Drug Delivery Technology®

February 2007 Vol 7 No 2

Combination Products in Europe & Asia

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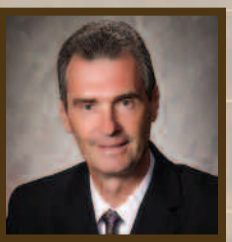

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Europe & Asia

"As American companies develop new medical devices and combination products, they will need to continue to be aware of recent and upcoming changes in the regulatory environment of each European and Asian country that presents a potential marketing opportunity. As these products grow more sophisticated, so does the regulatory process that is set in place to protect the consumers who will be benefiting from them."

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"To overcome the aforementioned limitations of conventional topical and oral modes of administration for retinal delivery, local delivery approaches are currently being investigated. The intravitreal and periocular routes are alternatives that can deliver greater dose fraction to the retina, resulting in dose reduction and reduced systemic toxicity."

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Market News and Trends

MediVas Announces Collaborations With PacificGMP & Pfizer

PacificGMP, Inc., and MediVas, LLC recently announced they have formed a collaborative effort to develop a commercial-scale production process for MediVas' next-generation subunit vaccine utilizing MediVas's novel amino acid-based Poly(Ester Amide) copolymers (PEA). MediVas' polymers are the first of a new generation of absorbable and biocompatible drug and biologic delivery platforms. Under this collaboration, PacificGMP will work with MediVas in developing the capability of manufacturing large quantities of subunit vaccines to protect against such diseases as seasonal and pandemic influenza, among many other potential candidates.

PacificGMP will utilize its expertise in disposable bioprocessing and its unique technology to scale up the production process and manufacturing for MediVas' initial candidates. Use of this disposable bioprocessing technology will allow for faster production, with greatly reduced overall manufacturing costs. This process also mitigates the possibility for cross-contamination in production, which should ultimately result in vaccines that will be available to the public in a much shorter time period.

MediVas' infectious disease and immunology platforms include rapid response formulations for next-generation vaccines. MediVas' lead preventative vaccine program represents a novel process to develop and manufacture vaccines for both seasonal and pandemic influenza. In addition, the company is also developing therapeutic vaccines with a lead program targeted against certain cancers.

"We continue to advance our capabilities in developing important next-generation biocompatible drug delivery solutions," said Kenneth Carpenter, President and CEO of MediVas. "We are confident in our ability to create innovative new drug delivery technologies across multiple therapeutic areas. PacificGMP is ideally suited to allow us to take the next step and bring our new therapeutic technology into the clinic and then into the public sphere."

"PacificGMP is excited to assist MediVas with this important project. We anticipate that production of MediVas' subunit vaccines in disposable closed systems will be a significant milestone in the development of rapid response formulations for next- generation vaccines. We are delighted to announce this collaboration and to assist MediVas in moving forward with this novel technology," added Leigh Pierce, President of PacificGMP.

Using its proprietary family of biodegradable and biocompatible polymers, MediVas has developed a next-generation platform for the delivery of biologics. MediVas is utilizing its novel polymer technology in collaboration with some of the world's largest pharmaceutical companies, as well as on its own internal product development efforts, to create groundbreaking medical advancements. The more than $50-billion biologics market is the next frontier in medicine, and MediVas is uniquely poised to take advantage of this growing space. By combining therapeutic proteins and other biologics with a MediVas polymer, delivery routes that were previously unimaginable, such as oral, intranasal, inhaled, or subcutaneous injection, can become a reality. By opening up these delivery routes, MediVas' delivery system can make the administration of the biologic more convenient, more efficacious, and safer, leading to higher patient compliance and overall better health.

PacificGMP is a Contract Manufacturing Organization (CMO) that specializes in the development and manufacturing of biologics using disposable technology. PacificGMP has extensive experience in process development and production of antibodies, recombinant proteins, gene therapy, and vaccine products. PacificGMP assists drug developers through the early stages of process design, development, and scale-up to pre-clinical and clinical manufacturing.

MediVas also announced the signing of a collaborative research agreement with Pfizer. The agreement is focused on the research and development of advanced delivery methods for proprietary Pfizer compounds to treat diseases of the eye. By combining the fully biodegradable and biocompatible MediVas polymers with the Pfizer compounds, MediVas and Pfizer hope to create a product that can change the paradigm of how ophthalmic treatments are administered. Financial terms of the agreement were not disclosed.

Commenting on the announcement, Kenneth W. Carpenter, MediVas' President and CEO, said, "We are excited to enter this relationship with Pfizer, and we are confident that by combining Pfizer's compounds with our best-in-class polymer delivery system we can help to increase patient compliance and significantly improve treatment of diseases of the eye. We look forward to moving this collaboration ahead quickly and to entering into a broader relationship with Pfizer."

Organon Partners With Huya to Identify & Develop Chinese Biopharmaceuticals

Organon, the human healthcare business of Akzo Nobel, recently announced it has signed a collaboration agreement with HUYA Bioscience International, LLC, (HUYA) to search for new, proprietary biopharmaceuticals or pharmaceutical compounds. As part of this collaboration, Organon has acquired an equity interest in HUYA, a biopharmaceutical company focused on developing Chinese biopharmaceutical products.

HUYA, with offices in San Diego and Shanghai, identifies, licenses, and develops Chinese drug candidates for commercialization in Western markets. Under the collaboration agreement, HUYA will support Organon in the sourcing and development of pharmaceutical or biopharmaceutical compounds in three specific therapeutic areas.

“This is an important strategic opportunity for Organon. It is consistent with our research strategy to forge closer links with China’s highly skilled and motivated scientists and significantly expands our own ongoing biotech research programs and capabilities,” said David Nicholson, Executive Vice President Research and Development at Organon “We are very excited by this investment and the prospect of closely collaborating with HUYA.”

Mireille Gingras, President and Chief Executive Officer of HUYA, added, “We are delighted to share the Organon knowledge and harness their extensive expertise in drug development in three specific therapeutic areas. We believe this collaboration is the first one between a biopharmaceutical and biotech company to jointly identify and develop investigational drugs in China. HUYA is highly experienced and uniquely well positioned with our large network of life science contacts and operating history in China to capitalize on the emerging biotech industry there.”

No financial details of the transaction were disclosed. The announcement follows other research collaborations that Organon has entered into with other leading Chinese biotech companies, such as Shanghai Genomics and HD Biosciences in the last year.

Market News and Trends

elbion Acquires Late-Stage Product Candidate for Treatment of Alcohol Dependence

elbion NV, a leading European drug discovery and development company, recently announced it has acquired a number of product candidates from the French

biotechnology company DrugAbuse Sciences. The most advanced candidate, Naltrexone

Depot, a sustained-release formulation of naltrexone, will become elbion's lead product, and the company expects it to enter pivotal Phase III clinical trials in 2007. A second asset acquired is Buprenorphine Depot, a sustained-release buprenorphine indicated for the treatment of opiate addiction. The acquisition of the DrugAbuse Sciences candidates was made in return for a financial consideration including elbion shares. Full financial terms were not disclosed.

Naltrexone Depot is a novel, sustained-release formulation of naltrexone, an antagonist that blocks receptors in the brain and is used in the treatment of opiate and alcohol abuse. Unlike conventional naltrexone dosage forms (ie, daily tablets), Naltrexone Depot is designed as a simple once-a-month intramuscular injection, which elbion believes will offer significant advantages in the treatment of alcoholism where patient treatment compliance is a major limiting factor.

Previous clinical trials with Naltrexone Depot have shown encouraging results with a trend toward greater levels of abstinence from alcohol for patients receiving treatment compared to those on placebo. elbion intends to begin a pivotal Phase III trial in 2007 with an improved formulation of Naltrexone Depot.

The company is collaborating on formulation development work with Brookwood Pharmaceuticals, a US drug delivery company, and acquired a license to certain Brookwood technologies as part of the asset acquisition. Brookwood will supply the product for trials.

Bernd Kastler, CEO of elbion, said, "This agreement brings us another advanced clinical product to add to our pipeline and one which we believe can be a significant value driver for elbion. Alcohol dependence has a profound effect on the lives of millions of people around the world, and we believe that Naltrexone Depot has the potential to play a major role in their treatment. We intend to initiate a well-designed Phase III program with an improved formulation of the product, and then to commercialize Naltrexone Depot through our own sales and marketing operations in certain territories and through licensees in others."

"The announcement of elbion's acquisition of the Naltrexone Depot program and other assets from DrugAbuse Sciences is good news for the future of what we believe is a very high value product," added Patrick Langlois, Chairman of DrugAbuse Sciences. "We are confident elbion's clinical expertise and the plans they have put in place for the development and commercialization of Naltrexone Depot will allow the full potential of the product to be realized and bring value to DrugAbuse Sciences investors through their holdings in elbion."

Arthur J. Tipton, PhD, President and CEO, Brookwood Pharmaceuticals, said, "Brookwood Pharmaceuticals strongly believes in the technical and market potential of the long-acting naltrexone under development at elbion. We have developed a positive relationship with the senior team at elbion and are enthused to be working with such a dynamic organization. We look forward to accelerating to market important products for the treatment of alcohol and opiate abuse."

Buprenorphine depot is in preclinical development. elbion intends to develop the product for the treatment of opiate addiction.

Eyegate Pharma Closes $12 Million Series B Venture Financing

EyeGate Pharma, a specialty pharmaceutical company pioneering the use of iontophoresis technology to safely and non-invasively deliver therapeutics for ocular indications, recently announced it has closed on a $2 million extension of its Series B venture round, bringing the total of the financing to $12 million. This additional funding comes from The Nexus Group and brings the total venture investment in EyeGate to $16 million.

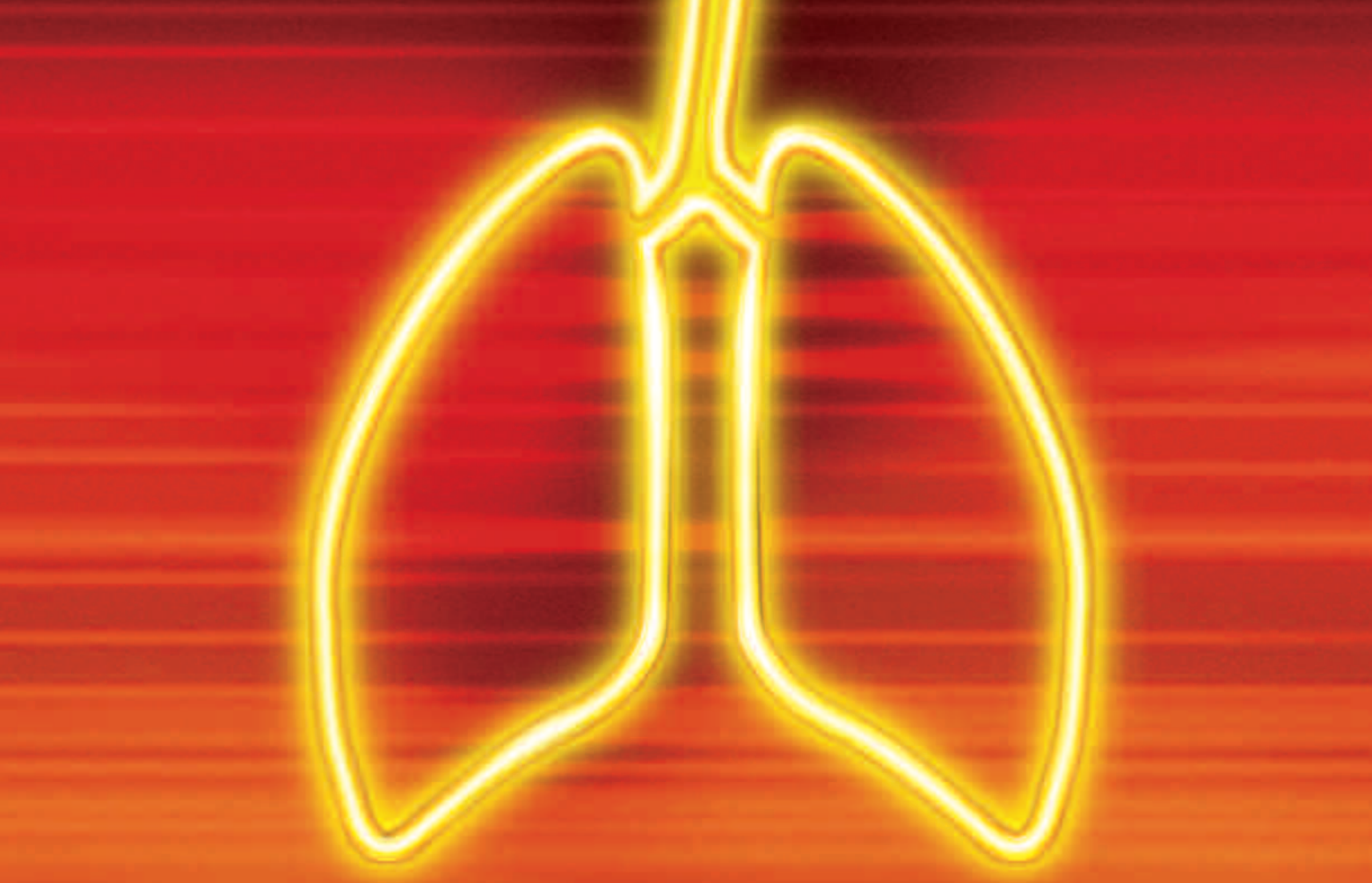
The first tranche of EyeGate's Series B round was co-led by Innoven Partenaires and existing investor Ventech, both of Paris, France. EyeGate had originally announced it had planned to secure funding for up to $10 million and in keeping the round open for potential US venture firms to become part of the syndicate, secured an additional $2 million in funding. As part of the transaction, Thomas E. Hancock, Principal of The Nexus Group, will be joining EyeGate Pharma's Board of Directors.

"EyeGate is pleased to welcome Nexus to our investor group and Tom Hancock to the Board of Directors," said Stephen From, President and Chief Executive Officer of EyeGate Pharma. "EyeGate will greatly benefit from his direction based on the depth of his experience in corporate, research, and banking roles. Adding a prominent US investor of Nexus' caliber is an important milestone for the company after beginning operations in Waltham, MA, in October of 2006."

Thomas E. Hancock added, "EyeGate has built an impressive ocular delivery platform with a strong intellectual property position that will address large markets with unmet medical needs. This platform fits well into the broader therapeutic ophthalmology space and has the potential to deliver a pipeline of commercially attractive compounds. It also provides significant opportunities for partnering. We are delighted to be working with the company and the other investors to build a leading company in this exciting area."

Mr. From continued, "The EyeGate II Delivery System represents a much needed safe and non-invasive alternative to ocular injections, implants, or eye drops for drug delivery with higher localized concentration to the front and back of the eye. This additional funding will help to accelerate EyeGate Pharma's clinical candidate for severe uveitis, which will be delivered using the EyeGate II Delivery System, into the clinic in the second half of 2007."

EyeGate Pharma was founded in 1998 with technology licensed from Bascom Palmer Eye Institute at the University of Miami. EyeGate's transscleral iontophoresis delivery platform, the EyeGate II Delivery System, was designed by ophthalmologists for ophthalmologists. This non-invasive system can be applied to safely deliver a wide range of therapeutics to both the anterior and posterior chambers of the eye. An 89-patient pilot study using the company's first-generation delivery device demonstrated exceptional patient tolerance with a significant decrease in inflammatory markers and a concurrent increase in visual acuity. A typical application takes less than 5 minutes and has been shown to be extremely well tolerated in patients suffering from severe uveitis and other inflammatory ocular diseases. Clinical studies utilizing the EyeGate II Delivery System are scheduled to begin 2H 2007.



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NWLS Signs Exclusive License Agreement Relating to Innovative Topical Drug Delivery

New Life Scientific, Inc., a company specializing in the development of new biotechnology products and pharmaceuticals, recently announced it has entered into an exclusive license agreement for two platform technologies (patent pending) that will allow formulation of topical drugs for various applications. The first technology involves topical formulation of prostaglandins that are temperature stable. NWLS will develop specific treatments for male erectile dysfunction (ED). The formulation is intended to allow treatment of ED (by simple application of PGE to glans of the penis) and female sexual arousal disorder (FSAD). The same technology will be used to formulate topical prostaglandin preparation for wound-healing indications.

The second technology allows for enhanced drug bioavailability from topical applications based on modification of solvency profile of drugs that have limited solubility, eg, itraconazole. This technology will be used for the formulation of topical drugs at concentrations higher than presently available for skin and nail fungal infections and other indications.

Wieslaw Bochenek, MD, PhD, company President and Chief Scientific Officer, said, "We are excited on the opportunity ahead of us. Presently available topical treatments for erectile dysfunction are cumbersome to use and never gained popularity. Our newly acquired technology will allow for creation of formulations that will offer ease of use and an excellent safety profile with negligible or minimal systemic effects. Wound healing and fungal skin and nail infections are major unresolved medical problems that still await more efficacious methods of treatment and which affect large numbers of people."

The company's Chairman and CEO, Henry Val, declared that the new platform technologies and the product that will be developed offer significant business opportunity for NWLS.

The National Institutes of Health estimates that more than 30 million American men suffer some degree of ED. Decision Resources Inc. estimates more than 76 million men suffer from ED in the seven most industrialized nations. At age 65, 62% of all men have some degree of erectile dysfunction (18% mild, 30% moderate, and 14% severe).

Female sexual arousal disorder (FSAD) is a less discussed sexual problem that continues to gain recognition and attract attention. Its main sign is persistent or recurrent inability to attain the lubrication-swelling response of sexual excitement, until completion of sexual activity. The data from the National Health and Social Life Survey indicate that approximately 30% of women report lack of sexual interest and close to 25% do not experience orgasm. Development of treatment for this condition constitutes one of the unmet needs.

New Life Scientific, Inc., was formed with the intent to develop and commercialize novel biotech/pharmaceutical products, including vaccines and stem cell- based treatment modalities, and to expand through its own research, collaborations, acquisitions, and in-licensing. The company has two subsidiaries: one subsidiary, PharmaTrials International (PTI), provides clinical trial services, market research, and services to enable pharmaceutical, biotech, and medical device companies worldwide to conduct research and to obtain regulatory approval of their products. The other subsidiary, Invamed Pharma, develops and commercializes pharmaceutical/biotech products coming from its own pipeline of in-licensed and reformulates existing products using proprietary technologies to improve the therapeutic potential of those drugs.

Biorigen USA, a joint venture of New Life Scientific, Inc. and Biorigen Srl, an Italian biotechnology company, is involved in development of adult stem cell-based therapies. Biorigen USA's major proprietary technologies include the use of biomaterials as a carrier for stem cells and growth factors, and other biomolecules to promote stem cell survival and biologic activity in tissue repair/regeneration after implantation and proprietary cell culture methods.

Insert Therapeutics Signs Collaboration & Option Agreement for Cancer Compound

Arrowhead Research Corporation recently announced that its majority-owned subsidiary, Insert Therapeutics, Inc., has entered into a collaboration agreement with R&D-Biopharmaceuticals GmbH to develop and commercialize conjugates of the potent anti-cancer compound tubulysin with Insert's proprietary drug delivery system, Cyclosert. The agreement provides a research license and an option for an exclusive license to develop and commercialize tubulysin-polymer conjugates.

"With this agreement, Insert has secured proprietary rights to one of the most potent anti-cancer compounds known," said Edward L. Jacobs, Insert's CEO and President. "The major challenge to its use as a cancer treatment has been toxicity. Linking tubulysin to Cyclosert could provide a fast track its use in humans." Tubulysins are naturally occurring cytotoxins that prevent cell growth and division by destabilizing microtubules. Data resulting from R&D's research indicate that tubulysin derivatives will offer significant advantages over currently used cancer treatments. Tubulysins have been shown to be 100 to 1000 times more potent than currently used chemotherapeutics, to be highly effective among multi-drug resistant cell lines, and to be non-immunogenic. By combining tubulysins and/or their derivatives with Insert's Cyclosert, it is expected that toxicity will be limited and targeting to tumors will be improved.

"We are excited to be unveiling this first additional pipeline compound at Insert," said R. Bruce Stewart, Chairman of Arrowhead. "We expect to announce additional therapeutic candidates in the near future."

Under the terms of the collaboration, R&D will supply Insert with tubulysin technology and material. The two companies will work jointly on the synthesis of the conjugate after which Insert intends to perform the preclinical testing. The agreement includes an up-front fee to R&D, research funding by Insert to R&D, milestone payments on clinical development and approvals, and royalties on product sales. Arrowhead has a 68% stake in Insert.

Arrowhead Research Corporation is a publicly traded nanotechnology company commercializing new technologies in the areas of life sciences, electronics, and energy. Insert Therapeutics, Inc., a majority owned subsidiary of Arrowhead, is using its proprietary nano-engineered, polymeric delivery system, Cyclosert, to design, develop, and commercialize delivery enhanced small-molecule therapeutics and nucleic acids. Cyclosert uses cyclodextrins as building blocks to create an entirely new class of biocompatible materials (linear cyclodextrin-containing polymers that are nontoxic and non-immunogenic at therapeutic doses). The company is pursuing this goal through its internal research and development and also through collaborations and partnerships with pharmaceutical and biotechnology companies. R&D-Biopharmaceuticals GmbH is a private biotechnology company focusing on the preclinical development and the commercialization of unique small molecules deriving from natural products for diseases with unmet medical need. The Company has exclusive access to the natural product class of the Tubulysins discovered by Prof. Höfle from the Helmholtz Centre for Infection Research in Germany and to other compound classes with promising potential for the treatment of cancer. The company is pursuing a partnering strategy to fully exploit the value of its natural products.

BioSante Initiates Phase III Study of LibiGel for Female Sexual Dysfunction

BioSante Pharmaceuticals, Inc., recently announced it has initiated a Phase III safety and efficacy trial of LibiGel (transdermal testosterone gel) in the treatment of female sexual dysfunction (FSD). The double-blind, placebo-controlled Phase III trial will enroll approximately 360 surgically menopausal women for a 6-month clinical trial, conducted under a Phase III protocol and IND reviewed by and on file with the US FDA.

As previously announced by BioSante, treatment with LibiGel in a Phase II study significantly increased satisfying sexual events in surgically menopausal women suffering from FSD. The Phase II study results showed LibiGel significantly increased the number of satisfying sexual events by 238% versus baseline (p less than 0.0001); this increase also was significant versus placebo (p less than 0.05). In this study, the effective dose of LibiGel produced testosterone blood levels within the normal range for premenopausal women and had a safety profile similar to that observed in the placebo group. In addition, no serious adverse events and no discontinuations due to adverse events occurred in any subject receiving LibiGel. The Phase II study was a double-blind, placebo-controlled study, conducted in the US, in surgically menopausal women distressed by their low sexual desire and activity.

"Based on discussions with the FDA and our positive results from the LibiGel Phase II study, we are moving forward into Phase III pivotal studies of women with low sexual desire, the largest component of FSD, also known as Hypoactive Sexual Desire Disorder (HSDD)," said Stephen M. Simes, President and CEO of BioSante.

"We are encouraged by the clinically significant improvement in sexual events with LibiGel treatment in the Phase II study," said Michael C. Snabes, MD, PhD, BioSante's key clinical development consultant. "Because there are no medications approved by the FDA for the treatment of this common disorder, there is significant demand by patients and their physicians. We are hopeful that if and when LibiGel is approved by the FDA that LibiGel treatment will be able to improve the sex lives of women with low sexual desire and activity."

"We are pleased to be moving into Phase III clinical development of LibiGel. Female sexual dysfunction is underserved by the pharmaceutical industry today. LibiGel may help address this unmet medical need. We believe two Phase III safety and efficacy trials plus 1 year of safety data are the essential requirements for submission and approval by the FDA of an NDA," said Mr. Simes. "With the initiation of this Phase III LibiGel trial and our recent FDA approval of Elestrin (estradiol gel), this is a very exciting time for BioSante."

LibiGel is a gel formulation of bioidentical testosterone designed to be quickly absorbed through the skin after application on the upper arm, delivering testosterone to the bloodstream evenly over time and in a non-invasive and painless manner. Though generally characterized as a male hormone, testosterone also is present in women and its deficiency has been found to decrease libido or sex drive. In addition, studies have shown that testosterone therapy can increase bone density, raise energy levels, and improve mood, in addition to boosting sexual desire and activity.

