50 years. As the developers of the first CFC-free MDI, we are experienced at overcoming the challenges that designing components for use with CFC-free propellants presents. 3M is the only MDI component supplier that manufactures both valves and canisters, allowing optimization of these components simultaneously, ensuring compatibility, while delivering the convenience of a single source. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3M.com/dds**.

Licensing Opportunities

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

Development Services

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

Prefillable Delivery Systems

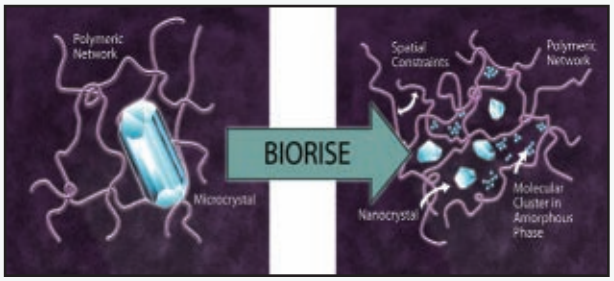
BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. Whether a glass or plastic prefillable syringe, a nasal spray system, a dry drug reconstitution system, an injection or self-injection device, BD 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**.

Technology Showcase

Specialty Pharma

CyDex Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on the development and commercialization of drugs specifically designed to address limitations of current therapies in selected established markets. We have developed a portfolio of product candidates utilizing our drug formulation technology (Captisol® cyclodextrins), which are a patent protected, specifically modified family of cyclodextrins designed to improve solubility, stability, bioavailability, safety, and/or dosing of a number of APIs. To maximize our internal resources, experience, and technology, we are focusing on the development and commercialization of product candidates for use in the acute care hospital setting. For those product candidates that likely will entail more extensive development and commercialization efforts, we partner with established pharma companies. We also outlicense our Captisol technology to third parties. For more information, contact CyDex at (913)685-8850 or visit **www.cydexpharma.com**.

Bioavailability Enhancement



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

New Auto-Injector Line

Elcam Medical recently launched its Flexi-Q line of auto-injectors for self-medication - the only fully disposable auto-injectors designed for life-cycle management. Flexi-Q DV is designed for drugs in vials in liquid or lyophilized form, and the Flexi-Q PFS is for drugs in prefilled syringes. Both incorporate our unique platform with flexibility in customization: dosage between 0.3-1.0 ml, needle length & gauge, viscosity, injection force, and injection time. Elcam Medical is a leading worldwide OEM supplier of Fluid Management, Drug Delivery, and Vital Signs Monitoring systems and devices. As an OEM partner, we have significant experience in partnering with pharmaceutical companies in many disease states and therapeutic classes. Our dedicated team of auto-injector engineers and technical staff has worked with many leading companies in the field. For more information, contact Elcam Medical at (201) 457-1120 or visit **www.elcam-medical.com**.

Combination Capsule Technology

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

Technology Showcase

Airless Bottle

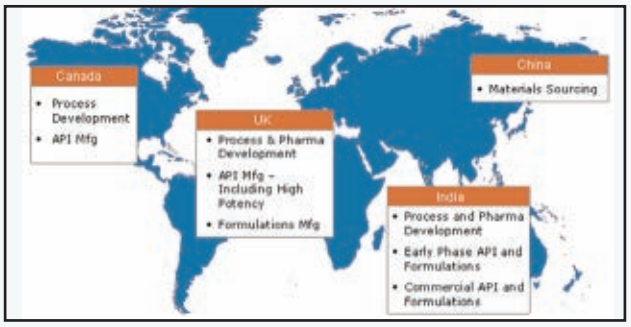
LABLABO's new EasyFoil bottle is fitted with a pouch consisting of an aluminum multilayer film rolled up and welded around a superior ring and an inferior cup, both produced in a thick plastic material. The film is composed of an exterior PET layer and an interior PP or PE layer wrapping a central aluminum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

