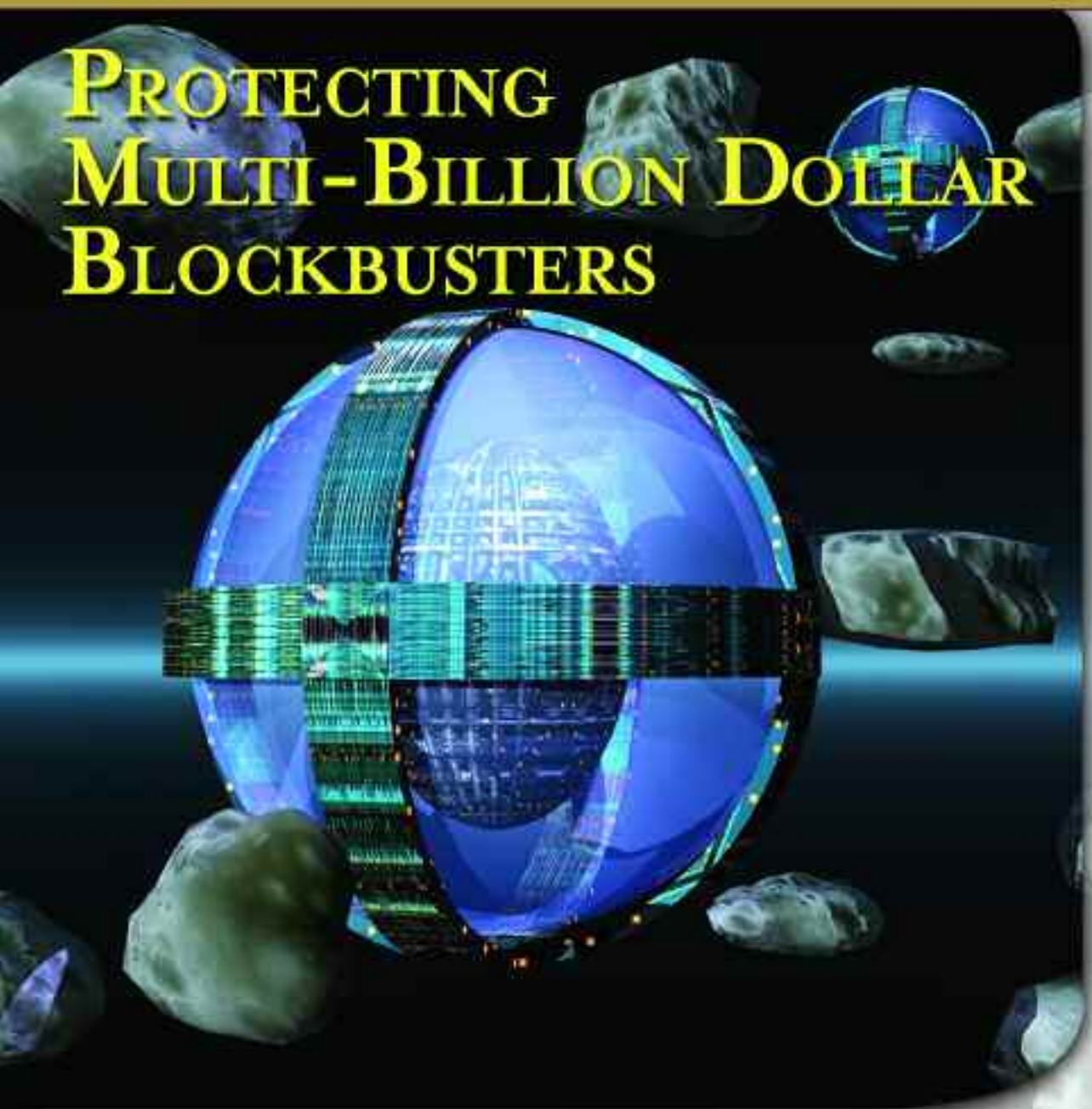
Drug Delivery Technology

October 2006 Vol 6 No 9

Protecting Multi-Billion Dollar Blockbusters



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

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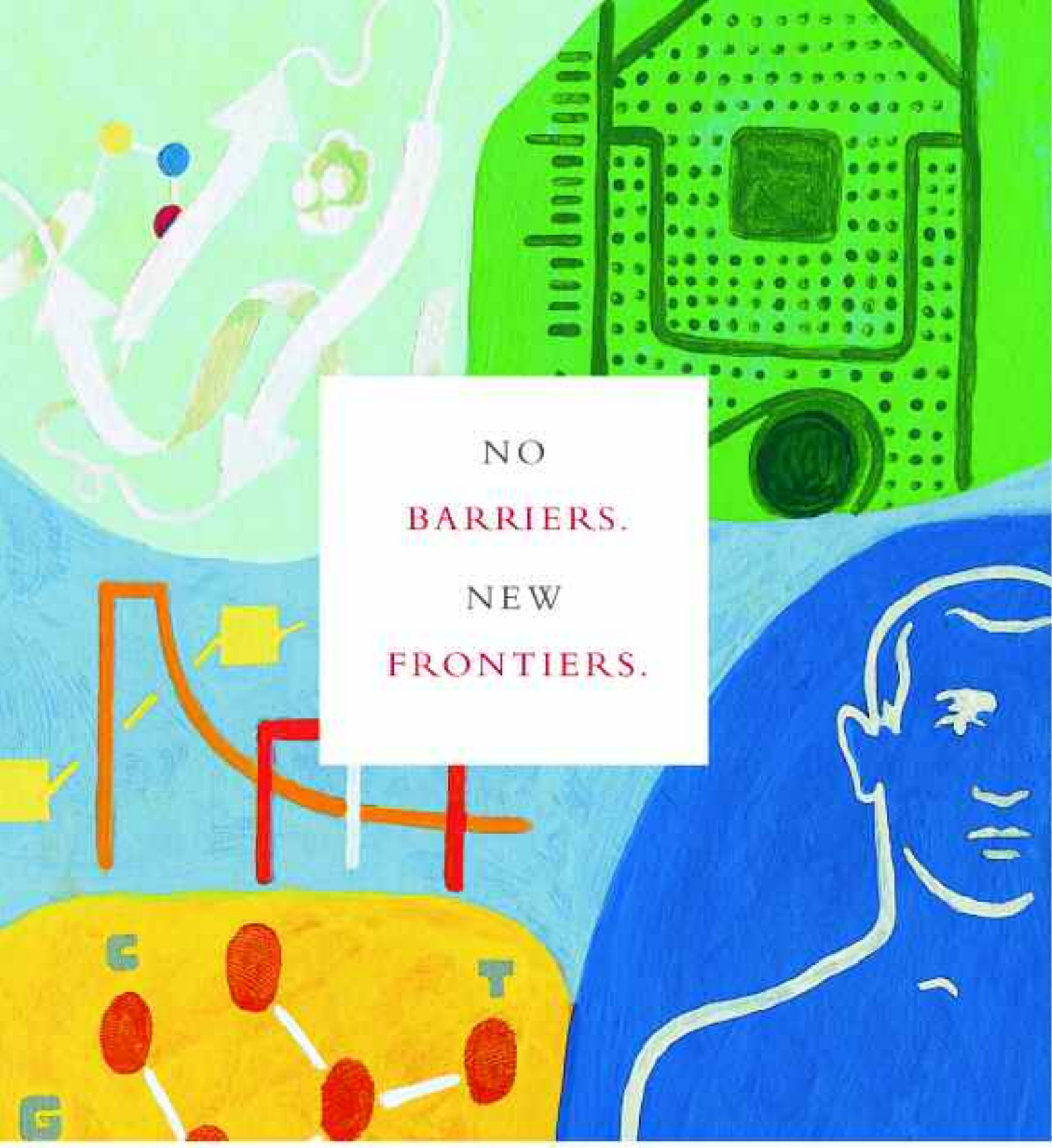

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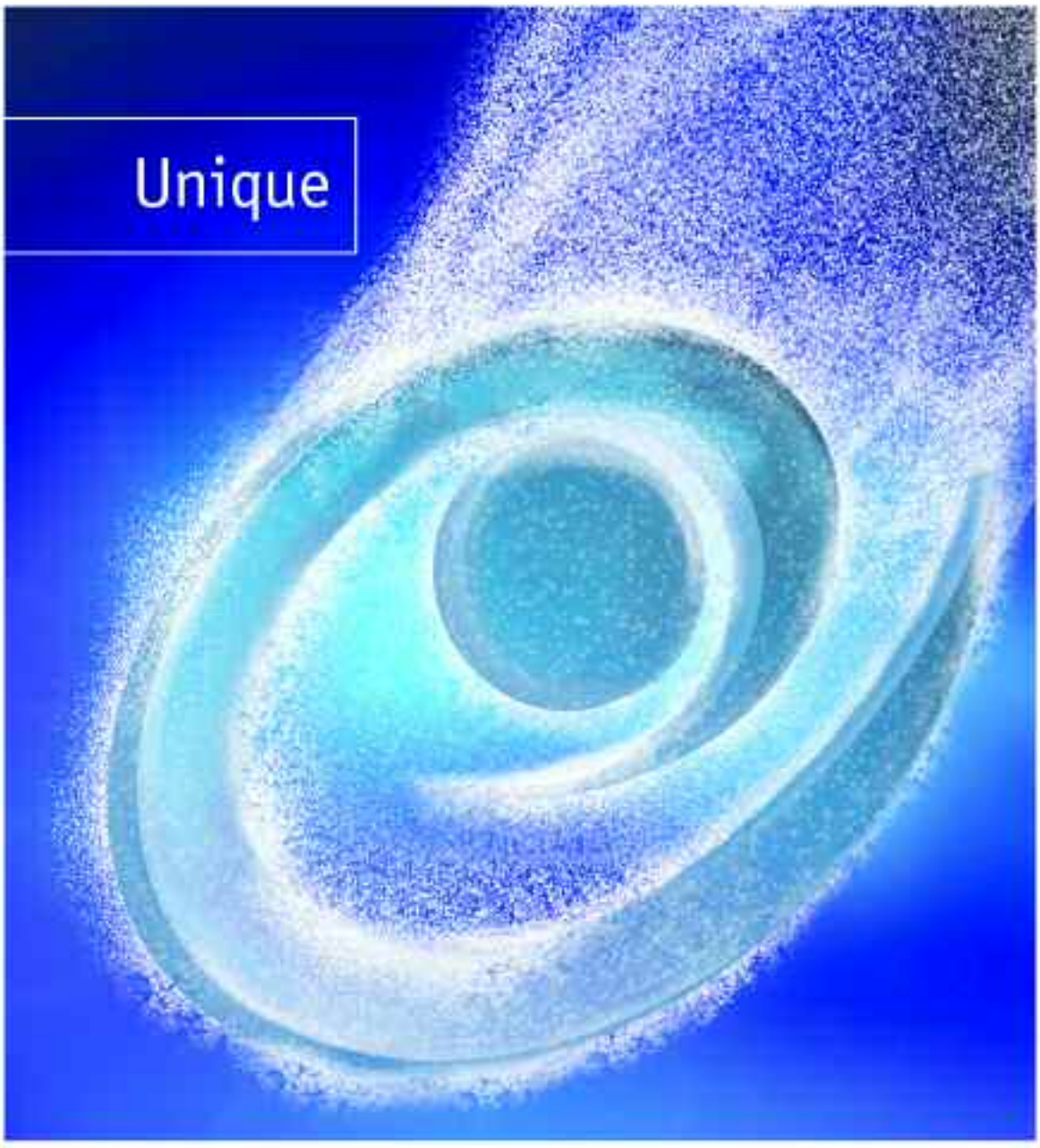

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Market News and Trends

Cell Therapeutics Announces Worldwide License & Co-Development Agreement With Novartis, Deal Worth up to $285 Million

Cell Therapeutics, Inc. recently announced an exclusive worldwide licensing agreement with Novartis for the development and commercialization of XYOTAX (poliglumex paclitaxel), an investigational agent in Phase III for the treatment of non-small cell lung cancer (NSCLC) and other cancers.

Total product registration and sales milestones for XYOTAX under the agreement could reach as much as $270 million. Novartis has also agreed to make a $15 million equity investment in CTI. CTI will have the option of co-detailing XYOTAX in the US under the direction of Novartis, under an agreement to be entered into if CTI exercises the option. The closing of the transaction is subject to antitrust regulatory clearance and certain other closing conditions.

XYOTAX is currently in Phase III clinical trials to test whether single agent XYOTAX provides improved overall survival compared to paclitaxel in women with NSCLC and poor-performance status.

The agreement also provides Novartis with an option to develop and commercialize pixantrone based on agreed terms. Pixantrone is an investigational agent designed to potentially increase anti-tumor activity and decrease the potential for cardiac toxicity associated with the currently marketed anthracyclines. If Novartis exercises its option on pixantrone under certain conditions, Novartis would pay CTI a $7.5 million fee and up to $104 million in registration and sales-related milestones.

"This agreement brings the strength of one of the most innovative leaders in oncology to the development and commercialization of XYOTAX, an agent that could be demonstrated in ongoing trials to prolong survival in women with lung cancer and potentially become the first gender-specific therapy for this disease," said James A. Bianco, MD, President and CEO of CTI. "It also provides pixantrone with potential access to a market leader in blood-related cancer therapeutics to fully maximize its commercial potential."

Mr. Bianco added "This collaboration takes CTI one step closer to rebuilding its commercial presence in the US and its goal of becoming a profitable cancer-focused company. It also allows us to continue our growth through an acquisition strategy looking for other novel targeted agents to add to our development pipeline and into our future commercial infrastructure."

CTI had also announced this past June that they have agreed on pathways for regulatory approvals for XYOTAX in recent meetings with the US FDA and the European Medicine Agency's Scientific Advice Working Party (SAWP). Lung cancer continues to be a major killer of men and women on both continents. In the US, lung cancer is now the number one cancer killer of women.

XYOTAX is a biologically enhanced chemotherapeutic that links paclitaxel, the active ingredient in Taxol, to a biodegradable polyglutamate polymer, which results in a new chemical entity. When bound to the polymer, the chemotherapy is rendered inactive, potentially sparing normal tissue's exposure to high levels of unbound, active chemotherapy and its associated toxicities. Blood vessels in tumor tissue, unlike blood vessels in normal tissue, are porous to molecules like polyglutamate. Based on preclinical studies, it appears that XYOTAX is preferentially distributed to tumors due to their leaky blood vessels and trapped in the tumor bed allowing significantly more of the dose of chemotherapy to localize in the tumor than with standard paclitaxel. Once inside the tumor cell, enzymes metabolize the protein polymer, releasing the paclitaxel chemotherapy. Preclinical and clinical studies support that XYOTAX metabolism by lung cancer cells may be influenced by estrogen, which could lead to enhanced release of paclitaxel and efficacy in women with lung cancer compared to standard therapies.

Pixantrone is an investigational agent under development for the potential treatment of various hematological malignancies, solid tumors, and immunological disorders. It was developed to improve the activity and safety of the anthracycline family of anti-cancer agents. Anthracyclines have been shown to be very active clinically in a number of tumor types. However, they are usually associated with cumulative heart damage that prevents them from being used in a large proportion of patients. Pixantrone has been designed to reduce the potential for these severe cardiotoxicities, as well as to potentially increase activity and simplified administration compared to the currently marketed anthracyclines.

Nastech Initiates Clinical Development of Rapid-Acting Insulin Nasal Spray for Diabetes

Nastech Pharmaceutical Company Inc. recently announced the initiation of a Phase I pharmacokinetic study designed to evaluate the safety, bioavailability, and glucose response of Nastech's proprietary, rapid-acting intranasal insulin formulation. The study will compare Nastech's intranasal formulation to an approved injectable product and to a recently approved new dosage form, Exubera (insulin human [rDNA origin]) Inhalation Powder. Nastech's insulin nasal spray could provide patients with a convenient, needle-free alternative, while avoiding possible pulmonary side effects or long-term toxicity associated with the inhalation of insulin.

This study is the first of several studies to select the formulation and determine the optimal insulin nasal spray dose that will be used to conduct subsequent safety and efficacy studies. This is designed as a dose-ranging study in which subjects will receive a single subcutaneous injection of insulin, a single administration of Exubera, and several different Nastech insulin nasal spray doses on separate days. Pharmacokinetic and pharmacodynamic parameters will be evaluated as well as tolerability of the insulin nasal spray doses.

"Nastech's initiation of human clinical testing marks a major milestone in our insulin nasal spray development program," saidd Steven C. Quay, MD, PhD, Chairman, President, and CEO of Nastech. "This product candidate utilizes Nastech's proprietary drug delivery technologies, which have demonstrated the ability to safely and effectively deliver large molecules through a non-invasive, intranasal route of administration. Nastech's insulin nasal spray could offer a patient- and physician-preferred form of administration that avoids an injection and the potential safety concerns of pulmonary delivery. The convenience and privacy afforded by a device the size of a pack of gum also should promote patient compliance, which could in turn translate into better diabetes control and outcomes. We look forward to rapidly advancing this program and finding an appropriate marketing partner."

Nastech is a pharmaceutical company developing innovative products based on proprietary molecular biology-based drug delivery technologies. Nastech and its collaboration partners are developing products for multiple therapeutic areas, including osteoporosis, diabetes, obesity, respiratory disease, and inflammatory conditions.

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Market News and Trends

Aradigm Announces Asset Sale of Intraject® Needle-Free Technology to Zogenix

Aradigm Corporation recently announced that, in furtherance of its plan to focus on its core pulmonary delivery expertise, particularly as it applies to the treatment of respiratory diseases, it has sold its Intraject subcutaneous delivery technology and related assets to Zogenix Inc., a newly formed privately held company. Zogenix plans to complete development and commercialize the Intraject sumatriptan product for migraine, and may seek to commercialize other products based on the Intraject technology. Under the agreement, Aradigm has received an upfront payment of $4 million, and may receive an additional milestone payment and a royalty on sales of both the commercialized migraine product, as well as any future products based on the Intraject technology.

"Strategically, the sale of this asset facilitates the continuous development of the Intraject product and preserves for Aradigm a share in its success, while enabling us to move forward with our plans to focus our resources and efforts on building a portfolio of products for our core pulmonary business," said Igor Gonda, President and Chief Executive Officer of Aradigm. "With a solid manufacturing and supply chain infrastructure for Intraject in place, we expect that Zogenix will be successful with sumatriptan and other Intraject products."

"Aradigm has done an outstanding job of developing Intraject to this point, and we look forward to carrying this effort forward," added Roger Hawley, CEO of Zogenix. "I am confident Zogenix can successfully take Intraject sumatriptan into the marketplace as a patient-friendly alternative for those who suffer from debilitating migraines."

Aradigm is developing products using its advanced AERx platform and novel formulations to enable patients to comfortably self-administer biopharmaceuticals and small molecule drugs. The company's AERx pulmonary platform is being developed to offer a rapid delivery solution for liquid drug formulations. Current activities include partnered and self-initiated development programs addressing the treatment of asthma, cystic fibrosis, pulmonary hypertension, pulmonary anthrax infections, and smoking cessation. In addition, Aradigm's AERx insulin Diabetes Management System (iDMS), which has been licensed to Novo Nordisk for development and commercialization in return for royalties, is in Phase III testing for type 1 and type 2 diabetes.

Under the agreements with Novo Nordisk, Novo Nordisk is responsible for all further clinical, manufacturing, and commercial development, while Aradigm and Novo Nordisk continue to cooperate and share in technology development, as well as intellectual property development and defense. Novo Nordisk also remains a substantial shareholder and investor in Aradigm.

Zogenix, Inc. is a privately held specialty pharmaceutical company focused on the development and sale of CNS and pain therapeutics. Zogenix raised $60 million in a Series A private venture financing co-led by Clarus Ventures and Domain Associates, LLC. Additional investors included BA Venture Partners, Thomas, McNerney & Partners, and Life Science Angels, Inc. Proceeds from the financing will go toward acquiring and commercializing products based on the Intraject technology in the migraine field and other CNS applications and seeking technology license agreements in other therapeutic areas. Zogenix will be responsible for executing the remainder of the product development program and plans to build a sales force and launch Intraject sumatriptan into the migraine therapy market.

Halozyme Initiates First Enhanze Technology Clinical Trial to Improve Subcutaneous Absorption of a Large Molecule Protein Therapeutic

Halozyme Therapeutics, Inc., a biopharmaceutical company developing and commercializing recombinant human enzymes, recently announced it has initiated and dosed the first three patients in a clinical trial of Enhanze Technology, Halozyme's enzyme-based drug delivery platform based on recombinant human PH20 hyaluronidase (rHuPH20), intended in this trial to enhance the absorption of a representative large molecule protein therapeutic.

"The initiation of this clinical trial takes us another step closer to further developing the full potential of the human recombinant form of hyaluronidase," said Richard C. Yocum, MD, Vice President of Clinical Development and Medical Affairs at Halozyme. "If rHuPH20 can be shown to enhance the absorption of large molecule therapeutics and confer benefit either by improved bioavailability, time to absorption, and/or reduced side effects, this method of drug administration may open up new strategies to treating patients with regard to doses administered, dosing intervals, patient tolerability, patient convenience, and health economics."

As a spreading agent, hyaluronidase has traditionally been used to accelerate the delivery of drugs and fluids, including local anesthetics, other co-injected drugs, and contrast agents, and for subcutaneous (SC) fluid replacement. Although a large body of clinical experience supports the benefits and safety of using hyaluronidase as an adjuvant to increase the absorption and dispersion of co-injected small molecule drugs, clinical studies are needed to support the benefits and safety of recombinant human hyaluronidase use with large molecule agents, such as monoclonal antibodies and other large molecule biologics. Concerns about the allergenicity and immunogenicity of repeat dosing of older, animal-derived hyaluronidase have limited the use of those products in many clinical settings. The recent availability of rHuPH20, along with its high purity and absence of both animal pathogens and risk of transmissible spongiform encephalopathies, has opened up the possibility of many more potential therapeutic uses of this enzyme.

This current clinical trial is designed to compare the pharmacokinetics (PK), safety, and tolerability of a large molecule protein therapeutic agent subcutaneously injected both with and without rHuPH20. The dose escalation, within-patient controlled study, will use escalating doses of rHuPH20 and substitute a standard SC injection of the therapeutic agent with an SC injection of the protein therapeutic agent combined with rHuPH20. The study will compare the bioavailability and other PK parameters, along with safety and tolerability, of the two SC injections, one with and one without rHuPH20.

SCOLR Pharma Engaged by Leading Consumer Products Company to Co-Develop Novel Application of its CDT® Delivery Platform

SCOLR Pharma, Inc. recently announced a research agreement with a global consumer products company to co-develop a novel application of its CDT drug delivery technology. Under the terms of the agreement, SCOLR will receive a research fee. If the program is successful, it is anticipated that the parties would enter a global license agreement to allow for application of SCOLR's technology.

"After consideration of multiple technologies and completion of diligence by our development partner, we are very pleased to have been selected from a competing group of drug delivery companies," said Alan M. Mitchel, Sr. Vice President of Business and Legal Affairs. "This agreement allows us to potentially capitalize on a new application of our CDT technology and may provide our partner with increased product differentiation. In addition to our previously announced relationships with Wyeth and Perrigo, this agreement is further recognition of the potential advantages of our technology and enhances the credibility of our formulation capabilities."

Daniel O. Wilds, President and Chief Executive Officer, added "We are gratified to complete our third collaboration with an important partner over the last 10 months. Each of these collaborations represents a significant and distinct business opportunity. We continue dialogue with potential partners regarding development of products incorporating our CDT platform and other types of marketing, manufacturing, or distribution opportunities with a focus on the pharmaceutical and OTC markets."

Based in Bellevue, Washington, SCOLR Pharma, Inc. is a specialty pharmaceutical company leveraging formulation expertise and its patented CDT platform to introduce distinctive and novel OTC products, prescription drugs, and dietary supplements. SCOLR Pharma's CDT drug delivery platform provides distinctive products with tangible benefits for the consumer and competitive commercial advantages for licensees.

Market News and Trends

European Commission Grants Orphan Medicinal Product Designation to Nektar's Amphotericin B Inhalation Powder

Nektar Therapeutics recently announced its Amphotericin B Inhalation Powder (ABIP) product has been granted orphan medicinal product designation by the European Commission for the prevention of pulmonary fungal infections in patients deemed at risk. This designation is based on a recommendation from the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMEA).

"Prevention of these serious fungal infections in the lung is a major priority, given the increasing incidence of invasive pulmonary aspergillosis in immunosuppressed patients," said Dr. David Denning, Professor of Medicine and Medical Mycology at the University of Manchester. "Any therapy that reduces the incidence of invasive pulmonary aspergillosis in particular is welcome, as these infections are frequently fatal, and can be expensive to treat."

According to the EMEA, orphan medicinal products are for diagnosing, preventing, or treating life-threatening or very serious conditions that are rare and affect less than 5 of every 10,000 persons in the European Union (EU). An orphan drug designation provides 10 years of potential market exclusivity if the product candidate is approved for marketing in the EU. It also allows for regulatory assistance in preparing the marketing application, free protocol assistance to optimize clinical development, reduced regulatory fees associated with applying for marketing approval, and direct access to the centralized procedure for Marketing Authorization Application through the EMEA.

"We are pleased to make continued progress in our ABIP program and look forward to using the scientific guidance and assistance available through the EMEA's Orphan Medicinal Drug Program," said David Johnston, Nektar Senior Vice President of Research and Development. "ABIP holds the promise of preventing fatal fungal infections that start in the lungs, can be very difficult to treat, and are associated with extremely high mortality rates in spite of currently available treatments."

In the US, the FDA granted both Fast Track designation and Orphan Drug designation to ABIP for prevention of pulmonary fungal infections in patients at risk for aspergillosis due to immunosuppressive therapy.

ABIP is under development for the prevention of pulmonary fungal infections, such as aspergillosis in high-risk immunosuppressed patients. The product is designed to target the site of infection directly with a novel formulation of amphotericin B, a broad spectrum, fungicidal drug. Nektar's innovative formulation and pulmonary delivery method could potentially eliminate systemic, dose-limiting toxicities found with current formulations of amphotericin B that are delivered intravenously.

Immunosuppressed patients, for example, those receiving organ or stem cell transplants, or chemotherapy or radiation therapy for hematologic malignancies, are vulnerable to opportunistic fungal infections, such as aspergillosis, which start in the lungs and spread throughout the body. Aspergillosis has a mortality rate of over 50%, and in some immunosuppressed patient groups, the mortality rate may be near 100%. Using ABIP for patients at risk of developing the infection may potentially reduce the incidence of these infections, as well as associated high morbidity and mortality and significant treatment costs. ABIP recently completed a multi-dose, dose escalation clinical study in preparation for pivotal trials to begin in 2007.

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Kurve Technology Achieves Clinical Success in Alzheimer's Disease Study

Kurve Technology, Inc., a leader in nasal drug delivery devices, recently announced the delivery of insulin by the ViaNase electronic atomizer significantly improved memory in patients with Alzheimer's Disease (AD) or Amnestic Mild Cognitive Impairment (MCI). In a recent study presented at the *International Conference on Alzheimer's Disease* by investigators from the Veterans Affairs (VA) Puget Sound Health Care System in Seattle, Washington, and the University of Washington School of Medicine, ViaNase intranasally delivered insulin or placebo to 24 study participants. Treatment was well-tolerated, with no serious adverse events or changes in plasma glucose or insulin levels.

Compared with the placebo-treated group, the insulin-treated group showed enhanced ability to retain verbal information after a delay. Although memory savings scores were no different between the two groups at baseline, they were significantly higher in the insulin-treated group at day 21. During the 6-month trial, ViaNase delivered over 1,000 doses without a single failure. Patients ranged in age from 65 to 95 years. A longer-term trial will begin soon.

"Intranasal insulin administration improved memory by about 20%," said VA Principal Investigator and Professor of Psychiatry and Behavioral Sciences Suzanne Craft, PhD. "This degree of memory improvement can be considered clinically significant."

Recent evidence suggests that disorders of insulin metabolism, such as insulin resistance and diabetes, increase the risk for developing AD. According to the Alzheimer's Association, an estimated 4.5 million Americans have Alzheimer's disease – a number expected to increase to 11 to 16 million by 2050. Finding a treatment that delays onset by 5 years could reduce the number of individuals with Alzheimer's disease by nearly 50% after 50 years.

"The ViaNase electronic atomizer performed flawlessly throughout the duration of the clinical trial period. In addition to improvement in daily function and memory, study participants and their caregivers found the device easy to use and extremely reliable," said Kurve Technology's CEO Marc Giroux.

Dermisonics' Insulin Patch Component of the U-Strip System Does Not Damage the Skin

Dermisonics, Inc. recently announced it successfully completed its HPT-3A human pilot trial of its proprietary U-Strip transdermal drug delivery system in patients with type-2 diabetes, demonstrating that an insulin-loaded proprietary patch does not cause skin damage or irritation. The company continues its HPT-2 human pilot trial, an approved investigational review board (IRB) study designed to demonstrate the ability of the U-Strip System to deliver controlled doses of insulin to patients, comparing the rate of delivery of insulin in comparison to an insulin pump. The company anticipates completion of HPT-2 by the end of 2006. This trial specifically examined the effects of the U-Strip insulin transdermal delivery system upon the skin of type-2 diabetic patients.