Market News and Trends

Sanofi-Aventis & Bristol-Myers Squibb Rumored to Have Signed Pre-Merger Deal

Sanofi-Aventis and Bristol-Myers Squibb Co could announce a friendly merger deal within the next few weeks to create the world's biggest drugs company, according to recent reports. In an unsourced story, French financial newsletter La Lettre de l'Expansion said a premerger deal was thought to have been signed late January. Buying Bristol-Myers would be a coup for Sanofi's ambitious chairman and veteran dealmaker, Jean-Francois Dehecq, who is due to retire from the French firm at the end of 2009. The acquisition of the US company, which has a market value of around $51.5 billion, would see Sanofi leapfrog Pfizer, Inc., as the biggest pharmaceuticals company in the world by sales and push GlaxoSmithKline Plc back into third place.

Sanofi and Bristol-Myers have long been tipped as possible merger partners, since they work together in marketing the hugely successful blood thinner Plavix, as well as Avapro for hypertension. A Sanofi spokesman said the company did not comment on press speculation. Still, many analysts and industry executives are convinced Sanofi will have been taking a long, hard look at US-based Bristol-Myers in recent months.

"This wouldn't surprise me," said WestLB Analyst Oliver Kaemmerer. "Sanofi needs increased exposure to the US market. They have substantially deleveraged their balance sheet since they took over Aventis, so they are prone to do something going forward."

Novartis Chairman and Chief Executive Daniel Vasella said only this past December that he believed such a deal could be in the cards. "I would not be surprised if companies, which are connected through products like Sanofi-Aventis and Bristol-Myers Squibb, think about a merger," Mr. Vasella told a Swiss newspaper.

Sanofi, with a market capitalization of $123 billion, is twice the size of Bristol-Myers, but its shares are less highly rated, and analysts believe an acquisition could significantly dilute Sanofi earnings. Bristol-Myers, whose shares have been buoyed in recent months in part by takeover speculation, trades on around 21 times forecast 2007 earnings while Sanofi gets just 13.3 times, according to Reuters data.

Analysts believe any final deal for Sanofi to buy its smaller US partner is likely to be contingent on the outcome of litigation surrounding the blockbuster Plavix. A key court case over Plavix patents opened in the US this past January, with the two allies fighting a challenge from Canadian generic drugmaker Apotex. A verdict is not expected before the third quarter of the year.

Most analysts bet Sanofi and Bristol-Myers will win the case, which could then clear the way for a full-blown merger. Bristol-Myers has been seen as vulnerable to a takeover for some time, following management upheaval, while Sanofi would benefit from adding the US company's many new experimental drugs to its pipeline.

"Bristol-Myers becomes a very attractive takeover prospect because it has very solid pipeline, once the Plavix issue is resolved," a second analyst commented.

DURECT Signs Posidur Manufacturing Agreement With Hospira

DURECT Corporation recently announced it has entered into a long-term manufacturing and supply agreement with Hospira Worldwide, Inc. for Posidur, DURECT's post-surgical pain management investigational drug, which is currently in Phase II clinical trials. Under the agreement, Hospira's One 2 One contract manufacturing services will provide DURECT's clinical and commercial supplies of Posidur on a worldwide basis. The two parties have begun manufacturing development activities in accordance with the agreement.

"Hospira's capabilities, expertise, and capacity in manufacturing parenteral products makes them an ideal partner for us, and the establishment of this agreement, following on the heels of our recent development and commercialization collaboration with Nycomed, now one of the 25 largest pharmaceutical companies in the world as a result of its Altana acquisition, is a second key milestone in our Posidur development program," said James Brown, Chief Executive Officer of DURECT.

"We look forward to supporting DURECT's manufacturing needs to help them bring Posidur to market around the world," said Anthony Cacich, Vice President and General Manager, Contract Manufacturing Services, Hospira. "Our collaboration with DURECT exemplifies how Hospira One 2 One partners with its clients from development to commercialization to deliver quality parenteral products and leading-edge technologies to market."

Posidur (Saber-Bupivacaine) is a long-acting local anesthetic under development by DURECT for the treatment of post-surgical pain. It is intended to be injected during surgery, where it continuously releases therapeutic levels of bupivacaine in a controlled fashion, providing up to 72 hours of uninterrupted local analgesia. Posidur's performance is due to DURECT's proprietary Saber delivery system, which is an injectable, biodegradable drug delivery technology that allows for less post-injection burst than is typical of polymer-based systems. On November 29, 2006, DURECT and Nycomed signed a $202-million agreement to develop and commercialize Posidur in Europe and other select countries. Posidur is currently in Phase II clinical development. DURECT and Nycomed anticipate moving the program into Phase III in 2007.

DURECT is an emerging specialty pharmaceutical company focused on the development of pharmaceutical systems based on its proprietary drug delivery platform technologies focused on treating chronic and episodic diseases and conditions. The company currently has a number of late-stage pharmaceutical products in development initially focused on significant unmet medical needs in pain management, with a number of research programs underway in a variety of other therapeutic areas.

Hospira is a global specialty pharmaceutical and medication delivery company dedicated to Advancing Wellness by developing, manufacturing, and marketing products that help improve the productivity, safety, and efficacy of patient care. With 70 years of service to the hospital industry, Hospira's portfolio includes one of the industry's broadest lines of generic acute-care injectables, which help address the high cost of proprietary pharmaceuticals; integrated solutions for medication management and infusion therapy; and the leading US injectable contract manufacturing business.

Altea Therapeutics Announces Positive Clinical Results for its Basal Insulin Transdermal Patch

At the 11th Annual Drug Delivery Partnerships Conference in Las Vegas this past January, Altea Therapeutics announced positive clinical results from Phase I human clinical studies for its basal insulin transdermal patch showing efficient, sustained, and constant delivery of insulin at therapeutic levels.

In a glucose-clamp study in normal subjects, Altea Therapeutics achieved constant insulin delivery at therapeutic levels over a 12-hour patch application period. The data show efficient delivery of the applied dose of insulin and demonstrate favorable pharmacodynamics of transdermal insulin delivery when compared to a subcutaneous injection of a long-acting insulin analog. Altea Therapeutics is developing both 12-hour and 24-hour transdermal patches based on its proprietary PassPort System to provide constant "basal" levels of insulin for people with type 1 or type 2 diabetes.

"We are delighted to achieve such promising results," said Dr. Eric Tomlinson, President and CEO of Altea Therapeutics. "These findings are very important to our clinical development program as they confirm efficient and constant delivery of basal insulin from our PassPort Patch. These results give us confidence that basal insulin transdermal patches can be a cost-effective alternative for people currently using insulin injections to manage their diabetes. A higher patient acceptance of a basal insulin transdermal patch over needle injections enables physicians to start subjects earlier on insulin in the management of type 1 and type 2 diabetes."

Market research conducted by Altea Therapeutics on its transdermal basal insulin product confirms significant market potential for a pain-free, convenient, and cost-effective alternative to repeat insulin injections. Approximately 40 to 50 million people with type 2 diabetes and 10 million people with type 1 diabetes worldwide require insulin therapy. The worldwide market for all forms of insulin was over $7 billion in 2005 and is estimated at over $11 billion by 2011. The basal insulin is the fastest growing market and generated over $2.6 billion in 2005.

Altea Therapeutics is an emerging specialty pharmaceutical company developing and commercializing products based on a new transdermal patch technology that can deliver sustained therapeutic levels of highly water-soluble drugs, carbohydrates, nucleic acids, peptides, and proteins in a convenient, painless, and cost-effective manner.

Altea Therapeutics has demonstrated in several clinical studies that its patented PassPort transdermal system achieves what existing patches are unable to do, namely the continuous delivery through the skin of compounds that are typically administered by needle injections.

The company is conducting several clinical trials in the US for its products, including for an insulin transdermal skin patch that provides continuous delivery of basal levels of insulin for people with diabetes, a fentanyl citrate transdermal skin patch that provides for rapid and safe management of moderate-to-severe pain, and an apomorphine hydrochloride transdermal skin patch for the convenient management of advanced Parkinson's disease. The company is also in preclinical development for a low molecular weight heparin patch for thromboses, parathyroid hormone analog for osteoporosis, and an atypical antipsychotic for the management of psychoses.

Penwest Pharmaceuticals Begins Next Study in Development of Nalbuphine ER

Penwest Pharmaceuticals Co. recently announced it has begun a Phase I safety study on a nalbuphine hydrochloride extended-release tablet formulation (Nalbuphine ER) that the company is developing for the treatment of pain. Nalbuphine ER is a controlled-release formulation of nalbuphine hydrochloride that Penwest is developing using its TIMERx drug delivery technology. It is designed to be taken as a twice-daily tablet.

The primary objective of the Phase I safety study is to evaluate the safety and tolerability of the drug in healthy subjects of escalating dosage levels during multiple-dose steady-state administration. The secondary objective is to evaluate the pharmacokinetics of nalbuphine during steady-state administration and the effect of different nalbuphine ER dosage levels on typical opioid-related side effects.

Alan F. Joslyn, PhD, Penwest's Senior Vice President of Research and Development, said, "This next step in the clinical development of nalbuphine ER demonstrates our progress in building our own product portfolio. We are conducting the Phase I safety study to enhance our understanding of the safety and pharmacokinetics of multiple doses of nalbuphine ER over the projected clinical dose range. We believe that, combined with the single dose safety and efficacy data we already have, this study will give us the information necessary to advance to the Phase II program we intend to begin in the first half of this year."

The study will employ a randomized sequential dose-escalation design, with a planned total enrollment of 32 healthy adult subjects in two separate alternating cohorts. The study will examine a total of four dosage levels. Each subject will receive treatment at two different dose levels sequentially, with a number of days at each dosage level until steady state plasma concentrations are achieved. The company expects subject participation to be complete by the end of February, with data available in the second quarter.

Penwest is a specialty pharmaceutical company dedicated to bringing to the marketplace innovative products that help improve the lives of patients. The company's goal is to identify, develop, and commercialize prescription products that address unmet medical needs, primarily for diseases of the nervous system. At the core of this strategy, Penwest applies drug delivery technologies, including its own proprietary technologies, to new and existing compounds to enhance their therapeutic profiles. The launch by Endo Pharmaceuticals of Opana ER (oxymorphone hydrochloride extended-release tablets) in mid-2006 demonstrates the execution of this strategy and the value of Penwest's TIMERx extended-release delivery technology. Penwest is currently applying its expertise to a pipeline of potential products that are in various stages of development. The company intends to commercialize these products independently and through third-party alliances.

Overcoming Formulation Challenges of Proteins & Peptides

By: Cindy H. Dubin, Contributing Editor

"The discovery of insulin in 1922 marked the beginning of research and development to improve the means of delivering protein therapeutics to patients. From that period forward, investigators have contemplated every possible route of delivery," says Larry Brown, Chief Technology Officer, Epic Therapeutics, Inc., a wholly owned subsidiary of Baxter Healthcare Corporation.

The company's research efforts have followed two basic pathways: one path has focused on non-invasive means of delivering proteins to the body; and the second has been primarily aimed at increasing the biological half-life of the therapeutic molecules. Thus far, the commercial successes of protein delivery by the nasal, oral, and pulmonary routes have been more opportunistic rather than the application of platform technologies applicable to every protein or peptide, stated Dr. Brown in his 2005 article, *Commercial Challenges of Protein Drug Delivery (Expert Opinion on Drug Delivery,* 2005;2(1):29-42).

In several limited cases, sustained delivery of peptides and proteins has employed the use of polymeric carriers. More successes have been achieved by chemical modification using amino acid substitutions, protein pegylation, or glycosylation to improve the pharmacodynamic properties of certain macromolecules. Today, commercial successes for protein and peptide delivery systems remain limited. The needle and syringe remain the primary means of protein delivery. Major hurdles remain to overcome the combined natural barriers of drug permeability, drug stability, pharmacokinetics, and pharmacodynamics of protein therapeutics.

The delivery of macromolecules may present the greatest challenge yet to the delivery marketplace, agrees Jack Aurora, Senior Director of Research and Development with the Perrigo Company. While many of these protein drugs are used for serious, life-threatening and chronic diseases, such as cancer, rheumatoid arthritis, hepatitis, and diabetes, the development of protein drugs is not without challenges. Due to their large size, charge, hydrophilicity, and enzymatic degradation, absorption through biological membranes is very limited. As a result, protein drugs are almost exclusively administered parenterally. The latter requires the drug to be in solution, but many proteins cannot be stored in solution for prolonged periods, due to their physicochemical instability. Thus, delivery of protein drugs is a challenge with respect to biological and formulation aspects.

But formulators are intrigued by the challenges, and the pharma companies for which they work are even more intrigued by the financial bounty. Today's market for peptides drugs is estimated to be $12 billion with an annual growth rate of 10%; the estimated market for proteins is much larger.

ORAL DRUG DELIVERY

To date, the development of oral formulations for the effective delivery of peptides, proteins, and macromolecules has been an elusive target. Poor membrane permeability, enzymatic instability, large molecular size, and hydrophilic properties are four factors that have remained major hurdles for peptide and protein formulations. In order to develop an efficacious oral formulation, the peptide must be protected from the enzymatic environment of the gastrointestinal tract (GIT).

This is where Cytogen Corp. is focusing its efforts. The company has been issued a patent covering its oral drug delivery agents — random peptide compositions that bind to GIT transportreceptors. These agents can facilitate transport of an active agent through a human or animal GIT.

According to Vernon Alvarez, PhD, listed inventor on the patent and a consultant to Cytogen, by binding (covalently or noncovalently) one of Cytogen's delivery agents to an orally administered drug or by coating the surface of nanoparticles or liposomes with the delivery agent, the drug can be targeted to specific receptor sites or transport pathways that are known to operate in the human GIT, facilitating its systemic absorption into the bloodstream.

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Controlled Release Coatings	X	X	
Microencapsulation		X	
Conventional Tablet Coating	X		
Solvent-Based Coating for Barrier or Taste Masking Properties	X	X	
Conventional Wet Granulation	X		X
Direct Compression	X	X	X
Solvent-Based Granulation		X	
Melt Extrusion	X	X	X
Bulk Laxatives	X		
Creams, Gels, and Ointments	X		X
Ophthalmic Preparations	X		
Suspensions	X		
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Mucosal Bioadhesives			X

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Cytogen's technology is based on proprietary peptides that facilitate the transport of macromolecules across membranes while preserving the structure and biological effects of the drug as well as the integrity of the intestinal membrane. The binding of Cytogen's delivery agents to these receptors has been confirmed in preclinical models, and successful *in vivo* delivery of both insulin and leuprolide in animal models has been demonstrated.

"Cytogen's proprietary technology may represent an important advancement for patients with a variety of disorders who can greatly benefit from the availability of an oral dosing option," says Dr. Alvarez. "Through future collaborations, we look forward to the development of products for oral administration that, until now, could only be administered by injection."

PULMONARY DELIVERY & SPRAY-DRYING

Pulmonary delivery is gaining increasing interest as an alternative method for the systemic delivery of various drugs, including proteins. A major advantage of the pulmonary route is rapid absorption, thus providing a useful administration to treat symptoms that come on suddenly or require a quick response. Moreover, the deep lung provides a higher bioavailability for protein drugs than any other noninvasive route of administration. Thus, pulmonary delivery may help to overcome poor patient compliance associated with the parenteral delivery of many of these protein drugs.

The main challenge for pulmonary delivery is to deliver the particles to the deep lung, especially the alveoli. Apart from proper design of the inhaler system, this requires that the particle/droplet diameter is within the range of 1 to 4 microns, making pulmonary delivery a significant technological challenge. For proteins, an additional challenge is the relatively low physicochemical stability of these drugs. In many cases, prolonged storage of peptides and proteins is only possible by drying the formulation, but even under those conditions, stabilizers are still required.

Proteins' susceptibility to proteolytic enzymes in the gut makes oral administration quite challenging. While various routes such as ocular, transdermal, nasal, and buccal have been tried, none of these have proved to be a potential alternative to the invasive injection, according to S.A. Shoyele and colleagues at 3M Health Care Ltd. However, various studies have been performed on the formulation of these proteins as aerosols for pulmonary delivery, and promising results have been obtained.

The pulmonary route is considered suitable for proteins because these are taken up through the epithelium in the alveoli, providing systemic delivery without the first-pass effect. To this end, the YKI Institute for Surface Chemistry (official name: YKI, Ytkemiska Institutet AB), an internationally leading industrial research institute in applied surface and colloid chemistry, is investigating spray-drying as a technology for producing particles that are large enough to avoid phagocytosis, but have a low density to allow delivery to the alveoli. The relationship between droplet and particle size has been investigated, and the company is currently studying formulation of proteins in particles for pulmonary delivery.

Spray-drying has recently been recognized as a viable method to dry peptides and proteins. The spray-drying process can result in aerodynamic particle diameters that are within the desired range for pulmonary delivery. Thus, spray-drying potentially provides a single-step preparation procedure of dry protein powders for inhalation.

However, there is still limited knowledge on how the process, as well as formulation strategies, affect the protein and powder stability. It is clear that certain stabilizers are required to protect the protein against some of the stress factors throughout the process, but these may have both positive and negative effects on the particle characteristics.

Epic's PROMAXX protein microsphere technology offers narrow control of microsphere size and the ability to vary drug-release profiles. PROMAXX consists of a simple, robust, gentle process that is water-based, which has been shown to preserve the drug's protein structure and activity. PROMAXX microspheres of proteins, peptides, low molecular weight drugs, and DNA are manufactured by adjusting formulation conditions to account for the specific physical/chemical characteristics of the molecule.

Microspheres may be engineered to either release drug immediately (for pulmonary delivery) or in specific cases yield sustained release (for injectable delivery). For example, microspheres with a 1- to 5-micron diameter are ideal for pulmonary drug delivery while larger microspheres (10 to 50 microns) can be used in injectable applications.

CONVERTING PEPTIDES & PROTEINS INTO SMALL MOLECULES

Many proteins and peptides are either in clinical use, or not used as drugs because of a lack of selectivity and poor absorption, distribution, metabolism, and excretion (ADME) properties. But advances in genomics, proteomics, and bioinformatics, and the sequences and three-dimensional structures of many new proteins with clinical potential will be discovered, according to Prof. Chaim Gilon, The Hebrew University-Givat Ram Campus, Faculty of Science Institute of Chemistry, Department of Organic Chemistry.

Researchers here have demonstrated a need for technology that will enable the conversion of peptides and active regions in proteins into small- or medium-size molecules with the appropriate ADME properties.

A new technology is being investigated that reduces the physical size of peptide and protein molecules. Libraries of novel macrocyclic molecules with spatial diversity are being developed to provide candidates for a variety of applications in human and veterinary medicine. The technology allows the manipulation of peptides and proteins to produce a series of molecules small enough to pass through cell membranes and other biological barriers. These small molecules can be used to build up libraries of lead compounds for therapeutics, diagnostics, and radiotherapy. The members of each library differ from each other in ring size as well as the conventional chemical and positional diversity, thereby allowing for the selection of the most active compound.

Prof. Gilon says that the new technological platform will enable molecules small enough to reach their intended target. In addition, the technology provides a method for modulating a protein- or peptide-mediated cell activity, such as proliferation, differentiation, cellular shape alteration, cellular elongation, or expression of various proteins, by combining cellular components and cell membranes or from cellular molecules.

The application of this technology to a variety of medical indications is being studied as an anti-obesity agent, for example. Studies on the oral bioavailability of these new macrocyclic compounds are currently being pursued.

THE FUTURE

"Interest in the delivery of proteins and peptides is increasing day by day," says Dr. Aurora of Perrigo. "However, due to the aforementioned constraints, this area of research offers an interesting challenge to conduct further research work and to achieve acceptable and cost-effective delivery of proteins and macromolecules for patients. It can also be expected that new drugs and improved treatment protocol based upon the outcome of ongoing research work will appear in the near future."

According to Dr. John S. Patton, Founder and Chief Scientific Officer of Nektar Therapeutics, "The drive to improve today's protein and peptide therapies comes from a need for greater safety and efficacy, decreased immunogenicity, and better delivery routes. More than 300 new drugs were approved from 1995-2000 that were improvements of existing medicines. Better drug delivery can increase patient compliance and therapeutic outcomes. The first waves of protein and peptide drug delivery focused on topical and nasal delivery as well as sustained-release delivery. The future lies in a paradigm shift that will see the first inhaled proteins and peptides." ◆

BIOGRAPHY

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

Smart Self-Injection: Incorporating Drug Stability Monitors Into the Injection Device

By: Stephen E. Zweig, PhD

ABSTRACT

Self-injection devices (autoinjectors, injection pens) allow for precise dosages of drugs to be injected by unskilled users in a wide variety of non-clinic environments. These devices are a convenient way to administer biotherapeutic drugs and are increasingly being used by the pharmaceutical industry for this purpose. However, because self-injection devices are frequently used outside of a normal clinical setting, there is an increased risk that the drugs may accidentally deteriorate due to inadvertent exposure to improper thermal conditions. The safety and effectiveness of drug injection devices can be improved by incorporating drug stability monitors into the injection device.

INTRODUCTION

For decades, self-injection devices have been used to administer medication in non-clinical settings, such as on the battlefield, at home, or while traveling. Although these devices have many different configurations, they generally consist of a combination of a drug storage container, a needle, and some mechanical means to allow a patient to easily self-inject the drug. There are many different types of self-injection devices of varying complexity, ranging from simple Syrettes™ and Uniject devices™ to prefilled syringes, spring-loaded autoinjectors, single-use injection pens, and highly sophisticated multiple-use injection pens. Due to their high convenience, self-injection devices, originally introduced for stable small molecule drugs such as morphine, are being used with an ever-growing array of cutting-edge biotherapeutic drugs.[1]

Because self-injection devices are designed to be used by unskilled patients in almost any situation, self-injection devices present some unique design and safety challenges. The devices must be robust, easy to use, and ideally contain one or more safety devices designed to prevent against accidental misuse. These safety devices can range from simple printed instructions for use to the

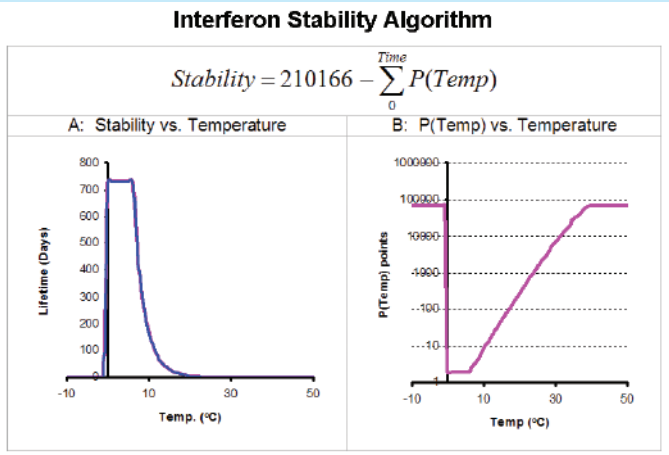

FIGURE 1

Injection pens are frequently used to administer various types of interferon. Studies have shown that an adverse temperature history can render some types of interferon immunogenic. Because neutralizing antibodies are known to be a common interferon treatment side effect, better stability monitoring with "smart" stability sensing injection pens may be desirable. Figure 1A shows a graph of the storage stability of a hypothetical interferon biotherapeutic that has a storage life of 2 years at 2°C to 8°C, 1 day at 25°C, and which should not be frozen. Figure 1B shows the corresponding LifeTrack stability P(temp) algorithm. The equation above the two graphs shows the complete LifeTrack stability equation. The LifeTrack monitor is programmed to sample the device's temperature and run the stability equation every 10 minutes. When the equation reaches zero (no life remaining), the LifeTrack visual display from a + to a -.

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complex mechanical safety interlock and dosage metering schemes present in many biotherapeutic injection pens.

Until now, however, one type of safety problem has been difficult to handle. Because self-injection devices are designed to be used anywhere, they are more likely to be subjected to storage and transportation temperatures that are more extreme than those encountered in a standard clinical environment. A self-injection device is at risk of being accidentally frozen, accidentally being left out at room temperature by a forgetful patient, or even accidentally being left in an automobile trunk during the hot summer. If the particular drug used in the device is temperature sensitive, there is a risk that the drug will become degraded. Because unskilled patients often use the self-injection devices, this degradation may not be detected.

Currently, there is no good measure to protect unskilled patients from the risk of injecting themselves with deteriorated medication. Fortunately, as this article will discuss, modern electronics have advanced to the point at which it is now feasible to address this issue. Electronic drug stability monitors, customized to the particular stability characteristics of the drug and self-injection device at hand, can provide a way to warn unskilled patients when the drugs have deteriorated.