Transdermal & Oral Films

LTS Lohmann Therapy Systems

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

Development & Manufacturing



Pharma Solutions is the Contract Development and Manufacturing division of Piramal Healthcare, a leading pharmaceutical company in India. Pharma Solutions is one of the very few Contract Manufacturing Organizations (CMOs) that can provide end-to-end support for bringing a drug to market or managing the life cycle of a launched drug.
We offer Clinical Phase API synthesis and Formulations Development services and scale-up to Commercial API and Finished Dosage form supply. We seamlessly integrate all contract manufacturing services across our global network of assets in North America, UK, and India to provide our customers with geographical flexibility, reduction in drug development times, and cost competitiveness across the product life cycle while maintaining high reliability and quality. For more information, contact Pharma Solutions at (732) 549-9451 or visit **www.piramalpharmasolutions.com**.

Knowledge Management

PharmaCircle™

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

Technology Showcase

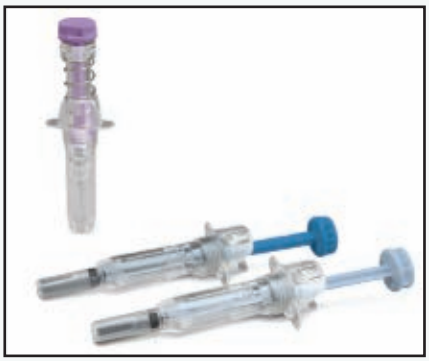
Contract Service Provider

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

Global Central Labs

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

Passive Safety Device



In response to the continued concern over unprotected needle exposures and the mandated Safety and Prevention regulations, Rexam has developed a fully passive safety device for prefilled syringes: the Safe'n'Sound. The Safe'n'Sound provides healthcare industries and patients with full protection from needlesticks to avoid any contamination. Compared to a standard syringe, the Safe'n'Sound system guarantees passive protection as the syringe retracts automatically in the system after the injection without any action by the user. Compact, light, and transparent, the Safe'n'Sound has only three components (a sleeve, a body, and a spring). For more information, contact Rexam at (847) 541-9700 or visit **www.rexam.com/pharma**.