The goal of the study was to demonstrate that insulin contained within the company's proprietary transdermal patch does not cause skin damage or irritation. The study was conducted upon 25 adult type-2 diabetic patients of both sexes, with an average time on disease of at least 10 years. A U-Strip Low Profile Transdermal patch, containing 75 units of insulin (enough for a 2-day supply for most diabetics) was fitted on the left upper arm and to the right side of the abdomen. The volunteers were tested over a 5-hour test period to determine any skin sensitivity to the insulin or to the adhesive border of the patch. During this study, no ultrasound was applied. The patches were loaded with conventional insulin, Humalog, which was supplied by Eli Lilly and Co. Abbott Laboratories supplied the glucose meters, FreeStyle Flash, which were used in the trial to verify that the insulin was not permeating through the skin on its own. No ultrasound was applied to the skin during this study, which tested the irritancy of the insulin contact upon the skin and to a lesser degree the border adhesive's irritancy factor.

The trial revealed no adverse skin reactions, no skin irritation, or skin damage among any of the volunteers. This study demonstrates that the insulin-loaded patch component of the U-Strip system does not damage the skin, even the skin of highly sensitive type-2 diabetics. The contract research organization that worked with the company on the trial reported no adverse reactions to the adhesive used in the insulin patches, but some minor adhesive residue was observed around the border of the patch in some of the volunteers. This residue was easily washed away and was not a source for redness, discoloration, or irritation.

Dermisonics' proprietary U-Strip system employs proprietary microelectronics and ultrasonic technologies with a drug-carrying patch to enable the painless delivery of large-molecule drugs through the skin's natural pores and hair follicles. This successful study, and the recently completed HPT-4 human pilot trial that demonstrated that the ultrasound component of the U-Strip System did not damage the skin of highly sensitive type-2 diabetics, are significant steps in achieving clinical approval for the U-Strip System.

FDA Approves Connetics Corporation's Verdeso Foam for the Treatment of Mild-to-Moderate Atopic Dermatitis

Connetics Corporation, a specialty pharmaceutical company that develops and commercializes dermatology products, recently announced that the US FDA has approved Verdeso (desonide) Foam, 0.05%, for the treatment of mild-to-moderate atopic dermatitis. Verdeso, previously referred to as Desilux, is a low-potency topical steroid and is the first approved product formulated in Connetics' proprietary VersaFoam-EF emulsion formulation foam vehicle. Connetics expects to begin marketing Verdeso to physicians in the fourth quarter of 2006 in 50-g and 100-g trade unit sizes.

"This approval allows us to bring a new and valuable option to physicians for treating children and adults with atopic dermatitis," said Lincoln Krochmal, MD, Executive Vice President of Research and Product Development for Connetics. "We look forward to commercializing the first product in our patented emulsion foam vehicle, formulated with emollient ingredients, and our first product approved for pediatric use. The low-potency corticosteroid desonide in VersaFoam-EF has been shown in our clinical trials to be safe and effective in children as young as 3 months of age. The ethanol-free vehicle in Verdeso is intended to provide an elegant, moisturizing, non-stinging product that absorbs quickly into the skin and does not feel sticky like an ointment or cream. In our pivotal clinical trial, burning sensation at the application site was reported by 3% of all treated patients and 1% of pediatric patients between 3 months and 3 years of age."

Thomas G. Wiggans, Chairman and Chief Executive Officer of Connetics, added "We have established leading brands in the topical mid- and super-high potency steroid categories with Luxiq and OLUX, respectively. With the addition of low-potency Verdeso, Connetics now offers physicians a complete line of topical steroids with enhanced cosmetic elegance, which we believe leads to increased patient compliance and satisfaction. Verdeso is a strong strategic fit for our dermatology sales force as well as the pediatric sales force we acquired earlier this year. Looking forward, we anticipate the potential approval of a second product using the VersaFoam-EF technology, Primolux, with a January 2007 PDUFA date."

Approximately 7.7 million prescriptions are written annually in the US by dermatologists for low-potency steroid products, and desonide is the leading topical corticosteroid in this market. The approval of Verdeso provides Connetics with its first low-potency steroid product and expands the company's topical steroid franchise to include a product offering in each of the three potency segments of the total $1.1 billion topical steroid market.

Connetics believes that its emulsion foam delivery vehicle is an important advancement in topical steroid therapy. The vehicle, which was granted a patent in May 2004, contains no ethanol and is reported by patients to have a moisturizing feel. The vehicle was developed by Connetics as a cosmetically and functionally elegant formulation to compete against creams and ointment-based treatments and to address a US market opportunity that currently exceeds $725 million annually.

Connetics owns worldwide rights to a number of unique topical delivery systems and has branded its proprietary foam drug delivery vehicle VersaFoam. This versatile topical drug delivery vehicle is available in three formulations, including VersaFoam-HF, VersaFoam-EF, and VersaFoam-AF. VersaFoam Hydroethanolic Formulation (HF) is neither hydrating nor drying. It dissolves rapidly at skin temperature (90° F to 95° F) and leaves minimal residue on the skin. VersaFoam-EF is an emulsion formulation that provides many of the benefits of ointments, creams, and emollient-cream vehicles, but with the cosmetic elegance of VersaFoam. VersaFoam Aqueous Formulation (AF) is a hydrating version of VersaFoam. Medications formulated with VersaFoam-AF are in development. VersaFoam formulations are designed to address specific patient preferences and skin types, and to have important functional benefits and cosmetic benefits compared with conventional delivery vehicles, such as creams, ointments, gels, and lotions. Each VersaFoam formulation is easy to apply and spread, disappears into the skin quickly, and offers the cosmetic elegance of a fine skincare product. In addition to Verdeso, Connetics' VersaFoam-based products are OLUX for scalp dermatoses and non-scalp psoriasis, Luxiq Foam for scalp dermatoses, and Evoclin Foam for acne.

Market News and Trends

Bentley Pharmaceuticals Announces Agreement with Cardinal Health for Scale-Up and Manufacture of Clinical Supplies for its Intranasal Insulin Program

Bentley Pharmaceuticals, Inc., a specialty pharmaceutical company, recently announced it has secured capacity at Cardinal Health's new North Raleigh facility for the scale-up and manufacture of clinical supplies of Bentley's intranasal insulin product candidate, facilitating the expansion of clinical trials.

The product candidate utilizes Bentley's proprietary CPE-215 drug delivery technology to deliver insulin directly through diabetic patients' nasal mucosa using a small, discreet nasal spray. The conventional treatment requires intramuscular injections several times a day.

Cardinal Health, a leading provider of products and services supporting the healthcare industry, will manufacture clinical supplies of Bentley Pharmaceuticals' intranasal insulin product under cGMP at its new, sterile manufacturing facility in North Raleigh, NC.

"This agreement with Cardinal Health is another important step forward in our intranasal insulin program and the CPE-215 delivery platform," said John A. Sedor, President of Bentley Pharmaceuticals. "Early results for the intranasal insulin product have been promising, and there is growing interest in alternative insulin delivery methods that are less intrusive than injection. We are excited to be working with Cardinal Health to continue to advance this program through global Phase II trials this year."

This agreement builds on an existing drug development relationship with Cardinal Health's manufacturing and analytical services facility in Research Triangle Park, NC, where Cardinal Health pulmonary and nasal experts worked with Bentley Pharmaceuticals to characterize the product.

"Bentley Pharmaceuticals leveraged multiple capabilities within Cardinal Health's development and manufacturing segment to prepare its intranasal insulin candidate for global clinical trials," said Shawn Gallagher, Vice President and General Manager of Cardinal Health's North Raleigh facility. "By using Cardinal Health's full range of solutions, from development to manufacturing to packaging and distribution, Bentley Pharmaceuticals maximizes its efficiency and relies on the same high-quality services through the entire drug development and commercialization cycle."

Bentley Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on advanced drug delivery technologies and generic pharmaceutical products. Bentley's proprietary drug technologies enhance or facilitate the absorption of pharmaceutical compounds across various membranes. Bentley also manufactures a growing portfolio of generic and branded generic pharmaceuticals in Europe for the treatment of cardiovascular, gastrointestinal, infectious, and neurological diseases through its subsidiary, Laboratorios Belmac, and markets these pharmaceutical products through its subsidiaries, Laboratorios Belmac, Laboratorios Davur, Laboratorios Rimafar, and Bentley Pharmaceuticals Ireland; and manufactures and markets active pharmaceutical ingredients through its subsidiary, Bentley API.

Pfizer & TransTech Pharma Enter Into Agreement for the Development & Commercialization of RAGE Modulators

Pfizer Inc. and TransTech Pharma, Inc. recently announced they have entered into a license agreement for the development and commercialization of small and large molecule compounds under development by TransTech. These compounds target the receptor for advanced glycation endproducts (RAGE) and have potential use in the treatment of Alzheimer's disease, a progressive illness that kills nerve cells in the brain afflicting some 18 million people worldwide.

Through the collaboration, Pfizer gains exclusive worldwide rights to develop and commercialize TransTech's portfolio of RAGE modulators. The most advanced molecules are TTP488, an orally available small-molecule compound that has completed a Phase IIa study in Alzheimer's patients and is currently in a Phase II study in patients with diabetic nephropathy; and TTP4000, a large-molecule compound that is expected to enter Phase I clinical trials before the end of 2006.

Under the agreement, TransTech will receive upfront and near-term milestone payments of $155 million and the potential for significant additional milestone payments for the successful development and commercialization of multiple RAGE antagonists in several indications. TransTech will also receive royalties on worldwide sales of products. In addition, Pfizer will provide TransTech up to $18 million during the research term to support continued expansion of the RAGE portfolio. The agreement is subject to clearance by US Federal Trade Commission.

"This agreement is an important step in Pfizer's commitment to neurosciences research and the development of new medicines for patients whose lives are impacted by Alzheimer's disease and other disorders," said Martin Mackay, PhD, Pfizer Senior Vice President Worldwide Research and Technology. "As a world leader in Alzheimer's disease therapy, we understand the need for new treatment options for this debilitating disease, which takes an enormous toll on our aging and elderly population."

"Our collaboration with TransTech advances our strategy to build upon Pfizer's broad internal research programs with high-potential, externally sourced product candidates and technologies. With this agreement, we have now signed 10 major deals for new products and technologies in a number of therapeutic areas in the past year, and our goal is to accelerate this activity by quickly seizing on new opportunities," added Mr. Mackay.

"We are extremely pleased and excited to be partnering our RAGE platform with Pfizer," said Adnan M.M. Mjalli, PhD, Founder, President, and Chief Executive Officer of TransTech Pharma. "We believe this transaction has the potential to be among the largest of its kind in recent years. Pfizer's deep commitment in multiple therapeutic areas coupled with their broad expertise and experience in the development and commercialization of new medicines, especially for the treatment of central nervous system diseases, were significant factors in our decision to go with Pfizer as the partner of choice to advance our current portfolio of RAGE inhibitors in a variety of potential indications."

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin superfamily of cell surface molecules with a variety of ligands that are associated with different diseases. Ligands of RAGE and their associated diseases include amyloid fibrils (Alzheimer's disease), advanced glycation endproducts (AGEs) (diabetes and renal insufficiency), amphoterin (tumors), and S100/calgranulins (inflammation).

TransTech Pharma is a privately held clinical-stage pharmaceutical company focused on the discovery, development, and commercialization of human therapeutics to fill unmet medical needs. The company's high-throughput drug discovery platform, Translational Technology, translates the functional modulation of human proteins into safe and effective medicines. TransTech has a pipeline of small molecule clinical and preclinical drug candidates for the treatment of a wide range of human diseases, including cardiovascular disorders, central nervous system disorders, type I/II diabetes, obesity, and cancer.

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Alexza Pharmaceuticals Initiates Phase IIa Clinical Trial for AZ-004 in Schizophrenic Patients With Acute Agitation

Alexza Pharmaceuticals, Inc. recently announced it has initiated a Phase IIa clinical trial with AZ-004 (Staccato loxapine). AZ-004 is an inhalation product candidate being developed for the acute treatment of agitation in schizophrenic patients. The Phase IIa clinical trial is a multi-center, randomized, double-blind, placebo-controlled evaluation of 120 patients in a clinical setting. Two doses of AZ-004 will be compared to placebo in this proof-of-concept study. The primary aim of the clinical trial is to assess the safety and efficacy of a single dose of AZ-004 in acutely treating agitation in schizophrenic patients. Assessments of a patient's agitation state will be conducted at serial time points using both standard agitation scales and objective measures of patient's movement over a 4-hour period, with follow-up assessments for the next 20 hours. The change in the PANSS Excited Component (PEC) scale will be the primary efficacy measure for the clinical study.

AZ-004 is the combination of Alexza's proprietary Staccato system with loxapine, a drug belonging to the class of compounds known as antipsychotics. In a Phase I dose-escalation clinical trial, AZ-004 was generally well tolerated at all doses tested, and there were no serious adverse events. Across all doses, pharmacokinetic analyses revealed that peak plasma levels were generally reached within the first few minutes after dosing, and AZ-004 exhibited good dose proportionality. Alexza believes the non-invasive nature and rapid pharmacokinetic properties resulting from administration via the Staccato system make AZ-004, if approved for marketing, a viable product candidate for treating agitation episodes in schizophrenic patients.

Alexza is an emerging pharmaceutical company focused on the development and commercialization of novel, proprietary products for the treatment of acute and intermittent conditions. The company's technology, the Staccato system, vaporizes unformulated drug compound to form a condensation aerosol that allows rapid systemic drug delivery through deep lung inhalation. The drug is quickly absorbed through the lungs into the bloodstream, providing speed of therapeutic onset that is comparable to intravenous administration, but with greater ease, patient comfort, and convenience. The company has four product candidates in clinical development; AZ-001 (Staccato prochlorperazine) for the acute treatment of migraine headaches, AZ-002 (Staccato alprazolam) for the acute treatment of panic attacks associated with panic disorder, AZ-004 (Staccato loxapine) for the treatment of acute agitation in patients with schizophrenia, and AZ-003 (Staccato fentanyl) for the treatment of patients with acute pain.

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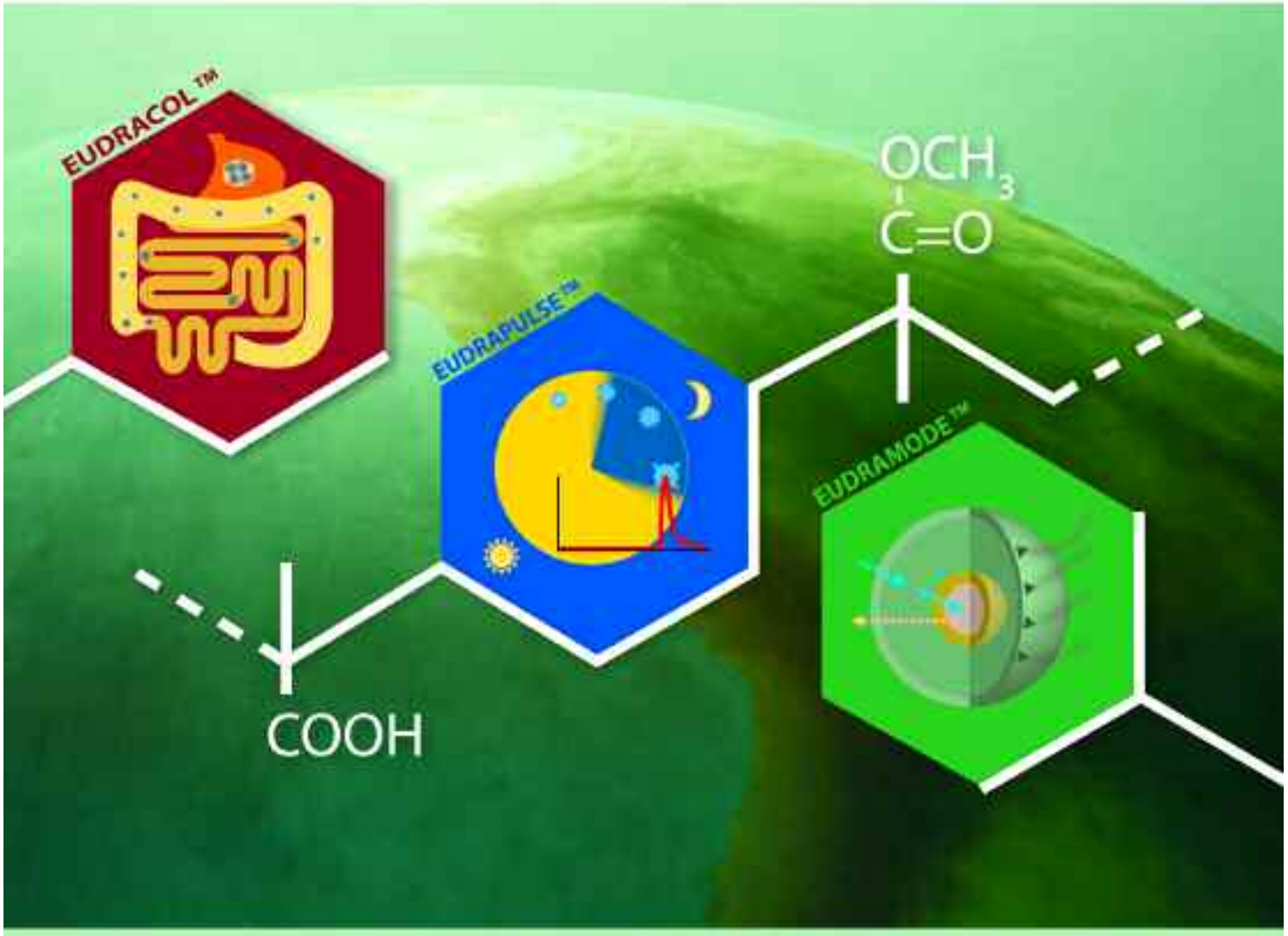

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COMBINATION UPDATE

Combination Products Revolutionize the Global Healthcare Industry

By: Christine M. Ford, MBA

In recent years, the combination products market has developed into a revolutionary industry. Initially, the FDA handled most products that crossed jurisdictional lines on a case-by-case basis. With two or more agencies responsible for reviewing each product, there were issues in clarifying which policies were applicable. In 2002, under the *Medical Device User Fee and Modernization Act* (MDUFMA), the FDA established the Office of Combination Products (OCP) to oversee the regulatory process for combination products. The OCP is responsible for assigning the product to the appropriate FDA center for jurisdiction. Since the establishment of the OCP, the FDA has reported a steady increase in the number of requests from cutting-edge combination product developers for presubmission meetings to seek advice on the best approaches for scientific and clinical testing and evaluation.

The definition of a combination product according to the FDA is as follows: two or more regulated components — drugs, medical devices, or biologics combined through physical or chemical means. These include drug-coated devices, drugs packaged with delivery devices in medical kits, and drugs and devices packaged separately but intended to be used together. Some examples of combination products include drug-eluting stents, surgical mesh with antibiotic coatings, spinal fusion putties, protein-coated implants to encourage bone regeneration, and single-device-integrated glucose meter/insulin pumps for diabetics. Many such products bring together the power of advanced therapeutics with the precision dosing made possible by sophisticated delivery technologies. Already valued at $5.4 billion in 2004, the global market for combination products is achieving annual growth of 10% to 14% percent a year.[1]

In the past year, numerous combination products have received a great deal of attention. One groundbreaking combination product is Pfizer's Exubera, an inhaled powder form of recombinant human insulin (rDNA) for the treatment of adult patients with type 1 and type 2 diabetes. Approved by the FDA in January 2006, Exubera is inhaled into the lungs through the patient's mouth using a specially designed inhaler. For the some 5 million Americans who take insulin injections, this product may allow for improved insulin management. It is the first new insulin delivery option introduced since the discovery of insulin in the 1920s. This new capability has revolutionized the drug delivery industry and provided the healthcare industry with the potential for unlimited possibilities for providing safe drug delivery via the systemic pulmonary route. This technology will benefit various areas of medicine, including pain management, oncology, osteoporosis, migraines, immunosuppression, and neurologic disorders.[2]

Another product of interest is Orthovita Inc's combination product Vitagel, which received pre-market approval (PMA) from the FDA in June 2006. Vitagel is a composite liquid hemostat used in surgical procedures as an adjunct to hemostasis. This technology offers an advantageous alternative when control of bleeding by ligature or conventional procedures is inefficient or impractical. Vitagel works by combining a thrombin/collagen suspension with the patient's own plasma. The resultant fibrin/collagen clot stems bleeding and provides a robust three-dimensional matrix for soft tissue healing. Vitagel is approved for use only in conjunction with the Cellpaker plasma collection system.[3]

Lastly, approved by the FDA in April 2006, Shire plc's Daytrana is the first and only transdermal methylphenidate medication approved to treat the symptoms of ADHD. This treatment provides physicians and parents with a new, practical way to individualize treatment for children with ADHD. The patch treatment provides an option for parents whose children have a resistance to oral medication and eliminates the need for children to take additional doses of medication during their school day. In addition, because the effect of the medication in Daytrana starts to decrease upon patch removal, the ADHD patch allows parents, at the direction of the physician, to vary the duration of effect of the medication up to the recommended 9-hour wear time.[4]

The aforementioned products represent only a handful of the innovative new products on the medical industry frontier. As the evolution of medical technology continues to progress globally, many experts predict that combination products will play a crucial role in the future because they hold great promise for advancing patient care. However, continued development of these technologies is not without challenges. Manufacturing, packaging, and regulatory considerations all present potential obstacles on the path to commercialization. Combination product manufacturers should bear in mind that the assessment process of the safety and effectiveness of these products may not yet be as timely and efficient in relation to the growth of the combination products industry. However, such concerns are only a telltale sign of rapid progression and exciting new advancements. ◆

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BIOGRAPHY

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

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BUSINESS DEVELOPMENT

Value Creation Through a Hybrid Business Model

By: Anthony Garramone and Debra Bingham

Creating value is the order of the day for every CEO. The idea is to design a workable business model that will create value for shareholders within a reasonable amount of time assuming a reasonable amount of risk. Almost everyone close to the drug delivery industry will agree that long-term value creation with a platform technology in and of itself is complicated now that pipelines are somewhat dryer, the client base is smaller, and the competition is greater than before. With strong enabling technology and good decision-making on partnering, a drug delivery model can provide the needed cash and skills to move a company forward. However, for long-term growth, most companies will have to look to product acquisition or development to create a strong internal pipeline of products independent of the whims of a partnership. The question is how far down the road toward the pharmaceutical product model does a drug delivery company have to travel?

SPECIALTY PHARMACEUTICAL MODEL – IS IT RIGHT FOR EVERY DRUG DELIVERY COMPANY?

The pharmaceutical industry is no different than other industries – you must create a product or service that meets an unmet need, you must differentiate from competition, and you must communicate the message clearly to your target audience. Drug delivery companies transitioning to a specialty pharmaceutical model may have difficulties with some or all of the aforementioned requirements. The current climate seems to value products more than enabling technology, and this fact has caused some drug delivery companies to begin a frenzied pursuit of a product-based specialty pharmaceutical business. On the other hand, some drug delivery company executives have realized that a pure specialty pharmaceutical business model is not always the best choice for near-term revenue generation. That business model requires significant investment, something for which most drug delivery companies are not well equipped.

For this reason, many drug delivery companies have chosen to pursue a hybrid model that allows both technology partnering and internal product portfolio creation. The key to success for these companies is to advance internal products and move toward a specialty model without losing track of building value in the platform technology. Leveraging the technology across both internal and select proprietary molecules and not limiting it only to internal opportunities would allow the most value to be derived from the technology. The hybrid model allows a company to leverage both internal development opportunities while accessing other markets by continuing to apply the technology to select, proprietary molecules. This approach allows these companies to create value that is not limited to that which could be created through the internally developed opportunities that could be pursued.

ARGUMENT FOR HYBRID BUSINESS MODEL

The economics of some partnered opportunities can be as lucrative as specialty pharmaceutical opportunities, which are either licensed out at a late stage or developed internally using the drug delivery technology. Typically, the

FIGURE 1

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opportunities available to specialty pharmaceutical companies fall below the radar and below the line in terms of market opportunity for big bio/pharma companies. While developing these can be lucrative, there is a significant amount of risk and development costs, which are funded by the drug delivery company. Alternatively, the value of the drug delivery technology when applied to a partnered program, especially an enabling technology, can garner a piece of what is in most cases a very large pie – this piece of the large pie can have as much value as having the whole pie in the case of the specialty pharmaceutical option – with lower risk and lower cost to the drug delivery company.

The bottom line is that the hybrid model (Figure 1) allows drug delivery companies to work across the entire continuum of opportunities that exist from the go-it-alone, speciality pharma model, to the partnered model, and therefore allows companies that pursue the hybrid model to "dial-in" and adjust the risk profile of their portfolio across more bandwidth than is possible for a pure-play company.

POSITIONING THE PORTFOLIO FOR VALUE CREATION

It is important to note that a hybrid model will require careful market positioning. The attraction of high-quality partners is as much due to market position and creative strategy as it is due to strong technology. It is critical that the company:

- Becomes an expert regarding technology capabilities
- Discovers and clearly communicates unmet market needs for the technology application
- Puts in place a formal process to quantitatively manage its portfolio
- Strategically drives IP portfolio to control its area of the market
- Develops a "story" – proprietary molecule partnering and internal projects and a clear message regarding strategy to investors and the public
- Develops or adopts an internal process for product concept generation

SUMMING IT UP

The successful companies will find a way to continue to add to and build on the drug delivery base while bringing in and developing innovative and relevant products. The industry needs drug delivery technology. There are still significant unmet needs around drug delivery. It is important that innovative and creative companies maintain a focus on deepening and strengthening proprietary drug delivery technology while at the same time keeping an eye to the horizon for products that fulfill a medical and/or market need.

Building value in the company using a drug delivery technology is more about making the right choices on partners and products to pursue, than it is about moving toward a specialty pharma business model. The market value of the company will ultimately depend on the strength of the portfolio and technology base. ◆

BIOGRAPHIES

Mr. Anthony Garramone is VP, General Manager of Epic Therapeutics, Baxter Healthcare. During his 20-year career in the life science industry, he has focused on early stage ventures from inception through product development. Mr. Garramone joined Epic Therapeutics in 1994 and since that time has held various senior management positions overseeing both operations and quality systems, and assisting in the development of company structure, organization, and strategic direction. He joined Epic (previously known as Middlesex Sciences, Inc.) as the Director of Operations and was promoted to Vice President of Operations in 1998. His responsibilities at that time included overseeing Research and Development, Quality Systems, Clinical Affairs, Analytical Development, and Intellectual Property. In this capacity, he helped Epic set-up on-site GMP operations, file its first Investigative New Drug (IND) Application, and generate the first clinical data on its PROMAXX technology. In 2000, Mr. Garramone was appointed President of Epic and was instrumental in positioning the company for acquisition by Baxter in 2002. As part of Baxter, he holds the title of Vice President, General Manager and recently was given the responsibility for all of Baxter's formulation technology platforms. Prior to joining Epic, Mr. Garramone was responsible for Operations and Quality Control / Quality Assurance at Transgenic Sciences (TSI). He helped establish and grow TSI from its founding as a venture funded company to a public offering. Before TSI, Mr. Garramone, who earned a BA in Biology from the University of Rochester, held senior technical positions in molecular biology at Integrated Genetics (now part of Genzyme Corporation).

Ms. Debra Bingham is a Founding Partner of Valeo Partners. She brings clients over a decade of specialized expertise in the pharmaceutical and biotech industries. At Valeo, her primary focus is in helping clients in the areas of business strategy, business development, growth opportunity assessment, and strategic partnering. Ms. Bingham leads Valeo's strategic partnering offering in affiliation with Stonecroft Capital, a DC-based investment bank, which provides full-service transactional capabilities from licensing to M&A. She spent the majority of the past 10 years working in the pharmaceutical industry assisting companies with strategic business assessment and business development. Ms. Bingham has authored many drug delivery business articles and technology reviews and is a featured speaker at industry trade conferences.

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FORMULATION FORUM

Formulation Strategies to Protect Multi-Billion Dollar Blockbusters

By: Contributor Cindy H. Dubin

INTRODUCTION

Nearly 70 branded drugs with annual US sales of $46 billion, including 19 blockbusters with annul sales of more than $1 billion each, are set to go off patent by 2010. The most recent of these was Merck's Zocor, the number two cholesterol-lowering medicine. In anticipation of losing its patent this past June, Merck struck a co-marketing deal with Schering-Plough in 2004 to sell Vytorin, a combination of Zocor and Zetia, discovered by Schering-Plough and co-marketed by the two companies. For Merck, Vytorin, which launched in 2004, has softened the blow of Zocor going off patent; the drug had sales of $2.4 billion last year. For Schering, Vytorin is projected to account for 70% of the company's earnings this year.

But it will take more than strategic partnerships for Big Pharma to compete with the generic market. Better life cycle management, earlier planning of drug delivery, and even morphing existing drugs are formulation strategies that Big Pharma should consider tackling to stave off generic competitors.

Coincidentally, Merck has slashed the price of Zocor for one insurance plan in which members will pay less for the branded drug than for the generic. Some consumer advocates fear that the practice will spark a movement among pharmaceutical companies, compounding other pressures they fear will weaken the generic industry.