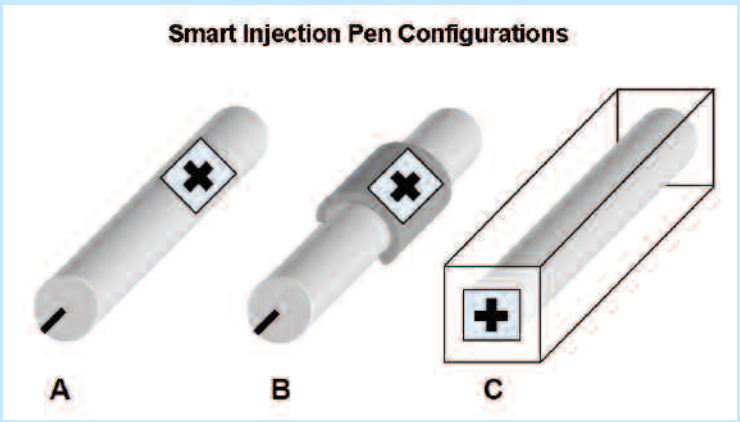

FIGURE 2

Shows three different ways to incorporate LifeTrack stability monitors into injection pens. A: Stability monitor incorporated as an integral part of the injection pen; B: Stability monitor incorporated as a clip-on to the injection pen; C: Stability monitor incorporated as part of the injection pen's external packaging. In cases A and B, the user can instantly assess the drug's fitness for use for the entire use-life of the injection pen. In case C, the user determines if the pen or cartridge is adequate for use before opening the outer packaging. Various refinements are also possible. The clip-on stability monitor shown in B may be initially stored with the drug cartridge, and then transferred to the injection pen when the drug cartridge is loaded into the pen. Alternatively, the injection pen in case A can incorporate a reset switch that resets the stability monitor to "fresh" whenever a new drug cartridge is added.

REVIEW OF INJECTION DEVICES

As previously discussed, the term "self-injection device" covers many different types of drug administration systems and drugs. One of the first and simplest types of injection device is the Syrette, used during World War II to self administer morphine to soldiers in battle. The Syrette consisted of little more than a plastic squeeze bottle containing an attached needle and a unitized dose of morphine (a relatively temperature-stable small-molecule drug).

Autoinjectors, essentially spring-loaded syringe-needle devices prefilled with a drug, also have a military history. Autoinjectors are designed to immediately release a unit dose of the drug when the user presses a button and are used to administer emergency medical drugs (epinephrine, lidocaine) and chemical warfare antidotes, such as Atropine and Pralidoxime choloride (2-PAM).

Epinepherine autoinjectors, such as the EpiPen® are popular in civilian life as well and are widely

used for treating anaphylactic shock.[2] Here, however, drug stability begins to become an issue. Epinephrine autoinjectors are somewhat temperature sensitive and ideally should not be frozen or subjected to high heat, but rather stored at room temperature between 15°C to 30°C. Temperatures outside this range can cause the epinephrine to deteriorate. Since in many cases, Epipen users need to have access to the pen while traveling, these storage recommendations can be difficult to follow. Fortunately, deteriorated epinephrine can be detected visually (it turns brown), and it is also relatively harmless. As long as enough undeteriorated epinephrine remains in the autoinjector to be effective in an emergency situation, deteriorated epinephrine is usually better than no epinephrine.[3]

Injection pens were originally developed for insulin self-administration by diabetics. Diabetes often takes a toll on both eyesight and hand-eye coordination, and diabetics, who needed to inject precisely metered amounts of insulin multiple times a day, had difficulties using traditional syringes. As a result, early work in injection pen technology began more than 50 years ago. By the 1980s, various types of modern injection pens were introduced with various types of digital dispensing mechanisms, including the NovoPen®, and NovoLet®. These devices have now evolved into highly sophisticated systems with complex mechanisms designed for accuracy and ease of use.

Insulin pens also have drug stability issues. Insulin is a small protein molecule that has a tendency to denature and aggregate when it is stored at adverse temperatures. As a result, insulin manufacturers usually recommend that insulin pens: 1) should not be frozen; 2) should be stored at 2°C to 8°C until use; 3) depending on the type of insulin, should not be stored above 30°C for more than 10 or 28 days. Although it is likely that diabetics frequently violate these stated recommendations, insulin is a comparatively robust molecule that withstands abuse well, and insulin pens have been widely adopted.

At the same time that injection pen technology was advancing, biotherapeutic technology was also advancing. In the past 20 years, a wide variety of therapeutic proteins designed to treat a wide variety of diseases have been introduced. Because many of these new biotherapeutics are used to treat chronic diseases, ways were needed to administer these drugs in non-clinical settings. Thus, not surprisingly, the biopharmaceutical industry has turned to injection pens for an increasing variety of protein-based biotherapeutics, including interferon, FSH, antibodies, growth factors, erythropoietin, and many others.

One problem, however, is that although the range of drugs administered by injection pens has increased, safety technology has not kept pace. Modern injection pens, originally developed for more temperature degradation-tolerant drugs such as morphine, epinephrine, and insulin, continue to lack drug degradation safety mechanisms. Unfortunately, as will be discussed in the next section, some biotherapeutic drugs are more temperature sensitive than insulin, and don't always degrade into easily detected or harmless forms if the drug injection device is accidentally stored under improper conditions.

REVIEW OF DRUG STABILITY

Drug stability is a complex topic that has been covered in depth by other authors.[4] Briefly, drugs can degrade from a wide variety of different chemical reactions. Each chemical reaction has its own unique kinetics and activation energy, and all show a strong degree of time-temperature dependency. Usually, the drug's ultimate stability is determined by the degradation mechanism that most clearly renders the drug unfit for use. This can be the mechanism that most quickly converts the drug into an inactive form, or alternatively the mechanism that most quickly converts the drug into

a potentially harmful form. In either case (assuming that the drug is otherwise packaged competently in a way that protects the drug from humidity, light, and other normal environmental stress), the "fitness for use" equation can usually be expressed as some function of time and temperature.

In the case of small-molecule drugs, this equation may be a simple Arrhenius decay equation that is relatively unaffected by the mechanical and chemical characteristics of the self-injection device in question. By contrast, in the case of biotherapeutic drugs, this decay equation may be a more complex function that, in addition to the chemical characteristics of the biotherapeutic, is also dependent on the mechanical and chemical characteristics of the self-injection device.

One important distinction between biotherapeutics and small-molecule drugs, however, is that in the case of protein-based biotherapeutics, stability "fitness for use" may not be limited by loss of activity, but rather may be limited by the formation of aggregated protein.[5] This is because the immune system is designed to attack aggregated proteins as "foreign." As a result, drug deterioration that results in a few percent conversion of a biotherapeutic protein from a non-aggregated to an aggregated state may have a negligible impact on the biotherapeutic's activity, but may render the biotherapeutic immunogenic. This is undesirable because patients may develop antibodies against the aggregated form of the biotherapeutic. These antibodies can diminish the effectiveness of the biotherapeutic (neutralizing antibodies), or occasionally even generate an adverse drug reaction. As a result, good stability monitoring is particularly important for biotherapeutics.[6]

Protein aggregation is complex. Usually induced by improper storage conditions (freezing or high temperatures), it is also affected by the surface properties of the drug containment system.[7] Each different drug injection device will, most likely, have its own unique immunological stability risk function. Thus, any stability-monitoring device must be capable of coping with this type of complexity. Fortunately, as will be discussed, modern electronic stability monitoring technology is capable of handing this complexity.

LIFETRACK® TECHNOLOGY

LifeTrack® technology is a new and accurate way of electronically monitoring drug stability.[8,9] The approach uses low-cost, low-power, rapidly programmable microprocessors to instantly warn users whenever drugs have deteriorated due to mishandling. The technique works by obtaining experimental time-temperature drug-stability data, abstracting this experimental data into a sophisticated stability algorithm, and embedding this stability algorithm into the LifeTrack stability monitor, which is then meshed with the self-injection device. The LifeTrack stability monitor electronically measures the device's temperature every few minutes and computes the impact that the storage at the observed temperature has had on the remaining lifetime of the drug in question. The stability monitor continually computes if the drug is still fit for use and displays the final result (+ = still good, - = expired) on an LCD visual indicator. The system can be miniaturized to fit into many types of self-injection devices, is capable of running for many years, and costs a few dollars per unit. An example of a LifeTrack stability algorithm is shown in Figure 1, and examples of injection pens equipped with LifeTrack stability monitors are shown in Figure 2.

INCORPORATING LIFETRACK INTO SELF-INJECTION DEVICES

Recent surveys have shown that injection pen users rank safe storage as extremely important, second only to overall reliability, ease of use, and injection pain.[10] Incorporating LifeTrack technology into self-

injection devices, particularly injection pens, serves several useful purposes. It makes these devices more robust from a human factors standpoint and lowers the frequency of adverse events. It also makes it more feasible to use low-stability drugs. It gives patients more freedom to travel, secure in the knowledge that their drugs are still good. Finally, it reduces waste. At present, perfectly good self-injection devices are discarded due to minor deviations from ideal handling conditions. With an embedded stability monitor, users better understand which deviations from ideal handling are significant, and which are not.

The essential elements of a LifeTrack stability monitor consist of a microprocessor chip, a button-size battery, a pinhead size temperature sensor, and a miniature LCD display. If the drug is sensitive to motion, light, or turbidity, these sensors can also be added. The electronic components are similar to those in a digital watch, millions of which are produced each year at a cost of about a dollar each. As Figure 2 shows, these stability monitors can be incorporated into self-injection devices in various ways.

Here, the key to success is high accuracy. The drug's stability in the self-injection device configuration must be assessed by careful experimentation, and an appropriate stability model selected. Although this stability model will likely differ between different drugs and injection devices, assuming good manufacturing quality control, it will otherwise be consistent. Once the appropriate stability model parameters are selected, these parameters can then be electronically downloaded into the memory of the LifeTrack microprocessors before shipment. Once activated, the LifeTrack stability monitors will then protect users from accidental use of deteriorated drug throughout the use-life of the injection device. This stability monitor transforms the self-injection device from a "dumb" device into a "smart" device, constantly on guard and protecting the user.

SUMMARY

Self-injection device technology represents a significant advance in pharmaceutical delivery technology. Self-injection devices enable sophisticated drugs to be administered by unskilled users in almost any environment. Although the "go anywhere" and "be used by anybody" characteristics of self-injection devices increase the risk of accidental use of deteriorated drugs, this risk can be reduced by stability monitors. Just as airbags and seatbelts are now a standard part of modern automobiles, drug stability monitors may eventually become a standard part of next-generation self-injection devices.

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BIOGRAPHY

Dr. Steve Zweig is the CEO of CliniSense Corporation. He earned his PhD in Biochemistry (Biophysics) from the University of California, San Diego. He conducted his post-doctoral work in Immunology at the NIH, and was an Assistant Professor of Pharmacology at Baylor College of Medicine. He is a former J&J (LifeScan) Research Director, and Founder of Avocet Medical, Inc., a medical diagnostics company.

Special Discussion

Growing Global Market for "Combination Products" Presents Regulatory Challenges for American Firms

By: John Sullivan and Henrik Elbaek, MSc (EE), MBA

The global market for medical devices and combination products is exploding. Standard & Poor's medical device and products industry report, in citing the most current Frost & Sullivan market research report, states that global revenues for the medical device and product industry reached $148 billion in 2004, up roughly 14% from $130 billion in 2003, with projections of $220 billion for 2006 and a 10% to 14% increase each subsequent year. Of this total, the US represented the largest market, 43% of the global revenues, followed by the European Union (30%) and Japan (11%). Within the European Union, Germany, France, Italy, the UK and Spain are the largest markets.

At Radius Product Development (www.RadiusPD.com), we have been dealing for years with the international regulatory issues regarding the introduction of combination products, through our offices in Beijing, Hong Kong, and Copenhagen. There have been and will always be perceived challenges in gaining approval to market new pharmaceuticals and medical devices in the US as well as Asia and Europe. The truly innovative products are being seen in the combination product category. Combination products have an inherent challenge with gaining approval because they require approval from multiple divisions of health administrations, like the US FDA.

Combination products integrate biologics, devices, and/or drugs into a combined therapy, treatment, or surgery. These products can be as simple as an antibiotic-coated bandage or as complex as a drug-coated stent, which inflates the artery while the drug breaks down the plaque and prevents it from developing. Another group is engineered biologics, such as grown cultures, blood, vaccines, and engineered tissues. Future developments could include such exotic products as device implants that contain an element of engineered biologics that help promote healing.

The complexity and nuances of combination products led the FDA to create the Office of Combination Products in 2002 to oversee the approval process, safety, and accountability of combination products. The FDA recognized the need for a central body that would help to translate new product applications into their component parts to ensure that the appropriate divisions are reviewing respective elements. While the path to regulatory approval is better defined in the US, it is only recently becoming clearer in Europe, and strides are being made in Asia to improve regulations and regulatory agencies.

ASIA: FOCUS ON JAPAN

Contrasting the state of Japan's Ministry of Health, Labor, and Welfare (MHLW) with the FDA, you see a system that is ripe with challenges for companies seeking approval of innovative combination products. Gaining approval for a medical device or pharmaceutical in Japan is rigorous and can be a frustrating

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"As American companies develop new medical devices and combination products, they will need to continue to be aware of recent and upcoming changes in the regulatory environment of each European and Asian country that presents a potential marketing opportunity. As these products grow more sophisticated, so does the regulatory process that is set in place to protect the consumers who will be benefiting from them."

process. Industry may also experience a market and medical practitioners that appear resistant to change and overly bureaucratic.

The following are examples of the lengthy processes required for approval in Japan and elsewhere in Asia:

- Approval times are typically 12 months for PMA (efficacy plus safety) devices versus 6 months in the US.
- Approval times for 510K (efficacy only) devices are 3 months in the US versus 4 months in Japan, 6 months in China and 6 to 8 months in Korea.

It is not uncommon for an American medical device manufacturer to have a product line that has been made obsolete by a new product in the US or EU, but which is still on the market in Japan, due to the effort and time required to gain approval. It should be noted that the time required to gain approval is lengthened not only by the process, but also for administrative reasons — the MHLW is perceived to be both understaffed and carrying a backlog of applications. The impact of these delays and lengthy processes is that new products providing better care are not being marketed as quickly as possible.

The effects on industry are more costs associated with managing the review process and more costs associated with maintaining product lines that are considered obsolete in other markets. The impact can be felt even at the manufacturing efficiency level, if the innovation in the product includes the introduction of new technologies that reduce manufacturing costs. In this scenario, both the American-based industry and the Japanese consumer are losing with the higher costs of using the older-generation product.

In recognition of these approval challenges facing the industry, the Japanese regulatory process was revised in 2005 to accommodate combination products, biologics, and medical devices, and to allow third-party review for approval. This process is in line with changes implemented at the FDA and in the EU. However, these processes and systems are new and will require a period of adaptation by regulatory personnel in Japan. Ultimately, these regulatory improvements will lead to a more efficient approval process, but will require that industry remain patient while long-standing practices are supplanted by new review methods.

EUROPE

In contrast to Japan, regulation is a much more efficient process in the European Union. However, just a few years ago, it was a difficult challenge, especially in the medical products area. Different member countries of the EU had varying requirements for approval. These rules affect the introduction of a product.

For medical devices in Europe, the Medical Device Directive (93/42/EEC) regulations provide guidance for gaining marketing approval through the declaration of conformance process. Ultimately achieving the right to bear the CE mark designates a device as marketable in the EU. The extent of the requirements for CE marking depends upon the product's classification.

To some degree, CE marking works on the honor system with non-combination, Class I products. All large European companies can actually CE mark themselves. For a new entrant in the market and for certain classifications of product, manufacturers are required to work with notified bodies (BSI, TUV, DEMKO, SEMKO) who will perform third party certifications of quality assurance systems and products. The

FDA and MDD regulations rules are similar, but for American companies, CE marking regulations present additional work to develop documentation that is not necessarily required by the FDA.

Under the EU regulation system, one country cannot have more restrictive regulations without a special dispensation. A country with very strict rules cannot enforce them if the other countries have more liberal rules. If a country tries to do so without being approved by the EU, it is considered a trade barrier and the companies can actually sue that country in the EU court.

Nevertheless, while European countries have a common set of rules, they each have their own authorities to handle approval of combination products, and they operate on different timetables. A combination product will typically have an unpredictable road ahead for regulatory approval in each country within the European Union.

MOVING FORWARD

As American companies develop new medical devices and combination products, they will need to continue to be aware of recent and upcoming changes in the regulatory environment of each European and Asian country that presents a potential marketing opportunity. As these products grow more sophisticated, so does the regulatory process that is set in place to protect the consumers who will be benefiting from them.

There are organizations working to harmonize methods of study, application, and review devices and pharmaceuticals. In the pharmaceutical industry, the International Conference on Harmonisation (ICH) is leading the effort, and in the medical device industry, the Global Harmonization Task Force (GHTF) is doing so. These organizations hope to harmonize the methods, clinical burdens, and documentation required to gain approval for pharmaceuticals and devices. The objective will be to reduce variations in regulatory pathways and expectations that are encountered by industry. Ultimately, there may be one process that allows the submission of the same application package to all target nations.

In the meantime, these organizations and their member nations are making great strides to reduce the varying complexities that industry (particularly medical devices and combination products) is currently confronting in gaining access to international markets. ◆

Headquartered outside Boston in Clinton, MA, Radius Product Development (www.RadiusPD.com) is an award-winning international product design and development firm that provides user research, industrial design, engineering, and manufacturing implementation for clients in the consumer and healthcare industries. The firm has offices in Chicago, Copenhagen, Beijing, and Hong Kong.

BIOGRAPHIES

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FAST-DISSOLVING TABLETS

Fast-Dissolving Rofecoxib Tablets: Formulation Development & Optimization Using Factorial Design

By: D.M. Patel, MPharm; N.M. Patel, PhD; and M.M. Patel, PhD

ABSTRACT

The purpose of this investigation was to develop fast-dissolving tablets of rofecoxib. Granules were prepared by wet granulation using a deposition method. The dried granules were then compressed into tablets. The tablets were evaluated for disintegration time and wetting time. A 3^2 full factorial design was applied to investigate the combined effect of two formulation variables: amount of crospovidone and mannitol. The results of multiple regression analysis indicated that for obtaining fast-dissolving tablets, an optimum amount of mannitol and higher percentage of crospovidone should be used. Response surface plots are also presented to graphically represent the effect of the independent variables on the disintegration time and wetting time. The optimized tablet formulation was compared with conventional marketed tablets for percentage drug dissolved in 30 minutes (Q_{30}). From the results, it was concluded that fast-dissolving tablets with improved rofecoxib dissolution could be prepared by balancing the quantities of soluble filler (mannitol) and disintegrant (crospovidone) in the formulation.

INTRODUCTION

Elderly persons have poor physiological and physical abilities due to the effects of aging. Hence, many elderly persons will have difficulties in taking conventional oral dosage forms because of hand tremors and dysphagia. It is difficult to administer tablets or capsules to patients who are uncooperative, on reduced liquid-intake plans, or are nauseated. To overcome these problems, mouth-dissolving tablets are an ideal option. The development of a fast-dissolving tablet also provides an opportunity for a line extension in the marketplace. Fast-dissolving/dispersing tablets are prepared by techniques such as tablet molding, spray drying, lyophilization, sublimation, or addition of disintegrants.[1-9] Rofecoxib is a non-steroidal anti-inflammatory, water-insoluble, tasteless drug. Hence, it was considered a suitable drug for the preparation of orodispersible tablets. The present work was undertaken to study the effect of variables on the characteristics of orodispersible tablets of rofecoxib utilizing factorial design.

MATERIALS

Rofecoxib was a gift sample from Torrent Pharmaceuticals Ltd., Ahmedabad, India. Croscarmellose sodium (CCS), crospovidone (CLP), low substituted hydroxypropyl cellulose (LHPC), and sodium starch glycolate (SSG) were gift samples from Zydus Cadila Healthcare Ltd., Ahmedabad, India. Mannitol was purchased from Laser Chemicals, Ahmedabad, India. All other ingredients used were of pharmaceutical grade.

METHODS

Preparation of Rofecoxib Tablets

A preliminary study was carried out for screening of four disintegrants namely, CCS, CLP, LHPC, and SSG. Mannitol was incorporated as a soluble filler to improve palatability, to impart cooling sensation and sweet taste upon dissolution. Granulation was carried out using the solid deposition method on superdisintegrants assuming that the method might enhance the wettability and dispersion of the drug particles that disintegrate from the tablets being that rofecoxib is hydrophobic and a water-insoluble drug. Disintegrant (CCS, CLP, LHPC, or SSG) was mixed with mannitol. The powder blend was mixed and kneaded with purified water to obtain a coherent

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TABLE 1

Batch Code	Variable Levels in Coded Form† X_1	X_2	DT (seconds)	WT (seconds)
F1	-1	1	6.66	8.00
F2	0	1	6.33	7.00
F3	1	1	5.33	6.66
F4	-1	0	4.33	5.33
F5	0	0	4.00	5.00
F6	1	0	3.33	4.66
F7	-1	-1	4.66	6.66
F8	0	-1	4.33	6.00
F9	1	-1	4.00	5.00
Coded Values	**Actual Values† X_1**	**X_2**		
-1	4	80		
0	8	85		
1	12	90		

***All batches contained 25 mg rofecoxib, 2% wt/wt talc, 1% wt/wt magnesium stearate, 0.5% wt/wt sodium lauryl sulphate.**

†X_1 is amount of crospovidone (mg); X_2 is amount of mannitol (mg).

DT indicates disintegration time; WT indicates wetting time.

damp mass. Rofecoxib was mixed with wet mass for 5 minutes. The damp mass was passed through a 30 mesh. The wet granules were dried in a hot air oven at 65°C for 1 hour. The dried granules were re-sifted through a 30 mesh and retained on a 100 mesh. The dried granules (30/100 mesh) were mixed with a glidant lubricant bland containing talc (2%), magnesium stearate (1%), and sodium lauryl sulfate (0.5%) for 3 minutes. This blend was compressed into tablets using an 8/32-inch diameter flat face round tooling on a Rimek-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad). The hardness of tablets was kept between 2.5 and 3 kg/cm^2. The prepared tablets were stored in a tightly closed glass container and evaluated for various parameters.

Evaluation of Prepared Tablets

Compressed tablets were evaluated for hardness, friability, wetting time, disintegration time, uniformity of dispersion, and drug content. Hardness was measured using a Monsanto type hardness tester. Friability was determined in a friabilator (model EF-2, Electrolab) by evaluating 20 tablets. A disintegration test was carried out using distilled water as a disintegrating media at 24 ± 2°C. One tablet was placed in each tube of a disintegration apparatus (model ED2, Electrolab, India). To determine wetting time, a filter paper was kept in a petri dish having a diameter of 9.5 cm and containing 15 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the filter paper. The time required to develop a red color on the upper surface of the tablet was recorded as wetting time. For uniformity of dispersion, two tablets were kept in 100 mL of water and gently stirred for 2 minutes. The dispersion was passed through a 22 mesh. The tablets were considered to pass the test if no residue remained on the screen. For drug content analysis, 20 tablets were accurately weighed and finely powdered. Quantity of powder equivalent to 20 mg of rofecoxib was taken into a 100-mL volumetric flask and dissolved in acetonitrile. Exactly 5 mL of the filtrate was diluted to 100 mL with distilled water and assayed for drug content at 237 nm using a double beam UV/Vis spectrophotometer (Shimadzu, model-1601).

Optimization of Formulation Variables

From the results of preliminary studies, a 3^2 randomized full factorial design was adopted to optimize the variables. In this design, two factors were evaluated (each at three levels), and experimental trials were performed at all nine possible combinations.[10] The amounts of disintegrant, crospovidone (X_1), and soluble filler, mannitol (X_2), were selected as independent variables.

The disintegration time and wetting time were selected as dependent variables. The formulation and evaluation of factorial batches (F1 to F9) is shown in Table 1.

The Response Surface Plot

The response surface plot was drawn using Sigma Plot software (Jandel Scientific Software, San Rafael, CA). Figures 1 and 2 show the plots of disintegration time and wetting time versus the amounts of crospovidone (X_1) and the amount of mannitol (X_2), respectively.

In Vitro Dissolution Study

The *in vitro* dissolution study was performed using a USP dissolution apparatus-II (model TDT-06T, Electrolab, India) at 100 rpm using distilled water or 1% w/v SLS in water or isopropyl alcohol: water mixture (30:70) as a dissolution medium.[11] The dissolution media was maintained at 37 ± 0.5°C. Samples were withdrawn at a predetermined time (30 minutes), filtered through a 0.45-micron membrane filter, diluted suitably with the dissolution media, and assayed at 237 nm.