Contract Manufacturing

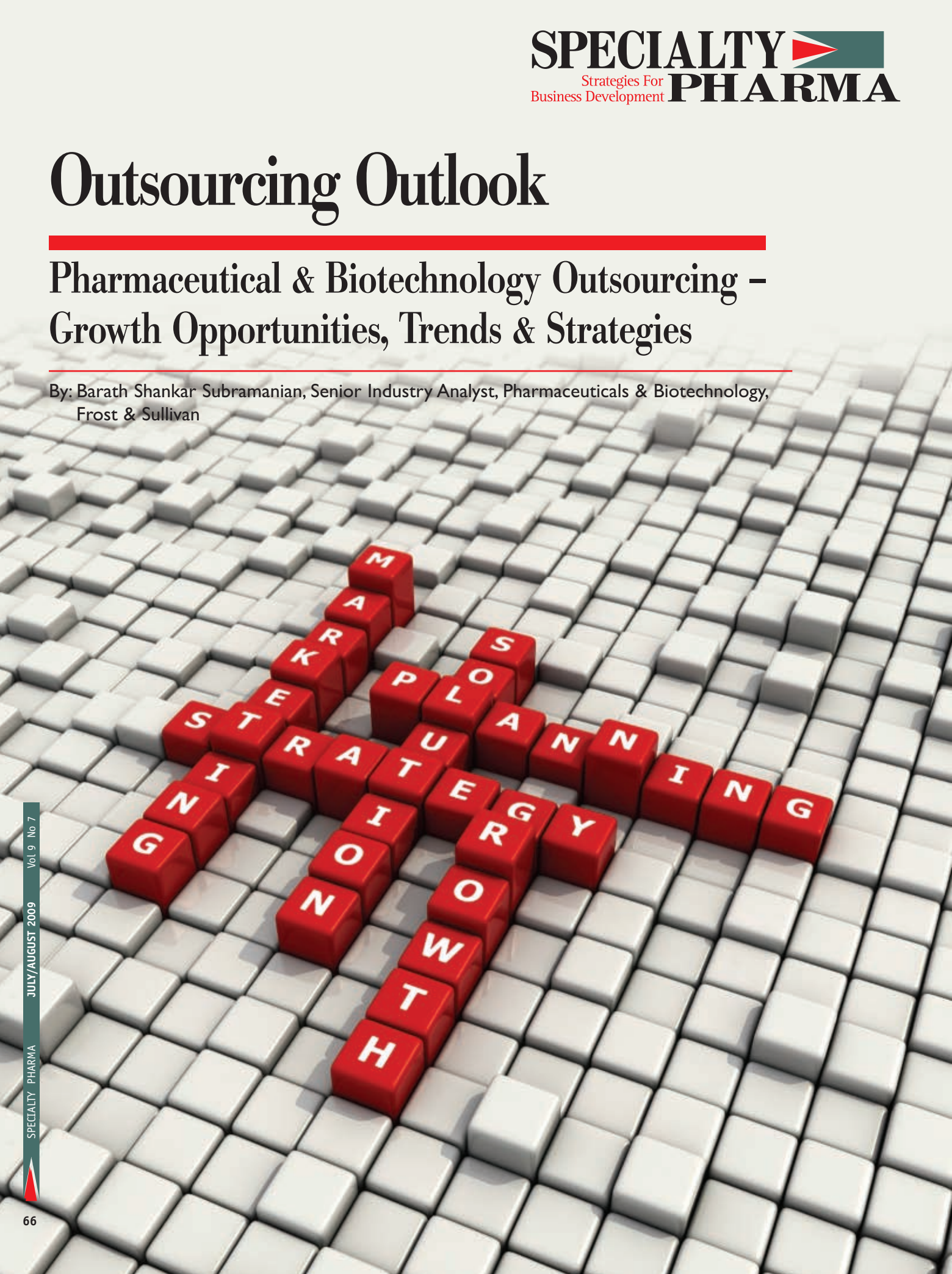
Stason Pharmaceuticals, Inc. has the experience and capabilities to manage the most challenging solid dose formulations. The company is a fully integrated cGMP contract development organization that provides complete turn-key drug development services for oral products. We offer services for both non-High Containment and High Containment Products. Stason offers a range of services for New Chemical Entities (NCEs), generics, and upgrades to existing formulations, and provides development and manufacturing services in its FDA-inspected facilities. We currently produce finished products at all scales through to commercial scale. All solid and semi-solid dosage forms are covered, including immediate- and delayed-release tablets and capsules, fast disintegrating tablets, creams, and lotions. For more information, contact Stason Pharmaceuticals at (949) 380-4327 or visit **www.stasonpharma.com**.

SPECIALTY PHARMA
Strategies For Business Development

Outsourcing Outlook

Pharmaceutical & Biotechnology Outsourcing – Growth Opportunities, Trends & Strategies

By: Barath Shankar Subramanian, Senior Industry Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan



Outsourcing as a concept within the pharmaceutical and biotechnology industry is becoming more integrated into the value chain, along with several other aspects, such as manufacturing, sales force, customized chemistry, and development services that are gaining traction. Despite the recent slowdown in the outsourcing markets due to the economic downturn, the potential for long-term growth remains fairly strong, backed by solid fundamentals. Contract Research Organizations (CROs) and Contract Manufacturing Organizations (CMOs) continue to make moves in acquisitions and strategic partnerships to strengthen their position in the outsourcing services market. The total pharmaceutical CMO market, which includes solid dosage and sterile and non-sterile semi-solids and liquids, is forecast to grow from $9.29 billion in 2009 to $15.02 billion by 2014 at a compound annual growth rate (CAGR) of 10.1% (Figure 1). In the short-term (2009-2010), we expect the slowdown to affect the expansion activities of small-to-medium CMOs. The tight credit situation, combined with recessionary effects, is expected to result in decreased expansion activities. However, given the growth prospects for this segment, combined with the flurry of generic versions of major blockbuster drugs, the prospects for CMO growth continue to remain bullish.