Consumer advocates say moves such as Merck's undermine generic companies' chances to generate the profits that fuel their ability to conduct research and challenge drug company patents — eventually resulting in fewer less-expensive medicines.

According to industry insiders, this has not stopped the switch of patients to the generic and is not an issue for the wider market for Zocor, which is why generic simvastatin has already taken over about 75% of total prescriptions for that product.

Drug Delivery Technology magazine recently asked some industry insiders how Big Pharma can survive the blow of blockbusters coming off patent. They are: Jack Aurora, PhD, Director Pharmaceutical Research and Development, Pharmascience Inc.; Ravi Kiron, PhD, MBA, Executive Director New Technology Assessment and Planning, Alza Corp.; Phil Smith, PhD, General Partner, S.R. One, Limited; Jay Trivedi, MS, MBA, Licensing & Development Programs, Patrin Pharma; and Daniel Ruppar, Research Analyst, Frost & Sullivan.

Q: As 19 blockbuster drugs are due to lose their patents by 2010, what formulation strategies does Big Pharma need to put into practice to compensate for losing those patents?

Jack Aurora: Big Pharma needs to change because of the growing disparity between the amount of money being spent and the number of successful drugs coming out of R&D. To survive in this competitive world, one may immediately think mega-merger. This eliminates overheads and duplications, but in the end, this does not give you a long-term viable solution. This is a short-term financial solution that takes longer and is expensive. Another short-term option being exercised by Big Pharma is authorized generics and licensing deals. It has been reported that the top 20 drug companies are becoming more dependant on licensing to build their pipelines. This trend will continue, but again, this option is not the best and is not a long-term solution.

So, there are a couple of options to exercise. One is to think creatively and squeeze more life out of expiring blockbusters by combining them with other drugs and marketing them as drug "combos" for new therapeutic indications. Another interesting option is to join hands with smaller biotechnology companies and be productive, eliminate overheads, and capitalize on inventions/research ideas of smaller organizations.

Buying your pipeline off-the-peg is one thing. But at the same time, these organizations need to bring new and better drugs to patients faster and more efficiently by reducing cost and time spent developing them. Increased emphasis has to be spent in the discovery and development phases, such as automated high throughput screening systems and targeted clinical trials through biological markers and/or genome-access tools. Moreover, regulatory requirements in terms of safety and efficacy

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need to be explored. With the advancement in pharmacogenomics more focused, smaller Phase III trials should be conducted to reduce the cost and time of the clinical phase of development. This will, in turn, reduce the regulatory approval time while still providing required data and confidence to the regulatory agencies. The question arises whether Big Pharma needs to perform all the R&D or outsource. It is wonderful to do yourself, but the golden rule is that you can always find someone else to do the job in a different and more efficient way.

Ravi Kiron: Various formulation strategies are being considered, and innovation in the traditional modes of delivery will bring about a new revolution in the way drugs are currently administered into the body. The opportunity for a clearly enunciated 505b2 strategy to launch once marketed drugs with a new delivery mode or route needs to be developed, and appropriate guidelines need to be communicated to the industry by the FDA and other regulatory bodies.

In addition, novel biological delivery formulation methodologies need a new lease on life so as to deliver the new crop of biotechnology products that are currently in development and that will need (very soon) a delivery option to be launched in the market.

Phil Smith: Formulators might want to consider polymorphs — a different crystal form of a chemical structure. A new polymorph can be patented and may be combined with salt form selection to produce a more stable pharmaceutical. Such an approach could allow for the development of a dosage form with improved solubility, reduced dosing frequency and/or amount, and hence better compliance and/or reduced side-effect profile to benefit the patient.

Jay Trivedi: The industry must understand that the concept of Life Cycle Management (LCM) begins at the launch of a product. As timelines are shrinking and competition is fierce, protecting Intellectual Property (IP) must be a part of the product launch strategy. In essence, LCM should be viewed as a Portfolio Optimization strategy at the time of launch rather than last minute efforts to respond to patent expiration.

The industry is learning this but for earlier products, the patent expiration will cause a significant financial blow to Big Pharma. The industry is already taking the usual steps, ie, pediatric trials to extend patent life, using alternate delivery routes, new formulations, and the use of drug delivery company's patented technology to extend product life. These are usual defensive steps and would help. In addition, they are also using the Authorized Generics strategy to reduce financial impacts.

Abbott executes a great example of an ideal LCM strategy with regard to Tricor. This is a 50-year-old molecule that still maintains a leading place in the market. It's a billion-dollar product on its own. As Tricor is reaching technological limitations for now, Abbott is teaming up with Astra Zeneca's Crestor for a combination drug. The drug is now in Phase III studies.

However, the key to growth is newer drugs that offer significant benefits over current treatments. Because development cycles are long and success rates are low, adaptation to newer technologies (eg, screening, genomics, and proteomics) will certainly help in finding new targets. In addition, acquisition or licensing of small technology firms is proving more beneficial both in the short-term as well as long-term for Pharma. More traditional approaches, such as R&D cuts and mergers, are temporary solutions and often result in disappointing results for long-term survival.

Daniel Ruppar: Big Pharma can exercise a variety of tactics, be it a new delivery method, next-generation product, or single pill combo for example. Where applicable, these all are able to yield an expanded IP position for the company and add revenue potential to their product line. GSK has three delivery forms for its migrane product, Imitrex. As Jay indicated earlier, Abbott maintains hold over fenofibrate patients by continuing to evolve TriCor, the latest using Elan's NanoCrystal technology. Overall, continuing product evolution through new formulation efforts can yield greater returns over what is possible with the initial product version launched in the market.

Q: Consider the case of Zocor and Merck's partnership with Schering-Plough to combine drugs. Will we see more of these partnerships to combine drugs? What is the advantage of this?

Jack Aurora: The interesting story of Zocor and Merck's partnership with Schering-Plough is an example of healthy growth and a stronger business relationship. In this specific case, the partnership has drawn upon the research expertise and marketing strength of both organizations and competes in the cholesterol management and respiratory therapeutic areas that would not otherwise be developed. Development and marketing costs have been split evenly, as well the sales.

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As we all know, success is tough to come by, and everything is expensive in this competitive world. We all need to think out of the box. In light of these eye-opening facts, we hope to see many more joint partnerships. Such strategies will help bring medicines to patient populations much faster and in a more efficient way. Moreover, such mutual partnerships will also help minimize the time and money spent on litigations and that in turn will reduce the cost and time of development of the new drugs.

Ravi Kiron: This trend of developing combination drugs will increase, although without any guidance from the regualtory bodies, it will be very difficult and a major hurdle for innovative smaller companies to launch in this space. Combinations will not only be two or more drugs together, but also a drug(s) and device together as a combination will also emerge in the marketplace throughout the next 5 years. For now, the success or failure of the Merck/Schering-Plough partnership will also spell the future of combination drug therapy.

Daniel Ruppar: The Merck/Schering-Plough partnership is an important one. As part of that, Merck and Schering took Merck's Zocor and combined it with Zetia, initially discovered at Schering, to create a new single pill, Vytorin. The companies have gained substantially through the partnership, launching Zetia and Vytorin, as both products have become global blockbusters. One major point for Merck in this is gaining the ability to continue to generate substantial revenues from the cholesterol space post Zocor's patent expiration this year.

Abbott has now done something similar through the initiation of a collaboration with AstraZeneca. That partnership combines Abbott's TriCor and their next-generation fenofibrate, with AstraZeneca's Crestor.

The overall advantage of this strategy is both companies bring individual strong points to the table, and sides of the product. Not only does the collaboration gain from the combination of resources, but in the splitting of development cost and risk. In cholesterol therapy, companies are looking more to combine products, especially in this statin plus a non-statin scenario as patients are looking for new ways to help them meet their lipid goals. This is yielding product development that wouldn't be possible right now from an IP standpoint without a collaborative effort. Both patients and the industry are able to benefit from that.

Jay Trivedi: Big Pharma used to compete with one another in the old model. Now, as patents are expiring, they are looking outward to create combination products. This requires an association with former competitors. We are seeing more joint ventures as a need of survival for both companies. You are already seeing this trend as already discussed in the aforementioned Merck/Schering and Abbott/Astra Zeneca partnerships. The goal is to utilize knowledge of individual products, create a product that offers synergistic benefits to patients, and generate new IP for these organizations. As I have discussed previously (Specialty Pharma magazine, March/April 2006 and July/August 2006), this is the future.

Q: How important is it for formulators to consider drug delivery earlier in the LCM of a drug to extend a patent in the long run?

Ravi Kiron: This is a key and relevant question that needs to be addressed by people at all positions and levels of the R&D Value Chain generation process. The value proposition for drug delivery, although accepted by most in theory and principle, is still not yet embraced by the decision-makers and the rainmakers of pharma drug discovery and development.

Drug Delivery should not be viewed as a rescue mission for candidates that have fallen by the wayside in the R&D process. Instead, if true partnership is established at the early stages of the R&D process, then the opportunity exists to improve the R&D pipeline on a number of fronts, including the following:

- Designing potent drugs that are more effective in addressing the therapeutic need.
- Ensuring proof-of-concept in early stages of the clinical evaluation, hence potential for the drug to actually be launched in the marketplace.
- More effective targeting by drug delivery reduces the potential for adverse events or side effects.
- Risk profile is reduced, therapeutic applicability enhanced, and cost to some extent also made more affordable because more numbers of drug candidates launched in the market results in competition.

All this would result in extending the revenue generation for a patented product to a longer timeline, ultimately benefiting the company and the industry.

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Unique Appearance

This new delivery system stands apart from look-alike products that crowd retail shelves.

Compounds

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JACK AURORA: Drug delivery is the backbone of the developed medicine. We can have a clinically effective and potent medicine discovered, but if the delivery system is not well understood and designed around the developed drug, failures will result in meeting expectations and declining profits. In addition, the extension of patent life is another important requirement for the company business and growth. This attribute will also require identification of the best delivery system, such as to extend, delay, or a combination of both, and/or alter the route of delivery to the target site of absorption. Moreover, time is of the essence here, and one should plan and start pooling ideas and having brainstorming sessions during the early phases of drug development rather than losing time later and compromising with the expectations and deliverables. Therefore, a formulator should review the therapeutic and physico-chemical attributes of the discovered drug (as being developed) at an early stage and arrive at the best delivery system for the desired stability and clinical efficiency. The strategy identified can always be modified at a later date, if required, due to newer facts and clinical attributes explored and identified.

JAY TRIVEDI: Ravi and Jack have put it well. Twenty years ago, not much attention was given to drug delivery. Now, companies are thinking ahead to various delivery technologies and routes. Again, LCM should be considered as a Portfolio Value Optimization at the time of product launch. It will require Marketing Managers to change their thinking from a short-term strategy (launch and market share, etc) to a more comprehensive optimization strategy and having a dialogue with relevant partners (eg, formulators, etc) prior to launch.

DANIEL RUPPAR: This can be very important in the maximization of a product's potential, be it therapeutically, or from the standpoint of revenues gained by the company. New versions that can expand the IP run are good for the industry; however, maximizing the effectiveness of a product through the exploration of drug delivery technologies is something that really can benefit patients through the marketing of potentially more effective drugs. As the Pharma industry is in the business of treating and curing disease, companies should really want to explore these options as early as possible in the development process.

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ADVANCED DELIVERY DEVICES

Gerresheimer Group/Bünder Glas – Set for Faster Growth With RTF® Sterile Syringes

By: H. Burkhard Lingenberg

INTRODUCTION

As a specialist in packaging and systems for pharmaceutics, the Gerresheimer Group established itself as a leading player in the world market a considerable time ago. With high-quality tubular and molded glass in every possible variant, it leads the field in America (with Kimble Inc.) and Europe and is currently making moves to become the largest pharma glass manufacturer in China as well. In parallel, this innovative and expanding Group, which manufactures in 21 locations around the world, is one of the top addresses for pharmaceutical plastic. It is also setting a breathtaking tempo in another field that represents one of the most important growth markets for drug delivery, namely the development and production of prefillable injection systems. Particularly in the exclusive segment of sterile all-glass syringes, Gerresheimer, with its German competence center Bünder Glas, today enjoys international recognition as a technology leader and is opening up for the pharmaceutical industry, including the industry in the US, highly attractive new dimensions for intelligent system partnership. The following article examines the background.

To date, the production lines of Bünder Glas have been turning out 100 million RTF® syringes a year, but from 2007, the figure will more than double. Gerresheimer is currently further expanding production of the high-caliber sterile systems, and there is no need to worry whether they will sell. Bünder Glas has never had any doubt about the success of its Ready-to-Fill concept. That part of the business is now actually growing faster than expected, and in all five continents of the world.

PRODUCT RANGE

Sterile syringes are by no means the only product category of Bünder Glas and in volume terms, not the largest. The Gerresheimer Business Unit, which concentrates primarily on glass-based Pharma systems, still sells the bulk of its syringes unsterilized. Each year, it delivers more than 200 million of these to the pharmaceutical industry, with very gratifying growth rates. In addition, there are system components for the injection, particularly matched cartridges. The glass range is complemented by plastic syringes characterized by extremely high barrier characteristics.

THE READY-TO-FILL CONCEPT IS SET FOR GROWTH

Even years after its launch, Ready-to-Fill is still proving to be a formidable growth generator with steadily increasing acceleration. For us, it is beyond question that the relationship between sterile and non-sterile syringe deliveries will be reversed in a relatively short time. The advantages of sterile syringes and particularly of a sophisticated partnership strategy are simply overwhelming. The complete systems do indeed represent more than just an advanced product group: they have pioneered the way for focus to be placed on the innovation potential of suppliers more strongly than ever before. Collaboration between the pharmaceutical industry and system manufacturers, from drug development right through to delivery, has now reached a new level.

THE READY-TO-FILL CONCEPT: HOW IT WORKS

First, in the filling process, Ready-to-Fill allows for considerable slimming of operations. From washing of unsterilized syringes through to their siliconization, assembly, and final sterilization, there is a long and technically time-consuming

FIGURE 1

Gerresheimer Group's Wide Range of High-Quality Pharmaceutical Packaging

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process chain which, in terms of drug production, is a foreign body: indispensable and by nature characterized by the highest possible quality requirements, yet not necessarily inextricable from the drug manufacturing process. Syringes are after all supplied from the outside. On delivery, sterile syringes have the entire procedure behind them. Established pharmaceutical manufacturers are increasingly making the change, and new entrants are able to plan on leaner production right from the start.

On the supplier side, the need on the pharma industry side for Ready-to-Fill syringes has created a more lasting change in the market. Around the world, only a very few system manufacturers are so far able to prepare syringes fully and in accordance with all the pharmaceutical regulations, and one of them is Bünder Glas. The pace of development is that this area is now moving at a speed and technical level hard to keep up with. There can be no doubt about how important it was to recognize at an early stage the opportunities offered by this concept, to believe in it, and consistently press ahead with its realization.

UNIQUE TECHNOLOGY CENTER

At a substantial investment cost, the parent company built a development and production center for its highly innovative systems subsidiary several years ago. From the start, this was designed for expansion. Technologically, it still enjoys a worldwide reputation as an exemplary facility. Prestigious special manufacturers were commissioned by Gerresheimer to design the delicate equipment for this development, contributing a wealth of their own ideas. With state-of-the-art ultra-pure water preparation and clean-room systems in class C, it is fundamentally compliant with pharmaceutical standards and precisely matched to the needs of pharmaceutical and biotech customers. The facility employs an experienced team with a penchant for tailor-made technologies.

ADVANCED SURFACE TREATMENT TECHNOLOGY

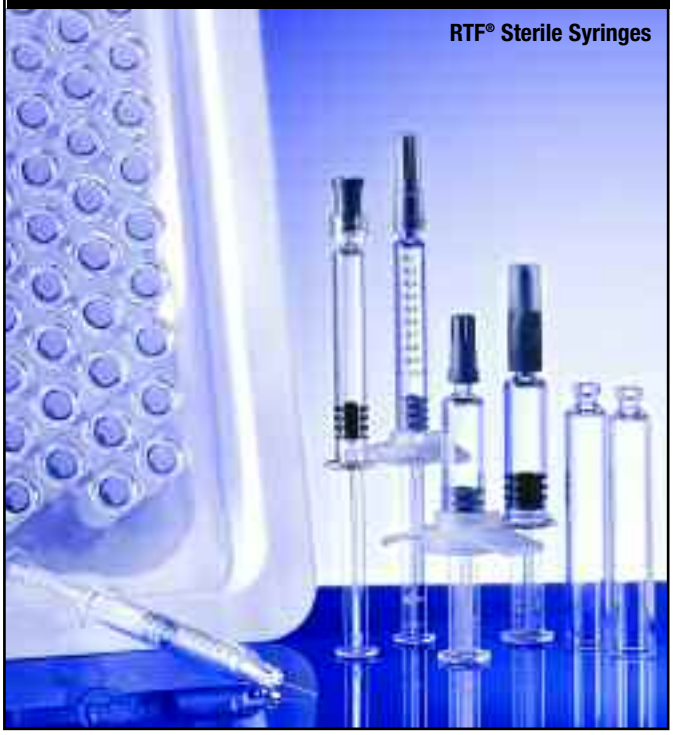
Clearly, such technologies reliably keep the products of this high-tech center at a very advanced level. A widely varied range of options for individual design and, for example, color-coding warrant mention in passing, but the critical strengths of the company lie in fine attunement of the syringe to the medication. To achieve this, Bünder Glas has at its disposal not only processes, such as spray siliconization as largely preferred in the pharma industry, but also baked-on siliconization, by means of which a particularly stable yet highly slide-conducive coating can be applied inside the syringe. This alternative is increasingly in demand, especially for the large group of sensitive biopharmaceutical injection preparations. A completely different process also tailored to very sensitive ingredients permits additional advance neutralization of the glass with ammonium sulphate. This allows for increased hydrolytic resistance of even Type 1 borosilicate tubular glass (known as neutral glass), which is generally used for syringes.

WIDE RANGE OF INNOVATIVE SYRINGE ACCESSORIES

As a complete supplier, the company also offers accessories. In this area as well, the development successes are impressive. Just a few months ago, the Gerresheimer Unit launched four newly developed and in part unique complementary components that immediately proved to be significant in the widely diversified product range. So it appears that the syringe family has managed to make RTF® even more attractive for doctors and patients in particular through the tangible improvement in comfort and safety.

With regard to delivery comfort, the dimensions and design of the needle play a key role. Together with Japanese partners, Bünder Glas has developed precision needles that slide almost painlessly through the skin, due in particular to exceptionally fine walls and long-ground points, but also to a specially developed process that permanently anchors the silicone coat to the metal. No less important is protection against deformation before use. With the Rigid Needle Shield (RNS), a dual-component casting combining soft elastomer on the inside and hard elastomer as an exterior shell, the syringe experts have achieved effective protection of the needle from the users and protection of the users from the needle, thus alleviating the widespread problem of injuries through new or (with often more serious effects) used needles.

FIGURE 2



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PharmaMedDevice has partnered with FDC *Reports' The Gray Sheet, The Silver Sheet,* and *The Pink Sheet* and BEACON, the producers of MEDi2005, to co-produce a conference program that will address the needs of the emerging combination products market, biomedical engineering community, and the exciting innovations taking place in drug delivery technology and healthcare. The conference program will provide life science companies with a roadmap for speeding new combination products to market and extend product lifecycles.

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FIGURE 3

RTF® Tub

Another system accessory, the Backstop, is also targeted precisely at difficulties frequently experienced in the medical practice and by self-injecting patients. This gives a better grip when applying pressure on the plunger, a particular benefit for patients with limited dexterity. It also prevents slip-ups while dissolving dried medications because the plunger is prevented from slipping out of the syringe as water is drawn in. With the Tamper Evident Luerlock Closure (TELC), Bünder Glas developers succeeded in integrating several functions in a single multi-component plastic element: the tamper-evident closure, the syringe closure, and the needle adapter. So any pharma manufacturer can use the system accessory immediately without the need for separate registrations. Bünder Glas ensures that familiar materials are used, but if clients prefer, it can insert precisely the same pharmaceutical rubber as the one they otherwise use.

INTERDISCIPLINARY EXCHANGES AT MAJOR VENUES

As a new product, the innovative sterile syringe is of interest to pharmaceutical and medical practitioners alike and is now a subject of increasing focus in forums of specific professional discussion. When the European branch of the Parenteral Drug Association (PDA) extended an invitation to such an event in Hanover 2 years ago and then late last year to Munich, Germany, Bünder Glas was among the initiators. The title of these international events was The Universe of Pre-Filled Syringes. The next series is coming up in Maryland this October in the Hyatt Regency Hotel Bethesda and bears the extended title of The Universe of Pre-Filled Syringes & Injection Devices. Bünder Glas will again have a key role in organizing this PDA symposium. Registration is possible on www.pda.org.

The Group sees its lecture work as a service and part of the constructive professional communication process. It is a key element of its philosophy that focuses generally on partnership-based thinking and know-how transfer – in the interest of openness in the profession as a whole, but particularly in direct customer relations.

FIGURE 5

RTF® Syringe Accessories: Nested Stoppers

FIGURE 6

RTF® Syringe Accessories: Bagged Stoppers

FIGURE 4

RTF® Processing Takes Place Under Clean-Room Conditions

THE PARTNERSHIP STRATEGY

Relationships are becoming closer and closer. In addition to pure supply commissions, customer-specific development work takes place, often including an extensive system partnership. In many cases, this starts in the early stages of drug development – for example with consideration of the basic delivery form of the relevant medication. All

FIGURE 7

the involved disciplines come together to examine the possibilities and limits for individual approaches and focus on the ideal solution from a wide range of viewpoints. This is without doubt the fastest way to achieve optimum drug delivery, in which the packaging becomes a really integrated component of the medication, and the system thus creates a synergy benefit.

Pharmaceutical companies in the US are also increasingly taking up the opportunity to integrate the specific competence of Gerresheimer systems specialists in their business concepts. In the local markets, Bünder Glas works with global Blue-Chip corporations as well as striving start-up companies. Many of them operate in the biotechnology and biopharmacy field in particular and demonstrate acknowledged innovative strengths.

As everywhere in the world, the major manufactures as well as SMEs profit in such cooperation agreements through the concentrated expertise in the field of pharma glass and associated materials, molds, and special processes – and on the other hand, through the package of services carefully designed by Bünder Glas to accompany each customer over the entire route of a project.

COMPREHENSIVE SERVICE STANDARDS

These services complement a product range that is FDA-licensed across the board and offers as a self-set minimum standard full compliance with the US, European, and Japanese pharmacopoeia requirements. In conformity with this, the Gerresheimer Unit offers its customers comprehensive technical documentation, life cycle management, and last but not least, systematic assistance with registration. There is no question that these are also in accordance with international standards and specially aligned to US requirements, with the company maintaining its own drug master files. From this area, the service for customers extends right through to comprehensive advice on process technology and logistics optimization.

BÜNDER GLAS IN THE US

In Doylestown, Pennsylvania, a small, highly professional team ensures that this concept is quickly and smoothly implemented, especially for American partners. Bünder Glas officially installed its own US representation just a few months ago and then quickly reinforced it in order to ensure greater local flexibility in terms of direct customer contact and technical service. Our systems business in the US is just taking off right now. To date, RTF® systems for the US account for 20% of the company's sterile syringe production. And confidence in the potential to make further inroads in the land of unlimited opportunities is certainly not in short supply in Bünder Glas. ◆

BIOGRAPHY

H. Burkhard Lingenberg, (for the whole Gerresheimer Group) directs both international marketing and corporate communications. He has spent decades personally involved in shaping the Group's marketing, sales, and image as a product manager, sales director, and contact person. He has considerable industry commitments outside the Gerresheimer Group, is active in the European Glass Association and the Federal German Glass Association (in the latter as Chairman of Communication), and acts as Chairman of the Advisory Board for the German Packaging Prize, which is awarded internationally. His particular interest is the field of drug delivery. The author can be reached via e-mail at b.lingenberg@gerresheimer.com or on the Group's website www.gerresheimer.com. The representation of Bünder Glas North America, which is headed by Chris King, can be reached by e-mail at cking@kimkon.com.

SUSTAINED RELEASE

The Properties of Chitosan as a Retardant Binder in Matrix Tablets for Sustained Drug Release

By: Dave A. Miller, Mamoru Fukuda, MPharm; and James W. McGinity, PhD

INTRODUCTION

Chitosan is a linear aminopolysaccharide obtained from the alkaline deacetylation of chitin. Chitin is the structural component in exoskeletons of crustaceans and is the second most abundant polymer found in nature.[1] Chitosan is both biocompatible and biodegradable, making it an attractive material for use in biomedical and drug delivery applications.

The name chitosan encompasses a series of polymers of varying molecular weights and degrees of deacetylation. The molecular weight of chitosan and the degree of deacetylation ranges from 50 to 2000 kDa and 40% to 98%, respectively.[2] The physiochemical properties of chitosan are strongly dependent on molecular weight and degree of deacetylation. Molecular weight determines the viscosity of chitosan solutions with higher molecular weights producing greater viscosity. In drug delivery applications, the molecular weight has been shown to significantly affect the release of drugs from a chitosan matrix. Lower molecular weight chitosans have been shown to promote wetting and dissolution of poorly water-soluble drugs, while higher molecular weight chitosans have been shown to retard the release of water-soluble drugs.[3,4]

The degree of deacetylation of chitosan dictates its aqueous solubility. Chitosans with a low degree of deacetylation (≤ 40%) are soluble in water up to a pH of 9, whereas highly deacetylated chitosans (≥85%) are only soluble up to a pH of 6.5.[5] This pH-dependant solubility leads to pH-dependant hydrogelation of chitosan matrices. In an acidic environment, the amine groups on chitosan molecules become protonated and consequently the molecules become densely positively charged. The high concentration of like-charges causes molecular repulsion and thereby swelling of a chitosan matrix. With an increase in pH, the swelling phenomenon is reversed as amine groups on the molecule become deprotonated and the repulsive forces are reduced. The addition of salts to solution also affects the solubility of chitosan. In general, the higher the ionic strength of solution, the lower the solubility of chitosan as charges on the polymer are neutralized by increasing the concentration of the counterion.[5] Consequently, the swelling properties of chitosan are also highly dependant on the ionic strength of the solution.

The swellability of chitosan is a property that makes the polymer very attractive for use as a retardant in matrix tablet formulations. In general, the mechanism of action for a matrix-forming binder in a tablet formulation begins with the hydration and swelling of the outer layer of the matrix to form a pseudo-gel layer.[6] Over time, the outer edges of the swollen gel layer erode and simultaneously the polymer layers beneath the gel begin to swell as the medium further permeates into the matrix. The dissolution of water-soluble drugs is controlled by both diffusion through and erosion of the pseudo-gel layer. Because chitosan is a swellable polymer with properties that can be tailored by varying the degree of deacetylation and molecular weight, it has been extensively investigated for use as a retardant polymer in matrix tablet formulations.

EARLY USES OF CHITOSAN IN MATRIX TABLETS

Some of the earliest work investigating the use of chitosan for sustained drug release from matrix tablets was done by Miyazaki et al and Sawayanagi et al.[7,8] In these studies, both researchers demonstrated that chitosan produced sustained drug release in acidic conditions; however, disintegration of the tablets occurred in water and occurred rapidly in simulated intestinal fluid of pH 6.8. In a study by Nigalaye et al, it was seen that when chitosan was used in a concentration of more than 50% of the total tablet weight, an insoluble non-erosion type matrix was formed in water.[9] Tablets containing 33% chitosan were fast-releasing, and at a level of 10%, chitosan functioned as a disintegrant. These researchers were able to reduce the quantity of chitosan required for sustained release to 10% by using citric acid and carbomer-934 P as acidifying agents to enhance the gelling properties of chitosan and reduce the disintegration of tablets in neutral pH.

Building on the findings of Nigalaye et al, Adusumilli and Bolton produced chitosan citrate complexes that formed viscous gels upon emersion in water.[10] The complexes were directly compressible and effective in retarding the diffusion of theophylline from matrix tablets in water by the formation of a viscous hydrogel. Akbuga also utilized the strategy of a chemically modifying chitosan to improve the sustained-release performance from matrix tablets by using the chitosonium salt of malic acid, chitosonium malate.[11] It was demonstrated that chitosonium malate exhibits far superior sustained-release properties to chitosan in pH 7.4 buffer as the altered form of chitosan was able to form a hydrogel at pH 7.4, whereas chitosan was not. Hence, the chitosonium malate tablets allowed for sustained drug release whereas chitosan tablets simply disintegrated.