RESULTS & DISCUSSION

Preliminary Trials

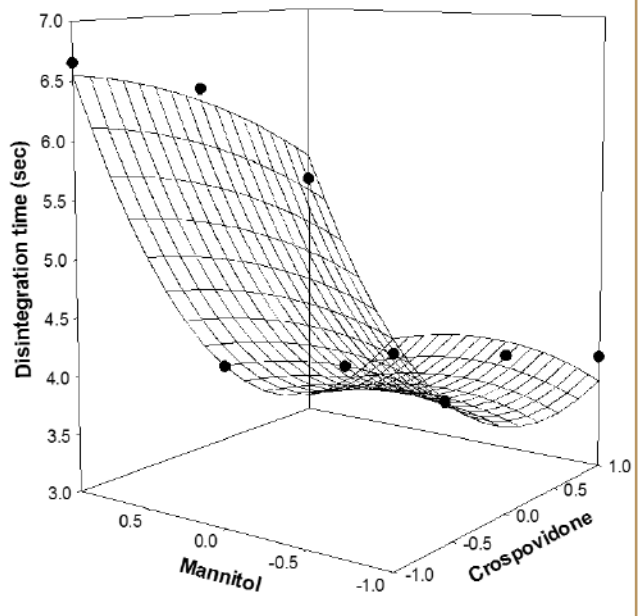
Four disintegrants were selected by keeping in mind that efficiency of disintegrants can be affected in different magnitudes by the presence of soluble filler in the tablet formulations. This expectation arises from the fact that the quantity of water penetrating into the tablet bed is limited. The soluble filler (mannitol) will compete for the available water, consuming it partially and leaving only a part of the total water penetrating the tablet for the development of force necessary for disintegration. The results of preliminary studies revealed that the tablets containing crospovidone exhibit quick disintegration and wetting followed by tablets containing croscarmellose sodium, sodium starch glycolate, and low substituted hydroxypropyl cellulose. The probable reason for delayed disintegration and wetting of the tablets might be slow water uptake or more gelling tendency of croscarmellose sodium, sodium starch glycolate, and low substituted hydroxypropyl cellulose than crospovidone. Hence, crospovidone was selected as a disintegrant for the further studies. The tablet granules failed to separate and hence, a small core remains even after wetting of the tablet. This may be due to formation of a network of wetted particles of disintegrant that counteract the disintegration force. From the preliminary study results, it was observed that the optimum concentration of crospovidone might be less than 15%.

Factorial Design

The amount of disintegrant (crospovidone, X_1) and the soluble filler (mannitol, X_2) were chosen as independent variables in a 3^2 full factorial design. The following statistical model incorporating interactive and polynomial terms was used to evaluate the responses: $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}+X_1+X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$.[1]

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and bi is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to

FIGURE 1



Response Surface Plot for Disintegration Time

TABLE 2

Coefficients For Disintegration Time

Response (disintegration time)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	3.99	-0.498	0.888	-0.167	-0.168	1.33
RM	3.89	-0.498	0.888	-	-	1.33

Coefficients For Wetting Time

Response (Wetting time)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	4.96	-0.612	0.667	0.08	-0.052	1.56
RM	4.96	-0.612	0.667	-	-	1.56

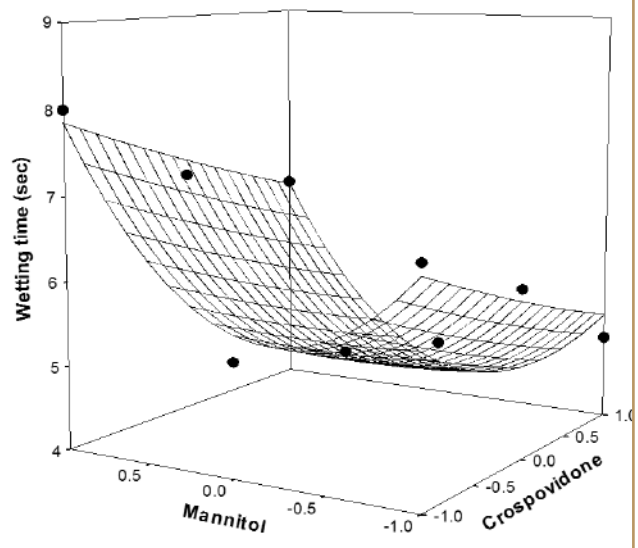
***FM indicates full model; and RM indicates reduced model.**

investigate nonlinearity. The data clearly indicate that the values of disintegration time and wetting time are strongly dependent on the selected independent variables. The fitted equations (full and reduced) relating the disintegration and wetting time responses to the transformed factor are shown in Table 2. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie, positive or negative). Table 3 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.[12] The high values of correlation coefficient for disintegration time and Wetting time indicate a good fit, ie, good agreement between the dependent and independent variables. The equations may be used to obtain estimates of the response as a small error of variance was noticed in the replicates. The significance test for regression coefficients was performed by applying the student F test. A coefficient is significant if the calculated F value is greater than the critical value of F.

Full & Reduced Model for Disintegration Time: The significance level of coefficients b_{12} and b_{11} were found to be $p > 0.05$, hence they were omitted from the full model to generate the reduced model. The results of statistical analysis are shown in Table 2. The coefficients b_1, b_2, and b_{22} were found to be significant at $p < 0.05$; hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{12} and b_{11} contributed significant information for the prediction of disintegration time or not. The results for testing the model in portions are shown in Table 3. The critical value of F for $\infty = 0.05$ is equal to 9.55 (df = 2, 3). Because the calculated value (F = 6.76) is less than the critical value, it may be concluded that the interaction terms b_{12} and the polynomial term b_{11} do not contribute significantly to the prediction of disintegration time and therefore can be omitted from the full model. From the reduced model generated for disintegration time, it can be concluded that amount of crospovidone (X_1) had negative effect while concentration of mannitol (X_2) had a positive effect on disintegration time. It means that as the amount of crospovidone is increased, the disintegration time decreases, while as the amount of mannitol is increased, the disintegration time increases. So, a high level of crospovidone and low level of mannitol should be selected for the rapid disintegration of the tablets. The data of the response surface plot (Figure 1) demonstrate that both X_1 and X_2 affect the disintegration time. It may also be concluded that the high level of X_1 (crospovidone) and low level of X_2 (mannitol) favor the disintegration.

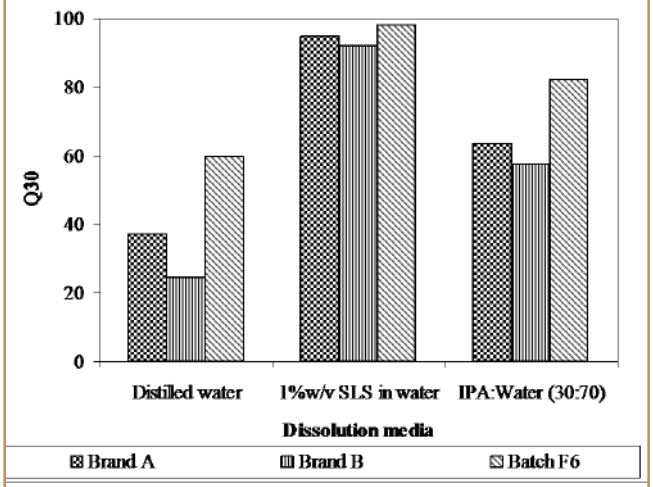
Full & Reduced Model for Wetting Time: The significance of the level of coefficients b_{12} and b_{11} were found to be $p > 0.05$; hence they were omitted from the full model to generate the reduced model. The results of the statistical analysis are shown in Table 2. The coefficients b_1, b_2, and b_{22} were found to be significant at $p < 0.05$; hence they were retained in the reduced model. The reduced model was tested in portions to determine whether the coefficients b_{12} and b_{11} contribute significant information for the prediction of wetting time or not. The results for testing the model in portions are shown in Table 3. The critical value of F for $\infty = 0.05$ is equal to 9.55 (df = 2, 3). Because the calculated value (F = 0.146) is less than

FIGURE 2



Response Surface Plot for Wetting Time

FIGURE 3



Comparative In Vitro Release After 30 Minutes

the critical value, it may be concluded that the interaction terms b_{12} and b_{11} do not contribute significantly to the prediction of wetting time and therefore can be omitted from the full model. From the results of multiple linear regression analysis, it can be concluded that factor X_1 has an inverse effect on wetting time, while factor X_2 has a positive effect. Hence, a high level of X_2 should not be selected for low wetting time. The data of the response surface plot (Figure 2) demonstrate that both X_1 and X_2 affect the wetting time. It may also be concluded that the high level of X_1 (crospovidone) and low level of X_2 (mannitol) favor the wetting of tablets. From the aforementioned discussion, batch F6 (disintegration time 3.33 seconds and wetting time 4.66 seconds) was selected as a promising batch.

Results of Evaluation

Hardness of the prepared tablets was found to be 2.5 to 3 kg/cm^2. Percentage friability of the tablets was observed in the range of 0.22 to 0.53 that was within the acceptable limit. The % assay found was 100% ± 5%, which was within the acceptable limit.

Comparison of Promising Batch With Marketed Formulations

Batch F6 was selected as a promising batch, and it was compared with two marketed samples (brand A and B) of rofecoxib tablets for Q_{30} in three different dissolution media as mentioned earlier. Scientists experienced with dissolution studies will appreciate the selection of three different categories, ie, with surfactant (SLS), hydro alcoholic liquid (IPA:water), and distilled water. The selection of three different dissolution media was done to discriminate the effect of dissolution media on dissolution. Rofecoxib follows Beer's-Lambert law in a concentration range 1 to 12 µg/mL in all the dissolution media used. All the media exhibited good correlation (R^2 greater than 0.99). From the results shown in Figure 3, it can be concluded that the tablets of batch F6 exhibited better *in vitro* drug dissolution after 30 minutes than the tablets of brand A and B in all the media used for dissolution studies. A stability study of batch F6 was carried out at 40°C in a humidity jar having 75% RH. Samples withdrawn after 3 months showed no change regarding *in vitro* drug-release pattern, hardness, wetting time, and disintegration time.

CONCLUSION

The results of a 3^2 full factorial design revealed that the amount of crospovidone and mannitol significantly affect the dependent variables, disintegration time, and wetting time. It is thus concluded that by selecting a proper amount of disintegrant and soluble filler in the tablet formulation, tablets with fast

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TABLE 3

For Disintegration Time

	DF	SS	MS	F	R^2	Fcal = 6.76 Ftable = 9.55
Regression						
FM	5	9.9404	1.9881	159.39	0.996	DF = (2, 3)
RM	3	9.7715	3.2572	78.94	0.979	
Error						
FM	3	0.0374	0.0125			
RM	5	0.2063	0.0413			

For Wetting Time

	DF	SS	MS	F	R^2	Fcal = 0.146 Ftable = 9.55
Regression						
FM	5	9.7888	1.9578	18.58	0.969	DF = (2, 3)
RM	3	9.7579	3.2526	46.85	0.966	
Error						
FM	3	0.3162	0.1054			
RM	5	0.3471	0.0694			

***DF indicates degree of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient; FM, full model; and RM, reduced model.**

disintegration can be produced with minimum efforts. It was also concluded that the deposition of the drug on disintegrant prior to tabletting is helpful to improve the drug dissolution.

ACKNOWLEDGMENTS

The authors would like to thank Torrent Pharmaceuticals Ltd., Ahmedabad (India) and Zydus Cadila Healthcare Ltd., Ahmedabad (India) for providing gift samples of rofecoxib and disintegrants, respectively.

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BIOGRAPHIES

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ADVANCED DELIVERY DEVICES

Needle-Free Injections Using a Spring-Powered Device for Subcutaneous, Intramuscular & Intradermal Injections

By: Richard R. Stout, MD, Maria J. Gutierrez, MD, Peter J. Freeland, MD, Melanie Fein, MD, Taylor D, Davis Y, Quiroz R, Correa O, Machado A, Landau S, Garcia M, Arencibia E, Chinery-Hesse N, Wai C, and Macias J

ABSTRACT

Purpose: The purpose of this study was to demonstrate that a needle-free "spring-powered" device could deliver Subcutaneous (SC), Intradermal (ID), and Intramuscular (IM) injections similar to a gas-powered device, such as the Biojector® 2000. The Biojector® 2000 has been used clinically for many years, thus providing a good standard for comparison with this spring device called the Vitavax.

Method: Sixty (60) healthy adult volunteers participated in the study. Each participant received three injections, SC, ID, and IM, and then a number of subjective and objective measures were used to assess the injection findings. These measures included verbal questioning as to overall impression, preference, pain, safety, positive experience, and likelihood of use. The objective measures included both a verbal and visual analog scale to assess pain as well as color, wetness, and induration at the injection sites.

Results: The data indicates the Vitavax system delivers SC, ID, and IM injections similar to the Biojector® 2000. Injection sensation (pain) was very similar to that reported in the literature for the Biojector® 2000, and other subjective findings were also similar. There were no adverse events in this study.

INTRODUCTION

The Biojector® 2000 Needle-Free Injection Management System (B2000) is a device that provides up-to-date jet injection technology and eliminates or reduces complications associated with previous devices (eg, cross-contamination from patient to patient, lacerations at the injection site, difficult device cleaning, cumbersome tanks, etc).[1-11] The B2000 permits the delivery of medications via the intramuscular, subcutaneous, or intradermal routes. Millions of injections have been administered successfully using the B2000 with no reports of major complications.

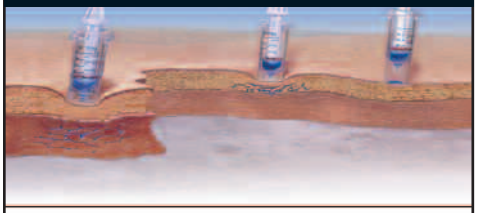
As an alternative, a device using spring technology that eliminates the need for a gas energy source might be beneficial for some markets. Such a spring device should perform SC, ID, and IM injections and have the same performance characteristics and pressure profile as the B2000, which has confirmed success with these three types of injections.

Bioject's engineering team has developed a new spring-powered injector known as the Vitavax (Figure 1). The Vitavax is based on the B2000 performance design but differs in that it uses a spring for its power source. In vitro testing documentation shows that the Vitavax pressure profile is virtually the same as the B2000. Additionally, extensive preclinical and clinical evaluations of SC, ID, and IM injections with the B2000 and the Vitavax have shown that the clinical performance of the two devices is essentially equivalent.

FIGURE 1

Vitavax Needle-Free Injection Device for SC, ID, and IM Injections

FIGURE 2



Left to Right – Needle-Free IM, SC, and ID Injections

DEVICE DESCRIPTION

The Vitavax is a needle-free injection system composed of a spring-powered injector device and a single-use disposable cartridge (needle-free syringe). The device is capable of delivering up to 0.5 ml SQ and IM, and 0.1 ml ID to children and adults without changes or adjustments; it uses multiple disposable cartridges (needle-free syringes) that are unique for each of these applications (Figures 2 and 3). The Vitavax is self-contained, manually powered, and requires no external power supply. The single-use cartridges are filled on site by a healthcare professional before each injection. Except for the power source, it is identical to the B2000 in use and performance.

Beyond clinical verification studies, the next generation of the Vitavax device will be offered with autodisabling disposable cartridges to ensure single-use compliance in immunization programs around the world. The Vitavax could also be employed in therapeutic applications, including self-injections. The Vitavax device is complete as packaged and requires no additional parts or modifications for full functionality.

METHODS

The Vitavax study was a three treatment, single blind, Phase I study conducted at a single clinical center. After meeting all eligibility criteria, a total of 60 healthy subjects, equally divided between males and females whose ages ranged from 18 to 56, were enrolled in this study.

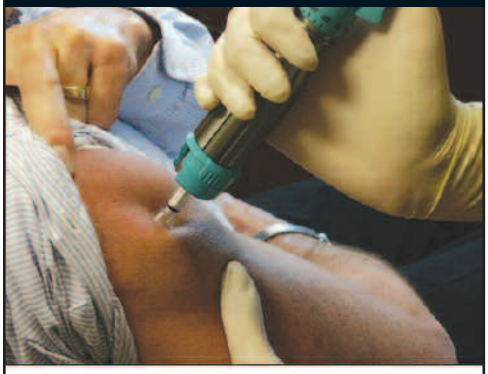
Comparisons were made between the intradermal (ID), subcutaneous (SC), and Intramuscular (IM) injections using the Vitavax.

Sixty (60) subjects received injections in the left or right arm as well as in the left or right abdomen; a block randomization scheme determined the site assignment. Using the Vitavax, all subjects were given injections as follows:

- 0.5 ml normal saline SC in the abdominal region;
- 0.5 ml normal saline IM in the deltoid region; and
- 0.1 ml of normal saline ID in the opposite arm.

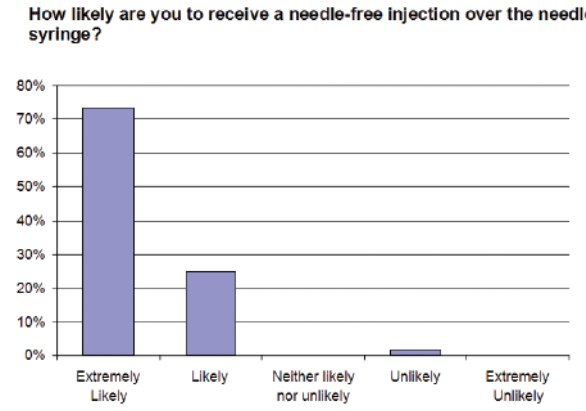
The order of the three injection methods was per the randomization schedule. The study consisted of an "Injection Phase" (Day 1) and "Follow-up" (Day 2). Immediately following each injection, a trained healthcare professional who had not witnessed the injections evaluated the injection sites. The sites were evaluated for surface wetness using a three-point scale, with 0 corresponding to no visible moisture, 1 corresponding to visible moisture without flow, and 2 corresponding to moisture with visible flow. Within 5 minutes after the injections, the degree of pain each subject experienced was elicited and documented via a Visual Analog Scale and a Verbal Scale. The injection sites were also evaluated immediately for local reactions (bruising, redness, and wheal formation). The follow-up, which

FIGURE 3



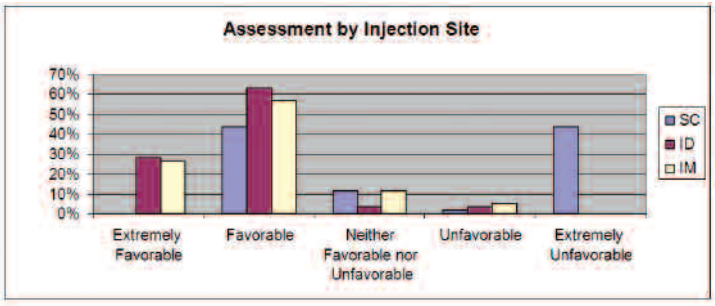
Subject Participant Receiving an Injection

FIGURE 4



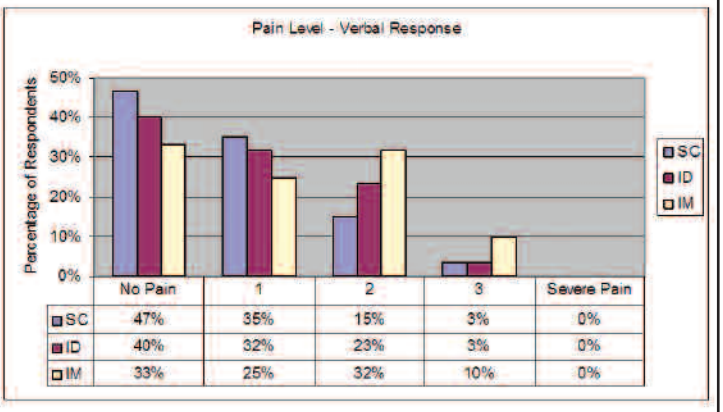
Overall Preference of the Vitavax Injections

FIGURE 5



Assessment by Injection Site. SC Injections Were Given in the Abdomen, IM and ID Were Given in the Arms

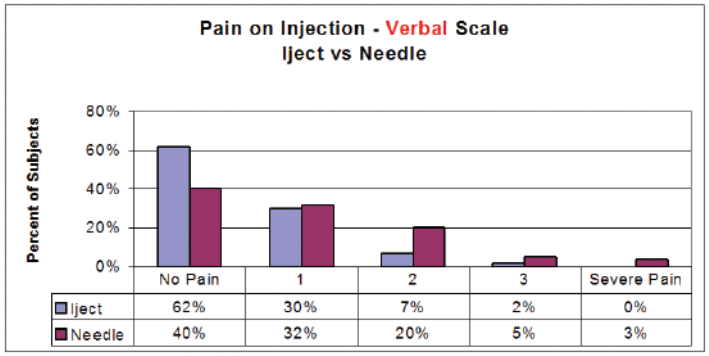
FIGURE 6A



	No Pain	1	2	3	Severe Pain
SC	47%	35%	15%	3%	0%
ID	40%	32%	23%	3%	0%
IM	33%	25%	32%	10%	0%

Pain Scores for SC, ID, and IM Injections

FIGURE 6B



	No Pain	1	2	3	Severe Pain
Ijject	62%	30%	7%	2%	0%
Needle	40%	32%	20%	5%	3%

***Drug Delivery Technology*, 2004;4(3):48-52. "SC Injections" Only**

consisted of injection site evaluations and a few questions regarding preference/subject acceptance, was conducted 24 hours after the initial injection. One specific question related to preference between needle-free and needle/syringe was "How likely are you to receive a needle-free injection over the needle and syringe?" Figure 4 shows that 73% indicated they are extremely likely and 25% indicated they are likely to receive a needle-free injection over a needle and syringe, with only 2% unlikely to use a needle-free device.

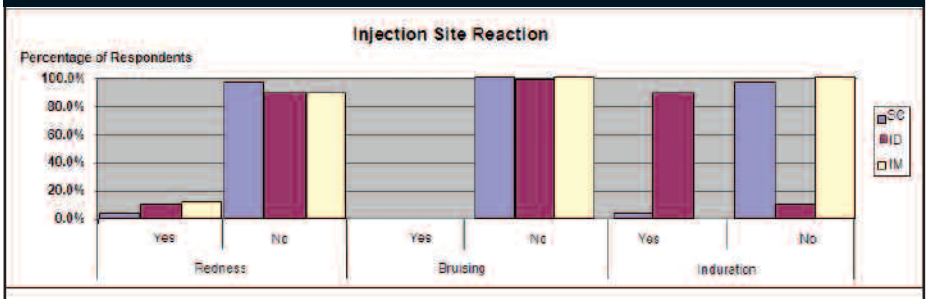
RESULTS

At the 24-hour follow-up, each subject was asked "What is your overall impression of each type of needle-free injection (SC, ID, and IM)?" In Figure 5, the subjective results indicate that overall, the ID injection was preferred over the SC and IM injections administered with the Vitavax. All the SC injections were administered in the abdomen, and many subjects indicated it was extremely unfavorable. It was believed that this was a sensitive area for this group of subjects and not an area they preferred for an injection, although the SC was reported less painful than the ID or IM.

Assessment of pain was performed within 5 minutes after the injection was given by a visual analog scale and a verbal scale, which are considered to be more objective than responses to questions posed by a coordinator. Using the visual analog scale, 40% of the subjects indicated they felt no pain with the SC injection followed by 33% who felt no pain with ID and 30% who felt no pain with IM. As Figure 6 shows, similar results emerged when reviewing responses to the verbal scale, which shows 47% of subjects felt no pain when given the subcutaneous injection followed by 40% who felt no pain with ID and 33% who felt no pain with IM (Figure 6A). Note that this pain data is very similar to data reported previously [*Drug Delivery Technology*, 2004;4(3):48-52] when the Ijject needle-free SC device was studied (Figure 6B), showing needle and syringe to report 40% no pain with a SC injection compared to Ijject showing 62% no pain. The Ijject needle-free device, which is similar to the B2000, had results comparable to the Vitavax. Thus again, needle free is reported less painful than a needle and syringe, at least for SC injections.

There were some interesting results seen in the pain data. Subjects overwhelmingly favored the intradermal injection; however, they felt that the SC injection caused less pain. It appears that the anatomical site (arm versus abdomen) of the

FIGURE 7



Injection Site Reaction With Each Type of Injection

injection participated in the subject's acceptance/assessment.

Other injection site evaluations included redness, bruising, induration, and wetness. Figure 7 shows only a small incidence of redness and no bruising reported. Induration (wheal formation) was found in 88% of ID injections, which is typical for ID injection placement. The remaining SC and IM showed none or no significant indurations. Wetness (surface moisture) was also reported in almost all ID injections but was minor, and there were little or no wetness reports with SC and IM (data not shown).