The CRO market has emerged as one of the fastest growing markets within the pharmaceutical and biotechnology industry and continues to drive innovation, productivity, and revenue growth. The US CRO market, which is the largest global CRO market with a share of over 56.6% of all global trials in 2006, grew from $4.8 billion in 2003 to $9.7 billion in 2008, with revenues doubling during this period (Figure 2).

This rapid growth in the market was driven by a variety of factors that include the emergence of specialty pharmaceutical and biotechnology companies as the engine for R&D growth and clinical pipeline expansion. The change in business model and supply-chain landscape of R&D has benefited the CROs significantly, due to the lack of infrastructure and financial resources within the tier 2 and tier 3 sponsor companies that carry out and manage their trials.

The primary source of business for CROs is the R&D budget allocation by sponsor companies. Due to the shift of business volume from Big Pharma and tier 1 companies that have R&D allocations of more than $500 million a year to tier 2 and tier 3 specialty pharmaceutical and biotechnology companies that have lower R&D allocations, business volume has significantly increased for CROs. The absolute revenue associated with this share of the business, however, is expected to be lower than Big Pharma sponsors.

With the slowing economy, companies are focusing more on the late-stage trials and cutting back on early stage work,

Figure 1.

which represents the biggest volume market for CROs. This is likely to have an impact on the overall market growth rate, which is expected to be lower - between 8% to 10% in 2009 and 2010 versus the low- to mid-teens originally forecast in 2008 by Frost & Sullivan.

Any major consolidation in the biopharmaceutical industry, as we are currently witnessing, could result in cutbacks in the number of service providers that with whom the newly formed entity works. This occurred in the late 1990s and early 2000s when the pharmaceutical industry went through a phase of major consolidation, resulting in a slowdown in the outsourcing services markets.

Figure 3 shows the skewed nature of the clinical development pipeline toward early stage development, with more than half of the pipeline between NDA and preclinical stages. In the current economic downturn, this segment is likely to be adversely impacted from decreased funding to early and development-stage companies. This is already resulting in the elimination of several of these companies and

Figure 2.

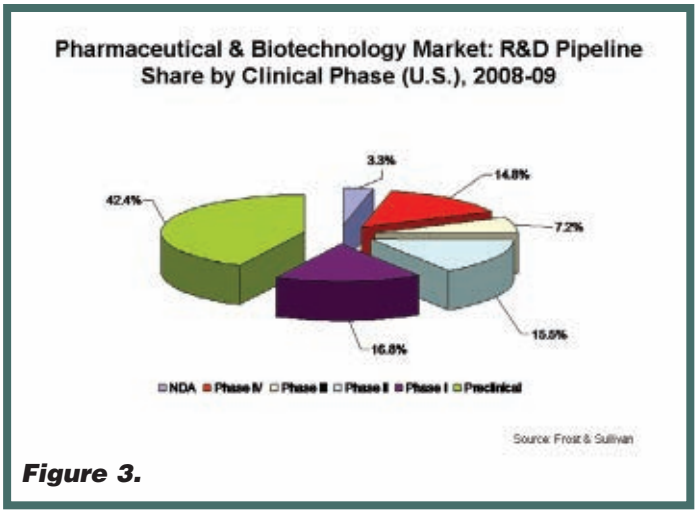


Figure 3.

could have a severe impact on market growth in the mid- to long-term. The implications of this could be further felt strongly amongst CROs and CMOs that provide services to these firms in terms of delayed payments, defaults, and cut-backs on pipeline candidates.