An investigation into the effect of excipients on drug release from chitosan matrix tablets was conducted by Kristmundsdottir et al.[12] In this

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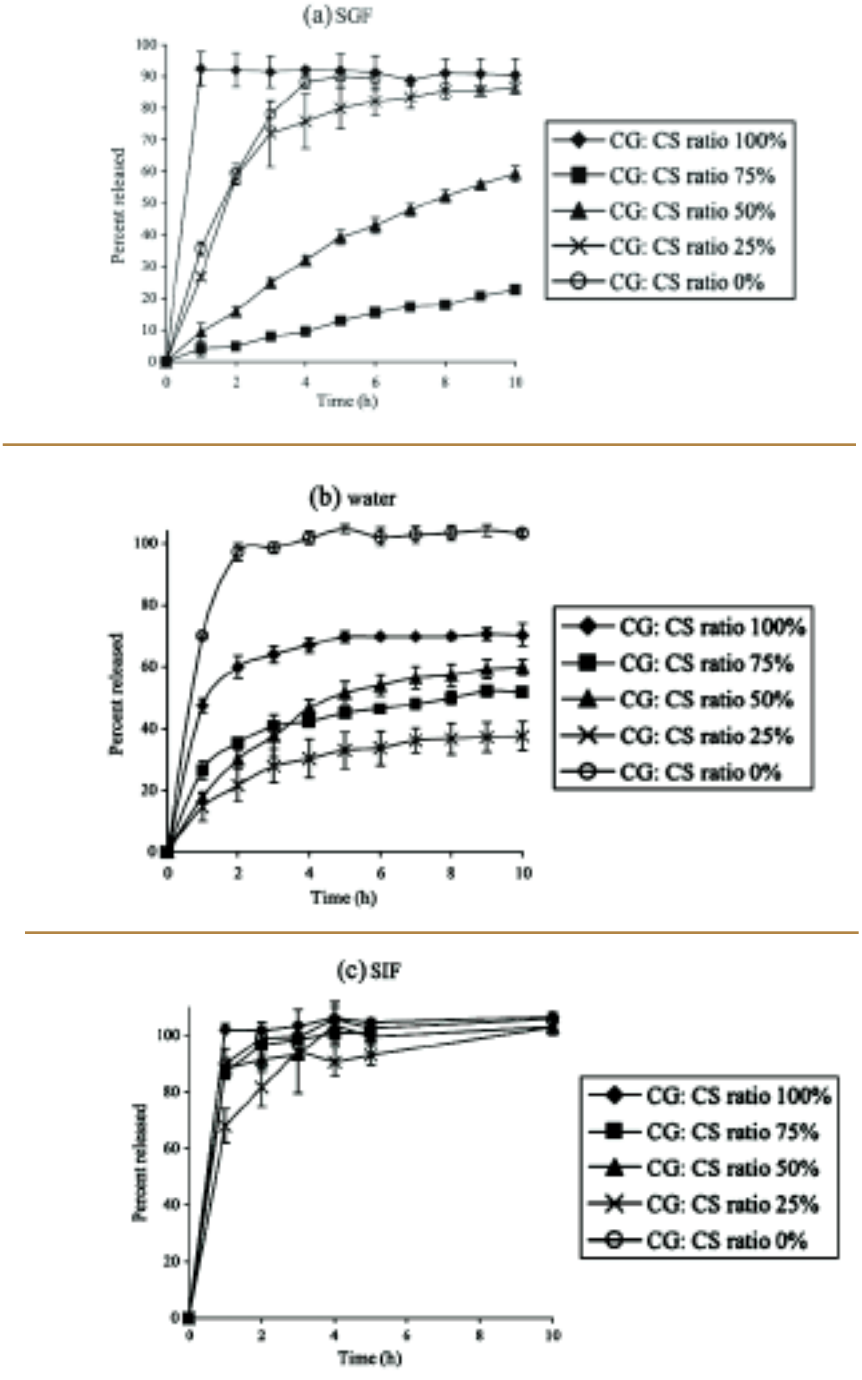
study, the authors note that tablets containing chitosan alone exhibited swelling on the surface in simulated gastric fluid, yet swelling was reduced when the tablets were transferred to simulated intestinal fluid. Consequently, the dissolution rate of diltiazem was decreased, indicating that dissolution was controlled via diffusion through the hydrated matrix. It was also observed that interactions between chitosan and various excipients can be utilized to further prolong drug release from chitosan-based matrix tablets.

COMPLEXATION OF CHITOSAN WITH ANIONIC POLYMERS PROLONGED SUSTAINED RELEASE

The work of Tapia et al in their examination of the influence of media pH, degree of polymerization, and degree of matrix swelling on the mechanism of diltiazem hydrochloride release from matrices based on mixtures of chitosan and alginate is a study that represents the next phase in the utilization of chitosan as a retardant polymer in matrix tablets in which anionic polymers were utilized to form complexes with chitosan to further prolong drug release.[4] In this study, the authors observed rapid drug release at pH 1.17 to 2.21, which was dependant on the degree of polymerization and quantity of chitosan in the formulation and related directly to the degree of matrix swelling. At pH 5.52 to 8.72, drug release was slow and controlled by the interpolymeric complex formed by the ionic interaction between chitosan and alginate. Similarly, Hasan et al combined chitosan and sodium alginate to produce a sustained-release matrix tablet for metoclopramide hydrochloride.[13] The authors were able to achieve first-order, diffusion-controlled drug release following a transition from acidic to neutral pH. In 2005, Tapia et al again examined the release mechanism of diltiazem hydrochloride from matrices based on chitosan in combination with anionic polymers in their study of chitosan-alginate and chitosan-carrageenan matrix tablets.[14] It was determined that the

FIGURE 1A, 1B & 1C



Dissolution profiles of diltiazem hydrochloride in various media from tablets containing carrageenan (CG) and/or chitosan (CS) in various ratios. (a) SGF (b) Water (c) SIF. Each plotted value is the mean of n=3 and SD is shown as error bar. [Reprinted from reference 15 with permission]

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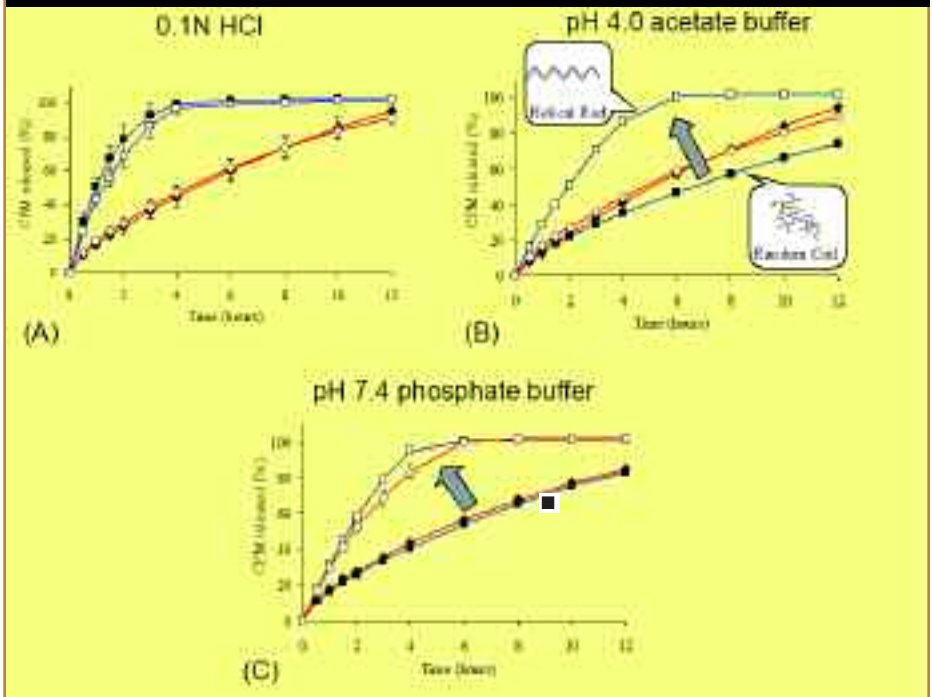
FIGURE 2



Influence of the ionic strength on chlorpheniramine maleate release from HME tablets prepared by formulations 2 and 3 in: (A) 0.1 N HCl, (B) pH 4.0 acetate buffer, and (C) pH 7.4 phosphate buffer (■) formulation 2, (□) formulation 2 in media containing 0.4M NaCl, (♦) formulation 3, (◇) formulation 3 in media containing 0.4 M NaCl at 37 ± 0.5 °C (USP 27 Apparatus 2, 900 ml, 100 rpm). Each point represents the mean ± S.D., *n*=3. [Reprinted from reference 17 with permission]

drug release from the chitosan-alginate matrix is controlled by a combined mechanism of diffusion and relaxation in which the medium permeation into the hydrogel did not damage the microstructure of the matrix due to its high elastic modulus. On the other hand, the chitosan-carrageenan matrix exhibited rapid erosion and tablet disintegration which occurred due to rapid medium uptake that fractured the microstructure of the matrix. It was therefore concluded that chitosan-alginate matrix tablets performed better with respect to sustaining drug release as a result of the robustness of the matrix.

Bani-Jaber and Al-Ghazawi also investigated chitosan-carrageenan matrix tablets in their study into the effect of polymer weight ratio, dissolution medium, and drug type on drug-release properties.[15] As can be seen in Figure 1, some ratios of chitosan and carrageenan showed excellent sustained release of diltiazem hydrochloride in comparison to single polymer matrices in simulated gastric fluid (SGF) and water; however, no sustained-release affect was seen from any combinations in simulated intestinal fluid (SIF). Thus, the authors concluded that interactions between the polymers depend entirely on the ionization of chitosan which is naturally achieved in simulated gastric fluid and was achieved in water due to the decrease in the microenvironmental pH by the acidic salt of diltiazem hydrochloride. However, ionization of neither chitosan nor diltiazem hydrochloride was possible in simulated intestinal fluid, and therefore, no sustained-release effect was observed. With diclofenac sodium, it was shown that no sustained drug release was achieved due to the basic nature of the drug salt, which did not act to ionize chitosan in water as had the acidic salt of diltiazem hydrochloride. A similar lack of polymer interaction was also seen with diclofenac sodium in simulated intestinal fluid.

Alsarra et al utilized sodium sulfate to crosslink chitosan by wet granulation in an acidic environment to achieve sustained-release tablets.[16] Ratios of 1:0.5 and 1:1 chitosan to sodium sulfate were seen to provide slow release of theophylline, while ratios of 1:2 and 1:3 showed fast drug release as a result of pore formation resulting from excess sodium sulfate. Drug release was shown to be dependant on molecular weight and quantity of chitosan in the tablet formulation. A comparison of the dissolution performance of the optimum formulation in water to its performance in SGF followed by SIF showed no change in dissolution rate, thus demonstrating pH-independent sustained drug release from matrix tablets of crosslinked chitosan.

COMBINING CHITOSAN-POLYANION MATRICES WITH HOT-MELT EXTRUSION FOR IMPROVED SUSTAINED RELEASE FROM MATRIX TABLETS

Recently, Fukuda et al examined the use of a combination of chitosan and xanthan gum in matrix tablets prepared by direct compression (DC) and hot-melt extrusion (HME).[17] Specifically, the authors examined the effect of pH, buffer species, and ionic strength on the release mechanism of chlorpheniramine maleate. Directly compressed tablets containing chitosan and xanthan gum exhibited pH and buffer species-dependent release with the most rapid drug release occurring in 0.1 N HCl. This indicated that the hydrogel formed by chitosan in acidic media did not adequately retard drug release from the DC tablet. Drug release from HME tablets containing only chitosan also showed pH and buffer species-dependant drug release with the release rates being slowest in 0.1 N HCl and 0.1 M acetate buffer. Thus, it was determined that a retardant hydrogel layer was formed by the intra-molecular hydrogelation of chitosan in these media, but was not formed in 0.1 M citrate and

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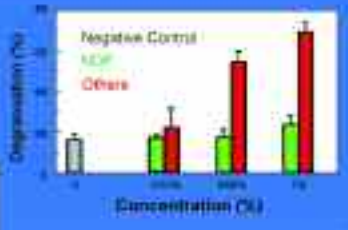

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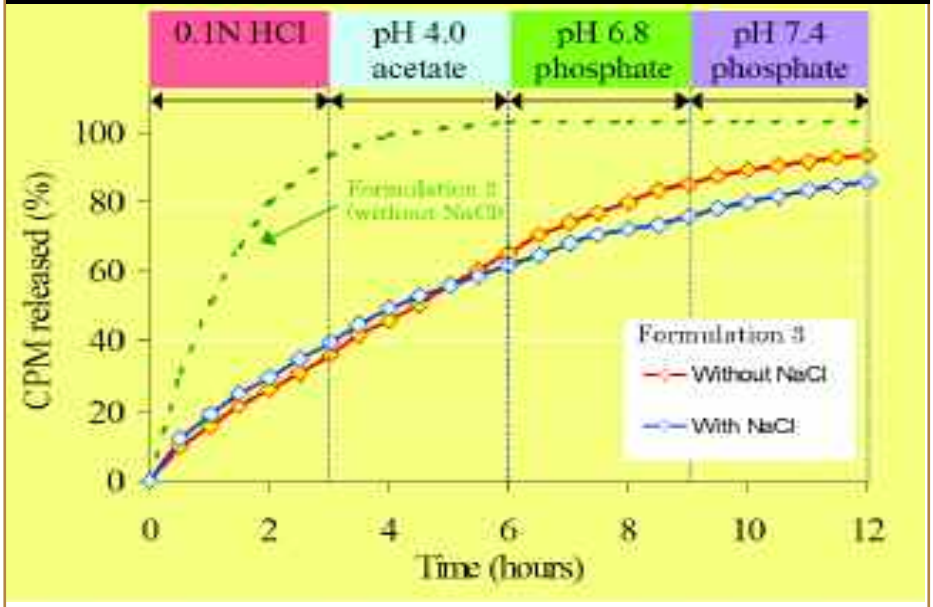
FIGURE 3



Media replacement study of HME tablets prepared from formulations 2 and 3.

phosphate buffers or in pH 6.8 and pH 7.4 buffers. The difference in drug release in the pH 4.0 buffers was explained by the difference in the solubility of chitosan in dilute acids. Because chitosan is more soluble in acetate buffer than in citrate and phosphate buffers, hydrogelation occurred more readily and thus drug release was retarded to a greater extent. Drug release from HME tablets containing only xanthan gum were also seen to be pH and buffer species dependent. Drug release from these tablets was rapid in acid owing to the lack of hydrogel formation because xanthan gum remains un-ionized in acidic media. At pH 4.0, drug release was buffer species dependant as xanthan gum existed in a more ionized state in acetate buffer than in citrate and phosphate buffers, and hence drug release was slower in acetate buffer. In pH 6.8 and 7.4 buffers, drug release was sustained as the gelation of xanthan gum occurs readily at neutral pH.

Interestingly, HME matrix tablets containing both chitosan and xanthan gum showed pH and buffer species-independent release, whereas the same directly compressed formulation exhibited pH and buffer species-dependant drug release. The most notable difference between the HME and DC tablets was the reduction in drug release in acid with the HME tablets versus the DC tablets. The authors determined that this reduction is due to retardation of the rate of medium uptake resulting from the difference in the state of polyethylene oxide (PEO) in the tablets. With the DC formulation, PEO exists as a dispersed powder with polymer chains in the coiled state, whereas with the HME formulation PEO exists as a polymeric matrix that served as a barrier for medium uptake and therefore reduced the gelation rate of chitosan in acid.

In addition to examining the effect of media pH and buffer species, the authors also examined the effect of ionic strength on drug release in 0.1N HCl, pH 4.0 acetate buffer, and pH 7.4 phosphate buffer. The results of this investigation are shown in Figure 2. It can be seen from this figure that CPM release rates from the HME tablets containing only xanthan gum (formulation 2) in pH 4.0 acetate buffer and pH 7.4 phosphate buffer containing 0.4 M NaCl were significantly faster than without 0.4 M NaCl. This was explained as being due to the change in polymer configuration from a random coil to a helical rod with increasing electrolyte concentration. The helical rod polymer configuration reduces the extent of intra-molecular hydrogelation of xanthan gum, and thus increases drug release. Alternatively, the HME matrix tablet formulation containing both chitosan and xanthan gum (formulation 3) was not affected by a change in ionic strength in 0.1N HCl and pH 4.0 acetate buffer, indicating that the retardation mechanism in acidic media from these tablets was not affected by a configuration change of xanthan gum. However, it was seen that at pH 7.4 drug release was much faster with 0.4 M NaCl due to the lack ionization of chitosan at that pH and the lack of ionization of xanthan gum due to the electrolyte concentration, which prevented both intra- and inter-molecular hydrogelation of chitosan and xanthan gum.

Drug release from HME tablets containing both chitosan and xanthan gum was also evaluated using a pH switch dissolution test with and without 0.4 M NaCl. The results of this study are shown in Figure 3. It is seen from this figure that the drug-release profile from HME tablets containing both chitosan and xanthan gum (formulation 3) was not affected by the ionic strength of the media. This was attributed to the hydrogel, which formed in 0.1 N HCl that served to retard drug release in all subsequent media. This sustained release was not seen with the HME tablets containing only xanthan gum (formulation 2) due to the prevention of intra-molecular hydrogelation of xanthan gum during the acid phase.

From crosslinking studies, it was determined that over the spectrum of pH changes, the sustained release of CPM from chitosan-xanthan gum matrix tablets was due to the synergistic effects of

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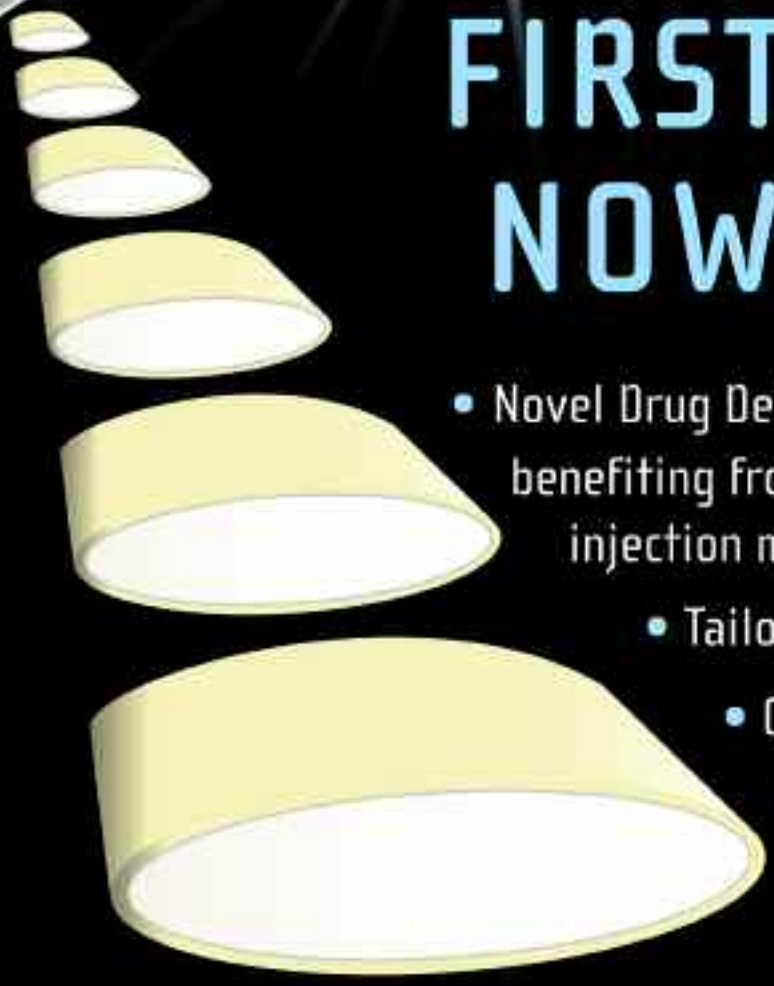

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chitosan and xanthan gum hydrogelation. The sustained release of CPM at low pH was primarily the result of intra-molecular hydrogelation of chitosan, although the inter-molecular hydrogelation between chitosan and xanthan gum also acted to somewhat reduce the rate of drug release. Retardation of drug release at pH 4.0 was due to both intra- and inter-molecular hydrogelation of chitosan and xanthan gum, and the extent of inter-molecular hydrogelation was dependent on the buffer species and ionic strength. Sustained drug release at pH 6.8 and 7.4 was solely due to intra-molecular hydrogelation of xanthan gum as chitosan is un-ionized and insoluble at these pH values.

In summary, from this study, it was seen that HME matrix tablets containing PEO, chitosan, and xanthan gum exhibited pH and buffer species-independent sustained release that was attributed to the synergistic effects of these polymers. In its melt-state orientation, PEO reduced the uptake of acidic medium and thus reduced the rate of chitosan hydrogelation and drug release. The combination of chitosan and xanthan gum provided a synergistic hydrogelation effect that provided sustained drug release over the entire spectrum of gastrointestinal pH. It was seen that ionic strength did not affect the hydrogelation of chitosan-xanthan gum HME tablets in acidic media. It was also seen that the hydrogelation that occurs in acid was maintained as the media pH and ionic strength was increased and hence sustained drug release was achieved over the spectrum of gastrointestinal pH levels independent of electrolyte concentration.

CONCLUSION

The biodegradability, biocompatibility, and unique physiochemical properties of chitosan make it an ideal material for biomedical and drug delivery applications. Of its potential applications in drug delivery, one of the most promising is its use as a basis for sustained-release dosage forms. The functionality of chitosan as a retardant binder in matrix tablets has been extensively investigated, and it has been shown to exhibit sustained-release capabilities in acid as well as in neutral pH when combined or complexed with other excipients. In particular, the combination of chitosan with anionic polymers has been shown to produce sustained-release drug profiles from matrix tablets over the range of gastrointestinal pH due to a synergistic gelation effect. Additionally, combining a chitosan-anionic polymer matrix with an advanced processing technique, such as hot-melt extrusion, has been shown to produce sustained-release dosage forms that exhibit drug-release profiles that are independent of pH, buffer species, and ionic strength of the dissolution media. With these recent advances, the potential of chitosan as the basis for sustained-release matrix tablets has been clearly demonstrated, and its future prospects for use in modified drug delivery systems are excellent.

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BIOGRAPHIES

Mr. Dave A. Miller is currently a PhD student at the University of Texas at Austin in the Department of Pharmaceutics. Mr. Miller joined the research groups of Dr. James W. McGinity and Dr. Robert O. Williams III in 2003 after earning his BS in Chemical Engineering. His current research focuses on the utilization of drug particle engineering and hot-melt extrusion for enhancing the dissolution properties of poorly water-soluble drugs.

Mr. Mamoru Fukuda is a Formulation Scientist at Kyorin Pharmaceutical Co., Ltd., in Tochigi, Japan. He earned his BPharm and MPharm from Nihon University, Chiba, Japan. From 2003 through 2005, he worked as a Research Scientist with Dr. James W. McGinity at the University of Texas at Austin. His research focused on the utilization of hot-melt extrusion for the production of novel drug delivery systems.

Dr. James W. McGinity is the holder of the Johnson & Johnson Centennial Chair in Pharmacy and is Professor and Division Head of Pharmaceutics in the College of Pharmacy, The University of Texas at Austin. He earned his BS in Pharmacy at the University of Queensland, Australia, in 1967 and his PhD in Pharmaceutics in 1972 from the University of Iowa. Prior to joining U.T. in 1976, he was a research scientist at the Squibb Institute for Medical Research in New Brunswick, New Jersey. Dr. McGinity's research interests and publications are in the areas of pharmaceutical technology and novel drug delivery systems. He has been issued 23 US patents. His present research interests center on solid dosage forms, aqueous film coating of pellets and tablets, powder technology, materials science, transdermal systems, and hot-melt extrusion. He has been the USA Editor for the European Journal of Pharmaceutics and Biopharmaceutics since 1995. Dr. McGinity has participated in several national and international scientific symposia and conferences. He has been a consultant to the FDA and to many pharmaceutical and chemical companies both in the USA and Europe. He is an AAPS Fellow and was the recipient of the 1999 Pharmaceutical Preparation and Particle Design (PPD) Award presented by the Society of Powder Technology Japan and more recently, the Takeru & Aya Higuchi Award (2004) and the AAPS 2005 Research Achievement Award in Pharmaceutical Technology. He is a past President of the Controlled Release Society and a charter member of Drug Delivery Technology' Editorial Advisory Board.


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PARTICLE ENGINEERING

Novel Particle Engineering Technology: A Review

By: Megha Barot, MPharm (student); Dharmesh M. Modi, MPharm; and Jolly R. Parikh, PhD

ABSTRACT

Micronization is an important procedure used in the pharmaceutical industry to reduce the particle size of active pharmaceutical ingredients (APIs). The spray-drying and milling techniques presently used to micronize drug substances cannot be used to process thermo-labile or physically unstable drug substances. Therefore, new micronization techniques, including cryogenic technology, particle precipitation technology, and crystallization by sonication technique are currently being perfected for future use in the pharmaceutical industry. This review highlights these potential solution-based particle formation technologies for drugs that cannot be processed by conventional micronization techniques.

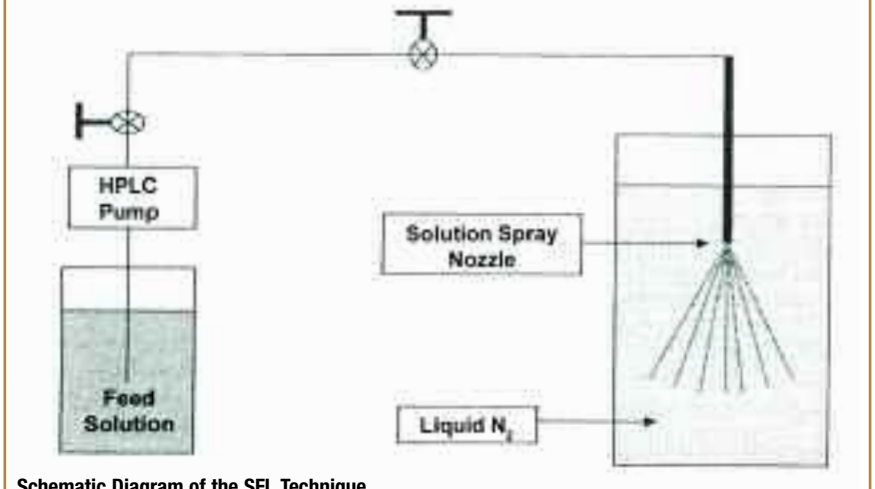
INTRODUCTION

Many potentially bioactive molecules have been rejected during the early stages of development because they are poorly water soluble and difficult to wet. Active pharmaceutical ingredients with poor aqueous solubility often demonstrate low bioavailability when administrated orally due to the dissolution rate-limiting absorption in the GI tract. Of particular interest is the poorly water-soluble, highly permeable APIs discussed in the Biopharmaceutical Classification System Class II (BCS class II).[1] Increasing the dissolution rate of poorly water-soluble APIs is a significant challenge to pharmaceutical scientists. Technologies that have been commonly used include mechanical milling, spray-drying, freeze-drying, and precipitation.[2]

Widely used mechanical techniques based on high shear or impaction, including microfluidization, high-pressure homogenization, and milling can be limited by low yields due to solid losses, high polydispersities in particle size, shear-induced particle denaturations, long processing times, high energy requirements, and the need for separating the product and processing agent.[3-5]

To overcome many of these limitations, particles may be formed from solution in semi-continuous spray processes, eg, spray-drying. It is a widely used technology. In these solution-based processes, it is often not possible to formulate a solvent that can dissolve both poorly soluble drug and hydrophilic stabilizer. Even if such a solution may be formed, the stabilizer may not coat the surface of the drug particle as it forms during solvent evaporation because the vapor surrounding the particle is highly hydrophobic.[6] However, because of use of elevated temperatures (on the order of 150°C), it is not always appropriate for use with thermo-labile compounds. Furthermore, the final product yield can be low, particularly in small-scale unit operations. In addition, it is difficult to form submicron particles in the aforementioned mechanical processes and spray-drying.[7] Although lyophilization or freeze drying is a promising technique for producing pharmaceutical powders, the freezing

FIGURE 1



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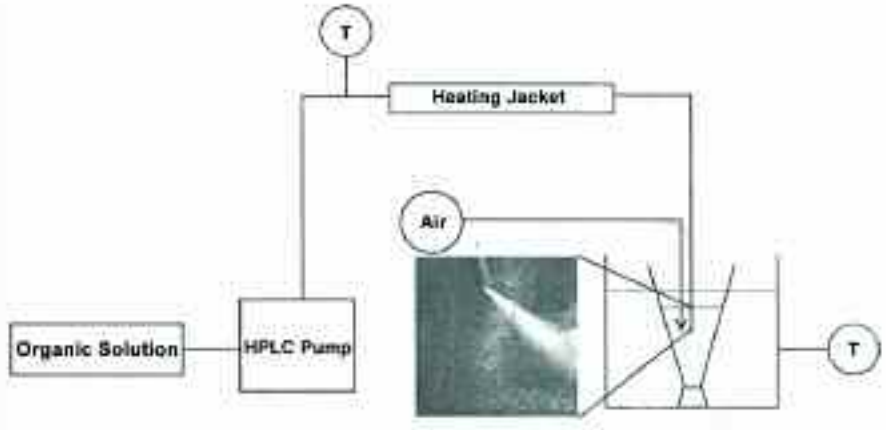
rate in some cases is too slow so that the solvent crystallizes as it is frozen.[8]

Relatively new solution-based phase-separation processes, such as rapid expansion from supercritical solution (RESS), and precipitation with a compressed fluid antisolvent (PCA), which is also referred to as the SAS or SEDS process, may be used to overcome many of the limitations of the aforementioned mechanical milling processes.[9,10] These two techniques involve the use of compressed liquid and supercritical CO_2 functioning as solvents or antislovents for phase separation of APIs and solvent by rapid expansion or change in solvent composition.[11] These processes often require less particle handling resulting in higher yields. These continuous or semi-continuous processes may be scaled up more readily than batch mechanical processes.[12]

In spray-drying, RESS, and PCA, the formation of a particle containing a poorly water-soluble drug and a water-soluble excipient is limited by the lack of solvent systems that will dissolve both hydrophilic and hydrophobic substances appreciably. The low solubility of water in CO_2 and similar compressed fluids limits its use as a solvent or cosolvent in RESS and PCA.[13,14] Because water is not very soluble in CO_2, ethanol has been used recently to aid water dissolution in the modified PCA process by mixing three streams of CO_2, water, and ethanol in a tri-axial-nozzle. The complicated nature of the resulting phase-separation and particle formation can make it challenging to control the particle morphology.[7] The high percentages of surfactants were often used to enhance solubility of API in the CO_2 and to stabilize the system as well. However, solid oral dosage forms often require high potency or a high API/surfactant ratio in order to achieve a therapeutic effect with tolerability to the API and minimal side effects from the excipients.