DISCUSSION

This study supports the successful evaluation of both subjective and objective assessment of the Vitavax for clinical applications. It demonstrates for the first time that all three types of injections (SC, ID, IM) can be administered with a spring-powered device. It also demonstrates the Vitavax performance to be the same or similar to that of the B2000. Eliminating an alternative power source, such as gas, chemical, or others that require alternative means, and using a self-powered spring makes the device much easier and accessible for worldwide usage.

With the Vitavax having the similar performance profile to the B2000, it may reduce the need for large amounts of detailed performance testing of a new generation needle-free device. The B2000 has demonstrated its successful performance over many years and millions of injections. The Vitavax only changes the energy source to provide a totally self-contained needle-free system for professionals and self-injection of any type for any injection needed.

In conclusion, the data clearly indicates the injection effectiveness and acceptability of the Vitavax jet injection technology system for SC, ID, and IM injections. From historical data and published studies, the B2000 has the same or similar clinical results. Due to patient fear of needles, it would have been difficult to perform a study giving three injections using a needle and syringe. Because all subjects were healthy volunteers and were not needle phobic, the actual results might be more favorable for needle free than reported in these results.

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BIOGRAPHIES

Dr. Richard R. Stout joined Bioject in April 1994 as Director of Clinical and Regulatory Affairs. He was promoted to Vice President of Clinical Affairs in December 1994. From 1992 to 1993, he was the Director of Clinical and Regulatory Affairs at EndoVascular Instruments, Inc., a developer of surgical devices and methods for endarterectomy and intraluminal graft placement. Dr. Stout acted as the Manager of Tachycardia Clinical Studies at Telectronics Pacing Systems from 1990 to 1992, an international medical device company involved in manufacturing and distributing cardiac pacemakers and implantable defibrillators. From 1987 to 1989, Dr. Stout was Director of Medical Programs at Biotronic, Inc., manufacturer and distributor of implantable cardiac pacemakers.

Dr. Maria J. Guitierrez is the Principal Investigator of Comprehensive Phase One, a division of Comprehensive NeuroScience, Inc. Born in Cuba, Dr. Gutierrez came to the United States in 1979. She studied medicine in Cuba and in the Dominican Republic and completed her residency in NEOUCOM at Canton, Ohio. Dr. Gutierrez completed a fellowship in Rheumatology at the University of Florida in Gainesville, Florida, and is board certified in Internal Medicine. Since 1999, she has served as Principal Investigator of Comprehensive Phase One, a research unit specializing in Phase I and early Phase II clinical trials.

IMPLANT TECHNOLOGIES

Implant Technologies Expected to Remain a Niche but Effective Method of Drug Delivery

By: Daniel Ruppar, Industry Manager, Pharmaceuticals & Biotechnology, Frost & Sullivan

ABSTRACT

The method of drug delivery is a concern for Pharmaceutical and Biotechnology companies for every project from the point of R&D conception. Implantable drug delivery is one technology sector that is often overlooked in the quest for companies to develop their next big drug. Implant technologies, with the ability to reduce the frequency of patient-driven dosing, and to deliver compounds in a targeted manner, have the capacity to provide a differentiated way to meet the therapeutic needs of patients. Overall, products utilizing implant delivery technologies are being utilized for niche therapeutic applications, such as certain oncology therapies or eye diseases.

INTRODUCTION

Many drugs, such as those based on protein and peptide hormones, are forced down the pathway of parenteral injection due to their PK/PD profile. Once a company seeks to explore other delivery methods, one that could be considered is the use of an implantable drug delivery system. This approach has been embraced by a variety of companies throughout the industry, many of which have successfully brought to market drugs utilizing implant technology.

In terms of related technologies, there are also devices that elute a drug in a targeted capacity, such as a drug-eluting stent (DES). This, however, is a hybrid product, with therapeutic outcomes a result of both the device and drug technologies. If one stays true to the concept of an implantable drug technology, then that relegates the discussion to products that have drug delivery as their main purpose and goal of therapy.

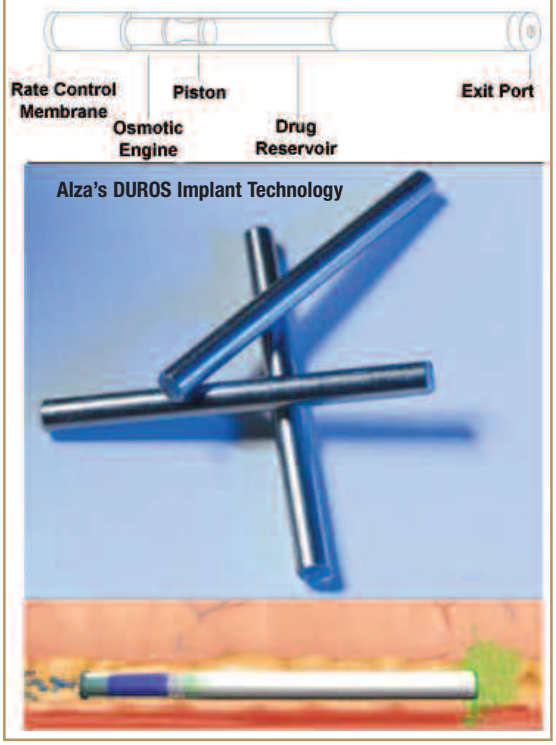
During the drug discovery process, companies often relegate their prospective development programs to one method of delivery for their research and development efforts. This is set on the front end, based on therapeutic targets and the compound types to which the company has rights, thus driving the focus of their R&D programs and clinical candidate development. Most drugs that are dosed to patients operate in a frequently dosed, systemic fashion to achieve the desired therapeutic goal. This is also usually achieved through the more common delivery pathways, including oral and injectable delivery.

In the maze of treatment types and drug regimens available to patients, there are places for other options to be developed and explored by the pharmaceutical industry. The use of implantable drug delivery, with the capacity for long-term controlled dosing and targeted delivery, is a niche that can be explored for product development, especially when there are potential synergistic benefits of having a drug dosed via that platform. This mechanism

FIGURE 1

Valera Pharmaceuticals' Hydron Implant Technology

FIGURE 2



of delivery is not expected to achieve massive use, but it could help patients with certain types of diseases or dosing/delivery needs. The following reviews some of the implantable drug delivery technologies and products that are being utilized and developed by pharmaceutical and drug delivery companies.

VALERA PHARMACEUTICALS

Valera Pharmaceuticals' Hydron Implant technology (Figure 1) is used in the marketed product Vantas (histrelin implant). Vantas received FDA approval on October 12, 2004, for the palliative treatment of metastatic prostate cancer. The company's Hydron technology utilizes polymer blends to deliver histrelin for a continuous 12-month cycle. The implant is inserted into the patient's upper arm in the physician's office under local anesthesia. In addition to the technology's use in Vantas, Valera has identified multiple other potential areas of therapeutic use, including antihypertensives, osteoporosis, antipsychotics, and corticosteroids.

The active drug in Vantas, histrelin, a lutenizing hormone-releasing hormone (LH-RH) agonist, was originally a parenteral injection product marketed by Shire Pharmaceuticals as Supprelin, indicated for the control of central idiopathic precocious puberty. Valera reformulated histrelin for this new use in Vantas.

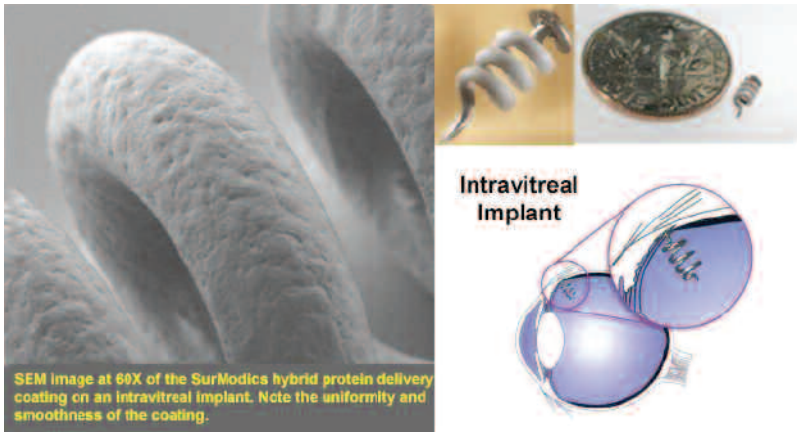
ALZA CORPORATION

ALZA Corporation's DUROS implant technology (Figure 2) is currently utilized in Viadur (leuprolide acetate implant) from Bayer Corporation. Viadur is used as a palliative treatment for advanced prostate cancer, over a 12-month implanted cycle. Previously, patients receiving injections of leuprolide acetate underwent dosing every 1, 3, or 4 months from products such as Lupron Depot (TAP Pharmaceuticals).

DUROS is a non-biodegradable implant technology that is able to provide systemic and tissue-specific delivery of small molecules, proteins, peptides, and DNA/bioactive macromolecules for up to 1 year. The titanium cylinder implant is powered by an osmotic engine.

FIGURE 3

FIGURE 4



SurModics' I-vation Sustained Drug Delivery System

DURECT CORPORATION

DURECT Corporation is involved in more than one type of implant technology. The company has licensed DUROS from ALZA Corporation for select indications and is also developing a catheterized version of the implant. The new catheterized version is to enhance the delivery of the drug to a precise and targeted location, such as a tissue, organ, or synthetic medical structure.

Additionally, DURECT has developed the DURIN biodegradable implant system (Figure 3). DURIN can deliver a wide variety of drug compound types and has the characteristic of not needing surgical removal once the therapeutic dosing cycle for the implant has been completed. This implant is also able to deliver the release of the drug through several mechanisms, allowing for multiple types of drug delivery profiles for products. Dosing profiles that are well suited for DURIN are ones that are needed for several weeks to several months. Overall, DURIN has the positive point of being a biodegradable implant not requiring surgical removal. However, it would not suit applications needing long dosing cycles, such as 12 months.

SURMODICS, INC.

SurModics' I-vation Sustained Drug Delivery System (Figure 4) is utilized in the company's I-vation TA intravitreal implant currently in clinical trials for the targeted delivery of triamcinolone acetonide to the posterior of the eye. This system offers drug delivery for as long as 2 years, and can utilize several different types of polymer systems to control a wide variety of therapeutic compound types. SurModics' proprietary Bravo polymer matrix coating that is utilized in the I-vation system was also used, in collaboration with Johnson & Johnson, in the Cypher drug-eluting stent.

PSIVIDA, LTD.

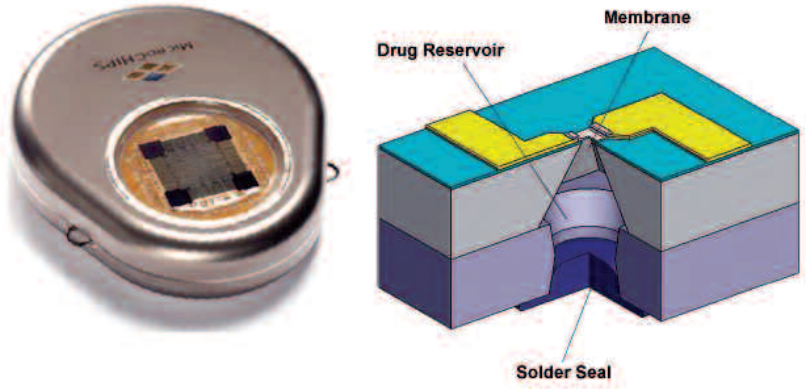
pSivida, through the 2005 acquisition of Control Delivery Systems, has two implant products for the treatment of back-of-the-eye diseases, Vitrasert and Retisert, both marketed by Bausch & Lomb. pSivida also has Medidur (Figure 5), an implant for Diabetic Macular Edema, in clinical trials. This next-generation product is able to be inserted into the patient utilizing an injection, rather than a surgical procedure, which is an attractive characteristic for this type of delivery form.

HOW TO ACHIEVE ACTIVE CONTROL

Once the implant is placed in the patient, the drug's dose control is set for the time the implant is to remain in the patient. This is governed by the formulation and technology utilized

FIGURE 5

FIGURE 6



Key to the implantable MicroChips device (top) are 100 ptramid-shaped drug reservoirs (bottom) about 50 micrometers wide at the top. A wireless signal from outside the body prompts the device to melt a thin metal metal membrane covering a specific reservoir, releasing a drug directly into human tissue. A solder seal holds the drug in place.

in the implant itself. Post implantation, the dose of the drug is not able to be adjusted without removal of the implant delivery system. The ability to actively control the dose could increase the use of implant technologies as a drug delivery method. Furthermore, it could be a widely desired product characteristic, once fully developed and marketed.

MICROCHIPS, INC.

MicroCHIPS is developing technologies for implant devices to enable not only passive delivery, but also active delivery of drugs (Figure 6). Utilizing the company's reservoir array technology to house the drug, products can be delivered through active control by using microprocessors or wireless telemetry that in turn initiate the opening of the reservoirs. This technology is an interesting step in implant technology in that it could provide patients and physicians with "smart" dosing control. One important difference with MicroCHIPS' active control technology relative to other implant technologies is the ability to provide different dosages over different periods of time, all the while controlled ex vivo. In addition to active control, the company's reservoir technology has the ability to be applied in a passive format with possible targeted use as part of several types of orthopedic implants.

THE BOTTOM LINE

The use of implant technologies is expected to remain a niche area for the pharmaceutical industry. However, this delivery application can be very effective in the right therapeutic use, especially for areas that are under-served by other dosing methods. Many products could bring added benefits to patients from the elimination of a repetitive dosing regimen, or through targeted site-specific direct delivery. However, finding those that translate to a beneficial marketed implantable product is something that we are only now starting to successfully see.

BIOGRAPHY

Daniel Ruppar is the Industry Manager of Frost & Sullivan's North American Pharmaceutical & Biotechnology analyst team. He focuses on monitoring and analyzing emerging trends, technologies and market dynamics in the Pharmaceutical and Biotechnology Industry in North America. Since joining Frost & Sullivan, Mr. Ruppar has assumed primary coverage of the cardiovascular sector, with recent work focusing on cholesterol therapy, diabetes, and thrombosis. He also has performed consulting duties for the Venture Capital industry. Prior to this, Mr. Ruppar spent 9 years in the pharmaceutical industry as a medicinal chemist. Additionally, he is a co-author of multiple scientific publications in peer-reviewed journals for his work in chemistry, is a co-inventor on four patents for his work in drug discovery, and has published articles in *Drug Delivery Technology*. He earned his BS in Biochemistry with a minor in Economics from Trinity University.

Developments in MDI Valve Technology Ensure Better Patient Compliance

By: John Olley

INTRODUCTION

Over a number of years, patients, practitioners, and regulators have expressed real concerns about the impact of poor regime assurance on the successful treatment of illness. It is becoming clear that in many cases, patient compliance can be better ensured with assistance from within the device itself. In time, more and more regime assurance and assistance features will be incorporated into everyday drug delivery devices. Indeed, as recently as 2003, the US FDA issued draft guidance recommending that dose counters be considered for all future pressurized metered dose inhaler (MDI) therapies.[1] The FDA and other regulatory authorities have also emphasized the need to produce less variable MDIs that deliver doses more accurately than the current requirement in the United States Pharmacopoeia (USP).[2,3]

Many devices in development now feature dose counters, but perhaps the most impactful technologies in drug delivery regime assurance are those that provide benefit invisibly that do not require the user to consider more information or learn further steps to gain advantage.

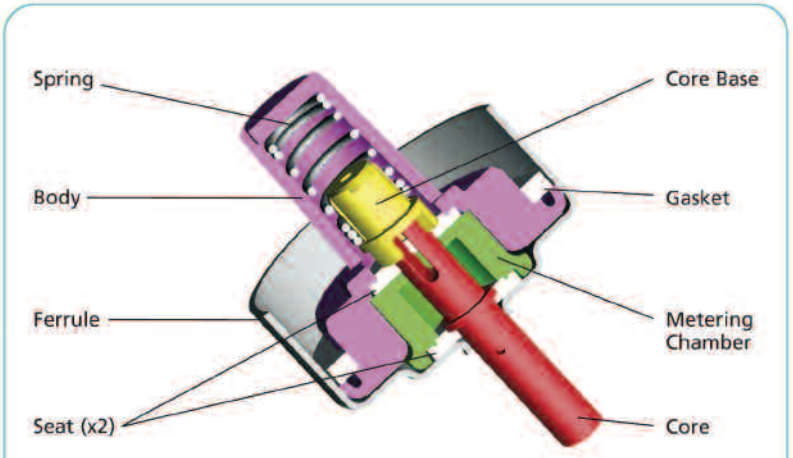
Loss of prime (LOP) and dose content variability are major patient compliance issues associated with all capillary retention valves fitted to MDIs.[4] This is because conventional MDI valves fill a metering chamber immediately after the last dose is fired, and this chamber may partially empty if the inhaler is inverted or left for some time. For the inhaler to then deliver an optimum dose, the patient should ideally fire one shot into the air to ensure the valve chamber is completely refilled from the main can reservoir. This requirement results in high levels of wastage and, of course, assumes that the patient has been shown how to use the inhaler properly or has read the (often ignored) Patient Information Leaflet that came with their medication. Often, this is not the case, so the only reliable method to ensure a full dose is taken is to recommend a regime based on two puffs from the inhaler.

Many believe that other more expensive systemic therapies will account for an increasing share of the MDI market in the coming years. As pharmaceutical companies consider delivering more expensive drugs via MDIs, and generic equivalents compete with more and more of the molecules that have historically been delivered in MDIs, the high wastage issue becomes of greater concern.

A NEW VALVE DESIGN

Bespak, a leading designer, developer, and manufacturer of specialty medical devices, has developed a unique MDI valve to eliminate LOP and improve dose content uniformity. The BK361 Easifill valve is designed to have fast

FIGURE 1



Schematic of the Bespak BK361 Easifill Valve

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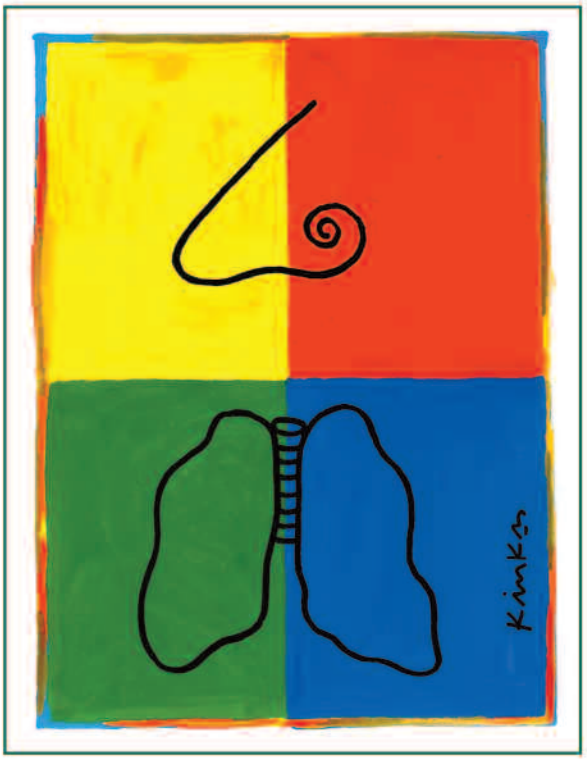

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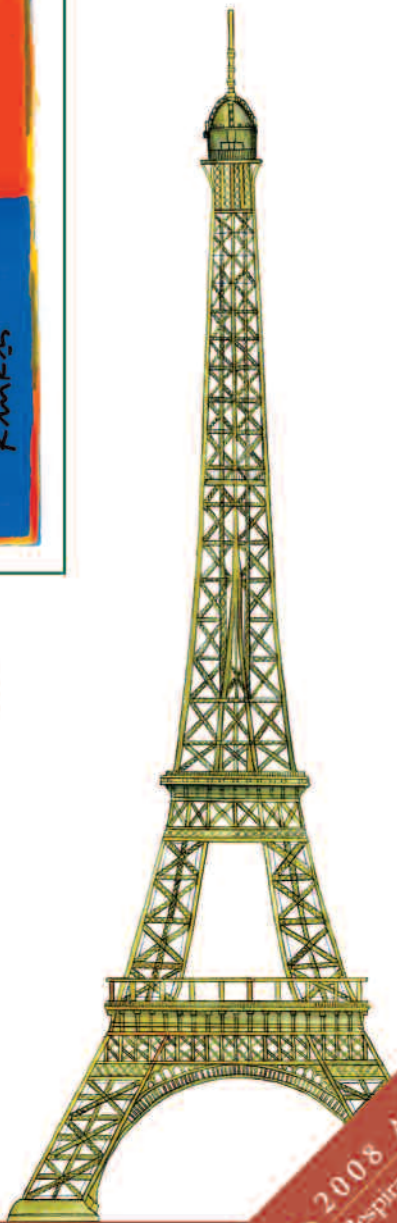

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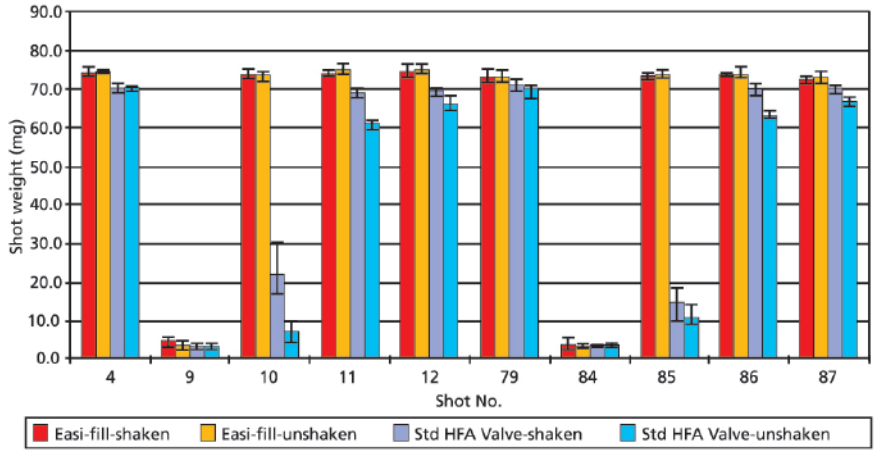
FIGURE 2



Through Life Shot Weight Data for Salbutamol MDIs Fitted With BK361 Easifill and Conventional HFA Valves (n=5)

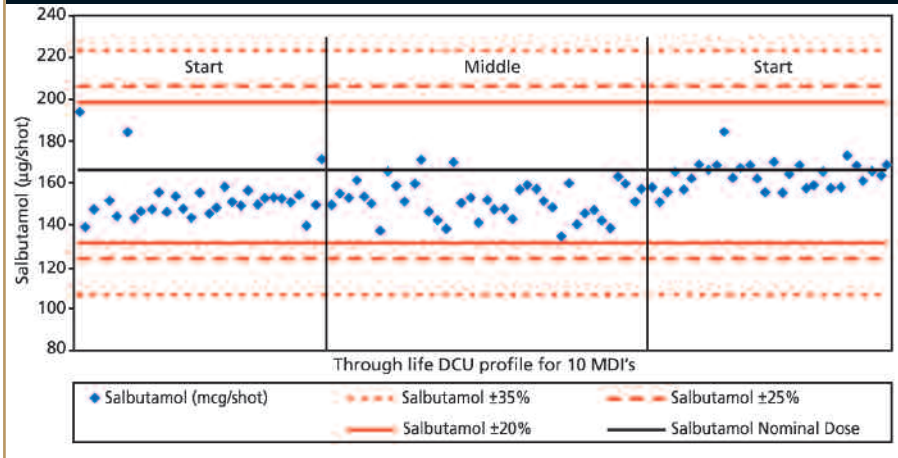
fill/fast drain characteristics that allow the metering chamber to fully refill after actuation or storage, eliminating LOP, reducing dosing variability, and therefore helping to improve patient compliance. The following paragraphs detail the methodology and results of testing the BK361 Easifill valve against a conventional capillary retention valve. Figure 1 shows a cross-sectional diagram of the BK361, which has a larger flow path than the standard metering valve and therefore is able to fill and drain easily.