The Importance of Partnerships & Equity

In these difficult times, the companies that tend to perform well and exceed market expectations are those that have been able to strategically partner with their sponsors. Strategic partnerships had been the recent buzz phrase in the industry, especially during the boom times. However, these established relationships help service providers survive cycles in the economy as sponsors look to cut costs and outsource a greater amount of "non-core" operations to their strategic partners.

Overall, there has been a surge in private equity (PE) interest in the contract services market. In the recent past, JLL Partners acquired PharmaNet and Patheon in 2009. Catalent was acquired by the Blackstone Group in April 2007, and Genstar Capital picked up a minority interest in the deal. Genstar Capital reacquired PRA International in 2007, a company which they held before it went public in 2004. Sequoia Capital made a significant investment in an Indian CRO GVK Biosciences in 2007.

The investment horizon for PE firms in companies is typically around 5 to 6 years. The recent investments in these CROs and CMOs by PE firms justify the growth potential that has been touted for the CMO and CRO markets over the long-term and could further drive more transactions. Also, several publicly traded CROs have been hit by the downturn, and the stock prices and valuations have fallen significantly, making investments in these areas cheaper for PE firms. It is likely that there could be more deals, especially amongst top-tier CROs that have a strong history of producing steady operating cash flows (a key metric for acquisition by PE firms). These acquisitions are expected to bode well for the industry, as the PE firms are likely to focus on leveraging CRO and CMO cross-functional efficiencies and improve the working profile of these companies.

We are likely to see the emergence of a new layer in the supply chain that not only focuses on bringing lower fixed cost alternatives to their sponsors, but also provides an expanded breadth of services that could enable them to take products from NDA all the way to commercialization and post-commercialization support.

The Strength of Long-Standing Relationships

The long-term success of top CMOs has been built on the back of strong long-standing relationships with major industry participants. CMOs that offer additional value-added, upstream, and downstream services have remained consistently successful. Proprietary drug delivery platforms have also played an important role in ensuring the continued success of these mutually beneficial partnerships. The core strength in manufacturing, which is backed by a strong network of global manufacturing locations across several key regions and harmonized for quality and technology, plays an important part in leveraging the strengths of different regions.

CROs, such as Covance and PPD, have shown the way forward by entering into partnerships with Big Pharma companies in which they lease and run the facility for a specific period of time. CMOs could essentially replicate the model, especially because Big Pharma companies have announced the closure of several plants, and CMOs look to expand.

Conversion of Brand Awareness to Brand Preference

Top CMOs are renowned for their breadth of services, global reach, and strength of their brand. In a survey of 155 pharmaceutical and biotechnology executives, as a part of a Frost & Sullivan Voice of the Customer Analysis of the US Pharmaceutical and Biotechnology Contract Manufacturing Markets, there was a clear distinction between CMOs that had a high brand awareness and preference. The market leaders

with strong conversion rates are CMOs that have stayed ahead of the industry curve with strategic initiatives and leverage the strength of their parent brand.

Pfizer CenterSource (PCS) is well positioned to garner a greater share of the rapidly growing contract manufacturing business by having the highest brand awareness, as well as brand preference in both pharmaceutical and biotechnology markets. The backing of the strong brand name of Pfizer Inc., one of the largest global pharmaceutical companies, has helped its contract manufacturing business significantly in building a strong business. Pharmaceutical and biotechnology companies are increasingly demanding sterile manufacturing capabilities, and PCS has been able to align its service offerings with the expectations of the market.

Customer-Focused Alignment of Services

Baxter is considered a top choice for manufacturing outsourcing and is one of the leading CMOs in the sterile manufacturing market, especially prefilled syringes and lyophilized vials. The key to Baxter's success in this market has been its ability to provide flexible capacity that enables its customers to expand from small-scale to large-volume manufacturing quite seamlessly, depending on variations in demand.

CMOs not only need to adopt a highly customer-focused approach to its clients, but also constantly evaluate their needs and measure their satisfaction on an ongoing basis to ensure quality services. By maintaining multiple channels of communication with clients, CMOs can ensure continuous engagement of its clients and flow of information.