FIGURE 2



Schematic Diagram of the EPAS Technique

However, it is highly challenging in current particle engineering technologies to achieve high dissolution rates for poorly water-soluble APIs with high potency because only a small amount of stabilizing excipient(s) can be used in the process.[15] The objective of this article is to provide a comprehensive review of novel solution-based techniques that are promising in producing high-potency micronized powder with increasing dissolution character.

CRYOGENIC TECHNOLOGY

Spray-Freezing Into Liquid (SFL)

SFL is a novel cryogenic atomization technology in which either an aqueous or an aqueous-organic co-solvent solution containing an API and pharmaceutical excipient(s) is atomized directly into a compressed liquid, such as compressed fluid CO_2, helium, propane, and ethane or the cryogenic liquids nitrogen, argon, or hydrofluoroether.

SFL technology was created by the adaptation of several atomization processes. SFL is derived in part from the PCA process, which utilizes liquid-liquid impingement between an organic or organic/aqueous feed solution through a nozzle that is submerged into compressed CO_2 fluid. In PCA, the solvent must be miscible with compressed fluid CO_2 to produce drug particles from micro-droplets. With the novel SFL technology, the solvents are frozen during the spray and are not required to be miscible with the cryogenic liquid in contrast to PCA.[16]

In traditional spray-freezing into vapor over liquid (SFV/L), the feed solution is atomized through a nozzle positioned at a distance above the boiling refrigerant. The droplets may begin to solidify while passing through the vapor gap and then freeze completely as contact is made with the boiling refrigerant liquid.[17,18] Spray-freezing into halocarbon vapor over liquid has been performed by Briggs and Maxwell.[19] Halocarbon refrigerants present problems. Chlorofluorocarbon are deleterious to the ozone layer.[20] The relatively new ozone-friendly hydrofluoroalkane (HFA) refrigerants are expensive alternatives to the CFCs. However, both HFA 134 and HFA 227 are good solvents for a number of drugs, including steroids and danazol. Thus, if an HFA refrigerant were used as the cryogenic medium, the HFA could solubilize the API and consequently decrease the

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TABLE 1

Process	API Load	Protein Denaturation/Drug Degradation	Temperature Range (ºC)	Organic Solvent Required	Pressurized System	Compressed Fluid as Solvent/Antisolvent
PCA/SAS/SEDS	Low	Yes	45 to 80	Yes	Yes	No/Yes
RESS	Low	Yes	>100	No	Yes	Yes/No
Spray-freezing into halocarbon refrigerant vapor	Low	No	-20 to -25	No	Yes	No/Yes
Spray-freezing into halocarbon refrigerant liquid	Low	No	-20 to -25	No	Yes	No/No
Spray-freezing into liquid N_2	High	No	-196	Yes (if antisolvent extraction is utilized)	No	No/No

Comparison of the Micronization Techniques Using Either Compressed Fluids or Cryogenic Liquids

potency of the powder formulation.[21]

To alleviate drug loss due to solvent extraction by halocarbon refrigerants, an inert cryogen with poor solvent capacity must be used.[12] Gombotz et al developed spray-freezing in to nitrogen vapor over liquid technologies for the purpose of capturing frozen API particles following atomization.[22,23] As the atomized droplets pass through the vapor gap above the liquid nitrogen, they may collide and coalesce. The particle morphology is not quenched until the droplets are fully solidified on contact with the liquid nitrogen phase below the vapor. Each of these factors may broaden the particle size distribution.

In the novel SFL technology, the solution is sprayed below the surface of the cryogenic liquid phase to avoid particle growth in the vapor gap described previously for the conventional SFV/L process. The liquid-liquid impingement that occurs as the feed solution impacts the cryogenic media results in intense atomization into fine micro-droplets that freeze instantaneously. The SFL particle engineering technology has been used to produce micronized powders, which contain an amorphous API molecularly dispersed within an excipients matrix, for the purpose of enhancing the aqueous dissolution of insoluble or poorly water-soluble compounds.[24]

A schematic representation of the SFL apparatus is shown in Figure 1. A pressurized syringe pump is used to propel the feed solution from the solution vessel through an insulated nozzle that is submerged beneath the surface of the cryogenic liquid. Nitrogen is the cryogen of choice because it is inexpensive, environmentally friendly, inert, and may be used at atmospheric pressure, unlike CO_2. Because of the ultra-rapid freezing rates achieved by atomizing the feed solution directly into liquid nitrogen, a cryogenic suspension containing the dispersed frozen microparticles is produced. The SFL micronized powder can then be separated from the liquid N_2 by using a fine sieve to collect the powder. The frozen powder is then dried.[16] To obtain dry micronized SFL powders, the frozen solvent(s) must be sublimed. Generally, vacuum freeze-drying (eg, Tray lyophilization) was used to remove the solvents while maintaining the structure of the microparticles. Because of difficulty with vacuum requirements, vacuum freeze-drying is not a preferred processing technique in the pharmaceutical industry. Therefore, a technique has been devised that is capable of freeze-drying at or above atmospheric pressure. This technique, atmospheric freeze-drying (ATMFD), uses cryogenic air to fluidize the powder, facilitating mass transfer rates in solvent sublimation.[25]

The SFL process offers a variety of advantages relative to the aforementioned traditional technologies. Because of intense atomization, the formation of high surface area droplets, low intrinsic temperature of liquid N_2, and ultra-rapid freezing rates, the time for phase separation of solutes within the feed solution are minimized. Therefore, the API molecules may be dispensed homogeneously throughout the solidified excipient matrix of the frozen microparticle. After lyophilization, the dried microparticle retains the shape of the micro-droplet, but is highly porous due to

the channels created as the solvent(s) are removed. The API is molecularly dispersed within a homogeneous microparticle.[16]

PRECIPITATION TECHNOLOGY

Evaporative Precipitation Into Aqueous Solution (EPAS)

EPAS is a novel solution-based spray process reported to produce amorphous micron and sub-micron size particles of a poorly water-soluble drug coated with a hydrophilic stabilizer to enhance dissolution rates. This novel particle engineering technology utilizes rapid phase separation to nucleate and grow nano- and microparticles of water-insoluble drug substances.

During EPAS, the API is first dissolved in a low boiling liquid organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution, as shown in Figure 2.[12] Intense atomization leads to rapid evaporation of the small organic droplets in the aqueous solution. The rapid evaporation produces large supersatuation of the drug.

The resulting rapid nucleation of the drug has the potential to produce amorphous instead of crystalline particles.[7] Because the amorphous form of a pharmaceutical solid has a higher chemical potential than the thermodynamically stable crystalline form, it can exhibit an enhanced dissolution rate and bioavailability. A key challenge is to stabilize the amorphous solid to prevent crystallization during storage.[26] The glass transition temperature (Tg) of an amorphous pharmaceutical solid can have a significant influence on its physicochemical stability.[27]

The particles may be stabilized by a variety of stabilizers, generally nonionic and ionic stabilizers consisting of homopolymers, block copolymers, and low molecular weight surfactants, which is present in either or both the organic and aqueous phases. The stabilizers adsorb onto the newly formed drug particle surfaces, consequently decreasing the surface energy and providing steric and/or electrostatic repulsion between particles. This process may be dictated by the thermodynamic and kinetic aspects of stabilizer adsorption. The stabilizer must adsorb on the newly created surface and attain a conformation that is conducive to stearic stabilization.[28] The stable aqueous drug suspension is dried by a variety of techniques, including ultra-rapid freezing in conjunction with lyophilization, or spray drying.[12]

The EPAS process offers a variety of advantages relative to RESS and PCA. Because the particle formation stage is distinct from the stage in which the aqueous solution is dried, EPAS has the potential to provide greater control over particle size and morphology.[7]

NOVEL SONICATION TECHNOLOGY

Solution Atomization & Crystallization by Sonication (SAXS)

This is a single-stage processing technique that uses ultrasonic waves to produce increased sphericity in crystalline particles within a well-defined particle size range. The SAXS process consists of three interdependent processes:

1. The production of aerosol droplets of the solute from a carrier solvent using a suitable aerosol generator to produce highly supersaturated spherical constructs of the API within a well-defined particle size for controlled crystallization. Although not limited to any particular atomization system, but use of an electrohydrodynamic (EHD) atomization system and a conventional air pressure atomizer is reported in literature.

TABLE 2

Drug	Technology Used	Purpose/Result	Reference
Danazol	SFL	Size reduction, improved dissolution	8,30,31
Carbamazepine	SFL	Improved dissolution	9,11,32
Insulin	SFL	Improved dissolution	17
Cyclosporine A	EPAS	Size reduction	3
Carbamazepine	EPAS	Increased drug dissolution	5
Itraconazole	EPAS	Increased drug dissolution	12,16
Danazol	EPAS	Increased drug dissolution	33
Paracetamol	SAXS	Crystalline particles in well defined size range	13

Summary of Research Work on Newer Drug Delivery Technologies for Insoluble Drugs

2. The collection of the highly supersaturated droplets in a crystallization vessel containing a nonsolvent of the drug. A common nonsolvent used was Cyclohexane (surface tension 24.98 mu/m).

3. The application of ultrasonic waves to a crystallization vessel to control and induce homogeneous nucleation and crystal growth. The ultrasonic frequency is continually swept at a frequency of between 35 KHz and 45 KHz.

By combining these processes and controlling relevant parameters, high-purity micron-size, sphere-like crystalline particles could be readily produced in a single-step (solution to particle) operation.

The major advantage of this low-cost technique relates to the use of any suitable aerosol generator, and the whole process can be carried out under atmospheric pressure and ambient conditions. Furthermore, it has the potential for even greater control of the surface characteristics and surface geometry of active compounds while maintaining high-through output and industrial scalability.[29]

CONCLUSION

Three novel solution-based particle technologies that can generate dry powders composed of either API alone or API in combination with pharmaceutical excipients were discussed. These constructive-based techniques, ie, EPAS and SFL, have provided a means of forming particulates with novel physico-chemical properties, such as low-density porous spherical particles having wetting and rapid dissolution properties, with low surface free energy and well-defined morphologic structures. The development of the novel particle engineering SAXS process may provide a key advance in controlling such characteristics through modifying the degree of sphericity and surface topography of the crystalline particles. In conclusion, developing drug delivery technologies for insoluble drugs is a promising area for continued research with the aim of improving their bioavailability and therapeutic effectiveness.

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METERED DOSE INHALER TECHNOLOGY

Improvement & Optimization of HFA Valve Technology

By: Guillaume Brouet, MSc, and Christophe Jacuk, MS (Engineering)

INTRODUCTION

Metered dose inhalers (MDIs) were introduced 50 years ago and remain today the primary delivery technology used to deliver drugs into the lungs. The need to phase out CFCs led to the initial introduction of HFA products over 10 years ago, and these products are now widely used in Western Europe as well as in the US. Reformulated MDIs with HFA propellant have improved overall efficiency; however, the behavior of HFA-based formulations and increased regulatory requirements has introduced a number of new constraints upon metering valve technology. The development of metering valves that meet all necessary functional and regulatory requirements requires careful selection and evaluation of valve concepts and materials of construction. This situation has led to the use of new design tools and the development of new generations of materials.

MATERIALS OF CONSTRUCTION

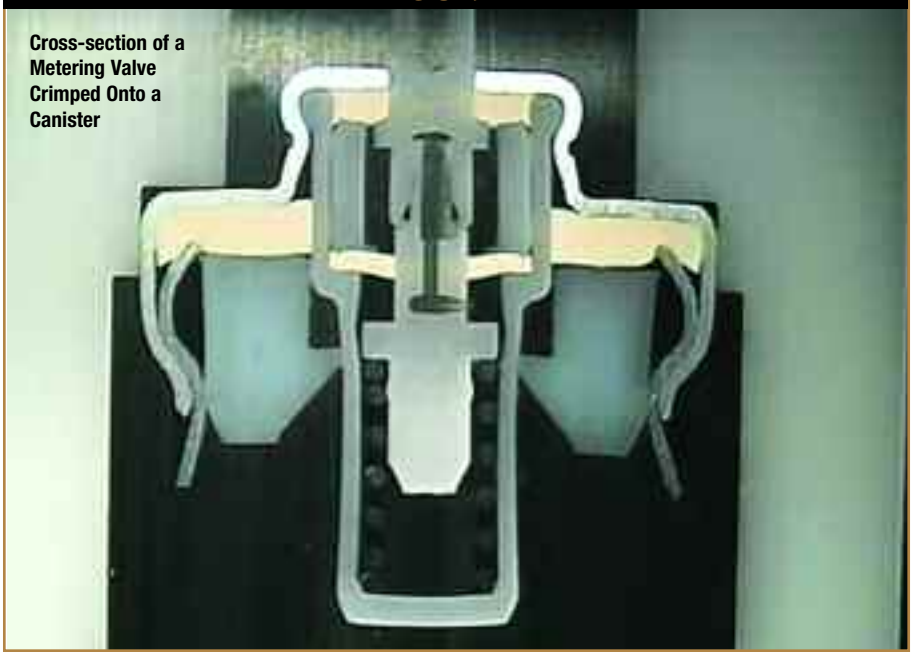
Many different factors need to be taken into account when selecting materials for use in metering valves in MDIs, including absence of toxicity, the need to be chemically inert, mechanical properties, and regulatory status.[1] As a result of these complex and potentially conflicting requirements, the list of possible materials is very short. All components in metering valves are in permanent contact with organic solvents as well as being exposed to very high pressures on a permanent basis. Moreover, components involved in the dispensing action are subject to a considerable amount of mechanical stress both from the manufacturing process (ie, valve assembly, crimping, pressure filling) and due to the level of interference that needs to be maintained between rubber gaskets and plastic components.[2] Figure 1 shows a cross-section of a metering valve crimped onto a canister. The effect of mechanical stress can be seen in the distortion of the valve body.

RUBBER GASKETS

The rubber gaskets are usually identified as the most critical components in a metering valve. Rubber materials currently used in metering valves include nitrile, EPDM, polychloroprene, and butyl. Specific rubber formulations have been developed for use in HFA metering valves such that the materials possess the correct properties in terms of swelling, elasticity, hardness, modulus, water vapor and propellant permeability, impurity profile, and being chemically inert.[3] These formulations are complex, and a typical list of ingredients used to produce a suitable rubber formulation is shown in Figure 2.

The impurity profile needs to be evaluated thoroughly as many rubber materials are known to contain organic compounds that may leach into the drug product through the solvent action of the propellent and co-solvent and are therefore a concern for patient safety.[4,5] This is particularly true for nitrosamines and polynuclear aromatics (PNAs), which are known to be human

FIGURE 1



Cross-section of a Metering Valve Crimped Onto a Canister

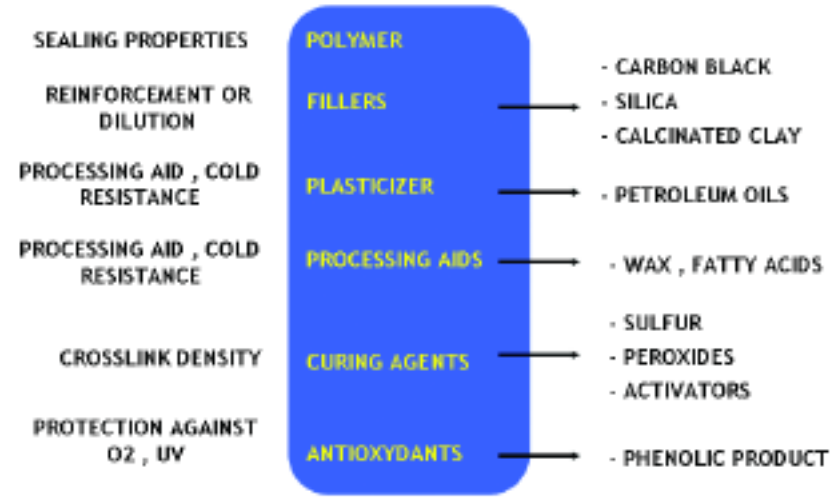
carcinogens and may be present if the initial formulation ingredients are not appropriately selected. Each of the aforementioned rubbers brings its own advantages and disadvantages (eg, nitrile gaskets usually exhibit very good mechanical properties but their water vapor permeability is relatively high). Rubbers can be combined to optimize the advantages of the different polymers and dilute the disadvantages. Examples of suitable combinations are materials, such as Polyolefin elastomer (POE), hydrogenated nitrile (HNBR), and bromobutyl (BIIR). HNBR/ Bromobutyl combinations may produce rubber gaskets with excellent mechanical properties combined with good barrier properties.

PLASTIC COMPONENTS

Plastics commonly used in metering valves include acetal resins (POM) and polyester (PBT) for the components that play a dynamic role in the dispensing action polyethylene and polyamide (Nylon 6,6) for non-moving components, such as the gathering ring. The requirements for valve components involved in the dispensing action in terms of modulus, hardness, and heat deflection temperature are such that only a few pharmaceutical-grade materials have shown acceptable levels of performance to date. The formulation of these materials is usually a straight blend of polymer with additives, such as antioxidants and lubricants. There is usually no safety concern associated with the use of these materials in metering valves. However, acetal resins have a tendency to release low levels of formaldehyde. Therefore, this phenomenon and the associated risks need to be thoroughly investigated for each product.

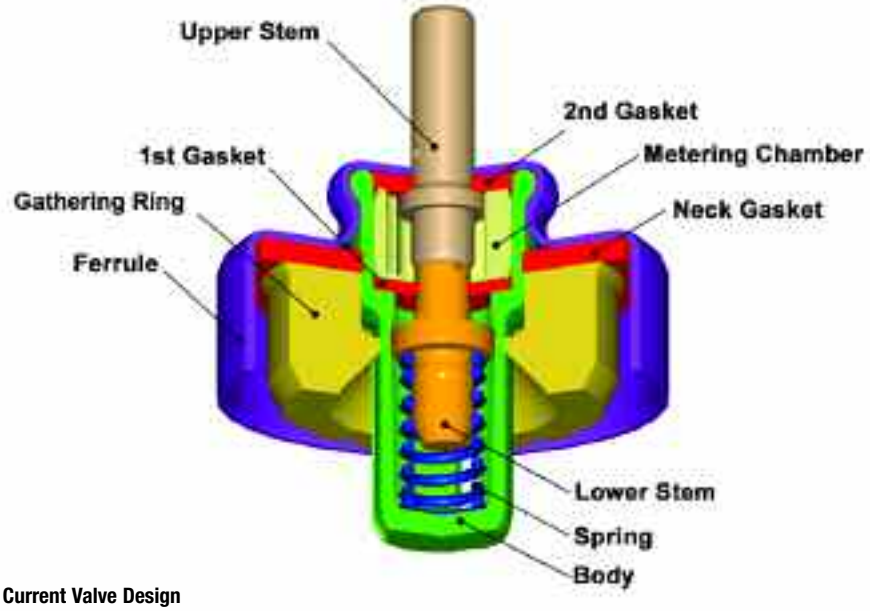
Most suppliers now offer specific pharmaceutical grades for acetal resin and PBT. These grades are of particular interest for the pharmaceutical industry as care is usually taken by the manufacturers to use safe ingredients and to produce these

FIGURE 2



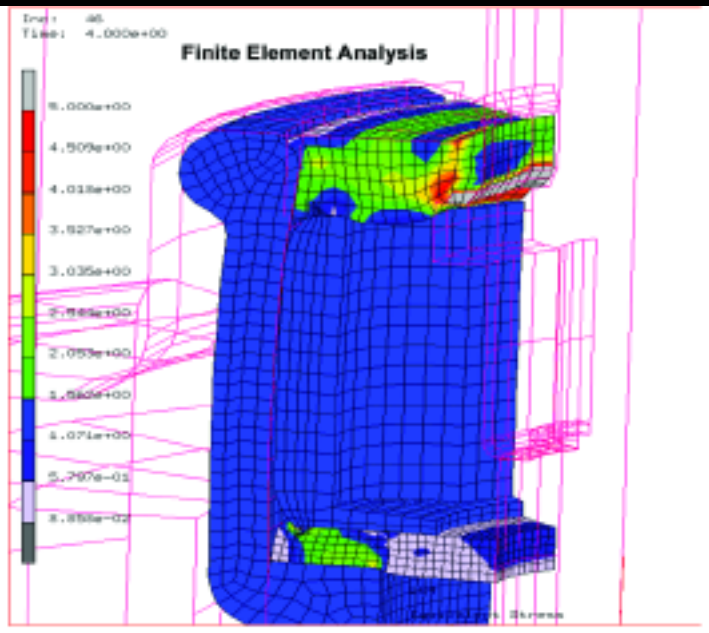
Rubber Composition

FIGURE 3



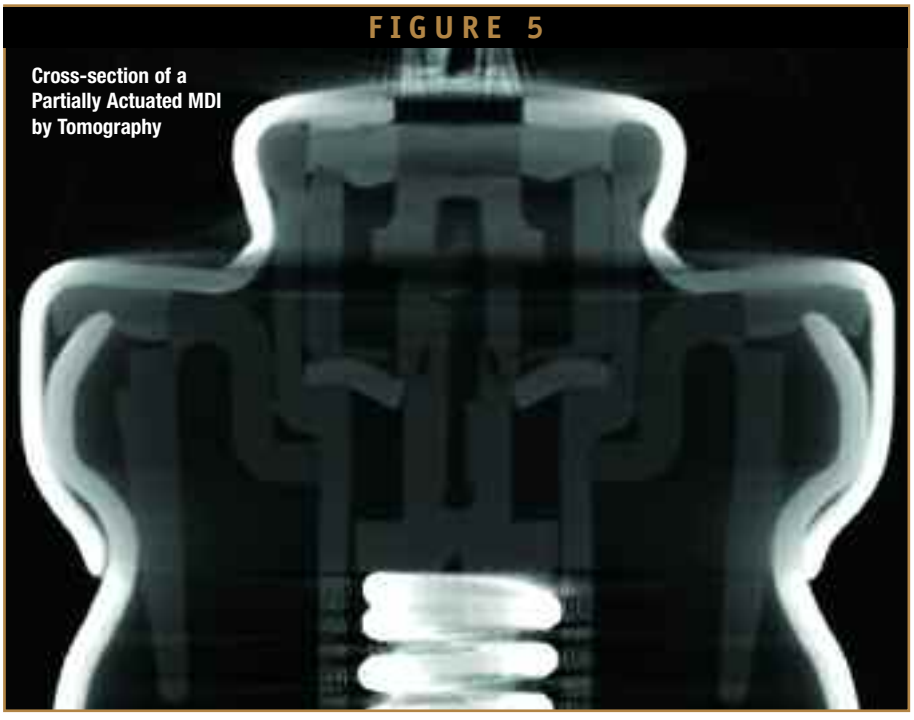
Current Valve Design

FIGURE 4



Constraint Distribution on Internal Gaskets by FEA

FIGURE 5



products in the appropriate quality environment (prevention of cross contamination, line clearance, etc).

DESIGN OPTIMIZATION

Optimization of the Shape & Dimension of Components

Retention valve designs have not changed tremendously since MDIs were first introduced on the market. All currently marketed products are based on a retention valve design (Figure 3). Other design concepts, such as rapid fill–rapid drain metering valves, are in development. The IT revolution made available powerful tools, such as FEA (Finite Elements Analysis) calculation, evaluation of rheological behavior of resins, and their injection molding, statistical tolerance analysis softwares, and FMEA (Failure Mode Effect Analysis). Through our experience of developing such valves and adapting them to customer-specific formulations, we have identified the technical aspects of metering valves that require further optimization/improvement. Through the use of these optimization tools, it has been possible to reduce the sensitivity of valve performance to manufacturing and processing parameters without radically changing the valve design.

Unlike most other drug delivery devices, the metering valve is subject to some extreme stress conditions. The overall manufacturing process of MDIs involves component assembly, crimping the valve onto the canister, pressure filling, and testing (which may include exposing the filled inhaler to elevated temperatures and therefore generate high pressure inside the canister). In the worse case, this stress can lead to irreversible deformations of the plastic components, which can negatively impact valve functionality and product performance.

Such deformations can be observed on the valve body as shown in Figure 1. These may arise from excessive force being applied to the neck of the canister and then transmitted through the ring and then onto

the body when the valve is crimped onto the canister. It has been possible to reduce the level of mechanical stress applied onto the valve body, by optimizing the ring. For example, using computer simulations and experimental design, the shape and dimension of the ring were modified so that it was able to absorb the mechanical stress introduced during the canister/valve crimping process. Whilst this new ring prevented mechanical stress being transferred onto the valve body, it was still able to play its role within the valve (ie, to reduce dead volume inside the canister at the end of product life, in addition to acting as a moisture sink to prevent excessive levels of moisture coming into contact with the drug product).[3]

Optimization of Gasket Compression

Retention-type metering valves have three sealing gaskets, two of which act to isolate the metered portion of the product and a static neck gasket to seal the valve against the canister (Figure 3). For optimal valve mechanical performance, the internal gaskets need to be compressed to an appropriate degree. The compression of the gaskets remains complex to manage as it results from the stacking of the components, gasket swelling (which will vary from one formulation to another), and mechanical stress induced during manufacturing and packaging.

In order to guarantee an optimal compression of the first and second gaskets (isolating the valve metering chamber), the behavior of these gaskets was investigated whilst mechanical constraints were applied. With the help of computer simulations, the distribution of mechanical constraints and resulting gasket deformations were investigated inside the valve mechanism as shown in Figure 4. All of these results combined with a detailed analysis of all design functions led to an optimal design of the metering chamber. Subsequent production of valves with the shape of this chamber demonstrated an improved distribution of mechanical constraints such that an optimal compression of the gaskets was maintained throughout product life.

The use of non-destructive analytical techniques can be used to confirm and to support the results obtained by computer simulations. For example, the analysis of a metering valve by tomography was used to evaluate the actual level of gasket deformation inside the valve mechanism when put in contact with the formulation. This can be seen in Figure 5, which shows a partially actuated metering valve. With the repeat of simulations and the analysis with non-destructive methods, the interference between the plastic components was finely adjusted to optimize shot-weight reproducibility and accuracy.

SUMMARY

The selection of valve design and materials of construction is a complex process and is critical to valve performance and product robustness. The use of tools, such as computer simulation of mechanical behavior and high-resolution tomography to visualize actual behaviour, has provided a significant contribution toward the design of more reliable metering valves.

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BIOGRAPHIES

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MICROFLUID PROCESSING

Process Optimization for Making Stable Emulsions Using Accelerated Dispersion Analysis by Multi-Sample Analytical Centrifugation

By: St. Küchler, Christina Schneider, D. Lerche, and T. Sobisch

INTRODUCTION

A common goal in the formation of stable emulsions during a homogenization process is to obtain the smallest possible particle size distribution of the dispersed phase. The emulsification process and process parameters (type of homogenizer, temperature, energy input, time, and homogenization cycles) used to achieve this goal depend on the desired characteristics of the emulsion. The use of a Microfluidizer® processor has shown to be both a flexible and proven method to achieve optimum product quality. In the search for the most effective emulsification parameters, a method for fast comparative emulsion stability measurements is required. The multi-sample analytical centrifugation (STEP™-Technology) allows the accelerated characterization of any demixing processes (creaming, sedimentation, phase separation) in addition to the quantification of time-dependent structural alterations (eg, flocculation, coalescence) without dilution of the samples. This paper demonstrates the effectiveness of analytical centrifugation as a technique for fast emulsion stability measurements in addition to homogenization parameter optimization.

MATERIALS & METHODS

Preparation of the Pre-Emulsion

A rotor-stator mixer (IKA) was used to form the pre-emulsion consisting of 88.5% water and 10% sunflower oil. Emulsifiers used were Tween-80 (1%) and Span-80 (0.5%). The ingredients were mixed at 10000 rpm for a total 120 seconds during which sample aliquots were taken at 30, 60, and 120 seconds. The pre-emulsion formed at the end of the 120-second mixing period was the basis for the final emulsions formed using the Microfluidizer processor.