METHODS

The performance of Easifill 50-µl valves fitted with RB700 EPDM elastomers was investigated using a model 0.4% salbutamol sulphate HFA 134a formulation containing 15% ethanol and oleic acid. A comparative priming study of BK361 and a conventional HFA valve was performed to assess each valve's ability to re-prime from empty. The procedure involved test firing each inhaler with 3 shots using a 5-second shake between shots. Shot 4 was fired, valve down. The nominal shot weight was established and indicated that the valves were primed. The device was then inverted (valve up) and shots 5 to 9 were fired, without shaking, to empty the metering chamber. The mass of shot 9 was noted to indicate exhaustion of the valve metering chamber. Shots 10, 11, and 12 were fired valve down to establish whether the valve could deliver a full shot from empty. The procedure was repeated at the end of the MDI life (nominal 100 doses).

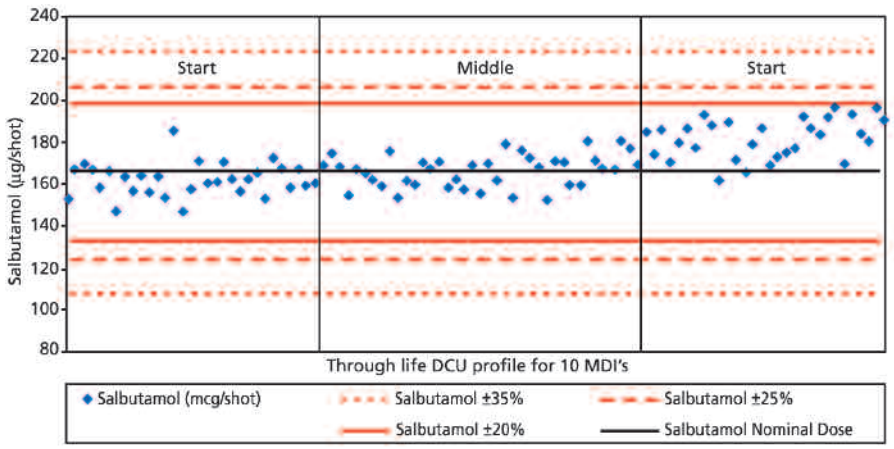
Dose content uniformity (DCU) was assessed for MDIs fitted with a BK361 valve at time = 0 and following storage at 40°C/75% RH (valve down) for 3 months. DCU was assessed through the life of 10 units at the beginning (3 shots), middle (4 shots), and end (3 shots) of the unit life according to USP methods. Salbutamol content was determined using a reverse phase HPLC method.

FIGURE 3



Through Life Dose Content Uniformity for Salbutamol MDIs Fitted With BK361 Easifill Valves at Initial (Ambient) (Start: 3 Shots, Middle: 4 shots, End: 3 Shots From 10 pMDIs)

FIGURE 4



Through Life Dose Content Uniformity for Salbutamol MDIs Fitted With BK361 Easifill Valves Following 3 Months' Storage (40°C/75% RH, Valve Down) (Start: 3 Shots, Middle: 4 Shots, End: 3 Shots From 10 pMDIs)

RESULTS & DISCUSSION

Figure 2 summarizes the results of the priming study and shows that following exhaustion, shots 10 and 85, actuated from MDIs packaged with Easifill valves, delivered a full dose. In contrast, MDIs fitted with standard HFA valves did not deliver a full dose when fired from empty. Figures 3 and 4 illustrate through life dose content uniformity of Salbutamol MDIs packaged with BK361 Easifill valves at time = 0 and following 3 months' storage at 40°C/75% RH, respectively. The results indicate that the DCU remains within the ± 20 % target limits through the life of the product.

CONCLUSION

The data indicate that the BK361 Easifill valve has fast fill/fast drain characteristics, that LOP has been eliminated, and that MDIs fitted with this valve do not require priming. DCU results at the start, middle, and end of unit life for the initial and 3 months time points indicate that all data were within the specification outlined by the FDA and well within the specification detailed in the USP.

Because the Easifill valve requires no priming, pharmaceutical partners can provide a drug delivery solution that gives a consistently accurate dose with a single actuation, resulting in greater regime compliance as patients need only take one puff of their inhaler rather than the two usually recommended. This reduces waste and, with the growing likelihood of more expensive molecules being delivered from MDIs, will almost certainly offer a significant economic advantage. Easily incorporated into new MDI designs, the business case for using the Easifill valve is further enhanced when considered in the context of the key benefits of MDIs as a delivery route, ie, the flexibility to deliver to a range of formulations, enhanced delivery to the lungs, and historically a speedier route to market.

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BIOGRAPHY

John Olley joined the Engineering Department at Bespak in 1974, having completed an indentured apprenticeship in injection mould tool making. Mr. Olley has served in several R&D functions at Bespak, where his knowledge and experience of Polymer Engineering and tool making has benefited the design and manufacture of many new products. In his current role as a Senior Development Engineer, he leads a team of engineers dedicated to delivering innovative design solutions for Bespak's proprietary next-generation projects.

Nanoparticles & Microparticles: Particle Engineering, Cell Uptake, In Vivo Disposition & Efficacy

By: Aniruddha C. Amrite and Uday B. Kompella, PhD

ABSTRACT

Composite nanoparticles and microparticles of drugs, including nucleic acids, are useful in either enhancing or sustaining ocular drug delivery and effects. Eye drops and their ingredients, including particulate systems, can be rapidly cleared due to tear drainage and blinking. Functionalization of nanoparticles is one suitable approach to facilitate rapid uptake of drug into the corneal and conjunctival epithelia. Drug delivery to the retina is more formidable. Periocularly administered particulate systems are offering a safer alternative to systemic and intravitreal modes of administration for retinal drug delivery. Nanoparticles and microparticles > 200 nm are retained in the periocular space for a few months, allowing sustained drug delivery and effects.

INTRODUCTION

Although the eye is a readily accessible organ for the administration of eye drops, the extent of drug delivery to the anterior segment tissues of the eye to treat disorders such as glaucoma is low following topical drop administration.[3] Even for lipophilic solutes < 500 Da, the extent of absorption is estimated to be less than 10%. For macromolecules, the absorption is much less or negligible. The reasons for low drug bioavailability include nasolacrimal drainage of applied drop aided by blinking, drug binding to tear proteins, and poor corneal permeability of solutes. Our investigations, as discussed briefly in this manuscript, are indicating that nanoparticle systems can overcome some of these limitations.[4]

A greater challenge is delivery of drugs to the posterior segment of the eye, which includes tissues such as the choroid, retina, and vitreous.[5] The topical route of administration yields low drug bioavailability in the anterior segment, resulting in little or no drug levels in the posterior segment, necessitating the development of alternative approaches. Although systemic administration (eg, oral dosing) can provide drug levels in the retina, the dose required to achieve therapeutic levels is high due to dose dilution throughout the body and the presence of the blood retinal barrier. Large doses needed with systemic dosing may lead to toxicity. To overcome the aforementioned limitations of conventional topical and oral modes of administration for retinal delivery, local delivery approaches are currently being investigated. The intravitreal and periocular routes are alternatives that can deliver greater dose fraction to the retina, resulting in dose reduction and reduced systemic toxicity. The intravitreal route provides the highest drug levels in the retina, but this route is associated with complications such as retinal detachment, cataracts, and hemorrhage. Periocular routes are safer compared to the intravitreal routes and we are investigating the effectiveness and safety of both periocular and intravitreal routes in delivering drugs to the retina.[5-7]

Several diseases afflicting the posterior segment of the eye, including diabetic retinopathy and age-related macular degeneration, require chronic treatment. Frequent injections either by the intravitreal or periocular routes compromise safety, and also lead to diminished patient compliance. Thus, sustained delivery systems that deliver therapeutic concentrations of drugs to the retina are needed. Our focus is biodegradable sustained-release systems, including nanoparticles, microparticles, and implants for this purpose. The advantage with the particulate systems is that they can be injected and do not require surgical placement and/or removal as is the case with implants. Nanoparticles can be further tailored to have unique properties for enhanced cellular entry, and hence, gene therapy.[4] This manuscript summarizes our investigations in particle engineering, biopharmaceutics and pharmacokinetics of particulate systems, and the safety and efficacy of particulate systems, primarily as they relate to ophthalmic applications.

NANOPARTICLE & MICROPARTICLE ENGINEERING METHODS

Particulate systems for ophthalmic applications can be prepared using a variety of materials, including proteins, lipids, and polymers. We prepared particulate systems using either proteins, such as albumin, or biodegradable

polymers, such as poly(lactide-co-glycolide) (PLGA) and poly(lactide) (PLA). The approaches for engineering nanoparticles and/or microparticles include emulsion polymerization, denaturation, or desolvation of macromolecules, solvent evaporation, ionic gelation, nanoprecipitation, milling, self-assembly, nanolithography, and supercritical fluid technology. The engineering methods for preparing particulate systems differ based on the type of carrier and drug materials utilized and the intended application. We prepared PLA/PLGA particles using the widely used emulsion-solvent evaporation method or unique approaches based on supercritical fluid technology. Using the emulsion solvent evaporation method and a probe sonicator, we prepared nanoparticles of budesonide and a vascular endothelial growth factor (VEGF) antisense oligonucleotide.[8,9] A similar technique was used in preparing microparticles of celecoxib, budesonide, and a peptide drug.[8,10,11] In this method, controlling the energy input from the probe sonicator, the duration of sonication, and the choice of emulsification system allow particle size control.

A key problem with the solvent evaporation methods such as the one described previously is the presence of residual organic solvent in the particles prepared. We have utilized new supercritical fluid extraction-based methods to remove the residual organic solvents form the particles.[11] A 30-minute exposure of supercritical CO_2 to PLGA particles formed using the emulsion solvent evaporation method reduces the residual organic solvent (dichloromethane) content form 4500 ppm to less than 25 ppm. In addition, supercritical fluid extraction-based methods can be utilized for the preparation of drug containing nano- and microparticles of PLGA.[12] We have recently extended supercritical fluid processing to encapsulate plasmids in PLGA (unpublished data). Using a solvent-free single-step supercritical fluid process, we prepared solid-state complexes of budesonide and hydroxypropyl-b-cyclodextrin.[13] To enhance aerosolization and reduce cellular uptake, large nanoporous particles with low bulk density can be prepared using supercritical fluid technology. Such an approach was successful in reducing the uptake of deslorelin containing PLGA particles by alveolar macrophages, thereby sustaining systemic delivery of a peptide drug from the lungs.[11,14] In a supercritical fluid process, several parameters, including the concentration of the drug/polymer, the flow rates of solute containing liquids or supercritical CO_2, the temperature and pressure conditions of the supercritical fluid, and the diameters and type of the capillary nozzles used for spraying can be varied to optimize the particle properties.[15,16] Thus, supercritical fluid process is a versatile process that allows for a finer control of particle properties.

TABLE 1

	Neural Retina (μm)	ONL (μm)	INL (μm)
Controls	304 ± 12	67 ± 4	35 ± 3
Cele-PLGA Microparticles	302 ± 5	67 ± 2	35 ± 2

Morphometric analysis of the rat retina. The thicknesses of the neural retina, outer nuclear layer (ONL), and inner nuclear layer (INL) were compared. Data are expressed as mean ± SD for n = 4.

NANOPARTICLE & MICROPARTICLE UPTAKE BY CELLS & TISSUES

The cellular uptake of nano- and microparticles can depend on various factors, including the chemical nature of the particle, its surface modifications, and size. We investigated the influence of size on particle uptake by retinal pigment epithelial cells (ARPE-19 cell line).[1] Studies using negatively charged fluorescent polystyrene particles (Fluospheres) ranging in size from 20 nm to 2 μm indicated size-dependent cellular uptake of particles, with the uptake increasing with size reduction (Figure 1). Uptake by these cells is relatively high due to the known phagocytic nature of these cells. While both nanoparticle and microparticle composites are capable of protecting the entrapped therapeutic agents from enzymatic degradation, nanoparticles can possibly enter the cells better, enabling greater drug delivery. We have demonstrated that PLGA nanoparticles of an antisense oligonucleotide for VEGF elevate the cell uptake of the oligonucleotide 4-fold.[9]

In an ex vivo bovine eye model (cornea), the uptake of negatively charged 20-nm nanoparticles in 5 min is 2.4%.[4] This uptake of nanoparticles can be further enhanced by functionalizing the nanoparticle surface. We demonstrated that functionalization of nanoparticle surface with ligands that bind to cell surface receptors, such as deslorelin and transferrin, can increase the corneal uptake of nanoparticles from an eye drop to 9% and 16% within 5 min. Further, using excised bovine eye tissues, we observed more efficient nanoparticle uptake and transport across the cornea and conjunctiva following particle surface functionalization.[4] This strategy can be utilized to increase the drug levels in the cornea or conjunctiva and some intraocular tissues after topical administration.

NANOPARTICLE & MICROPARTICLE DISPOSITION *IN VIVO*

Knowledge of disposition kinetics is essential in optimal design of delivery systems. Periocular routes are emerging modes of administration for sustained drug delivery to the retina via the transscleral pathway.[5] We have investigated the disposition of nanoparticles and microparticles after periocular administration to rats.[2] The rats received a periocular injection of either 40 µg or 400 µg (25 µl) Fluospheres, ranging in size from 20 to 2000 nm. Animals were euthanized at 0, 1, 7, or 60 days after treatment. The particles were quantified in the ocular tissues and the periocular space. The effect of surface properties, including charge and surface hydrophilicity, was evaluated using the 20- and 200-nm particles.

Subconjunctivally administered 20- to 2000-nm particles failed to reach the retina to any significant extent, and the larger particles (200 nm and higher) were almost completely retained at the site of administration for at least 2 months. The 20-nm Fluospheres disappeared rapidly from the periocular space with 15 ± 3% and 8 ± 3.5% particles remaining at the end of 1 and 7 days and no detectable levels at 60 days post-administration. The dose did not affect the retention behavior of any type of particles. The surface hydrophilicity did not influence the retention of the 200-nm particles. In contrast, for the 20-nm particles, the retention was greater for the hydrophobic particles as compared to the hydrophilic ones (Figure 2).

There is a cut-off size above which the particles are retained in the subconjunctival tissue. The particulate systems at or above 200 nm are retained at the site of administration for at least a period of 2 months, and this retention is not affected by dose or surface properties probably because these particles are above the cut-off size for rapid clearance. Thus, drug-particulate systems greater than 200 nm in size, formulated using biodegradable polymers, can be utilized for sustained drug delivery to the retina by the transscleral approach.

NANOPARTICLES & MICROPARTICLES FOR ENHANCED OR SUSTAINED DRUG DELIVERY

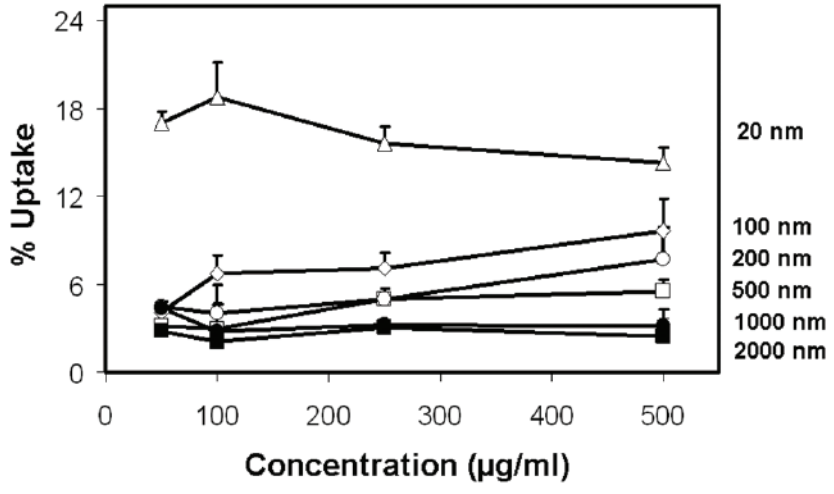
Sustained delivery is essential for treating several posterior segment ocular disorders. Periocularly injected biodegradable PLA/PLGA-based microparticulate systems sustain budesonide and celecoxib levels in the retina for at least 2-months.[6,17] The same sustained effect is not observed with the nanoparticles, although the nanoparticles sustain better as compared to the un-encapsulated drug.[8] This difference can be attributed to a high burst release followed by very slow release observed with nanoparticles.

NANOPARTICLES & MICROPARTICLES FOR THERAPEUTIC APPLICATIONS

Consistent with their ability to elevate cellular uptake of oligonucleotides, PLGA nanoparticles significantly inhibited the secretion of VEGF secretion from retinal pigment epithelial cells with efficacy comparable to that of Lipofectamine, a commonly employed cell transfection reagent.[9] On the other hand, the oligonucleotide alone is ineffective. In our gene therapy efforts using nanoparticles, albumin nanoparticles facilitated the cellular delivery and expression of superoxide dismutase 1 gene in retinal cells *in vitro* as well as *in vivo*.[18] Thus, nanoparticles are particularly useful in enhancing the delivery and effectiveness of macromolecules, such as nucleic acids.

Microparticles of PLGA are useful in sustaining the delivery and effects of

FIGURE 1

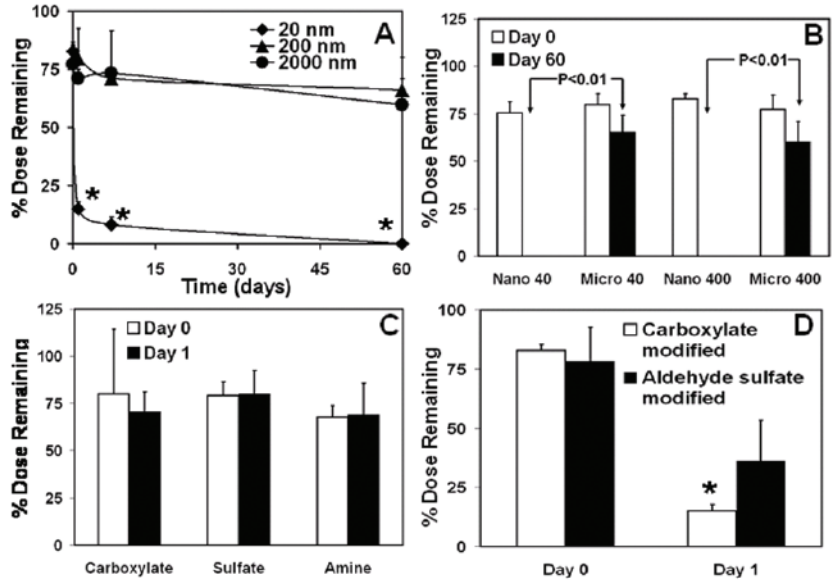


Size-dependent uptake of fluorescent-polystyrene nanoparticles and microparticles by retinal pigment epithelium (ARPE-19 cells). Confluent ARPE-19 cells grown in 48-well plates were exposed to nanoparticle suspensions of various sized nano- and micro-particles at concentrations ranging from 50 to 500 µg/ml for 3 hrs. The data are expressed as mean ± SD for n = 4. From Aukunuru et al.[1]

celecoxib in a rat model of early diabetic retinopathy. We observed that an ultra-low dose (75 µg) of celecoxib encapsulated into PLGA microparticles alleviates diabetes-induced oxidative stress in the rat retina.[10] The rats were made diabetic by an intraperitoneal injection of streptozotocin (60 mg/kg). One day following the injection, the development of diabetes was confirmed by measuring the blood sugar levels, and the rats were given a periocular injection of 75 µg of celecoxib solution or equivalent celecoxib encapsulated in microparticles. The rats were sacrificed after 14 days, and the retinas were removed and assessed for oxidative stress markers. The celecoxib-PLGA microparticles significantly reduced diabetes-induced elevations in thio-barbituric acid reactive species (TBARS: a marker of oxidative stress) and 4-hydroxynonenal (4-HNE: a marker of lipid peroxidation). However, they did not significantly reverse glutathione depletion observed in this model.

In a separate study, using a higher dose, we have demonstrated that celecoxib-PLGA microparticles have beneficial effects in reducing diabetes-induced elevations in VEGF (an endogenous vascular permeabilizing and angiogenic agent), prostaglandin E2 (PGE2; an inflammatory mediator and vascular permeabilizing agent), and vascular leakage for at least 2 months.[6,19] Diabetes was induced in rats using intraperitoneal streptozotocin (60 mg/kg). The animals were divided into 6 groups: normal, diabetic, normal + celecoxib microparticles, diabetic + celecoxib microparticles, diabetic + celecoxib suspension, and diabetic + placebo particles. After ensuring hyperglycemia, phosphate buffer saline (PBS) containing celecoxib-PLGA microparticles (750 µg of celecoxib), celecoxib (750 µg) suspension, placebo microparticles, or vehicle was administered to one eye by periocular injection. Two months post-administration, the animals were euthanized, and the retinal PGE2 secretion, VEGF protein, and vascular leakage (measured as vitreous: plasma protein ratio and a 4-kD FITC-dextran leakage assay) were estimated. Diabetes elevated PGE2 secretion, VEGF protein, the vitreous-plasma protein ratio, and blood-retinal barrier leakage by 3-, 1.7-, 3.1-, and 2.7-fold, and celecoxib-PLGA microparticles significantly reduced these elevations by 40%, 50%, 40%, and 50%, respectively. Neither the placebo-treated eyes nor the contralateral eyes in celecoxib-PLGA microparticle-treated rats showed significant effects. Further, celecoxib suspension failed to exert any significant effects. Thus, particulate systems sustain drug delivery and effects. The effectiveness is mainly due to local delivery of celecoxib to the retina in the dosed eye. Thus, celecoxib-PLGA microparticles are of therapeutic value for diabetic retinopathy. Potentially similar particulate systems can be utilized for treating other disorders of the back of the eye, including choroidal neovascularization and retinal degenerative disorders.

FIGURE 2



Microparticles and nanoparticles (> 200 nm) are retained in the periocular space for over 60 days following posterior subconjunctival injection. A) Retention behavior of 20-nm, 200-nm, and 2-µm carboxylate-modified polystyrene particles in the periocular space of rats for up to 60 days. B) Effect of dose on the retention of 20 nm and 2 µm particles. A dose of either 40 µg or 400 µg was injected and the retention behavior analyzed post 60 days. C) Effect of surface properties on the retention of 200-nm particles in the periocular space. Carboxylate (negatively charged, hydrophilic), sulfate (negatively charged, hydrophobic), or amine modified (positively charged, hydrophobic) 200-nm particles were injected into the periocular space of rats, and there retention was followed for a day. D) Effect of surface properties on the retention of 20-nm particles in the subconjunctival space. The data are expressed as mean ± SD for n=3-4. * Significantly different from Day 0 (P≤0.05). Based on Amrite and Kompella.[2]

SAFETY OF PARTICULATE SYSTEMS

Safety is of paramount importance in developing injectable, new drug dosage forms. We investigated the safety of periocular celecoxib-PLGA microparticle systems.[6] For the safety studies, non-diabetic Sprague Dawley rats were injected subconjunctivally with celecoxib-PLGA microparticles to one eye under anesthesia. The non-diabetic rats injected with PBS served as controls. The rats were euthanized

60-days post administration, and the periocular tissues and retina were assessed for toxicity using histology and morphometric analysis of the retina. The blood chemistry, body weights, and blood cell counts were used to assess any systemic toxicity. Celecoxib-PLGA microparticles did not cause any histopathological damage to the retina or the periocular tissues. The Masson trichrome staining of the periocular tissue, including the conjunctiva, revealed no difference in collagen staining pattern between the control rats and rats that were injected with periocular celecoxib-PLGA microparticles. The particles were well tolerated. There was no atrophy or degeneration of the retina, as evidenced by histological pictures and morphometric analysis (Table 1). There was no difference in the blood cell counts, body weights, or the blood chemistry profiles of the rats that were injected with celecoxib-PLGA microaprticles compared to controls. Thus, PLGA particles of celecoxib appear to be well tolerated and do not lead to any overt inflammation or toxicity when administered by the periocular route.

CONCLUSIONS

Nano- and microparticulate systems are useful for ocular drug delivery, both in the anterior as well as the posterior segments. These systems can offer several advantages, including enhanced cellular uptake and sustained drug release. In topical ocular delivery, limitations of the conventional systems, such as rapid clearance of the dosage form and inefficient uptake of some drugs by the epithelial cells, can be overcome to some extent by using functionalized nanoparticulate delivery systems. Nanoparticles, especially those functionalized with ligands for cell surface receptors, can penetrate into the cells probably through endocytotic mechanisms. Although nanoparticles can be used to sustain drug delivery, the effective sustainment is better with microparticles as compared to nanoparticles because of their low surface-to-volume ratio in comparison to the nanoparticles. For this reason and due to their better retention, nanoparticles > 200 nm and microparticles are of value in sustaining retinal drug delivery and effects for at least a few months. The ultimate choice of the dosage form will however depend on several factors, including pathophysiological considerations, treatment objectives, and several drug-related factors.