CMOs that are part of a larger pharmaceutical or biotechnology company can also draw expertise from the R&D division to help clients in addressing complex formulation challenges and improve productivity and efficiency of processes.

Summary

Long-term growth fundamentals remain strong for the CRO and CMO markets. The markets are experiencing two-tiered growth from Big Pharma, which is outsourcing work to lower fixed costs, while biotechnology and specialty pharmaceutical companies outsource work due to the lack of infrastructure.

As market leaders aggressively pursue strategic partnerships and acquisitions (Covance-Lily, PPD-AbCRO), the gap between tier 1 and tier 2 and tier 3 service providers is likely to widen. The demand for functional services, such as data management, logistics, translation, regulatory, and consulting services, is providing the additional level of growth beyond the base-level growth for CROs. Meanwhile, the demand for sterile manufacturing, secure tagging in packaging, regulatory, and consulting services is driving the additional level of growth for CMOs.

Overall, the CRO and CMO markets are expected to remain as two of the top growth areas within the pharmaceutical and biotechnology industries despite short-term effects of the economic downturn. ◆

Barath Shankar Subramanian

Senior Industry Analyst, Pharmaceuticals & Biotechnology, Frost & Sullivan

Barath Shankar Subramanian is a Senior Industry Analyst with the Frost & Sullivan North American Healthcare Practice. He focuses on monitoring and analyzing emerging trends, technologies and market dynamics in the Pharmaceuticals & Biotechnology industries in North America Since joining Frost & Sullivan in October 2004, Shankar has completed several research studies and consulting projects on Specialty Pharma, Contract Research and Contract Manufacturing.

Shankar has received acclaim for his research through articles and quotes published in Drug Delivery Technologies and Specialty Pharma.

Prior to this, Shankar was a Research & Development intern at IPCA Laboratories Ltd., Mumbai, India. He brings with him considerable analytical and quantitative experience, giving him a keen perception into the functioning of technology in the healthcare industry. Shankar holds a BS in pharmacy from the Birla Institute of Technology & Sciences (BITS), in Pilani-Rajasthan, India and is currently pursuing his MBA from the Tepper School of Business at Carnegie Mellon University.

Executive Summary

John E. Mordock
President & CEO
Neurologix, Inc.

Neurologix: Targeted Gene Therapies for Brain & CNS Diseases

Neurologix is developing a novel gene transfer therapy for the treatment of brain and central nervous system (CNS) disorders. The company's goal is to re-establish biological function at the molecular level by using a gene therapy approach to reintroduce natural proteins that are often deficient due to the particular disease state. Neurologix has already demonstrated feasibility for its approach in Parkinson's disease and is working to extend its therapeutic platform to the treatment of other serious conditions, including Huntington's disease, epilepsy, and chronic depression. Within each of these diseases, there are subsets of patients who are either refractory to standard pharmacological treatment or who have no therapy available to them. CEO John Mordock tells *Specialty Pharma* magazine of the opportunities and challenges presented by gene transfer technologies and why gene therapy offers unique benefits as a strategy for improving the treatment of chronic brain disorders.

Q: ***What is the scientific background behind the formation of Neurologix?***

A: Dr. Michael Kaplitt, one of Neuologix's founders, is an internationally recognized expert in the use of gene therapy in the brain and molecular neurobiology. He has published more than 40 papers and has edited two books on the subject, and he currently runs the laboratory for neurological surgery at Cornell Medical College. During his PhD program at The Rockefeller University, Dr. Kaplitt became very interested in the use of viruses to transfer therapeutic genes for the treatment of focal CNS disorders. As a neurosurgery resident at Cornell, he worked with deep-brain stimulation as an approach to the treatment of late-stage Parkinson's disease. Dr. Kaplitt had observed that if the inhibitory neurotransmitter gamma aminobutyric acid (GABA) - well known to be deficient in Parkinsonian patients - was administered into the

surgical site, there was a positive effect on the patient's brain activity. The challenge to exploring GABA's therapeutic potential, however, would be developing a method to re-establish its production within the targeted area of the brain on an ongoing basis.