Preparation of the Final Emulsions

In the Microfluidizer processor, the starting material is pumped under high pressures (up to 40,000 psi/2750-bar) through a patented interaction chamber in which the material is accelerated at high velocities through a channel of a fixed geometry. The velocity inside the interaction chamber reaches several hundred meters per second. The resulting very high shear rates and impact effects created inside of the interaction chambers lead to a highly efficient droplet or particle size reduction. Figures 1a and 1b show the principle of operation as well as the schematic of the interaction chamber. Various interaction chamber types and sizes are available for different applications. Y-type chambers (Figure 1a) in which the product stream is divided into two streams that impinge upon another and z-type chambers in which the product stream zig-zags through the interaction chamber are the two general types of interaction chambers available with different cross-sectional areas for different shear requirements.

For the described experiments, an M-110EH Microfluidizer processor equipped with an F20Y interaction chamber (75-µm minimum dimension) upstream, and a H30Z interaction chamber (200-µm minimum dimension) downstream was used. The effect of operating pressures (5000, 10,000, and 20,000 psi/345, 690, and 1380-bar) and system passes (1, 3, and 5) on both emulsions' stability and formation efficiency were investigated.

Analytical Centrifugation

Analytical centrifugation allows for the accelerated measurement of the separation process, and therefore gives the user a fast and accurate means of evaluating emulsion dispersion stabilities.[1] The stability analyzer LUMiFuge® measures the intensity of the transmitted light over the full sample length instantaneously as a function of time using the STEP-Technology (Space & Time Extinction Profiles) measuring scheme (Figure 1).

All data are stored and displayed in real time as a function of time and radial position, allowing for micron-

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scale accuracy and precise analysis of any changes in the dispersion characteristics. Up to eight samples can be analyzed simultaneously.

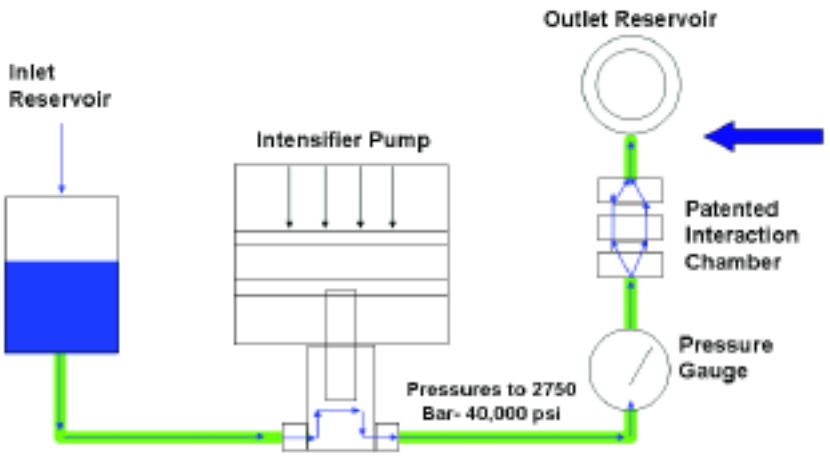
The separation behavior of the individual samples can be compared and measured in detail by analyzing the changes in the transmission at any part of the sample or by tracing the movement of any phase boundary. Based on these changes, the rate of clarification and the sedimentation/creaming velocity can be easily calculated. With the LUMiFuge, both of the calculations are performed semi-automatically.

Due to differences in stabilities, the respective emulsions were analyzed at 20 minutes (running at 1500 rpm) or 30 minutes (running at 3000 rpm), resulting in a corresponding acceleration of 290 *xg* and 1100 *xg*.

RESULTS & DISCUSSION

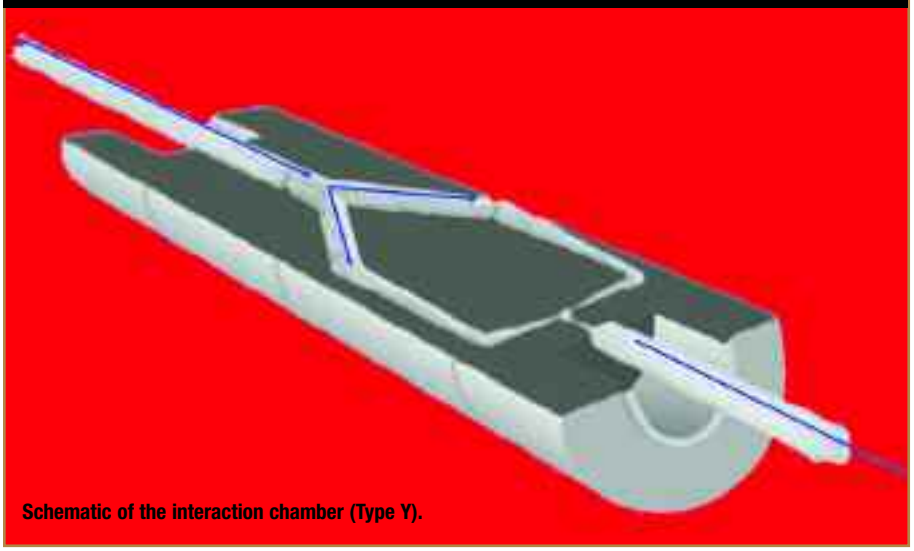
Figure 3 depicts the results obtained for the 5,000-psi (345-bar) emulsion after one pass through the Microfluidizer processor, ie, the progression of the transmission profiles as a function of time and space. The top of the sample and thus the air-liquid interface is at the 92.5-mm position (measured from the center of rotation). The bottom of the sample is at 114 mm. The first profile taken is shown in red. All subsequent measurements are depicted as lines having a red-green gradient, with full green indicating the last measurement taken. At the beginning of the analysis, the emulsion was well dispersed, and most of the incident light was absorbed. Therefore, the first transmission reading taken is very low (around 7%). Due to the density difference between the dispersed oil droplets and the continuous water phase, creaming will occur. This results in increasing light transmission percentages near the bottom of the sample as a function of time. The green transmission profile line indicates that complete clarification (100% transmission) occurred after 30 minutes for the lowest 1-mm part of the samples.

FIGURE 1A



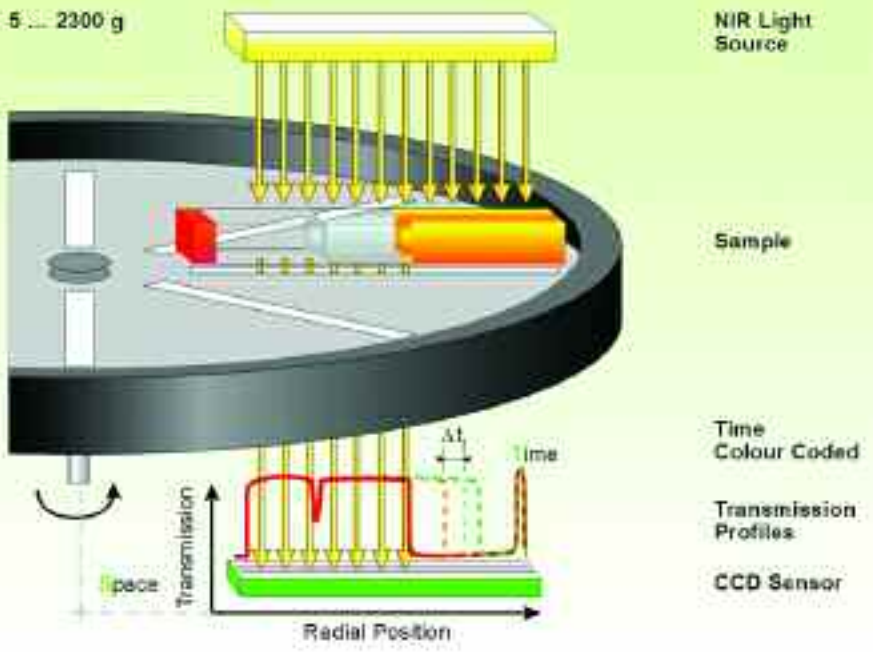
Principle of operation of the Microfluidizer® processor.

FIGURE 1B



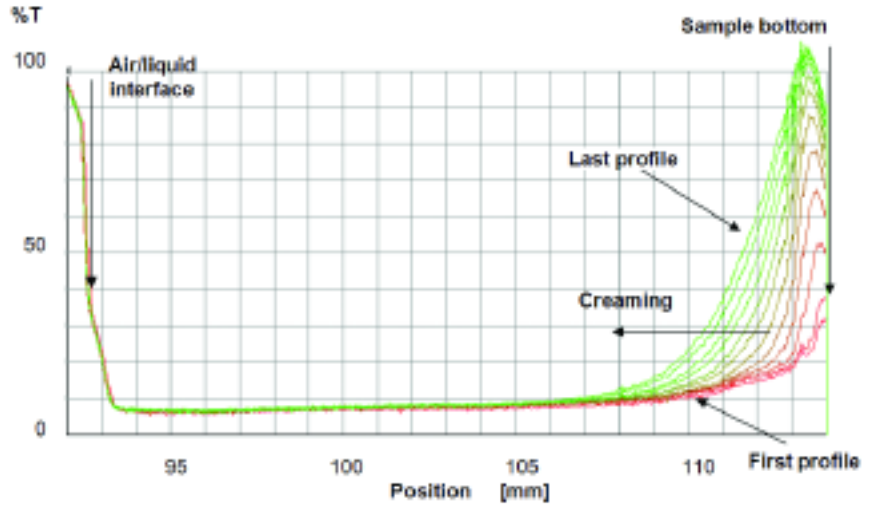
Schematic of the interaction chamber (Type Y).

FIGURE 2



Measurement principle of the multi-sample analytical centrifuge with photometric detection. Parallel NIR-light is passed through the sample cells, and the distribution of local transmission is recorded at preset time intervals over the entire sample length.

FIGURE 3



Progression of transmission profiles. Emulsion one pass at 5,000 psi (345-bar) (oil-in-water emulsion), 30 minutes centrifugation at 1100 xg, every 15th profile displayed.

Because the clarification of the samples occurs at the bottom of the sample first, it becomes clear that we are dealing with an oil-in-water emulsion (o/w). The STEP-Technology helps determine whether the emulsion is oil-in-water or water-in-oil without having this prior knowledge. For a water-in-oil emulsion, one would observe sedimentation of the water droplets, resulting in a clarification of the top of the sample.

The SepView software allows for a detailed and quantitative analysis of phase separation kinetics of water and oil and coalescence.[2,3]

In the following emulsion stability, ie, their separation tendency was quantified by the creaming velocity and the ratio of total liquid phase volume separated after a given time of centrifugation to the volume of the whole sample. Because the oil-water interface for this emulsion was not distinct during the creaming process, its position was measured along the 30% transmission line. Thus, after 30 minutes, the phase boundary moved from the bottom of the sample up to the position of 110.5 mm (Figure 3).

Pre-Emulsion Stability as a Function of Mixing Time

Because the raw emulsion was extremely unstable, a low acceleration setting (290 xg) was chosen for the LUMiFuge. As can be seen in Figure 4, the stability of the pre-emulsion is highly dependent on the length of mixing time using the rotor-stator mixer.

While the pre-emulsion showed great

instability for the 30-second mixing time, mixing the emulsion for 2 minutes does produce a stable enough emulsion to ensure consistent and reproducible behavior for the additional homogenization using the Microfluidizer processor.

Effect of Process Pressure & Cycles on Final Emulsion Stability

Even low homogenization pressures have a noticeably positive effect on the stability of the pre-emulsion, as depicted using only the first and last measured transmission profiles (Figure 5). The stability improves with increasing homogenization pressure, ie, the amount of water separated is reduced. The application of higher shear forces on the emulsion by increasing the homogenization pressure led to a remarkable increase in emulsion stability (Figure 6). At lower homogenization pressures (5,000 psi/345-bar), increasing the number of cycles resulted in progressively more stable emulsions. At 10,000 psi (690-bar) only the first two cycles showed meaningful increases in emulsion stability, with any additional cycles having only a marginal effect. At the highest applied pressure of 20,000 psi (1380-bar), the emulsion stability actually decreased slightly with an increasing number of homogenization cycles (over-emulsification).

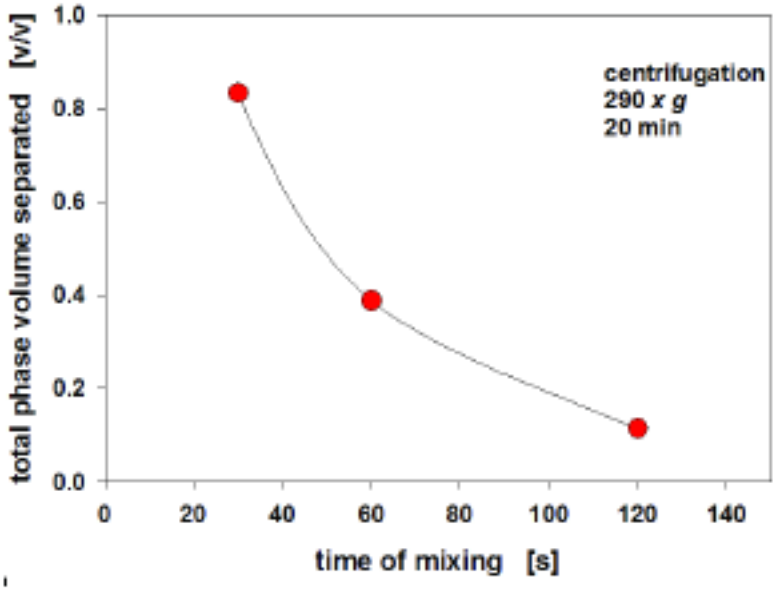
For this pre-emulsion then, it is more efficient to increase the homogenization pressure as opposed to cycles in order to achieve the highest stability toward creaming. As an alternative to measuring emulsion stability on the final phase-separation volumes, one can measure the rate of the phase-separation process in real time (Figure 7).

The differences in the slopes indicate different separation velocities. These separation velocities are also calculated semi-automatically by the software and can be used to predict the stability or shelf-life of the respective emulsion.

CONCLUSION

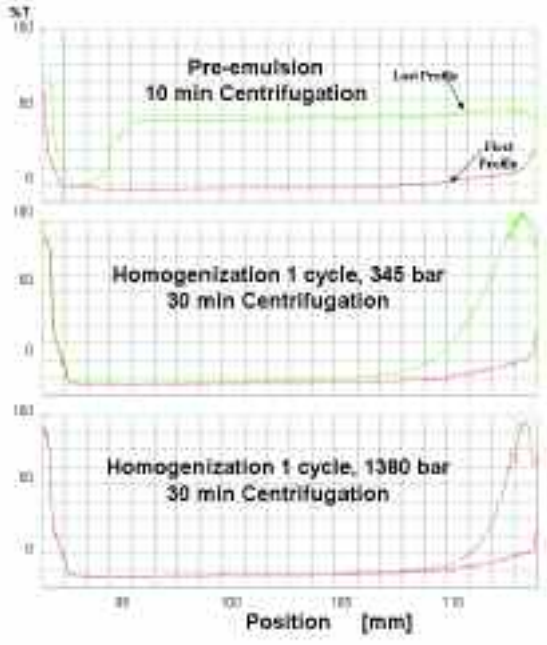
Using a water-oil emulsion, it was shown that homogenization using a Microfluidizer processor can significantly improve

FIGURE 4



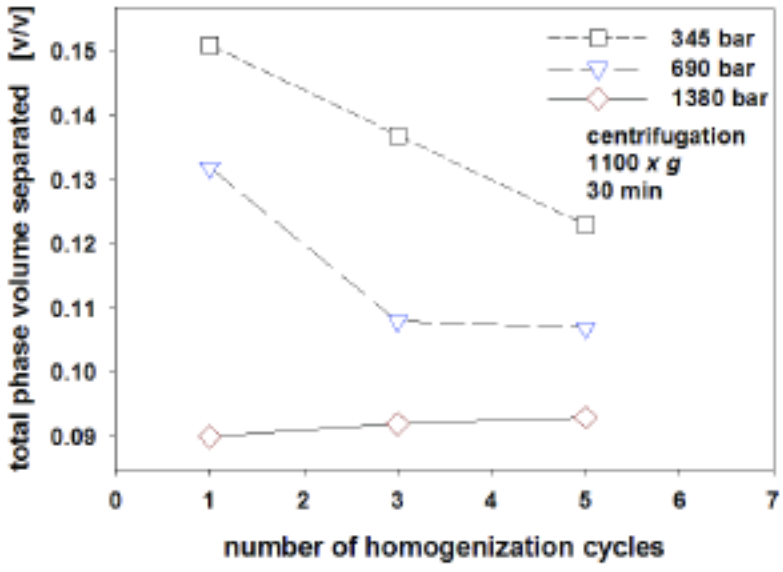
Effect of mixing time on the stability of the raw emulsion. Mixing with a rotor-stator mixer at 10.000 rpm.

FIGURE 5



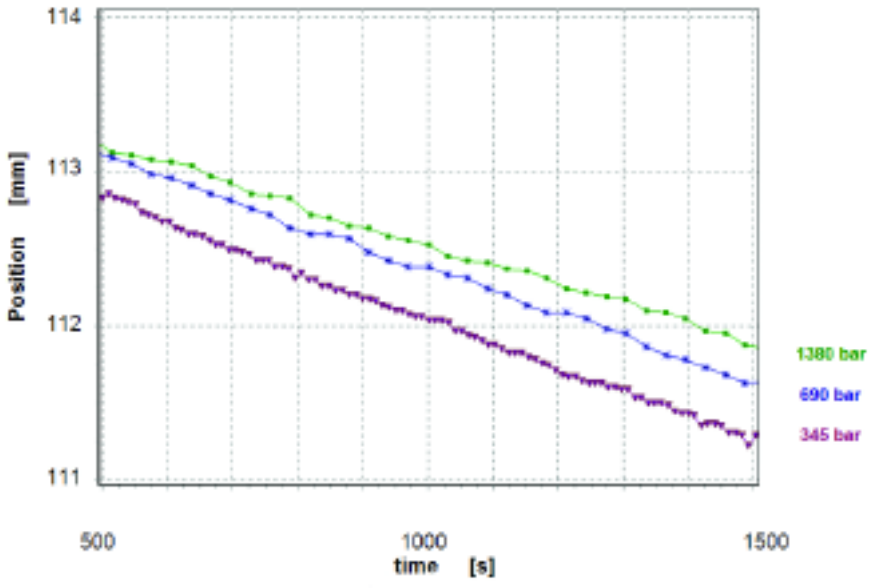
Effect of homogenization with the Microfluidizer® processor on emulsion stability. Comparison of the first and last transmission profiles, respectively, centrifugation at 1100 xg. Top graph shows the pre-emulsion, middle graph the same emulsion homogenized using 1 cycle at 5,000 psi (345-bar), bottom depicts pre-emulsion homogenized using 1 cycle at 20,000 psi (1380-bar).

FIGURE 6



Effect of the number of homogenization cycles and process pressure on emulsion stability.

FIGURE 7



Effect of homogenization pressure on emulsion stability after 5 homogenization cycles. Comparison of creaming kinetics (movement of the phase boundary), centrifugation at 1100 xg.

the stability of an emulsion. The optimal process parameters can be readily and accurately determined using multi-sample analytical centrifugation. The on-site use of such a technique then allows the operator in charge of quality control to immediately adjust and optimize the emulsification and homogenization process.

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BIOGRAPHIES

Ms. Christina Schneider is the European Sales Manager for Microfluidics. Prior to joining the team in 1999, Ms. Schneider was a Scientific Assistant at RWTH Aachen in Germany, where she earned her degree in Mineral Processing.

EROSION-BASED DELIVERY

Erosion Versus Diffusion – The Future for Controlled & Sustained Drug Delivery

By: Neena Washington, PhD, and Professor Clive G. Wilson

INTRODUCTION

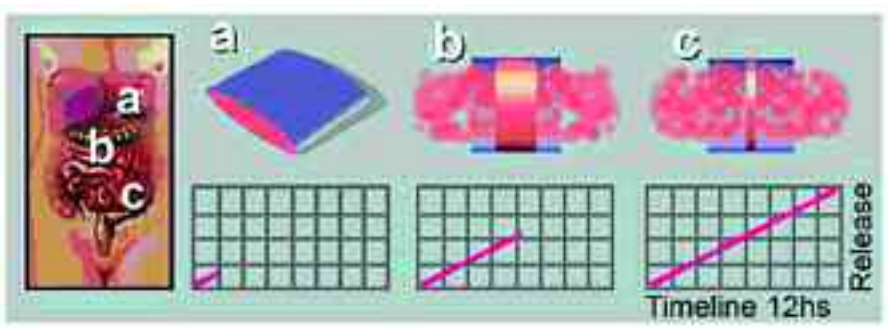
Traditionally, the most popular form of drug delivery has been ingestion of solid-dose forms. Virtually all drugs are initially marketed in "immediate-release preparations" that disintegrate within the first 5 or 10 minutes after the patient swallows them. Usually these types of tablets or capsules are taken between once and three times daily, as dosing any more frequently than this proves to be impractical and leads to a decline in patient compliance. Although many drugs can be dosed in this way, problems arise for instant-release preparations for drugs with short half-lives or small therapeutic windows. For these drugs, even with thrice-daily dosing, the required plasma concentration of drug cannot be maintained. It is these types of drugs that especially lend themselves to controlled and sustained drug delivery. This type of delivery system does not disintegrate soon after ingestion, but remains intact and delivers the drug in a controlled manner to a greater length of the gastrointestinal tract. This type of drug delivery is not new as it has been in existence for over 30 years, but the challenge is to be able to reproducibly achieve therapeutic plasma concentrations of drugs over a sustained period via the gastrointestinal tract, regardless of the lifestyle of the patient.

The majority of commercially available controlled-release drug delivery systems rely almost exclusively on aqueous diffusion through a matrix or through a membrane to cause drug release. This causes a problem for delivery of poorly water-soluble drugs, and apart from the Oros® tablet (ALZA Corporation), which uses osmosis to drive drugs from a solid unit, there are few drug delivery devices meeting this market opportunity.[1] The Egalet® technology (Egalet a/s, Denmark) is relatively new to the market, but offers some distinct advantages over more conventional controlled-release dose forms.[2,3] The primary advantage is its ability to deliver water-insoluble compounds in a controlled manner. This can be achieved because drug release from the Egalet® dosage forms involves the processes of erosion rather than diffusion. An added advantage is that active compounds entrapped in the Egalet® matrix are also protected from oxygen and humidity and therefore, the technology appears suited for chemically unstable substances and thus may increase in shelf-life.

The Egalet® Constant-Release system consists of two components: coat and matrix. The drug is distributed evenly throughout the matrix, which is eroded by gut movements and gastrointestinal fluids as it travels through the gut (Figure 1). The drug-release mechanism is believed to be surface erosion, effected through water diffusion, polymer hydration, disentanglement, and dissolution. The matrix is designed to erode when in contact with available water but, at the same time, it is desirable that water does not diffuse into the matrix until the point of release, thus avoiding hydrolysis and diffusion and reducing the effects of luminal enzymatic activity. A balance is required where the erosion is as fast as the diffusion of water into the matrix. The diffusion of water into the edges of the matrix producing only a hydrating/dissolving thin layer and leaving a dry core even after 4 hours can be distinctly shown by Nuclear Magnetic Resonance (NMR) imaging studies (Figure 2).[4]

To ensure a gradual release of the active substance(s), the matrix has to be eroded in a heterogeneous manner,

FIGURE 1



Constant release from the Egalet® tablet. a) Egalet® tablet reaches the stomach and release of drug begins b) Egalet® tablet during release c) Almost complete release of drug.

EROSION-BASED DELIVERY

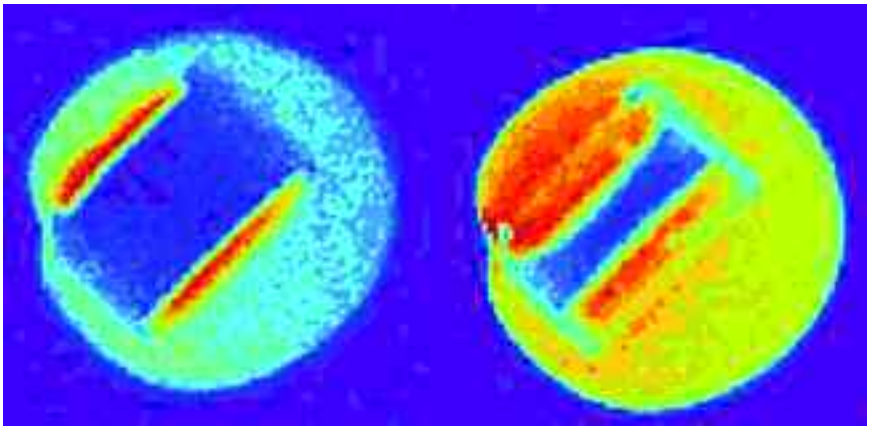
the opposite of homogeneous erosion or erosion occurring simultaneously throughout the matrix. The rate of drug release from an Egalet® unit can be altered by adjusting the composition of the polyethylene oxide (PEO) carrier within the matrix. A possible explanation for this effect is that when molten PEO cools and solidifies, it produces a structure that is partly crystalline and partly amorphous, containing cracks or fissures. Water will penetrate rapidly through the fissures, causing the surface and deeper layers to begin to dissolve simultaneously. This results in gel formation. A similar effect can be obtained if PEG-monosterate and PEG are melted together and then cooled. The PEG/PEG parts will align, whereas the monosterate groups will tend to be left on the surface of the particles, rendering the fissures hydrophobic and impassable to water. This results in heterogeneous erosion because the erosion proceeds layer by layer. This matrix gives a zero-order release profile of drugs *in vitro* independent of pH but directly dependent upon rate of agitation. Figure 3 shows the *in vitro* release of caffeine from an Egalet® dose form demonstrating zero-order kinetics.

Most conventional controlled-release dose forms use a polymer that hydrates, and it is only after the hydration of the outer layer is complete that the drug can diffuse out (Figure 4). Erodible barriers allow surface hydration of the unit, which then releases drug as the tablet disintegrates.

This almost inevitably results in a lag before drug release occurs. Another disadvantage of these systems is that the surface area is constantly being reduced as the tablet erodes therefore drug release is not linear. The advantage of the Egalet® dose form is that the surface area available for erosion does not change with time and hence delivery can be more precisely controlled.

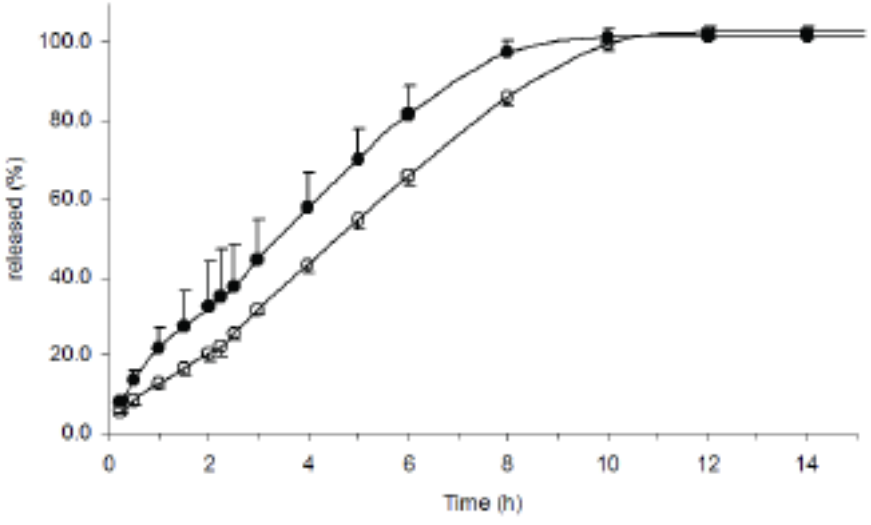
The proof for a controlled-release system is how well the *in vitro* data correlates with the *in vivo* data. One such study has been performed using the Egalet® Constant- Release system containing caffeine and samarium oxide in a scintigraphic study.[5] The samarium oxide was included in the dose form as it can be activated to $^{153}Sm_2O_3$ upon

FIGURE 2



NMR Image of Egalet® dosage units after 0.5 and 4 hours.

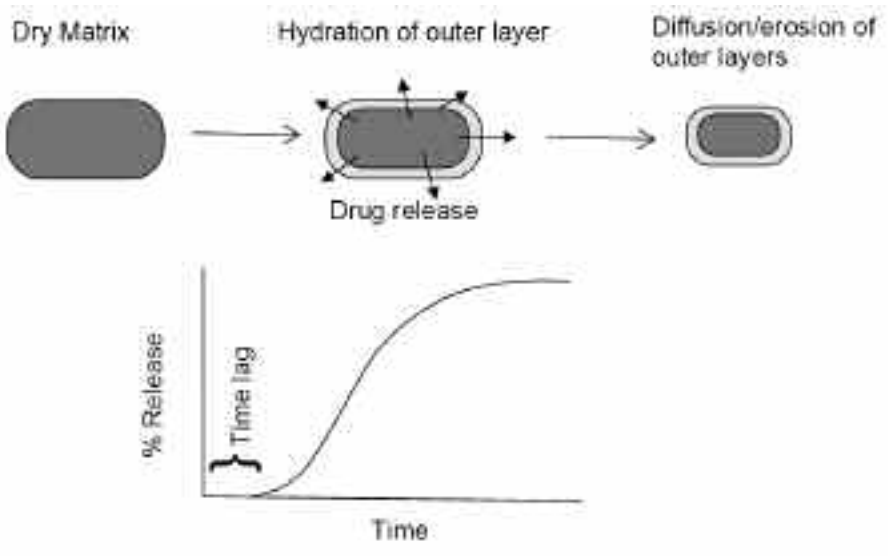
FIGURE 3



Dissolution of caffeine from non-irradiated Egalet® systems (○) for 4 minutes (n = 6 + sd). For comparison, the effects of neutron activation on the release profile of caffeine from the Egalet® are shown (•) (see later text). The dissolution medium was 0.1 M HCl for the first 2 hours, then phosphate buffer pH 6.8 for the next 22 hours. Rotation rates were 100 and 50 min-1, respectively.