ACKNOWLEDGMENT

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BIOGRAPHIES

Aniruddha C. Amrite is a graduate student at the University of Nebraska Medical Center in Omaha, working under the supervision of Dr. Uday B. Kompella. His current research focus is the retinal delivery of low molecular weight drugs as well as macromolecules using nanoparticles and microparticles. His research was recognized with the overall first place award for his oral presentation in the 2005 Midwest Biomedical Research Forum. Also, he received the UNMC and UNMC College of Pharmacy first place awards for his oral presentation at the 2005 Midwest Biomedical Research Forum. In 2006, he received a travel award from the American Association of Pharmaceutical Scientists (AAPS) and a research award from the American Association of Indian Pharmaceutical Scientists (AAiPS). Mr. Amrite served as the 2005-2006 Chairman of the UNMC AAPS Student Chapter. He earned his BS in Pharmacy from the University of Pune, India.

Dr. Uday B. Kompella is an Associate Professor and Chairman of the Pharmaceutical Sciences Graduate Program in the Department of Pharmaceutical Sciences at the University of Nebraska Medical Center (UNMC) in Omaha. His research interests include drug and gene delivery for treating corneal angiogenesis, age-related macular degeneration, diabetic retinopathy, and lung cancer. He has been published extensively, received numerous grants, and held leadership positions in several professional organizations. A 1997 recipient of the AAPS New Investigator Award in Pharmaceutics and the Pharmaceutical Technologies, Dr. Kompella's research was recently recognized with an AAPS Fellow Award (2005) and a UNMC Distinguished Scientist Award (2006). Dr. Kompella serves as an Editor for the Journals, Pharmaceutical Research and Clinical Research and Regulatory Affairs. He serves as an Editorial Board Member for the journals Drug Delivery Technology and Expert Opinion on Drug Delivery. Dr. Kompella earned his BS and MS in Pharmacy in India and his PhD in Pharmaceutical Sciences from the University of Southern California.

DRUG DELIVERY Executive

3M Drug Delivery Systems

3M Drug Delivery Systems: Providing Customer-Focused Solutions

3M Drug Delivery Systems is a global leader in inhalation and transdermal drug delivery systems, providing world-class product development, components, and manufacturing to pharmaceutical and biotechnical companies. This organization combines the agility of a leading drug delivery company with the extensive resources of a major multinational company. 3M products are manufactured and sold in more than 60 countries on 6 continents. Business partners benefit from 3M's in-depth expertise and wide-ranging resources, including global regulatory affairs, lean manufacturing, and 15 core technology platforms that give 3M Drug Delivery Systems the flexibility to offer customized solutions to meet their customers' needs. Drug Delivery Technology recently interviewed James Vaughan, 3M Drug Delivery Systems General Manager, on his organization's strategic direction.

James Vaughan
General Manager
3M Drug Delivery Systems Division

"Speed-to-market is important. Between drug discovery and commercialization, our vertical integration helps our partners get to market sooner."

Q: Can you tell our readers some things about 3M Drug Delivery Systems they may not know?

A: That's a timely question because there's been some confusion in the marketplace recently. 3M Drug Delivery Systems is part of 3M Health Care, one of the company's six major businesses. Our mission is to provide world-class innovative products and services to help healthcare professionals improve the practice and delivery of patient care. This past November, we sold one segment of that business – branded pharmaceuticals. But, let me assure you, 3M Drug Delivery Systems is totally separate and continues to be a strong strategic fit within 3M.

Q: How does your business model benefit partners?

A: What our pharmaceutical partners value most is the access they have to all of 3M. For example, we have global regulatory expertise. 3M has worked closely with the Food and Drug Administration and other regulators around the globe for many years, and we understand the challenges and the complexities involved. Also, we have scientists around the world and can tap into their expertise and knowledge. Our customers benefit from our global reach, our world-renowned technical community, and our manufacturing capabilities. Speed-to-market is important. Between drug discovery and commercialization, our vertical integration helps our partners get to market sooner.

Q: How do 3M's core technologies add value?

A: When you think about the word innovation, 3M is top of mind. Our name is synonymous with innovation. And our partners have access to 3M's entire range of technologies and the bright minds behind them. In fact, this past fall, we opened the 3M Innovation Center in St. Paul, MN. It's a one-of-a-kind facility that showcases how we make uncommon connections that result in unique solutions for our customers. Our customers are immersed in innovation, and it really unlocks the potential business opportunities that we have with our partners.

So whether we're focused on product development or problem solving, our partners take advantage of some 15 core technologies. For example, the same microreplication technology that is used to make street signs more easily visible is being applied to a new drug delivery technology we're developing. And 3M's world-renowned films and adhesives are also good examples of other core technologies that we use extensively in product development.

Q: We're curious about the new microreplication technology you just mentioned. Can you tell us more about it?

A: Yes, it's called Microstructed Transdermal System or MTS. It's a state-of-the-art microneedle system for transcutaneous or intradermal drug delivery. We're looking for a pharmaceutical partner to bring this new transdermal technology to market. This new technology has great potential for a wide variety of molecules, and it can enhance the efficacy of vaccines. It's a user-friendly and well-tolerated design, and the technology can be adapted to meet a partner's application requirements.

Q: You also provide transdermal and inhalation components to the marketplace. How does this fit into your overall business strategy?

A: Components are an important part of our business. Transdermal components include many varieties of backings, membranes, thin and flexible films, liners, and foam tapes. We can modify or design components to solve unique problems. In fact, about 80% of the transdermal patches on the market today contain at least one 3M component. That's a clear reflection of the quality of our products – even our competitors want to use them!

The same can also be said for the components we provide for metered-dose inhalers. We're a major supplier of metered-dose inhaler components. And we've been on the forefront, for example, of dealing with challenges like CFC-free propellants. There's the potential for chemical or physical interactions between CFC-free propellants and the components. We thoroughly understand formulation properties and can optimize container/closure systems. Our components are available to our partners and are also available to pharmaceutical companies that are developing their own metered-dose inhaler systems.

Q: You mentioned manufacturing services. What does 3M offer?

A: Manufacturing is a core strength of 3M, and this is particularly evident within the Drug Delivery Systems Division.

We have facilities worldwide, and we can offer a full range of advanced manufacturing resources through the entire life cycle of a product. We provide pilot to full-scale commercial manufacturing, including Schedule C-II and C-III capabilities. Our ability to design customized manufacturing processes is very important because some partners come to us at the product development stage and others already have a fully developed product that requires production. We have product registrations in more than 60 countries, and all of our work complies with global regulatory guidelines, including cGMPs.

We also use LEAN manufacturing principles and tools in our facilities. The focus is on eliminating waste in the supply chain. That's any activity that doesn't add value to the customer. We don't just reduce material waste, we look at everything we do. We're reducing cycle time and inventory and improving service levels. LEAN manufacturing is a logical extension of our commitment to Six Sigma. We've learned throughout the past 5 or more years how to be lean thinkers, and we can leverage that experience on behalf of our partners.

Q: A lot of drug delivery companies eventually become specialty pharmaceutical companies. Why has 3M sustained a true drug delivery business model?

A: I think we have a clear vision. We know what we're good at, and we stay focused on that. We've run a successful and stable organization for many years. As a result, we are very customer-oriented and cost effective. Our partners have unique circumstances, so each collaboration is also unique to meet their needs. We're in a fast-changing industry and that kind of flexibility is important.

There's a big gap between a concept on paper and a product ready for market. We work closely with partners to incorporate their drug molecules into successful delivery systems. It's one thing to hold a patent and quite another to deliver a real product that has met all of the regulatory requirements and can sustain itself after commercialization. 3M has a long-standing reputation of developing practical and ingenious solutions that other firms simply can't provide. We've been global leaders in this industry for 50 years, and, as a company, we bring more than a century of innovation to the marketplace. That's the unprecedented experience we offer. ◆

LECITHIN ORGANOGELS

Lecithin Organogels as a Drug Delivery System: A Review

By: I.M. Shaikh, MPharm; K.R. Jadhav, MPharm; V.J. Kadam, PhD; and S.S. Pisal, PhD

ABSTRACT

For many systemically acting drugs, the oral route has been the preferred route of administration. However, oral administration of many therapeutic agents has been reportedly subjected to extensive presystemic elimination by gastrointestinal and hepatic metabolism. Topical administration of therapeutic agent offers many advantages over oral and invasive methods of drug delivery. However, as skin is an exceptionally effective barrier to most chemicals, very few drugs can permeate it in amounts sufficient to deliver a therapeutic dose. Therefore, systems that make the skin locally more permeable and thereby enable transdermal delivery are of great interest. Under certain conditions, soybean lecithin in an apolar, organic solvent forms an entangled, dynamic network of long and flexible wormlike, multimolecular aggregates.[1] This so-called lecithin organogel is characterized by a considerably high viscosity and by a complete optical transparency. A number of therapeutic agents have been formulated as lecithin organogels for their facilitated transport through the dermal and transdermal route with some very encouraging results. Lecithin organogels have also been tried successfully for the ocular route. This review discusses salient features, formation, and various applications of lecithin organogels as drug delivery systems.

FEATURES OF LECITHIN ORGANOGELS

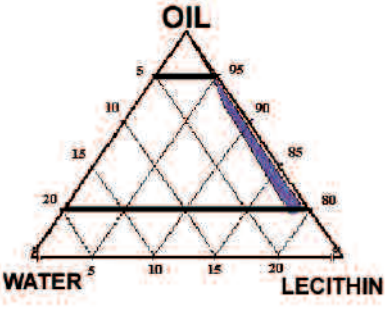
Some of the features of lecithin organogels can be characterized by the following bullet points:

- Use of biocompatible, biodegradable, and non-immunogenic materials makes lecithin organogels suitable for long-term use.[2-4]
- Lecithin organogels can solubilize lipophilic, hydrophilic, and ampiphilic guest molecules, including enzymes (due to reverse micelle formation).[5-7]
- Lecithin organogels are thermoreversible in nature. Above 40ºC, they become solvent, and when the temperature is decreased, they revert to gel state.[7]
- Lecithin organogels are thermodynamically stable systems and isotropic in nature.[8-11]
- Lecithin organogels are moisture insensitive, and being organic in character, resist microbial contamination.[1,11,12]
- Spontaneity of organogel formation, by virtue of self-assemble supramolecular arrangement of surfactant molecules, makes the process very simple and easy to handle.[11]
- Lecithin organogels, prior to gelling (ie, before the addition of polar phase), exhibit Newtonian behavior but follow Maxwell's rheological (viscoelastic) behavior on addition of polar phase.[13]

LECITHIN

A Frenchman named Maurice Gobley observed phosphtides, isolated them from egg yolk in 1846 for the first time, and named them lecithin. In the 1920s, the Bollmann extraction process made it possible to obtain large quantities of lecithin from soya beans. Lecithin is mainly a complex mixture of phospholipids, glycolipids, and triglycerides. In chemical terms, lecithin is a natural mixture of phosphatides that is phosphatidylcholine (20% to 31%) (PC), phosphotidylethanolamine (PE), and phosphtidylinositol (PI) in combination with fatty acids, carbohydrates, and other

FIGURE 1



Schematic Diagram of Pseudoternary Phase Diagram (Blue Patch Shows Organogel-Existing Area)

LECITHIN ORGANOGELS

substances. Lecithin is a trivial name for 1, 2-diacyl-sn-3-phosphocholine.[11] Soya bean lecithin contains 1.7% palmetic, 4% stearic, 8.6% palmitoleic, 9.8% oleic, 5% linolenic, 4% linoleic, and 5.5% C_{20} and C_{22} acids. Lecithin is made up of ubiquitous phospholipids that account for more than 50% of the lipid matrix of biological membranes. Lecithin organogels are readily obtained by adding a minimal amount of polar solvent, such as water, to a solution of lecithin in organic solvents.[1] It was Scartazzini and Luici who first provided information about lecithin organogels in an article published in 1988.[1]

FORMATION OF LECITHIN ORGANOGELS

Lecithin organogels are formed by three different components, including organic solvent, a polar phase, and an organogellator [lecithin]. The composition of these three components required for organogel formation is determined from a pseudoternary phase diagram.

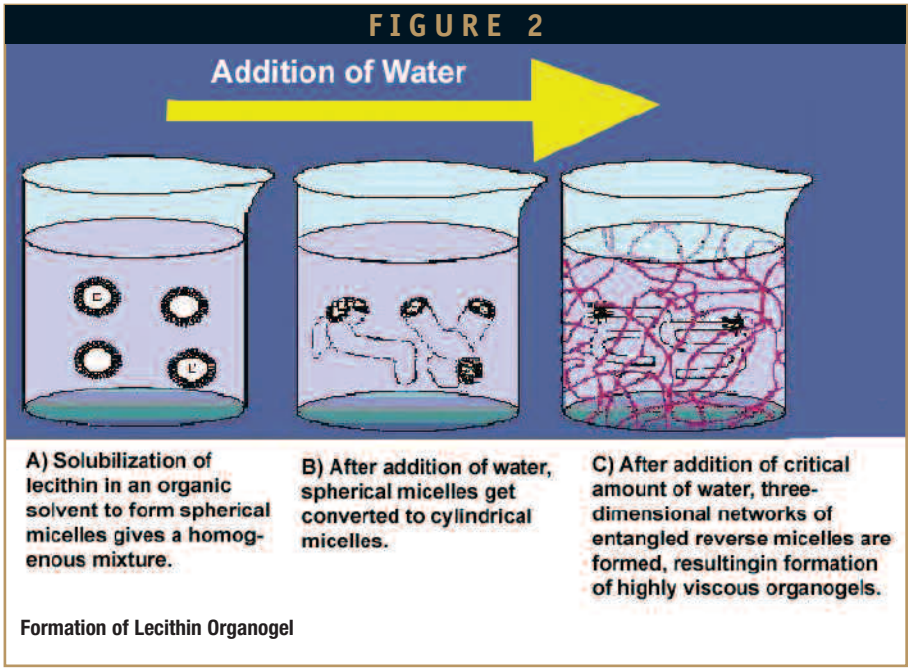
Organic Solvent

More than 50 organic solvents have been reported to form organogels with water as an aqueous phase.[1] Among various organic solvents, fatty acid esters, such as Iso Propyl Myristate and Iso propyl palmitate, have been widely used for lecithin organogel formation, but structural investigations have only been performed on systems based on hydrocarbons, ie, cyclohexane, iso octane, and decane.[11,13,14]

Polar Solvent

A series of polar solvents have been studied in order to reveal those capable of producing the thickening effect on hydrocarbon and fatty acid ester solutions of lecithin. Water has been used extensively as a polar solvent for organogel formation.

FIGURE 2



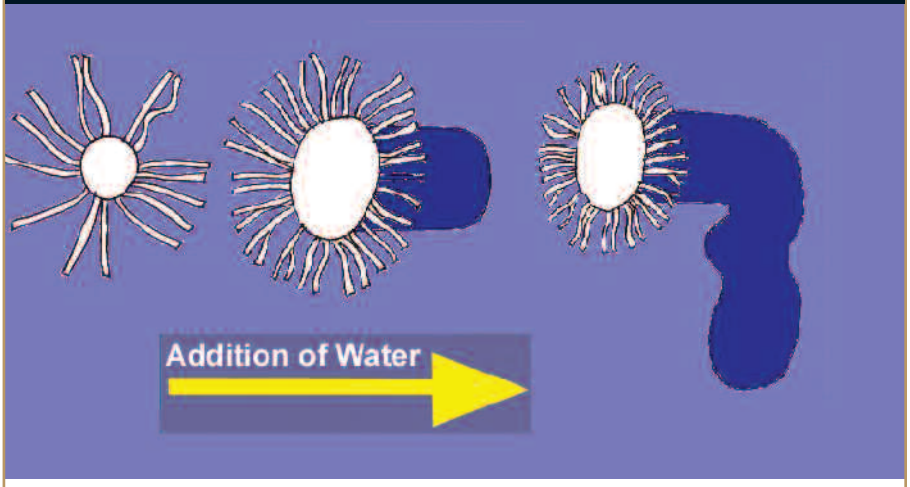
Formation of Lecithin Organogel

However, it has been established that glycerol, formamide, and ethylene glycol (in addition to water) have the ability to induce organogel formation.[11] The ability to promote thickening of lecithin solutions has correlated with the polarity of molecules. The correlation is particularly pronounced in the series of such structurally related compounds as glycerol, ethylene glycol, and 1, 3-propanediol. It has been inferred from the results that the difference between gelforming and non-gel-forming polar solvents is caused by their orientation and localization in the polar moiety of a lecithin molecule. In a proposed model of the organogel, the solvent molecules bridge phosphate groups of neighboring lipid molecules, thus allow their association into tubular aggregates through an extensive ribbon-like hydrogen bonding network.[11]

Organogellator-Lecithin

Organogellator-lecithin is a trivial name for 1, 2-diacyl-*sn*-3-phosphocholine. It belongs to a biologically essential class of substances termed phosphoglycerides or phospholipids. The latter form the lipid matrix of biological membranes and also play a key role in cellular metabolism.[15] As a biocompatible surfactant, it is widely used in every day life, including human and animal food, medicine, cosmetics, and manifold industrial applications.[16,17] Synthetic lecithins containing residues of saturated fatty acids failed to form organogels.[9,11,18] The gelling formation was also not observed with hydrogenated soybean lecithin.[11] These studies indicate the importance of lecithin in the naturally occurring form, which contains unsaturated fatty acids. Unsaturation in phospholipid molecules is a desired property for the formation of lecithin organogels. This may be attributed to its impact on the nature of self-assembly in which the phospholipid molecules associate and form the microstructures. The unsaturation contributes to the volume factor of the non-polar region of phospholipid molecules and may alter the value of critical packing parameter (CPP), favoring the formation of reverse micellar structures. And most likely, the size of such

FIGURE 3



Transformation of Spherical Micelles to Cylindrical Micellar Aggregates

structures is also one of the crucial factors that play an important role in the gelling process. In addition to the effect on CPP and size of the microstructures, the property of unsaturation can also be interpreted in terms of degree of hydration of phospholipid molecules that it provides. In contrast to the saturated hydrogenated phospholipids, unsaturation in phospholipid molecules would result in better hydration of the polar head group, thereby increasing the area per lipid polar head group. Consequently, a larger area and relatively smaller volume would favorably alter the spontaneous curvature of lipid monomers for the formation of micelles and subsequently their self-assembly to form a micellar network. Additionally, the purity of lecithin also plays a critical role in the organogel formation. Poorly purified lecithin does not possess gel-forming properties, and it has been demonstrated that lecithin should contain at least 95% phosphatidylcholine content for the preparation of organogels.[1,11,13] The high-purity grade lecithin is not only expensive but also difficult to obtain in large quantities. However, recent reports indicate the incorporation of synthetic polymers, ie, pluronics in LOs, for their usefulness as cosurfactants and stabilizers.[19-22]

It has been shown that the inclusion of pluronics as a cosurfactant makes the organogelling feasible with lecithin of relatively lesser purity.[22] The term "pluronic" refers to a series of non-ionic closely related block copolymers of ethylene oxide and propylene oxide.[23] Also known as poloxamers, poloxamer polyols, or Lutrols®, these are primarily used in pharmaceutical formulations as co-surfactants, emulsifiers, solubilizers, suspending agents, and stabilizers. These pluronic-containing LOs have been termed "pluronic lecithin organogels."

PHASE-BEHAVIOR OF ORGANOGELS

The phase-behavior of a ternary system of lecithin/organic solvent/polar solvent is mainly governed by the concentration of polar solvent and lecithin; the same is defined in terms of the parameter, nw, ie, the molar ratio of polar solvent to lecithin (nw = polar solvent/lecithin).[1,11-13,24,25] It is noted that the organogel as a homogenous phase exists over a very narrow range of polar solvent concentration.[24,27] Initially, with the addition of water, the thickening effect is observed at a certain specific molar ratio of water to lecithin. After this threshold concentration, further addition of water leads to a sharp increase in the viscosity and the formation of an organogel. For lecithin organogels prepared using isopropyl palmitate as the organic solvent, this sharp increase in viscosity is observed at nw = 3.[28] The organogel state is maintained up to a particular molar ratio of water to lecithin, designated as ncr. At the state in which nw is equal to ncr, the maximum viscosity of organogel is achieved. On continuing the water addition above the ncr, ie, at nw > ncr, the three-dimensional network collapses, and separation of the homogenous organogel takes place via a two-phase system consisting of low viscous liquid and a compact organogel or jelly-like phase. For lecithin organogels prepared using isopropyl palmitate as the organic solvent, this stage is observed at nw = 5-6.[28] A schematic of the pseudo ternary phase diagram for lecithin organogels is depicted in Figure 1.

MECHANISM OF GEL FORMATION

The first prerequisite for gel formation is the balance of intermolecular interaction amongst the gelator molecules (eg, Hbonding, vander Waals interactions, etc) and between gelator and solvent molecules. The latter helps in the formation of a continuous three-dimensional network. The simplest mechanism of gel formation involves shifting the balance of intermolecular and intramolecular attractions of the gelator molecules and organic solvent. This should result in a comparative increase in the intermolecular attraction amongst the gelator molecules and a comparative decrease in the interaction between the gelator molecules and solvent (eg, by addition of critical amount of water). This leads to the formation of a molecular dispersion that further results in the formation of a three-dimensional network in which the organic

solvent molecules are trapped (Figure 2). The gelation of the lecithin solutions in organic solvents is induced as a result of the incorporation of a polar solvent. Lecithin, when being dissolved in non-polar media alone, self-assembles into reverse spherical micelles at a concentration of about 0.01 mM.[29] The enormous uniaxial growth of these spherical-reverse micelles and subsequent transformation into tubular or cylindrical micellar aggregates (sphere-to cylinder transformation) is triggered by the addition of small and critical amounts of polar additive as shown in Figure 3. The molecules of polar solvent, on addition, bind in stochiometric ratios to the hydrophilic head portion of the lecithin molecules in such a way that two adjacent lecithin molecules are bridged together by one polar molecule.[9,13] This leads to the formation of linear networks, from hydrogen bonds formed by the polar molecules and phosphate groups of lecithin molecules, and in turn, to the one-dimensional uniaxial growth of lecithin-reverses micelles. Further increase in the amount of polar additive results in the formation of flexible, long tubular micelles with a 2.0- to 2.5-nm radius and hundreds to thousands of nanometers in length.[24,25] After reaching a critical length, these extended micelles begin to overlap, entangle themselves, and build up a transient three-dimensional network.[10,11,30-34]

BIOTECNOLOGICAL APPLICATIONS

Organogels in Enzyme Immobilization

There are various enzymes that are pharmaceutically important (Table1).[35] Enzymes immobilized in organogels offer considerable potential for use in organic synthesis. The following are advantages of enzymes immobilized in organogels:

- They have the ability to disperse the biocatalyst at a molecular level.
- It is possible to incorporate regenerable cofactors.
- They are efficient in that they can be reused.
- They are suitable to larger-scale synthesis.
- Organogels are stable when in contact with organic solvents as an external phase.
- Enzymes immobilized in organogels also tolerate high substrate concentrations.
- Enzymes immobilized in organogels are also useful in conducting the reactions at sub-zero temperatures. Temperature-sensitive compounds and rearrangements or racemization can be avoided by conducting reactions at low temperatures.
- Enzymes immobilized in organogels also tolerate high-substrate concentrations.