In the mid 1990s, Dr. Kaplitt collaborated with Dr. Matthew During, a world-renown virologist, identifying a transgene capable of stimulating GABA production in the brain as well as an appropriate vector for delivering that transgene into cells. The scientists selected adeno-associated virus (AAV), which is non-pathogenic and non-replicative. The virus has shown to be safe and is currently being used in approximately 30 human clinical trials.

Q: *So Parkinson's disease is Neurologix's lead program? What is the current status of your work?*

A: Neurologix completed its Phase I study in 2006, which was the first gene therapy study approved by the FDA for Parkinson's disease. In December 2008, we began treating patients in our Phase II trial, a bi-lateral randomized, sham-surgery controlled study designed to further establish the effectiveness and the safety of the treatment. The trial is being conducted at up to 10 US medical centers that will enroll approximately 40 patients, with completion of enrollment expected in the second half of the year.

Phase I results, published in *The Lancet* and *PNAS*, indicated that the treatment was safe and well-tolerated in patients with advanced Parkinson's disease, with no evidence of adverse effects or immunologic reaction related to the treatment. The trial, in which treatment was confined to only one side of the brain, also yielded statistically significant clinical efficacy and neuro-imaging results in the cerebral cortex of the brain. Additionally, we found the functional data to be highly correlated to a decrease in metabolism in subjects in both the "off" state, when they are not responding to pharmacological therapy, and in the "on" state, when they do benefit from standard Parkinson's disease drugs.

Q: *Describe the delivery system for this procedure that was developed with Medtronic.*

A: It is a fluid infusion system that is the first to be used to deliver genetic material directly to targeted neuron clusters within the brain. Our approach is highly dependent upon the infusion system to simplify the gene delivery procedure and reduce the amount of time the patient is in the operating room.

Q: *Is Parkinson's disease your only current focus?*

A: No, we are looking at a number of other CNS disorders. The brain is a particularly fertile area for the use of gene therapy that can be delivered directly to targeted brain cells via a surgical approach. It has been very difficult to treat brain disorders systemically, due to the presence of the blood-brain barrier, as the dosage rates must be so high that side-effect levels often become unacceptable. So our approach represents a new platform for the potential treatment of a number of CNS illnesses.

Most recently, we have focused on Huntington's disease, an inherited chromosomal deficiency that leads to progressive nerve degeneration. The XIAP gene (x-linked inhibitor of apoptosis protein) has a neuroprotective property that may modify the progress of the disease. In two rodent models, not only did we prevent further cell death, we have shown signs of reversing motor dysfunction in the animals treated.

We have also developed a strong preclinical basis for the treatment of epilepsy and depression using AAV to deliver therapeutic genes to focal areas of the brain.

Q: ***What is likely to be your second indication to go into clinical trials?***

A: It will most likely be Huntington's disease. We have very strong preclinical data supporting our approach using the XIAP transgene. We will again be using the non-pathogenic AAV to deliver the gene. Moreover, the biology of Huntington's disease is pretty well understood, and we believe our therapeutic approach is consistent with the biology of the disease. We have seen strong interest from some of the Societies that are looking for therapies for Huntington's patients, so there is the possibility of some financial support for our efforts as well.

Q: ***What kind of market opportunities do you see for your products?***

A: We know that there are about 500,000 patients with late-stage Parkinson's disease who are refractory to pharmacological treatments. About half of those individuals may be contraindicated for surgery, leaving about 250,000 patients within the United States who might benefit from our approach. Moreover, that market is growing substantially as a function of demographics - some published marketing reports expect those numbers to double within the next 10 years.

With respect to Huntington's disease, that is an orphan indication with an "at-risk" patient population in excess of 100,000 and a potential undiagnosed market that is at least as large. No approved therapy for Huntington's disease currently exists.