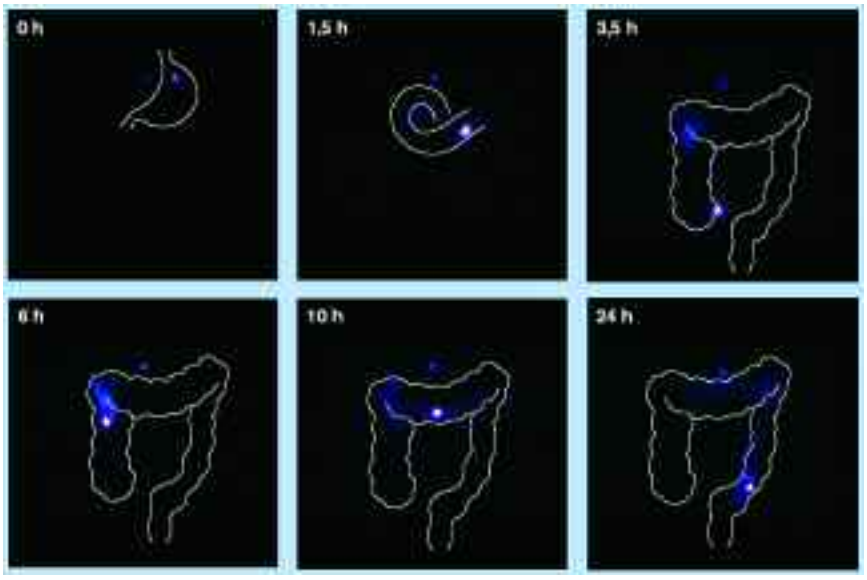
EROSION-BASED DELIVERY

FIGURE 4



Demonstrates how hydration of the outer layers of the matrix and dissolution add a time-lag before drug release from conventional matrix preparations.

FIGURE 5



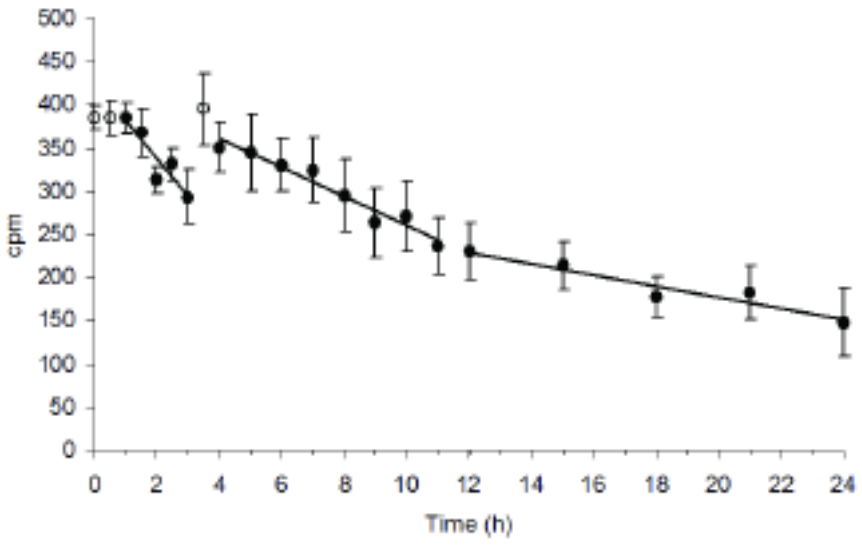
Scintigraphs of the gastrointestinal transit of the Egalet® unit containing a radiolabel in one subject at 0, 1.5, 3.5, 6, 10, and 24 hours after administration. Location of the dosage form 0 h = stomach, 1.5 h = end of the duodenum 3.5 h = ileo-caecal junction, 6 h = ascending colon, 10 h = transverse colon, and 24 h = descending colon.

irradiation, which is visible to the gamma camera. The effect of the irradiation on the *in vitro* release characteristics of caffeine can be seen in Figure 3. The activated dose forms were dosed to 6 healthy volunteers and an example is shown in Figure 5.

The *in vivo* release consisted of three linear phases with constant slopes (Figure 6). The rate of drug release was reduced when the Egalet® unit crossed from the small intestine into the colon and again when it moved from the transverse colon to the descending colon. It is likely that this reflects both the reduction in motility and water associated with these regions, which will affect the rate of both erosion and dissolution of the drug.

One issue with controlled-release technologies is that it can be a lengthy and costly process to tailor the dose form to match the required *in vivo* release profile of the drug. Often, only a few different designs are tried *in vitro*, and only the most promising one or two are selected from their *in vitro* release data to be tested in humans. The Egalet® unit manufacturing process consists of a conventional two-color, injection molding process. The premixed powders (usually in the form of extruded granulates), which are used to form either the active matrix or plug, are fed into the mold. A reciprocating injection-molding process allows sequential molding of the shell and the core contents within the dies. This design provides an efficient manufacturing process coupled with high accuracy in dimensions, weight, and content. It also allows for flexibility in dosage form design at minimum cost. This has been significantly demonstrated in the development process of a once-daily antihypertensive drug.[6] The aim was to replace the twice-daily doses of the marketed immediate-release drug with a single dose of the controlled-release

FIGURE 6



Release of the $^{153}Sm_2O_3$ from the Egalet® unit in the gastrointestinal tract of the subjects (Mean + sem). Cpm = counts per minute. Linear fit lines are shown for the three phases evident (small intestine, ascending and transverse colon, descending colon).

Egalet® formulation. Initial studies look very promising, and the ability to alter the geometry of the Egalet® has allowed it to be easily tailored to match the required pharmacokinetic data.

SUMMARY

The concept of erosion technology for sustained-release appears to have a number of advantages over more conventional delivery systems. In summary, these advantages include the ability to deliver poorly water-soluble drugs; zero-order release (the rate of which is dependent on gastrointestinal motility and water availability); and easily tailor dosage form manufacture to obtain the desired release profile by altering size, width, and matrix composition.

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BIOGRAPHIES

Dr. Neena Washington has worked extensively both in academia and the pharmaceutical industry. She earned her BSc (Sp. Hons) in Physiology and Pharmacology from Sheffield University prior to earning her PhD in Pharmaceutics at Nottingham University. Her main areas of interest are the *in vivo* behavior of dosage forms and the use of imaging techniques, particularly gamma scintigraphy in the visualization of dosage form behavior in man. Her clinical interests are in the fields of gastrointestinal, respiratory, inflammation, and oncology.

Professor Clive G. Wilson holds the JP Todd Chair of Pharmaceutics at Strathclyde University in Scotland, although currently he is on a sabbatical research period. His work has focused on the use of imaging techniques in formulation research, and he has received the Amersham and Pfizer awards in recognition of his contribution to this field. His main areas of research are the relationship between gastrointestinal physiology and drug absorption and the problems of ocular drug delivery. He has supervised more than 40 PhD students and has authored over 400 publications that include original articles, reviews, and six books. The publications reflect his interest in imaging, physics, drug absorption and metabolism, and pharmacokinetics. He is a member of the editorial board of the *European Journal of Pharmaceutics and Biopharmaceutics* and Editor of the *Taylor & Francis* series in pharmaceutical technology.

DRUG DELIVERY Executive

Azopharma
Contract Pharmaceutical Services

AZOPHARMA: LEADING THE FUTURE OF DRUG DEVELOPMENT

Mr. Phil Meeks
Chief Executive Officer
Azopharma

"This allows us to not only develop products for customers as I've been discussing, but also effectively help discover new molecules, which really transforms Azopharma from a product development company into a product development company that has discovery capabilities. I'm very excited by this recent phase in our growth."

Azopharma was founded in 1993 and is a contract product development organization, providing preclinical services, synthetic services, characterization services, preformulation services, formulations development, methods development and validation, quality control testing, stability services, clinical trial material manufacturing, potent compounds development, and regulatory consulting. Azopharma supports solid oral dosages (tablets, capsules), liquid dosages (injectables, suspensions), topical dosages (creams, ointments, lotions), inhalation dosages (nasal, MDI, DPI), drug substance and excipients, biopharmaceuticals, and medical devices and drug/device combinations. The company is registered with the DEA for testing all schedules of controlled drugs and has individual licensing for manufacturing on an as-requested basis. Its sites are fully cGMP compliant and have an excellent inspection record. Drug Delivery Technology recently interviewed Phil Meeks, CEO of Azopharma, to discuss the future of drug development and Azopharma's novel approach to developing Phase I clinical trial material.

Q: Azopharma's novel approach to speeding clinical trial material into the clinic is called Phase I Express™. What is Phase I Express?

A: Phase I Express is our proprietary approach for expediting drug development for new compounds entering clinical development activities. This approach differentiates Azopharma from other contract research organizations in two fashions. First and foremost is our scientific integrity, and second is our increased speed in getting compounds into Phase I activities. Phase I Express systems have been used successfully in all dosage forms, at least from an NDA perspective. So, it applies to all dosage forms, including solid oral, inhalation, topical creams, etc.

Q: Can you describe Azopharma's business model in support of Phase I Express?

A: Azopharma is a contract product development organization (PDO). We've been in business in South Florida for about 15 years. We have approximately 100 scientists and chemists in our company,

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most of whom have advanced degrees. Our capabilities start out in the preclinical arena and go all the way through to generation of clinical trial materials. The integration of our focused but exhaustive services into a proprietary project management system allows us to move through the clinical development cycle in a timely fashion while still maintaining excellence in quality and scientific areas.

In the preclinical toxicology area, we are able to support a full range of animal studies. We can develop small rodent models, dog models, rabbit models, and pig models, and we also have the ability to do non-human primates with two different species of monkeys and even baboons.

In our preformulation area, we perform studies such as salt selection, polymorphism evaluations, evaluation of API and excipient/excipient interactions, execution of PKa studies, and all the other requisite scientific studies needed prior to going in to a formulations development program.

When those activities are completed, we launch into formulation development, which is one of our core services. Our formulation team is able to handle multiple dosage forms, such as solid oral, which could be a tablet or capsule. Also, we're able to develop respiratory products, such as MDIs and inhaled solutions. Additionally, we're able to develop semi-solids, such as creams, ointments, and lotions in addition to other dosage forms utilized in the industry.

Following formulations, we offer a full range of analytical support. This includes all the analytical facets of formulation development. For example, we have a structural chemistry group that is able to elucidate structures of chemical compounds, a group that can perform reference standard characterizations, and an analytical methods development and validation group. We're also able to do release testing, stability storage, and stability testing. So, in essence, we're a full-service analytical house able to fully support a customer's formulation efforts.

We have also recently expanded our regulatory department in support of our expanding Phase I development programs. This allows us to complete requisite regulatory filings in a timely manner and to assist in getting products out faster into the marketplace for our customers.

This allows us to not only develop products for customers as I've been discussing, but also effectively help discover new molecules, which really transforms Azopharma from a product development company into a product development company that has discovery capabilities. I'm very excited by this recent phase in our growth.

Q: What time savings could a customer expect to find with Phase I Express compared to industry standards for development of clinical trial materials for Phase I studies?

A: Well, while I'm not versed on what the entire industry is doing, typical timings on getting a molecule into a Phase I clinic could be around 8 to 12 months or longer. Azopharma is able to do this in less than 6 months.

Q: It seems as if Azopharma is really moving into unique areas of the market in support of full development programs for Phase I, including cytotoxic and respiratory. Could you discuss both of those and what you see in the future as Azopharma's visionary?

A: Let's start first with potent compounds. A lot of the easy compounds have already been taken by now, so what happens is that you have a lot of compounds that are out there that have toxicity concerns. As we develop these compounds for customers, we need to be concerned first and foremost about the safety of employees. Therefore, we have certain processes and procedures in place to ensure that we have a safe working environment for these molecules. What we have at Azopharma is a series of containment suites and containment centers, as we call them, allowing us to help keep our employees safe, while at the same time allowing them to work on developing molecules that may ultimately help a lot of people.

Our team is able to work on the compounds without ever touching them, from a mortar and pestle approach all the way through to encapsulation techniques. And as one last safety precaution, upon exiting the facility, although they theoretically have never come in contact with the compound, we have a safety mist shower system that showers off the garment, which is then removed, and the employee is able to leave the facility unharmed. Additionally, we monitor employees, both before working with various molecules and during, for levels of exposure to a particular compound. So, we're able to take very highly potent compounds and safely work on them at very low levels.

Regarding respiratory dosage forms, we recently hired various industry veterans in the areas of inhalation and respiratory therapies who have a lot of experience with inhaled solutions, DPIs, MDIs, and nasal sprays. We are actively developing several products of which we are exploring unique therapies for molecules that may be able to be delivered via the nasal cavity or the lung. This expands Azopharma's capabilities into this very specialized market, and we're seeing good demand, particularly from the European marketplace.

Q: Azopharma has grown significantly over the past few years emerging as a market leader in the drug development arena not only domestically but in Europe as well as in Asia. Would you touch on what you believe is the core reason of Azopharma's success?

A: We have been very fortunate. Throughout the past 3 years alone, we've grown our revenue base ten-fold. We've been able to do that by remaining a profitable organization, and I'm very proud of that. In essence, it all boils down to the people. We have to hire the right scientists with the right experience and the right mindset, and we've been able to execute on that mission. We aspire to hire the best scientists, train them to focus on customers, and couple that with excellent quality. Thanks to our great people, we really have made our presence known out there in the marketplace. Moving forward, we look to continue to be a market leader in pharmaceutical product development by adhering to our core values. ◆

Drug Delivery Showcase

Inhalation & Transdermal Delivery

3M Drug Delivery Systems is a global leader and innovator for inhalation and transdermal drug delivery. From drug discovery to commercialization, 3M offers innovative and proven technology, product development services, global regulatory expertise, commercial manufacturing, and a broad range of customizable system components. 3M's technology, expertise, and experience can provide pharmaceutical and biotech companies with differentiated products, speed to market, and increased probability of technical and commercial success. 3M's proven track record includes development of the first MDI, HFA MDI, and the first stand-alone 7-day transdermal system. Products manufactured by 3M Drug Delivery Systems are currently sold in more than 60 countries on 6 continents. The company combines the agility of a leading drug delivery company with the resources of a major, multinational corporation, providing expertise in product development, regulatory, and manufacturing to get its partners to marker sooner. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3m.com/dds**.

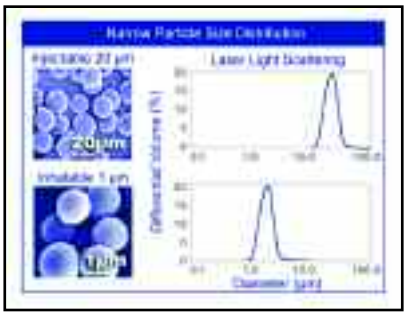
Osmotic Technology

OROS® technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs. OROS can be used to deliver high drug doses meeting high-drug loading requirements. L-OROS™ technology, adapted for liquid formulations, can enhance the bioavailability of drugs with low solubility. Targeting specific areas of the GI tract, OROS technology may provide more efficient drug absorption and enhanced bioavailability. L-OROS can also enhance the bioavailability of drugs with low solubility. For many drugs, zero-order is not the optimal delivery profile. OROS can be tailored to meet patterned delivery profiles to optimize a drug's therapeutic efficacy. For more information, contact ALZA Corp. at (650) 564-5000 or visit **www.alza.com**.

Excipient Portfolio

Excipient Portfolio
BASF puts the resources of the world's largest chemical company to work for its customers. One example of the company's powerful excipients portfolio is Kollidon® CL, which accelerates dissolution. BASF's comprehensive portfolio of excipients includes a full range of coatings, binders, disintegrants, and solubilizers, backed up by its experience, expertise, and technical service. BASF's skilled and experienced chemists and pharmacists respond to calls within one business day to answer questions about formulations, solid or liquid dosage, delivery systems, and manufacturing. The company also offers high-quality active ingredients, pharmaceutical finishing, and exclusive custom synthesis. For more information, contact BASF Pharma Solutions' Technical Services Line at (800) 469-7541 or visit **www.basf.com/pharma**.

Pulmonary Formulation



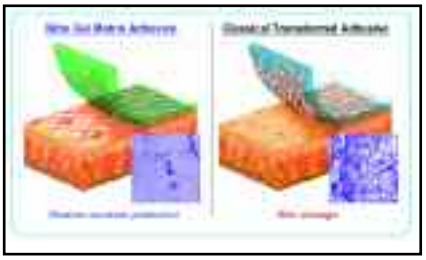
PROMAXX, Baxter Healthcare Corporation's proprietary drug delivery technology, is designed to enhance formulation success. The protein microsphere technology offers narrow particle size distribution ideal for delivery to and through the lung. This versatile platform can be applied to a variety of drug classes and has the potential to improve stability of the starting material. Baxter's experience with technology transfer offers clients the option to integrate formulation processing equipment with their manufacturing process. The PROMAXX manufacturing process consists of a simple, robust, gentle process that is water-based whenever possible. This has been shown to preserve the drug's protein structure and activity. Pulmonary formulation challenges? Let Baxter help you overcome them. For more information, contact Baxter Healthcare Corporation at (781) 440-0100 ext. 281 or visit **www.baxterbiopharmasolutions.com.**

Drug Delivery Showcase

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**.

Gel Matrix Adhesive Technology



Conventional transdermal technology has relied upon traditional pressure-sensitive adhesives, which include primarily acrylate-, silicone-, and rubber- or polyisobutylene- based polymers, as the primary matrix to adhere the patch to the skin. With these traditional adhesive types, a significant amount of stratum corneum cells are removed and transferred to the adhesive surface, resulting in damage and irritation to the skin. The technology employed by Aveva and Nitto Denko is based upon a proprietary adhesive composition, which addresses these problems. This Gel-Matrix adhesive has unusual properties that allow for exceptional adhesion and wear to the skin without the removal of a significant amount of stratum corneum cells. This allows for unique properties, including the ability to reapply patches while reducing skin damage and irritation. For more information, visit Aveva Drug Delivery Systems at **www.avevadds.com**.

Contract Manufacturer/Supplier

Buender Glas GmbH is a business unit of the Gerresheimer Group headquartered in Duesseldorf, Germany. As a specialist in pharmaceutical glass systems, Buender Glas concentrates primarily on problem solutions relating to all aspects of injections. The company is an international technology leader in the growth market of prefillable syringes and cartridges. Its particular specialities include sterile all-glass syringe systems under the trademark RTF® (Ready-to-Fill). For the production of sterile syringes, Buender Glas has a unique technology center in which state-of-the-art ultrapure water-processing plants and clean-room systems in the 10,000 class set the basic standards. The company's products comply at least with the European, US, and Japanese pharmacopoeia requirements and are FDA registered. For more information, contact Buender Glas North America, Chris King, at (267) 895-1722 or visit **www.buenderglas.com**.

Advanced Delivery Technologies

Cardinal Health is the global leader in providing outsourced pharmaceutical development services, drug delivery technologies, contract manufacturing, packaging, and product commercialization services, serving the worldwide pharmaceutical and biotechnology industries. The company offers the broadest range of dose-form development and manufacturing options in the industry - from traditional and proprietary oral forms to sterile products, from inhaled forms to topicals. Cardinal Health holds more than 1,500 patents and patent applications for drug delivery systems. Technologies include soft gelatin capsules; Zydis® fast-dissolve dosage form; EnCirc®, EnVel®, and EnSolv® for oral modified-release products; lyophilization; inhaled technologies; and topical Microsponge® for timed-release and DelPouch® for unit dosing. For more information, contact Cardinal Health at (866) 720-3148 or e-mail pts@cardinal.com; or visit **www.cardinal.com/pts**.

Drug Delivery Showcase

Polymers & Delivery Technologies

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

Drug Development Services

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

Controlled Release Technologies

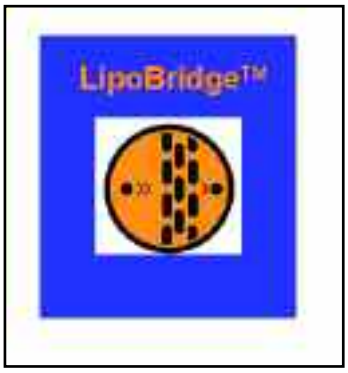
Egalet a/s is a drug delivery company focusing on formulation and development of oral controlled-release products using its proprietary drug delivery Egalet® and Parvulet® technologies. The company has four products in clinical development, two of which are entering into late-stage pivotal studies. The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

Orally Disintegrating Tablets

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

Drug Delivery Showcase

BBB Transporter



Lipobridge™ compounds facilitate transport of drugs across the blood-brain-barrier (BBB) and into the CNS. Short chain oligoglycerolipids have been shown to facilitate the delivery, distribution, and uptake of pharmaceutical actives into the CNS and thereby permeate the BBB. Data shows that some of these molecules can increase drug concentration reaching the CNS by a factor up to 100 without toxic side effects. Demonstrated in several laboratories, intracarotic injections of a simple mixture of Lipobridge and model compounds or pharmaceutical actives can be delivered into one or both hemispheres of the brain allowing for increased concentration in a selected hemisphere. This permeability has been shown to be reversible and has been demonstrated that the carrier itself is excreted unmetabolized. For more information, contact Genzyme Pharmaceuticals at (800) 868-8208 or visit **www.genzymepharmaceuticals.com**.

Sub-Q Protein Delivery

Would you like to convert your drugs from IV to subcutaneous (Sub-Q) delivery or enhance the dispersion of your existing Sub-Q compounds? With Enhanze™ Technology, microgram quantities of a fully human recombinant enzyme act as a "molecular machete" to clear the subcutaneous "jungle." Based upon this mechanism of action, co-delivery with Enhanze is anticipated to permit the Sub-Q administration of large volumes (up to 10 cc) of antibody drugs, speed onset of action relative to Sub-Q delivery without Enhanze, and improve patient comfort. For more information, contact Mark Wilson, Vice President of Business Development (Halozyme Therapeutics) at mwilson@halozyme.com or (858) 794-8889; or visit **www.halozyme.com**.

Manufacturer & API Specialist

Hovione is a fine chemicals company that specializes in the process development and manufacture of active pharmaceutical ingredients and regulated intermediates. Dedicated to solving the problems associated with the industrial production of complex chemical entities, the company's expertise in process chemistry and regulatory compliance to cGMP standards is based on more than 40 years of experience. Over that time, its ability to provide customers with timely solutions that are dependable and economical has given them a worldwide reputation for superior customer service. Hovione's business is 50% custom synthesis for large pharma and biotech companies and 50% generic products. More than half of today's sales consists of products launched less than 5 years ago. For more information, visit Hovione at **www.hovione.com**.

Iontophoresis Technologies

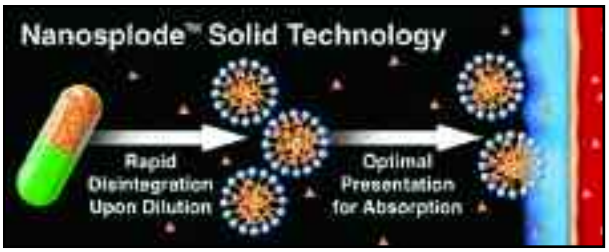
IOMED is a leader in the development, manufacture, and sale of active drug delivery systems that employ iontophoresis. IOMED's versatile transdermal and trans-scleral technology allows for custom delivery profiles for local and systemic applications. The company is actively pursuing opportunities to utilize its non-invasive drug delivery systems in combination with specialty pharmaceuticals to offer unique products designed to satisfy unmet medical needs. Licensing, co-development, and marketing agreements are available. For more information, contact IOMED at (801) 975-1191 or visit **www.iomed.com**.

Drug Delivery Showcase

Physical Characterization Workshop

IWPCPS-9 Ninth International Workshop on Physical Characterization of Pharmaceutical Solids, June 24-20, 2007, in Boston, MA, will be presenting information about cutting- edge methods for solid-state characterization, reviewing most recent regulatory issues, and presenting the latest research results in drug development and future outlooks. There will be 5 days of a Commercial Industry Exhibition with vendors of analytical, state-of- the-art pharmaceutical equipment who will introduce their newest instrumentation and software. Supporting companies include GSK; Boehringer Ingelheim; Amgen Inc; AstraZeneca; Sanofi-Aventis; Setaram; Teraview, UK; Panalytical; Lederer & Keller, Germany; Otago University, New Zealand; University of Toho, Japan; PerkinElmer; TA Instruments and more. For detailed information and abstract submission, visit our website **www.assainternational.com/workshops/IWPCPS_9/IWPCPS_9.cfm** or contact us at workshops@assainternational.com or +1 203 312 0682.

Solid-Lipid Dispersions



For diseases requiring rapid and superior therapy, drug absorption from a conventional solid dosage form of drugs with poor absorption potential is often slow and suboptimal. Nanosplode expands the dosage form options of Lipocine's Lipral (for optimal oral bioavailability) and Hydroance (for optimal non-invasive delivery of hydrophilic drugs with poor oral absorption potential) delivery technologies, while preserving their respective performance attributes. Nanosplode offers novel compositions and processes to produce practical solid dosage forms utilizing a broad spectrum of lipid materials. These materials are generally accepted lipid and other formulation excipients already in approved food or drug products. For more information, contact Lipocine, Inc., at (801) 994-7383 or visit **www.lipocine.com**.

New DDS Facility

NOF CORPORATION has been supplying Activated PEGs, high-purity phospholipids, and high-performance Polysorbate to pharmaceutical companies throughout the world. Its Activated PEGs have been used to conjugate with protein drugs so that PEG-stabilized drugs can circulate longer in the bloodstream with improved efficacy. NOF's new DDS plant for manufacturing Activated PEGs has started commercial operation under cGMP since October 2005. The new three-story, 200,000-sq-ft DDS plant now offers a five-fold increase in production capacity. The company's Activated PEGs and new plant have been attracting increasing attention from pharmaceutical companies across the globe. In addition, a new DDS Research Laboratory has just been established in the new building next to the DDS plant to accelerate the development of new products for DDS and satisfy customers. For more information, contact NOF Corporation at (914) 681-9790 or visit **www.nof.co.jp/dds**.

Pharmaceutical Product Development

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

Drug Delivery Showcase

Metering Delivery Devices

Rexam Pharma is a leading specialist in drug delivery devices and primary pharma packaging. The company has a recognized expertise in a wealth of different areas, including inhalation devices, such as dry powder inhalers and valves for pressurized metered dose inhalers; metering pumps and airless systems for topical or transdermal gels; spray pumps for topical or systemic use via the nasal or the buccal and sublingual routes; and injectors and implanters. With comprehensive resources in innovation, development, and industrialization and full GMP manufacturing, Rexam Pharma stands out as a partner of choice. For more information, contact Rexam Pharma at (914) 640-1310; mailboxpharma@rexam.com or visit w**ww.rexam.com/pharma**.

Controlled Delivery Platform

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

Sensor Technology

CMOSens (see-mo-sens): is a basic technology that is setting standards for high-precision sensor systems. Merging a semiconductor chip (CMOS) with sensor technology makes it possible to achieve highly integrated system solutions characterized by excellent sensor precision, digital intelligence, and reliability. The sensor component, amplifier, and A/D converter form a single unit on the same silicon chip. The digital intelligence of the CMOSens sensor facilitates output of a fully calibrated, temperature-compensated signal. The integral CMOSens "intelligence" of the chip thus allows measurement data to be output using a standard digital interface, such as SPI, for extremely straightforward processing. Due to a compact single-chip design, sensors based on CMOSens Technology have excellent resistance to electromagnetic interference (EMC), which is a significant technical advantage of this highly modern sensor technology. For more information, visit Sensirion, Inc. at **www.sensirion.com**.

Formulation Solutions

SPI Pharma is a worldwide leader in custom formulation solutions for pharmaceutical and neutriceutical manufacturers. By offering raw materials, processing capabilities, and advanced application technologies, the company has become a valued source for complete custom delivery systems. This provides a competitive advantage for its customers' formulations. SPI's broad product line includes excipients, antacid actives, and formulated systems. All products are produced under cGMP manufacturing guidelines suitable for pharmaceutical and neutriceutical applications. Core processing capabilities include precipitation, hydrogenation, crystallization, spray drying, granulation, micronization, suspensions, and encapsulation. Some advanced applications include solid dosage formulation, viscous suspensions/blends, DC chewing gum, effervescent systems, chewable/quick-dissolve tablets, and customized granulations. For more information, contact SPI Pharma at (302) 576-8554 or visit **www.spipharma.com**.