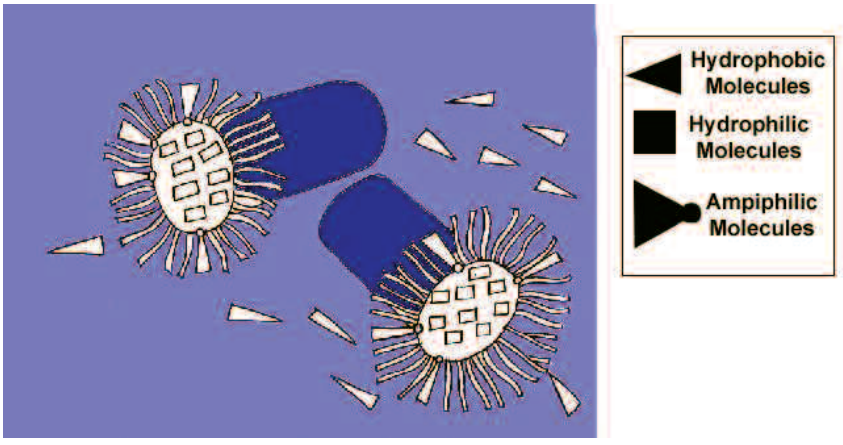
Pastou et al have immobilized lipases from Rhizomucor miehei and Candida antarctica in lecithin organogels formed with agar and hydroxypropylmethyl cellulose.[35] It was found that both lipases keep their catalytic function after entrapment in the gels, catalyzing the esterification reaction of 1-propanol with fatty acids in non-polar hydrocarbons at room temperature.[35] Stamatis and Xenakis have immobilized Pseudomonas cepacia lipase in lecithin organogels using gelatin, agar, and carrageenan as gelling agents. Gels prepared from gelatin and agar are found to be most suitable for the esterification of 1-propanol with lauric acid in hydrocarbon solvents. These gels have excellent operational stability in addition to being biocompatible.[36]

PHARMACEUTICAL APPLICATIONS

Lecithin Organogels as a Topical Drug Delivery System

Lecithin-based organogels have been proposed as a matrix for topical delivery of drugs. The mechanism, which is offered for enhanced penetration, is that lecithin disorganizes the structure of the skin slightly and thus increases the penetration of various drugs. This may be due to the interaction between the skin lipids and the phospholipids in the gels. Topical administration of a

FIGURE 4



Solubilization of Hydrophobic & Ampiphilic Guest Molecules in Reverse Micelles

lecithin organogel formulation containing a therapeutically effective amount of digoxin has been found to be effective for the treatment of muscle spasm as well as in the management of peripheral or neuropathic pain.[37] Friedman has reported the subcutaneous delivery of cyclobenzaprin, a muscle relaxant, using lecithin organogels as topical vehicles.[38] The muscle relaxant administered in lecithin-IPM organogels is shown to provide immediate relief of pain resulting from bruxism (tooth grinding) and tooth clenching. Remarkably high skin penetration of phytosphingosine or sphingosine, a Protein Kinase C (PKC) inhibitor, incorporated in lecithin organogel gels has been reported.[39] The prepared organogel-based formulation was found to effectively inhibit the PKC activity in the skin and mucocutaneous junction, thus useful in the topical treatment of keloids and hypertrophic or burn scars. It was also shown to be effective in psoriasis, psoriatic arthritis, or any other inflammatory condition of the skin that involves PKC. It is inferred that for those orofacial disorders that are regional, near the surface, and chronic, lecithin organogels are more advantageous over systemic administration of drugs because of the rapid onset of action with low side-effect profile. In one such study, significant improvement in the analgesic action of ketamine hydrochloride and amitryptiline hydrochloride formulated in lecithin organogels has been reported.[40] The use of these compounds for topical pain relief is otherwise limited due to their poor skin penetration and partitioning properties. Lecithin organogels have also been found to be an excellent matrix for the delivery of a macromolecules with a molecular weight of 33000 daltons.[41] Organogel systems have also been used as a matrix for transdermal transport of different therapeutic compounds. Willimann and Luisi were the first to study lecithin organogels as matrix systems for transdermal transport of drugs.[42] The authors investigated the transdermal delivery of scopolamine (an active drug against motion sickness) and broxaterol (a bronchodilatory agent) employing lecithin gel composed of 200 mM of lecithin in a biocompatible solvent IPP, in two separate studies. Scopolamine and broxaterol were solubilized in the gel up to a concentration of 40 mg/ml and 75 mg/ml, respectively. Significantly higher transdermal flux of scopolamine in lecithin-IPP gel was observed in comparison to that of drug in aqueous solution. Analogous results were obtained with broxaterol incorporated in lecithin organogels. Likewise, there is good solubility data regarding the following lecithin organogel compounds: β-estradiol 17-acetate, β-estradiol diacetate, β-estradiol 17-valerate, β-estradiol 17-enanthate, β-estradiol 17-cypionate, iso sorbide dinitrate, nifedipine, and clonidine.[42] This increase in solubility is attributed to the presence of lecithin-reverse micelles, which have ability to solubilize hydrophilic, hydrophobic, and ampiphilic guest molecules (Figure 4).[33] Bhatnagar et al have investigated the trans-skin permeability of propranolol hydrochloride, a poorly permeable and water-soluble drug incorporated in lecithin organogels, across human cadaver skin.[43] Significantly enhanced (approximately 10 times higher) permeability of micellar-borne drug across the human skin was observed employing drug in a 200-mM lecithin/iso-octane/water organogel system in comparison to that of pure drug in solution form or emulsified in petroleum jelly. The transdermal delivery and efficacy of various NSAIDs formulated in lecithin organogels has also been investigated. Grace et al have assessed the efficacy and safety of 2% diclofenac in lecithin organogels in the treatment of pain associated with mild-tomoderate osteoarthritis, and this novel topical formulation of diclofenac was found to possess a remarkable therapeutic value.[44] Dreher et al incorporated indomethacin and diclofenac in lecithin organogels [IPP (10 ml), soy lecithin (1.9 g), water (135 µl)], and the transdermal delivery of both the drugs were found to be higher using lecithin organogels vis-à-vis drug in IPP alone as the vehicle.[2] Aboofazeli et al have formulated lecithin organogels containing ketorolac tromethamine.[45] The effect of formulation variables on the release profile of the drug from MBGs through intact guinea pig skin and various artificial membranes was then determined experimentally. It was observed that as the lecithin concentration increased from 40% to 50% and then 60% w/w in formulations, a significant decrease in ketorolac tromethamine release was obtained. A remarkable increase in the drug release was also observed in formulations containing 6.5% w/w of KT compared to those containing 1% w/w of the drug. Increasing the water content of the organogels also resulted in an increase in KT release. Shippen et al have studied transdermal delivery of progesterone incorporated in lecithin organogels.[46] Nicardipine, a calcium channel blocker, because of its low dose, short half-life, and extensive first-pass metabolism, has been incorporated in an LO system in order to achieve systemic absorption through the topical route.[47] In another study on the potential of lecithin organogels in transdermal delivery, Bonina and coworkers formulated methyl nicotinatelecithin-IPM organogels and tested them in vivo with human subjects.[48] The results showed rapid induction and intense persistence of methyl nicotinate-induced erythema. The solubilization of piroxicam, to increase its transdermal permeation rate, has also been attempted by incorporating the drug in a LO consisting of lecithin/IPM/water.[49] A significant inhibition of carrageenan-induced rat paw oedema was observed with an organogel formulation of piroxicam vis-à-vis marketed transdermal product after 3 hours. Thus, with the inflow of several research reports on the varied fundamental aspects of

TABLE 1

ENZYME	APPLICATION	SOURCE
L- Asparginase	Anti-Tumour	Pseudomonas acidovorans, Acinetobecter sp
Serratio peptidase	Antioxidant, Anti-inflammatory	Serratia marcescens
Lipase	Digest lipids	Candida lipolytica, Candida rugosa, Aspergillus oryzae
Laccase	Detoxifier	Trametes versicolor
Protease	Anti- Tumour	Bacillus polymixa

Enzymes of Pharmaceutical Importance

LOs, along with some promising results on the front of drug delivery, these systems can be seen as potential tools in the field of topical drug delivery applications.

Lecithin Organogels as an Ophthalmic Drug Delivery System

Most ocular treatments call for the topical administration of drugs in the tissues around the ocular cavity. Various types of dosage forms have been developed for ocular drug delivery, which include drops, suspensions, ointments, ocuserts, more recently, eyelid skin delivery systems. Eye drops are the most widely used and most popular but suffers from the drawback that a majority of the medication is immediately diluted by tears and is rapidly drained out by the constant tear flow. Therefore, only a fraction of administered drug is absorbed to target tissue and thus, repeated administration of eye drops becomes essential, leading to poor patient compliance and undesirable side effects.

Suspensions have a disadvantage in that the rate of drug release is dependent on the rate of dissolution of drug particles, which vary due to constant change in composition and outflow of lachrymal fluid. In order to increase the therapeutic efficacy, one of the methods suggested is to increase the viscosity so as to prolong the contact period. But, the addition of viscosity builders, such as CMC, did not improve the situation much and in the case of water-insoluble ointments, immediate vision was affected. Lecithin-based organogels offer a potential ophthalmic drug delivery system that may overcome the aforementioned difficulties. These gels:

- present a unique feature of being able to incorporate lipophilic, hydrophilic, as well as amphoteric bioactive compounds;
- are transparent and hence even their long-term presence in the ophthalmic cavity does not affect vision;
- released drug at a steady rate because of the three-dimensional network of the gel; and
- because of their high viscosity and organic solvent as a continuous phase, are difficult to wash off.

Three formulations of organogels have been prepared by Fresta et al using lecithin as a gelator and organic solvents (paraffin, isopropyl palmitate, and cyclooctane).[50] Cyclooctane gels have been found to be toxic, and paraffin-based gels have been found to be the safest, whereas isopropyl palmitate gels cause mild morphological changes. Hence, lecithin-based organogels hold good potential as ophthalmic drug delivery systems owing to their very low toxic potential, coupled with their unique ability to incorporate lipophilic, hydrophilic, as well as amphoteric compounds. In the case of drug delivery, the presence of stable barriers permits a slow delivery of pharmaceuticals. This is likely the rationale for the performance of lecithin organogels made of isopropylmyristate as a carrier of timolol maleate in glaucoma therapy. On contact with the lachrymal fluid, a stable emulsion forms, leading to a controlled release of timolol maleate.

CONCLUSION

Lecithin organogels are emerging as novel drug carrier systems for drug molecules with diverse physico-chemical properties and macromolecules like proteins and peptides. The discovery of biocompatible substances, such as lecithins capable of gelling various organic solvents, has opened a new area in the development of novel drug delivery systems. These exhibit pharmaceutically useful properties like thermo reversibility, ability to incorporate all types of drug molecules, increased resistance to microbial contamination, and reduced risk of irritation. The concept of drug delivery through lecithin-based organogel systems has been studied extensively for various routes of drug administration, such as dermal, transdermal,

and ophthalmic. The drug release from most of the organogel systems is controlled by a simple diffusion process. However, not much work has been done on the usefulness of these systems for the other routes of administration, and their potential for these remains to be uncovered.

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DRUG DELIVERY Executive

Xcelience™
Xcelling the Science of Formulation Development

Derek Hennecke
Chief Executive Officer
Xcelience

"Our values are quality and speed. I say it in that order for a reason. We are passionate about getting our sponsors' products to the clinic, but we don't cut corners with quality. Our people give us confidence in our quality. But for speed, well, that's where technology comes in."

XCELIENCE: EXCELLING & ACCELERATING ITS PARTNERS' SCIENCE

Xcelience is a Tampa-based formulations company that's making waves in the biotech and pharmaceutical industries by formulating and manufacturing products with unprecedented speed. The small but rapidly-growing company produces solid, semi-solid, and liquid dosage forms, manufactures batches for stability testing, scales up and produces pilot batches, and manufactures clinical trial supplies from Phase I through to Phase IIb. It has a clean compliance record in North America, and several European QP reviews under its belt. Drug Development Technology recently spoke to Derek Hennecke, Chief Executive Officer of Xcelience, to learn more about the company as well as its drug development and manufacturing solutions.

Q: Xcelience is an unusual name. Can you tell our readers more about it?

A: We wanted a name that reflected our values. Our core values are quality and speed. We want to provide top-quality custom-made products for clients who need them, yesterday. The first half of the name should make you think of excellence, or excelling; but also of accelerating. The latter half is from the word science. Thus, Xcelience is about excelling and accelerating science.

Q: Is your company new to the market?

A: Not at all. The company was formed in 1997. In 2006, we changed ownership and launched a new name and a stronger focus. Our experienced scientists continue to be our core strength.

In fact, we are very proud of our compliance record and multiple European QP reviews. Xcelience is a privately held company with no private equity funding, no debt, and a strong cash position. This is different from our competitors, many of whom are on an acquisition spree or have recently been put on the selling block. Xcelience's investors are long-time devotees of this business. They're not going anywhere. Our management brings years of experience as well. Take Vice President Randall Guthrie, for example, who received a Presidential Citation at this year's 20th anniversary meeting for his longevity and dedication to the AAPS (American Association of Pharmaceutical Scientists). Randall has 30 years of experience in the Pharmaceutical Service Industry.

Q: Xcelience claims to be faster than anyone else at helping companies get their drugs first-in-man. How do you do this?

A: Part of being the fastest is having the best technology, and I'm going to talk about the Xcelodose™ later on. But first, let me tell you that technology is just one piece of the picture. A machine alone isn't going to give you speed, and certainly isn't going to give you quality and speed together. For that you need the right people.

It really starts with having experienced scientists. We hire the best. Job applicants comment on how tough our interviewing and background checks are. There are several rounds of interviews, and I insist on meeting every serious candidate before they are presented with an offer. If there is any doubt in any of the management teams' minds, we keep looking. We just can't afford to have people on staff who can't pull their own weight, because if they can't, they're going to let the whole team down. Top-rated, experienced scientists, simply put, are the secret to quality.

As I mentioned earlier, our values are quality and speed. I say it in that order for a reason. We are passionate about getting our sponsors' products to the clinic, but we don't cut corners with quality. Our people give us confidence in our quality. But for speed, well, that's where technology comes in. For this, we make a point of always having the latest and best technologies, but certainly the gem in the field is the Xcelodose technology.

Q: Please tell our readers more about the Xcelodose.

A: We were the first CRO in North America to introduce Capsugel's Xcelodose technology (Xcelodose is a trademark of Capsugel BVBA). This unique technology allows us to fill capsules with drug substances alone, thereby eliminating the need for excipient compatibility and preformulation activities.

This substantially abbreviates the drug development process by reducing the need for costly and time-consuming formulation and possible inaccuracies associated with hand-filling. In turn, it reduces the time taken to reach the first-in-man clinical trial decision point, which allows an increase in throughput of candidate compounds for development.

The Xcelodose is a precision powder micro-doser and automated encapsulator with a fill range of 100 micrograms to greater than 100 milligrams. It directly fills active pharmaceutical ingredients (APIs) into capsules (without excipients) at a rate of several hundred capsules per hour. Obviously, it's particularly suited to producing clinical trial material for use in clinical trials. This reduces timeline slippage and (something that particularly endears it to me) improves quality as well, with improved accuracy of 2% standard deviation.

Q: Tell us about your experience with controlled-release formulations?

A: We've been doing controlled-release formulations regularly throughout the company's history. For example, a sponsor gave us a low density, low melting point API. If that wasn't enough, it was also unstable in the presence of water and had lot-to-lot variation. An API densification process was used to make the API suitable for uniform filling into hard capsules for Phase I pharmacokinetics studies. The PK data and preformulation characterization of the API, through determination

of pKa, solubility in various solvents, moisture uptake, DSC, and TGA was used to design and develop a controlled-release tablet for continued clinical study. In the end, a suitable dosage form was developed, and the sponsor filed a patent to protect its intellectual property.

Q: Where do you see the drug delivery challenges coming in the future?

A: Our new ads use the slogan "send us your biggest challenge." The increasing complexity of drug development means, simply put, that there are fewer and fewer simple cases.

For example, many people have reported the difficulty of formulating low soluble and/or low permeable drugs in our collective futures (classes II to IV of the BCS). Even after the development of a suitable formulation, it is important to develop the analytical methods. In one case, a sponsor requested a formulation of an NME below 10 µg/gram for a topical application. A suitable semi-solid dosage form was found, but it was difficult to extract the NME from the drug product. A series of experiments lead to the discovery that one of the components in the drug product was deteriorating the HPLC column and needed to be removed prior to analysis. We developed an extraction method and included a step to precipitate out the interfering excipient. The supernatant was collected, rinsed, and evaporated before being brought to a total volume of 5 mL. This low total volume was necessary for analysis of related compounds at a very low level. In the end, we recovered 100% of the NME from the drug product, and the method has been validated for use in routine testing of clinical supplies.

Q: Does your company have any new plans for the coming year?

A: Always! I can tell you two things we plan to implement right away, and one we won't implement at all. We plan to extend our services via our website, **www.xcelience.com**, through two major projects. We'll launch an online pharmaceutical forum, which will open the dialogue of drug development and where we can answer questions and provide advice on line. We are also starting an **Xpert consulting** service spearheaded by our Scientific Director, Dr. Steve Bannister. His 23 years of experience in managing and consulting in the pharmaceutical industry will help our growing client base to plan, execute, and evaluate the development of drug products. And the one thing we won't do? Xcelience will not be developing its own NDAs. We believe that would be a disservice to our clients. Once a CRO starts to pursue an NDA, there are only two possible outcomes, neither of which serves the sponsor. Either the NDA is successful and the company starts diverting its top talent and resources to it and putting sponsors next in line; or the NDA fails, creating a cash pit. This ultimately leads to cutbacks and shuffling of resources to cover shortfalls. Given the loyalty our sponsors have shown us throughout the years, we feel no temptation to pursue NDAs. If we do our job right and our sponsors are successful, they return to us and we ride along on their success. Everybody is happy. ◆

Drug Delivery Showcase

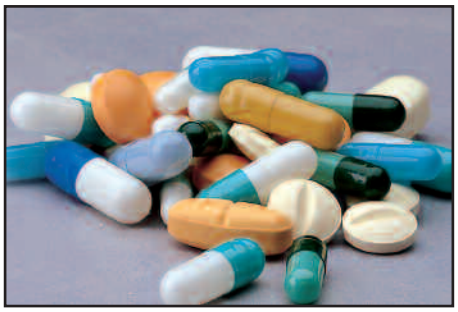
Devices & Packaging

Rexam Pharma is a leading specialist in drug delivery devices and primary pharma packaging. The company has a recognized expertise in several areas, including inhalation devices, such as DPIs and valves for pMDIs; 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. Rexam Pharma is now launching Evipharm and Secupharm, new filled-in-line desiccant caps, associated with their standard range of pill jars. These new innovative closures were developed in the Rexam Pharma plant in Offranville, a state-of-the-art facility with a long-standing experience in pharma containers and closures. For more information, contact Rexam Pharma at (914) 640-1310; mailboxpharma@rexam.com or visit **www.rexam.com/pharma**.

Stability Monitoring Technology

CliniSense LifeTrack® technology can solve your stability headaches. Our high-accuracy stability monitors precisely mimic your product's actual time-temperature stability characteristics. Unlike earlier generation temperature monitors, LifeTrack monitors cope with temperature excursions in a realistic manner. LifeTrack warns the user when the product is genuinely deteriorated, and doesn't give "false alarms" for unimportant temperature excursions. Experiment with the power of LifeTrack technology today. Our LifeTrack demonstration units allow your stability and R&D groups to immediately evaluate if this approach is right for your product. Simply enter your stability data onto one of our spreadsheets, flash program a LifeTrack demonstrator with your product's stability characteristics, and go! For more information, contact CliniSense Corp. at (408) 348-1495 or visit **www.clinisense.com.**

Oral Modified-Release Technologies



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

Moisture/Solids Analyzer

Arizona Instrument LLC has released the newest firmware enhancement of the Computrac® MAX® 2000XL moisture/solids analyzer, the 4.36 Advantage. The new Advantage firmware utilizes the industry-proven, RAPID Loss-on-Drying methodology, providing the testing accuracies and reliability required by the pharmaceutical industry, but it now includes 3 key feature enhancements to comply with the expanding requirements and policies of governing bodies, SOP certification processes and equipment verification standards. These new features include User Login/Tracking to track and manage user testing activities, Balance Verification to provide in-field balance check and reporting, and Balance Mode to allow the instrument to function as a stand-alone. For more information, contact Arizona Instrument at (800) 290-1414 or visit **www.azic.com**.

Drug Delivery Showcase

Licensing Opportunity

AVEVA Drug Delivery Systems
A Nitto Denko Company

Aveva Drug Delivery Systems is a drug-enabling company focused on underserved patient populations through the use of its proprietary Transdermal Drug Delivery technologies. Aveva is a wholly owned subsidiary of the $5.3-billion Nitto Denko Corporation, one of the world's largest manufactures of Transdermal Drug Delivery products. Aveva recently concluded its preclinical assessment of a selective beta2-adrenergic bronchodilator, albuterol, for the treatment of reversible obstructive airway disease. The product successfully met both the stability and flux permeation endpoint criterion. Aveva's product would be the first US 505(b)(2) approved patch product for the treatment of asthma, a market which had global revenues exceeding $12.5 billion in 2005. Aveva is currently looking for a partner to collaborate on the development of this novel application. Please contact Brian Guy (Director, Business Development) at (954) 624-1271 or visit **www.avevadds.com**.

Controlled Delivery Platform

Controlled Delivery Technology CDT

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February 2007

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EXTERNAL DELIVERY

Why CEOs Are Underpaid!

By: John A. Bermingham

The departure of Bob Nardelli from Home Depot has really fired up a lot of people recently. Not because he was asked to leave Home Depot by the Board of Directors, but because he left with a $210-million dollar severance package. Sheesh! A $210-million package for failing in your job and getting fired? We should all be so lucky. The guy was really overpaid, right? Well, maybe not.

When Bob Nardelli was passed over for the CEO position at G.E. by Jack Welch, Mr. Nardelli became a hot property to lead another company. I am certain that Bob Nardelli was not just looking at Home Depot but was instead being courted by several companies to become their CEO. So what did it take to convince Mr. Nardelli to take the Home Depot position instead of going to another company? How about a $210-million severance package negotiated up-front, amongst other perks, before he took the position.

So looking at the supply/demand ratio, Mr. Nardelli being the supply of one and many companies competing in the demand column for his services, the cost was very high to land him. I don't know of any CEO who thinks he or she is over paid, me included. I said in a previous article that being a CEO is the best job in the world and the worst job in the world. Just depends on the day. May I now include the most underpaid job in the world?

I think that pressure is the number one issue that every CEO faces because the ultimate responsibility for the company rests with the CEO, and every move made is put under a microscope and can make or break an empire. As Harry Truman said, "The buck stops here," and every CEO faces the same issue. The final decision, right or wrong, rests with the CEO.

Adding to the pressure are the time demands, both personal and professional. CEOs are on call 24/7, and their days are not necessarily under their control. Early morning (7 AM) arrivals at the office are commonplace, and late-evening departures are as well. Most CEOs eat lunch on the run. Attendance at special events, charities, etc is expected. And being at home does not relieve you from your company responsibility. You still have complicated financial and strategic documents to read that you could not accomplish at the office, conference calls, e-mails, and telephonic Board Meetings are some of the at-home issues a CEO faces.

Then there is the travel (several trips a month). Very early morning wake-ups, hassles at the airport, delayed flights, dinners consisting of a bag of pretzels on board, late arrivals at the hotel to find that they do not have your reservation, etc. Don't forget the missed anniversaries, birthdays, special family events, you name it.

Yes, it is true that many professions face the same demanding hours and travel requirements, but does the job security of thousands and retirement plans of millions rely on your decisions? People who save lives for a living are excluded as their services are priceless. There is much more, but I don't want you to think that I'm whining. Well maybe a little.

Now if you look at what a CEO does for a living, what is that person's worth to the company to make those sacrifices? What does it take financially to keep them motivated and hard working? What should it cost to have a person successfully lead a company that makes billions? What about compensation for the hours worked? Most CEOs work 70 to 80 hours per week to include weekends. What is that worth?

So here is the final issue on CEO compensation. Question: How much should you pay a CEO to lead the company to success? Answer: Whatever it takes. Okay, back to Mr. Nardelli and Home Depot.

I think that the Home Depot compensation committee should have pegged Bob Nardelli's severance agreement to performance-based metrics. If the Board chose to release him without cause, then there should have been a much lower guaranteed minimum with upside depending on his performance against those metrics over the duration of his time with the company. But then again, Home Depot may not have landed him with that kind of deal. So was the $210-million dollar severance package worth it? Ask the shareholders! ◆

BIOGRAPHY

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

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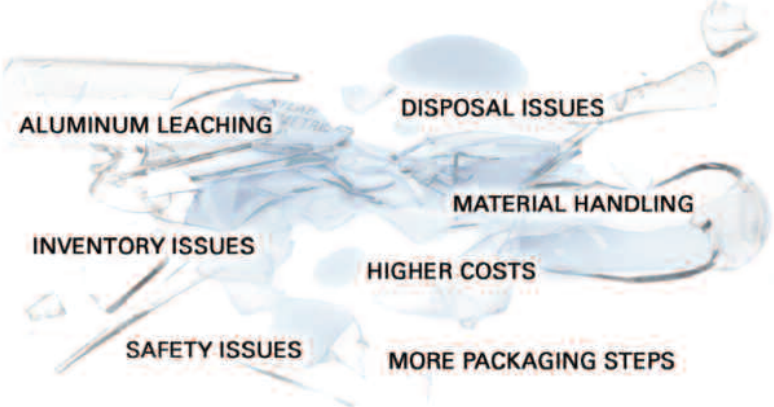

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