Q: ***Does Neurologix plan to take its products through to commercialization on its own or to partner? And if the latter, at what stage?***

A: With respect to Parkinson's disease, at the end of our Phase II trial, which we believe is a major inflection point, we want to enlist at minimum an international partner to help us expand our development work to Europe. Whether we also look for a US partnership at that point will depend on who our European partner is and what our need for cash is at that time. Our position has always been to take development forward as far as possible ourselves before we are forced to give up value. However, if someone came in and made an extremely strong offer for worldwide rights at the end of Phase II, we would obviously consider it because we want to do what is in the best interests of our shareholders.

Huntington's disease is different because it is an orphan indication. We may develop and commercialize this indication ourselves or do it on a co-marketing basis. We are still at an early stage in this program, but given the nature of the disease, the small market, and high value for an effective therapy, it is something the company might actually take forward itself. ■

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Part-Time Productivity: Your Boss Does Notice!

By: John A. Bermingham

People believe I am crazy because I typically arrive at the office at 6:30 AM. Sometimes I arrive even earlier. I do this because I want to be focused on what needs to get done that day, that week, and that month. I want to get ready for the day before anyone arrives so when the bell rings, I am focused and ready for the day's work. I want to have plenty of time to meet with our people and to walk around to see how everyone is doing.

Certain people show up for work anywhere from 15 to 30 minutes late every day. They spend the first few minutes getting coffee and socializing. Then they will make a few personal calls inside the company and outside. They will check their company and personal e-mails, and then look at their schedule for the day. By the time lunch rolls around, they might get in 1 or 2 hours of real work.

After lunch, they may get in another 2 or 3 hours of returning e-mails, so by the end of the work day, they may have put in 3 to 5 hours of real work. Then, because they arrived late to work that day, they stay late another half hour and then leave. Of course, the last 30 minutes is spent chatting with others.

I once had an executive who reported to me who had a six-figure salary plus bonus. Shortly after joining the company as the new CEO, I noticed he arrived every morning at 7:30 AM and was out the door every afternoon at 5:00 PM sharp. While most of the new management team stayed until 6:00 PM or later, this executive left every day at exactly 5:00 PM.

Being that we were in the early stages of the company's turnaround, I brought this to his attention. After explaining why I believed this was an issue and that a lot of important objectives were accomplished after 5:00 PM, he agreed to stay later every day from then on. So he adjusted his time in the office to be from 8:00 AM to 5:30 PM. If you are wondering, yes, I did give him an opportunity to work for another company shortly thereafter.

When I first started out in the business world, I discovered that the senior executives and fast risers in a company were those people who arrived early and focused all day on the important tasks that needed to be accomplished. They worked hard and put in the hours that would ensure successful accomplishments for the company as well as themselves.

One of the important lessons I have carried with me for my entire career was something the Japanese President of Sharp Electronics, USA said to me. I was new and relatively young at the time, having recently become Sharp's 31-year old National Sales and Merchandising Manager and still wet behind the ears.

We were talking about the hours that he and I were spending in the office, and he said the following to me. "John, it is not the hours that you spend here. It is what you accomplish that is important to me." Basically, it is not just working hard that matters, it is working smart as well. I have never forgotten that wonderful piece of advice.

Too many people believe time spent in the office equates to productivity. As most of you probably know already, it doesn't. It only means they are spending a lot of time in the office.

In order to be productive and have a significant impact in your company and for your career, you have to work hard and you have to work with efficient intelligence. You have to be focused the entire day, well organized, and very budget-conscious with your time, not letting others impose on your schedule or interrupt you achieving the goals and objectives set for the day.

Following the advice of Sharp's President, I always think about the fact that it is not what you tried to do, it is what you accomplished that counts. ◆

BIOGRAPHY

John A. Bermingham is the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 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.

2009 CRS Young Investigator Award

Justin Hanes
Professor, Chemical and Biomolecular Engineering
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