Drug Delivery Showcase

Silicone-Coated Papers & Films

Loparex specializes in thin coatings on flexible webs in the manufacture of release liners for medical pressure sensitive adhesive (PSA) products. The major categories that define the medical PSA market include: Transdermal Drug Delivery Systems, EKG/ECG Electrodes and Electro-Medical Devices, and Wound Dressings. Key performance characteristics of release liners for medical PSA products include: complete traceability, cleanliness, moisture resistance, and die-cutability. Manufacturing release liners that satisfy the requirements of both manufacturer and end user is critical. Because of our continuing commitment to leading-edge technologies in chemistry and substrate development, Loparex is uniquely qualified to develop a release liner designed for your unique application. Look to Loparex for all your medical device release liner needs. For more information, contact Loparex, Inc., at (888) 327-5454, ext. 2671 or visit **www.loparex.com**.

Spray & Dispensing Systems

Ing. Erich Pfeiffer GmbH is a leading manufacturer of pharmaceutical spray and dispensing systems, based in Southern Germany. The Pfeiffer product range is extremely versatile and offers dispensers for nasal, oral, and topical drug administration. Specific user needs are met by a choice of mechanical or electronic devices for multidose and unitdose applications. More than 5 decades of experience, dedicated innovation, and an uncompromising commitment to quality are behind the Pfeiffer dispensing systems, which are supplied to customers across all 5 continents. Customer requirements are integrated into the development process from the very early stages to ensure that user needs for safety, ease, and effective drug administration are met. Building on these strong foundations, Pfeiffer is committed to researching new systems for future therapies and applications. For more information, contact Pfeiffer of America at (609) 987-0223 or visit **www.pfeiffer-group.com**.

Product & Development Services

Given that the capsule dosage form had its genesis in pharmaceutical products, it is easy to understand why CAPSUGEL strives to go far beyond supplying high-quality capsules. CAPSUGEL's main mission is to assist its customers in the development of new products and line extensions. The company offers a wide range of specialized services to its pharmaceutical customers, for example, it can help provide appropriate technical information on a wide array of topics, such as formulating products for immediate or modified release. Also, its most recent technology can help experts in pharmaceutical development to formulate poorly soluble products. CAPSUGEL can assist in the technical transfer issues associated with scale-up and validation, and it has successfully proven its ability to design the best capsule and packaging that assures the highest level of customer satisfaction. For more information, visit Capsugel at **www.capsugel.com**.

Specialty Excipients

Developed by Huber Engineered Materials, a trusted name in calcium carbonate, silica, silicates, and other specialty excipients, RxCIPENTS® FM1000 is a fast-melt technology with numerous benefits to formulators and brand managers. RxCIPIENTS® FM1000 is an excipient that enhances tablet disintegration. It's fast, with tablet disintegration in 5 to 30 seconds, and strong, with a low tablet friability allows for standard packaging. It provides consistent tablet disintegration and is the excipient you can formulate in house without the need for a drug delivery company. Formulation scientists who are bringing new products to the market or brand managers who are forecasting line extensions of existing products can begin test formulations with RxCIPIENTS® FM1000 today. For more information, visit Huber Engineered Materials at **www.rxcipients.com**.

Drug Delivery Showcase

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Westech Instrument Services Limited specializes in the marketing and manufacture of all types of instrumentation for the measurement and collection of particulate and dust. The company has an intimate knowledge and understanding of existing devices, technologies, and trusted methods as well as access to many different sampling technologies and equipment manufacturers. Westech will find and design solutions to the most demanding sampling tasks, often through the innovative application of known technologies, for all types of aerosol, including ambient, automotive, emission, pharmaceutical, and biological. Westech also provides a comprehensive service and support program for all particulate monitoring systems in the field, including a maintenance and calibration service for the pharmaceutical industry and a UKAS-compliant traceable calibration service for the environmental monitoring market. For more information call Westech Instrument Services at (678) 627-8110 or visit **www.westechinstruments.com**.

Laboratory Testing Services

BioScreen is a full-service laboratory in industrial microbiology and analytical chemistry. The company is US FDA registered, ISO 9001:2000 Certified, DEA registered, and California State Certified to test drinking water. It now offers analytical reports direct from the Internet with electronic signature, and a blend of science and business with a service-oriented approach. BioScreen is capable of executing USP methods when required as well as designing or researching specialized methods for a unique product or process. The company has also participated in numerous projects for IND, NDA, and ANDA submissions to the FDA. There are four corporate divisions: Pharmaceutical & Biotechnology Services; Medical Device; Cosmetic, Household & Industrial Products; and Midwest Clinical Trials (Human Clinical & Claim Substantiations). For more information, contact BioScreen Testing Services, Inc., at (800) 229-9057 or visit **www.bioscreen.com**.

Reconstitution Device

Duoject has recently introduced the new Smart-Rod XR: Xpress Reconstitution system for staked-in needle syringes. The system is designed to fit a wide range of syringes and pharmaceutical cartridges for pen-injector applications. The development of Duoject's technologies in reconstitution and drug delivery of solid-form injectables is driven by a commitment to achieve similar user advantages as found in liquid prefilled syringes. Streamlining the reconstitution process reduces the need to develop stabilized aqueous drug formulations. Duoject designs and develops transfer and delivery devices for injectable drugs. Its unique expertise is focused on solid-form drug reconstitution and suspension devices for a wide range of indications. Customized versions of its innovative and patented device platforms are made available for license to biotechnology and pharmaceutical clients. For more information visit Duoject Medical Systems Inc. at **www.duoject.com**.

Device Development & Manufacturing

Throughout the past 9 years, BC Tech has grown to be one of the most comprehensive contract Medical Product Design, Development, and Manufacturing companies in California. It is established medical equipment manufacturing company with more than 100 medical devices completed for its satisfied national & international customers. BC Tech designed and developed its 20,000-square-foot facility to facilitate the flow of its multidisciplinary teams and their specialized equipment. BC Tech's seasoned teams have fine-tuned a development process that consistently yields highly effective medical products for its customers. BC Tech's medical equipment development and medical product manufacturing teams provide a highly effective outsourcing solution for companies seeking FDA-registered and ISO 9001-compliant medical equipment. For more information, contact BC Technology, Inc. at (831) 459-6464 or visit **www.bctechinc.com**.

DRUG DELIVERY Executive

élan

ELAN DRUG TECHNOLOGIES: UNLOCKING THE BILLION-DOLLAR NANO-PHARMA MARKET

Mr. Paul V. Breen
Executive Vice President & Head
Elan Drug Technologies

"Companies need to take a more critical look at their portfolios. Pharmaceutical companies focus on their R&D, yet significant opportunity exists in reformulation. They need to look at their entire portfolio – examining products that have not achieved their potential due to suboptimal delivery as well as those that have performed well but are coming under increasing pressure due to newer kids on the block."

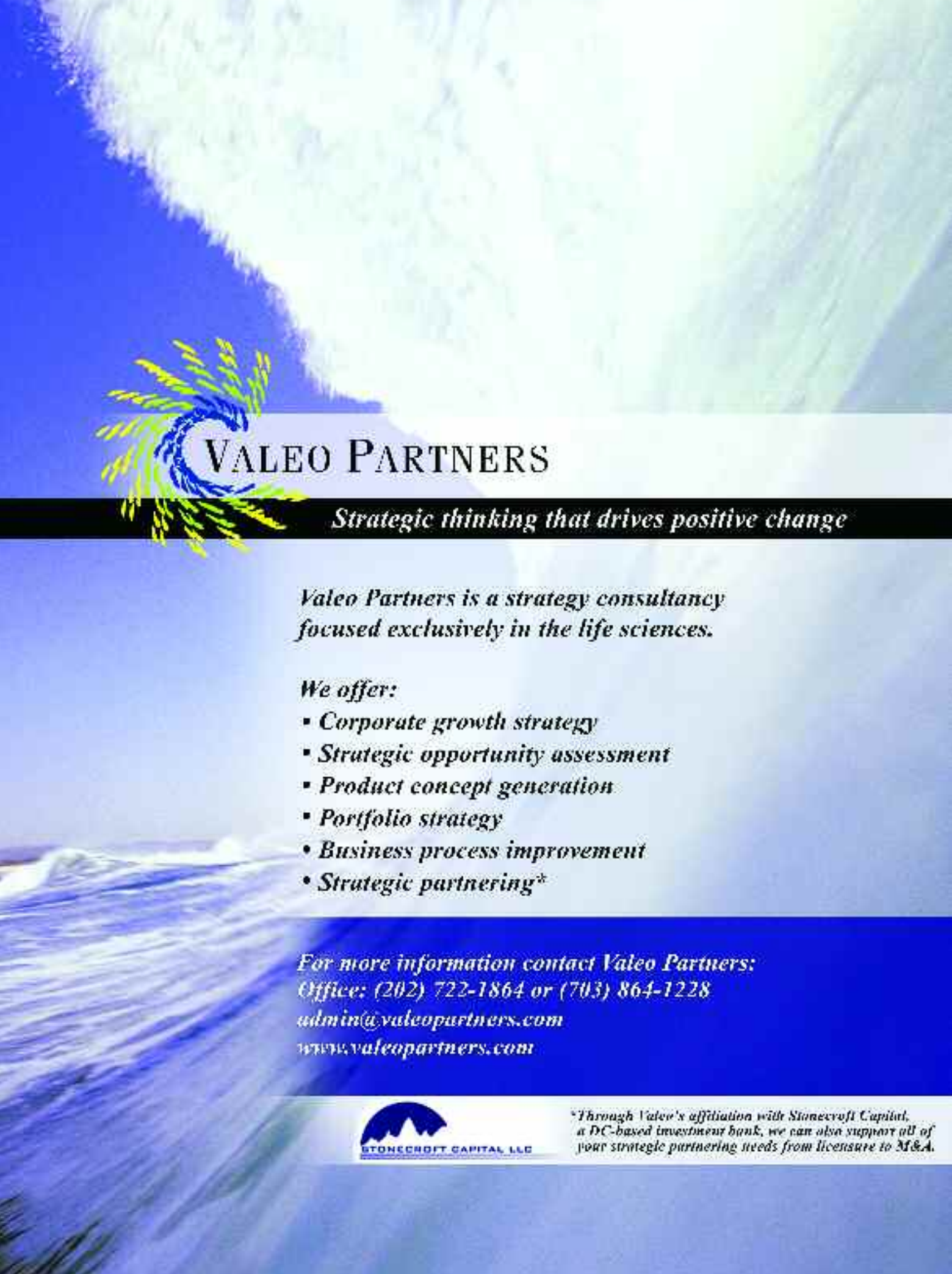
Elan Drug Technologies' (EDT's) key business is focused around product development and optimization of drug compounds. Their lead technology, NanoCrystal® Technology, applicable to poorly water-soluble compounds, has been incorporated into common dosage forms and has the potential for substantial improvements to drug performance. Now successfully used in the launch of four products in the US, the NanoCrystal technology has contributed to more than $1 billion in annual in-market sale of these drugs. As the EDT group begins to reap the reward of investing in this technology, Drug Delivery Technology caught up with EDT's Head and Executive Vice President, Paul V. Breen to find out more about this exciting technology and future plans for EDT's overall business.

Q: For our readers who may not be familiar with it, can you please describe your NanoCrystal® technology?

A: NanoCrystal technology involves manipulating the particle size of the drug at the nano-scale – somewhere between the width of a DNA strand and an atom. By reducing particle size to less than 400 nanometers, the exposed surface area of the drug is increased, and thus improving its ability to be absorbed. Applicable to poorly water-soluble compounds, the drug in nano-form can be incorporated into common oral, injectable, and inhaleable dosage forms. When you acknowledge that over 40% of drugs in the clinic have solubility problems and industry analysts are predicting the drug market for nanotechnology will be worth over $200 billion by 2015, you begin to realize the vast potential this technology offers both the industry and ultimately patients. NanoCrystal technology is now our most exciting technology within EDT.

Q: What makes this technology unique?

A: It is the science behind the technology and its successful commercialization that make it unique. There are a number of companies developing approaches to overcome poor water solubility, but few have made it to commercial launch with their technologies, with very few having commercial-scale manufacturing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capabilities. The NanoCrystal technology now has four products launched in the US, contributing to over $1 billion in annual in-market sales.

Q: What benefits does this technology offer? Can you provide some examples?

A: This technology offers tangible patient benefits, which is obviously the most important thing, so it is not just technology for technology's sake. For example, one commercialized product using our technology provides a 600% improvement in bioavailability; in another instance by applying our technology, a four-fold reduction in dosage volume is achieved. For a number of compounds, the food-fasting effect, which is a patient compliance issue, is eliminated. It is very pleasing to see a technology in which the company has invested time, effort, and money bear fruit and offer clear benefits to patients. Offering clear benefits such as these is a very plausible way of overcoming the drug challenges many companies now face with their aging pipelines.

Q: How significant is the challenge that aging pipelines pose to pharmaceutical companies?

A: Extremely significant. Despite research spend reaching an all time high, New Chemical Entity (NCE) approvals were down 55% in 2005. Several of the major pharmaceutical companies in 2005 failed to win approval for an in-house NCE, and the cost of that failure is high. Prudent Life Cycle Management (LCM) strategies need to be developed to optimize a company's portfolio. To date, LCM strategies to manage existing products have not been universally applied or have been applied too late. Over $80 billion worth of pharmaceutical products will go off patent in the next 5 years, which is a major cause of concern for many in the industry.

Q: What in your opinion is the solution?

A: Companies need to take a more critical look at their portfolios. Pharmaceutical companies focus on their R&D, yet significant opportunity exists in reformulation. They need to look at their entire portfolio – examining products that have not achieved their potential due to suboptimal delivery as well as those that have performed well but are coming under increasing pressure due to newer kids on the block. And they need to do this earlier than they have to date. This industry often ignores the success of reformulations because it is not as glamorous as a new product. There are numerous examples of products that have enjoyed long life with the aid of successful reformulation strategies – Cardizem®, Effexor®, Fosamax®, Wellbutrin®, and Adderall® to name a handful.

Q: Is Life Cycle Management always an option?

A: For any product to be successful, it needs to have a clear clinical/medical benefit. A reformulated product, with minor clinical benefits over the original, isn't going to cut it anymore. The difference has to be medically relevant, marketable, and where possible, patentable. A Life Cycle Management strategy based on little perceivable advantages

over the original will count for nothing. By applying our NanoCrystal technology, we have proven that we can develop distinctively differentiated products through reformulation.

Q: Please discuss an example of a distinctively differentiated product through reformulation.

A: We were approached by a company that had a product on the market for the treatment of anorexia and significant weight loss in patients with AIDS. However, this compound, which was used to stimulate appetite, was a thick viscous liquid that was difficult to swallow and had to be taken with food. Using our NanoCrystal Technology, we formulated a superior, more palatable product with a significantly lower dose than the original product. The viscosity was reduced 16-fold, the volume swallowed reduced by 75%, and probably most significantly, it could be taken with or without food – a significant benefit for those with poor or no appetite. We have plenty of other examples of how we have given our client companies truly differentiated products, be they poorly water-soluble compounds or not. We would consider ourselves the ideal partner for a company that has a drug with suboptimal delivery.

Q: What qualities makes Elan an ideal partner?

A: We have not only technologies to overcome common drug optimization problems, but also a proven track record. Thirty products have been launched in over 40 countries using Elan's technologies. Since 2001, we have assisted seven pharmaceutical companies launch seven technology-enhanced products in the US. That makes us the most productive drug technology firm throughout the past 5 years. The cohabitation of development and manufacturing capabilities on the same sites is also a benefit to many companies as it allows for streamlined scale-up and transfer to commercial-scale manufacturing activities. Also, we are comfortable working with large and not-so-large companies. Our current client list includes such companies as Merck, Wyeth, and Abbott as well as smaller companies, such as MAP and EntreMed.

Q: What lies ahead in he future for Elan Drug Technologies?

A: We will continue to capitalize on this technology we have developed. We have over 70 compounds now in development using our NanoCrystal Technology. We have also been working very diligently in strengthening our technology patent estate – at present, we have more than 1,400 patents and patent applications. Our facility in Athlone, Ireland, has also been upgraded and now has significantly more space and capacity to manufacture NanoCrystal technology-derived products. In our Pennsylvania facility, we have over 60 scientists working on further enhancements of the technology. Today, more than 2.5 million patients worldwide use drug products based on, or enhanced by, Elan's technologies. We hope throughout the next few years to increase this number significantly, offering truly distinctive, robust, and commercially sound products that benefit our clients and ultimately patients. ◆

Preservative Free Applications

Facing the Challenge of Broadening the Benefit Spectrum

By: René Bommer, PhD, and Jochen Kern

INTRODUCTION

The positive market reception for the Advanced Preservative Free system provided the Pfeiffer development team with a new, highly complex challenge. In the market, there was a clear demand for extending the benefits of the Advanced Preservative Free nasal pump to other applications. What would be the best response? René Bommer and Jochen Kern from Ing. Erich Pfeiffer GmbH, Radolfzell, Germany, trace the development from a mono-product line to the new Cartridge system, a modular product.

THE ADVANCED PRESERVATIVE FREE HERITAGE

Launched in 2003, the Pfeiffer Advanced Preservative Free system is a multidose system for the application of preservative free solutions via the nasal route. Patented filter technology prevents bacteriological contamination of the drug product on its metal-free path. This mechanical device is 100% sealed and has interchangeable secondary packaging. Since its launch, the Advanced Preservative Free system has offered producers of unpreserved nasal medication

FIGURE 1
The Advanced Preservative Free System From Pfeiffer

Preservative Free *Applications*

around the world an effective solution and won a number of prestigious design awards.

FINDING A SOLUTION FOR NON-NASAL & PRESERVED APPLICATIONS

The development of a new system, integrating all of the benefits of its predecessor, had two specific goals. It needed to be suitable for applications other than nasal and for solutions containing preservatives. These objectives marked the start of an intensive 2-year development phase at Ing. Erich Pfeiffer GmbH in Radolfzell, Germany. The brief was to develop a modular system to accommodate these diverse application needs and, if possible, set new standards in flexibility and customization. It was also necessary to maintain the established performance levels of the Advanced Preservative Free system, including low actuation force, strong priming and re-priming action, plus the emission of a smooth spray.

CARTRIDGE FAMILY READY FOR SAMPLING

Now, in the third quarter of 2006, the new, modular Pfeiffer Cartridge system is ready for sampling. This follows an extensive testing period as well as independent verification of the system's microbiological properties by the Qualis laboratory in Constance, Germany. Designed as an open platform, the family comprises otic, topical/oral, and nasal sprays as well as a nasal drop dispenser. Preserved and non-preserved solutions can be accommodated and dispensed by this product family. There are options of crimp, screw, or snap-on closures, plus a choice of colors, material, and designs.

For all of the applications, the pump functionality is essentially the same, leading to a smooth spray and high-performance reliability. In the topical version, the tip-seal is smaller in size, but the mechanical properties remain constant. For nasal applications, there is a choice of two devices with the spray and drop dispenser. The Cartridge pump can be integrated into existing processes and products, and the interchangeable design aims at giving customers branding opportunities to support their product differentiation. Standardized filling procedures and assistance with regulatory affairs are key elements of the accompanying customer support package that has been created parallel to the development, ready for the market introduction.

FIGURE 2
A Cross-Section of the Advanced Preservative Free System

A TWO-DIGIT LIST OF UNIQUE BENEFITS

The measurable results of this development process can be summarized in a verified two-digit list of unique benefits. Some are tip-seal driven, others related to microbiological integrity, and several more are expressed in specific usage characteristics.

Propriety Tip-Seal Technology

The propriety and patented Pfeiffer tip-seal and the special micro-filter with its textile

FIGURE 3
A Two-Dimensional Shot of the Cartridge System

membrane equip the Cartridge system to prevent microbes entering the system and to stop the clogging of the tip of the pump. This is key when dispensing crystalline solutions, such as throat medication containing sugar or steroidal medication. The sealed mechanism brings reliable protection against evaporation and particles or dust. Eliminating the risk of evaporation is crucial when dispensing a range of substances, for example, those containing alcohol with its volatile behavior.

The tip-seal is instrumental to the system's proven priming and re-priming action, leading to a significant reduction in drug wastage. This protection against a loss of prime means, for example, that even after a 2-week period of inactivity in a bathroom cupboard, the Pfeiffer Cartridge spray will dispense the correct dosage in the appropriate concentration.

A Metal-Free Route

The Pfeiffer Cartridge system facilitates a fully metal-free path for the pumps' contents. This feature is expected to have a meaningful impact in the rapidly growing field of homeopathic medicine for instance. Being highly diluted, homeopathic medicines are extremely sensitive to contamination, even from the mild scent of everyday substances, such as peppermint or coffee. Any contact with metal during dispensing would be detrimental to medicines of this type and potentially render them completely ineffective. From a regulation point of view, it is also a source of confidence and efficiency for pharmaceutical manufacturers to be able to completely eliminate the need for tests relating to metal content in dispensers, for example, where active pharmaceutical ingredients, such as proteins and peptides, are concerned.

THE CUSTOMIZATION CHALLENGE

In developing the new Cartridge system, Pfeiffer faced challenging demands for flexibility, without compromising any aspects of performance, dependability, or user-friendliness. The resultant modular product family is geared to allow the relatively simple customization of the dose volume. Regardless of changes in the outer dimensions of the package, for example, to accommodate products specifically for adults or children, the overall spray package height remains constant, regardless of the dosage. Filling flexibility is also facilitated by the ability to integrate the production of two dose-volumes in the same line.

The concept behind the secondary packaging is two-fold. From a design and marketing perspective, the aim is to offer clear product differentiation without complexity. From the development point of view, the constant design of the primary packaging aims to fulfill regulatory criteria at the start, independent of the parallel development of the secondary packaging (including interchangeable finger flange). More specifically, because the primary package is not adjusted, its registration remains valid, so there is absolutely no need for usability trials or other related, resource-consuming administrative activity.

RARE HARMONY BETWEEN SCIENCE & MARKETING

The Cartridge family has the clear objective of ensuring that scientifically proven characteristics translate directly into sales and

FIGURE 4
The Pfeiffer Cartridge Family

marketing advantages for pharmaceutical manufacturers. The resultant modular system is unusual in its ability to provide the market with reliable performance excellence and a clear competitive business advantage, all under the umbrella of flexibility. Minimum investment is thus required to bring maximum success on the market, through using one dependable dispensing solution for many formulations and applications. In the Cartridge family, marketing and science meet in a win-win situation to satisfy the toughest efficiency, performance, and design requirements of the increasingly competitive global pharmaceutical market. ◆

ACKNOWLEDGEMENT

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BIOGRAPHIES

Dr. René Bommer is Director of Business Development at Pfeiffer Pharma Division. He earned his PhD in Chemistry (1990) from the University of Constance in Germany. His areas of research focused on carbohydrates and antigens. He was a Research Associate at the Scripps Clinic in LaJolla, focusing on monoclonal antibodies and at Byk-Gulden Pharmaceuticals in Germany. Following a lectureship at the University of Buenos Aires in Argentina, he joined Pfeiffer, a developer and manufacturer of mechanical dispensing systems for pharmaceutical applications.

Mr. Jochen Kern is Sales Director Europe and Associated Marketing Director at Pfeiffer Pharma Division. He earned his MBA from the University of Applied Sciences of Constance in Germany. He joined Pfeiffer in 1996.

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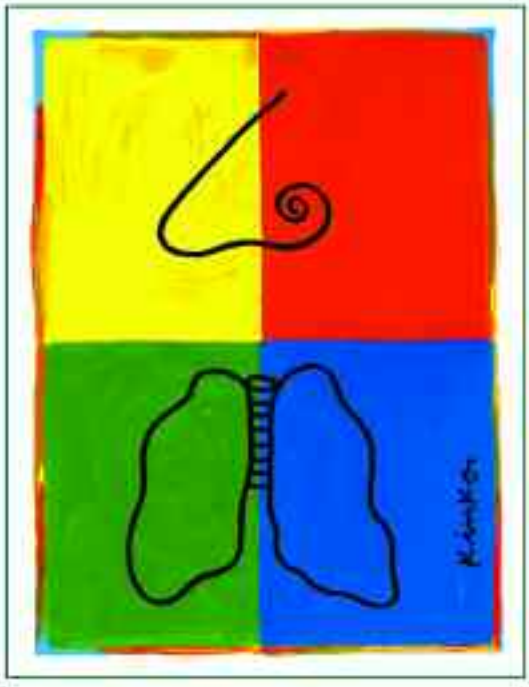

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The Yes Person Filter Factor, Part II

By: John A. Bermingham

As last issue's article discussed, *The Yes Person Filter Factor* can be a serious problem for anyone. So what can you do about it? I believe that you have to establish a culture in your management style that allows for mistakes to be made.

I am not asking you to accept repeated mistakes by the same person or mistakes that are caused by people who don't care, don't work hard, don't follow policy, or are not conscientious. People like that should not have a place in your company or department to begin with.

I'm referencing those people who make an honest mistake while working hard to achieve something. People who are doing something. I have a rule in my companies that I refer to as *Rule 27*.

In my opening Town Hall Meeting with all people at a new company, I always talk about *Rule 27* and reference it in the future as needed. I learned *Rule 27* when I was a newly graduated Corporal from the cryptography school at Fort Monmouth, New Jersey, where I was assigned to work at the officer's crypto school. On my first day on the job, I decided to prove my worth by making preventive maintenance adjustments to the cryptography equipment in the officer's school.

After completing those adjustments, I found that none of the crypto equipment worked, and there was a class the next morning using that equipment. Terrified and humiliated, I went to my boss, Sergeant Nick DePalo, a crusty old Sergeant First Class just back from Vietnam, and explained to him what I had done. I expected to be on Kitchen Police (KP) for the rest of my life.

Sergeant DePalo looked at me and said, "Corporal, always remember *Rule 27. Rule 27* states that people who don't make mistakes aren't doing anything. Now go fix those crypto machines."

I never forgot *Rule 27* nor Sergeant Nick DePalo. We quickly became great friends. So I always tell this story to our people and add that in my management style, people never get in trouble for making an honest mistake. Admit to it, help to fix it, learn from it, and move on. If people are doing things, they are going to make mistakes. You get in trouble when you make a mistake and hide it, filter it, or try to blame it on others, not taking accountability.

Once you establish that culture, you stand by it and immediately take out those people who don't get it or choose not to participate in the culture of surfacing mistakes. They are easy to spot in a *Rule 27* culture, and you must act quickly. Then *The Yes Person Filter Factor* will quickly disappear, and others will not tolerate Yes people either. ◆

BIOGRAPHY

John A. Bermingham joined Ampad as President and CEO in August 2003 when Ampad was acquired by group of investors composed of an affiliate of Crescent Capital Investments, himself, and another private investor. He also serves as Chairman of the company's Board of Directors. Previously at the helm of numerous industry-leading companies, Mr. Bermingham brings more than 20 years' experience in guiding enterprises to new levels of performance. Most recently prior to joining Ampad, Mr. Bermingham held the positions of Chairman, President, and CEO of Centis, Inc., a diverse multinational manufacturer and marketer of office, storage, and human resources products. Prior to joining Centis, Mr. Bermingham successfully leveraged the potentials of two start-up companies, raising capital, forging key relationships, and establishing the structure and direction that would pave the way for future growth and achievement. Among his many career highlights in the role of President and CEO for companies serving the office products industry, Mr. Bermingham successfully reorganized Smith Corona Corporation, restoring the company's stability, profitability, and reputation. At Rolodex Corporation, he refocused operations and a strategic vision for a dramatic turnaround in corporate culture, and phenomenal increases in both revenue growth and cashflow. Mr. Bermingham's expertise in leveraging technology and optimizing resources for the business products/services markets has also been deployed at industry giants, such as AT&T Consumer Products Group, and by having served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes. Earning a BA in Business Administration from Saint Leo University in Florida, Mr. Bermingham has also completed the Harvard University Graduate School of Business Advanced Management Program.

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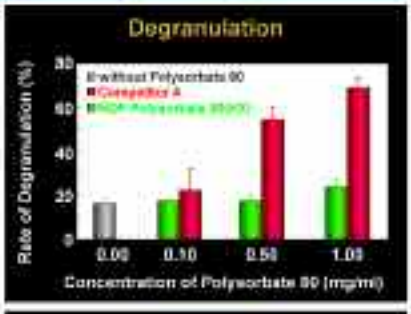

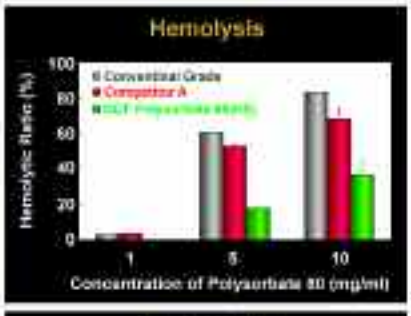

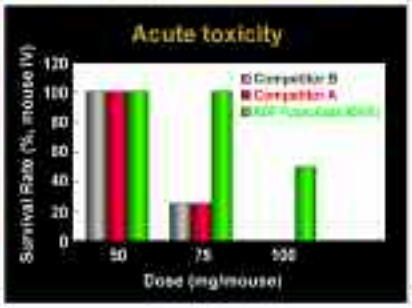

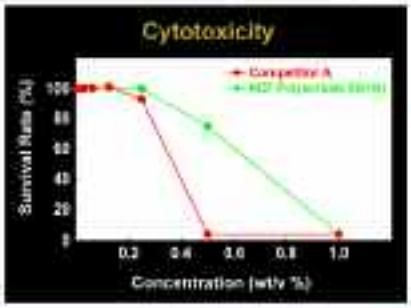

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