Drug Delivery® Technology

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Fast-Dissolving Delivery Systems

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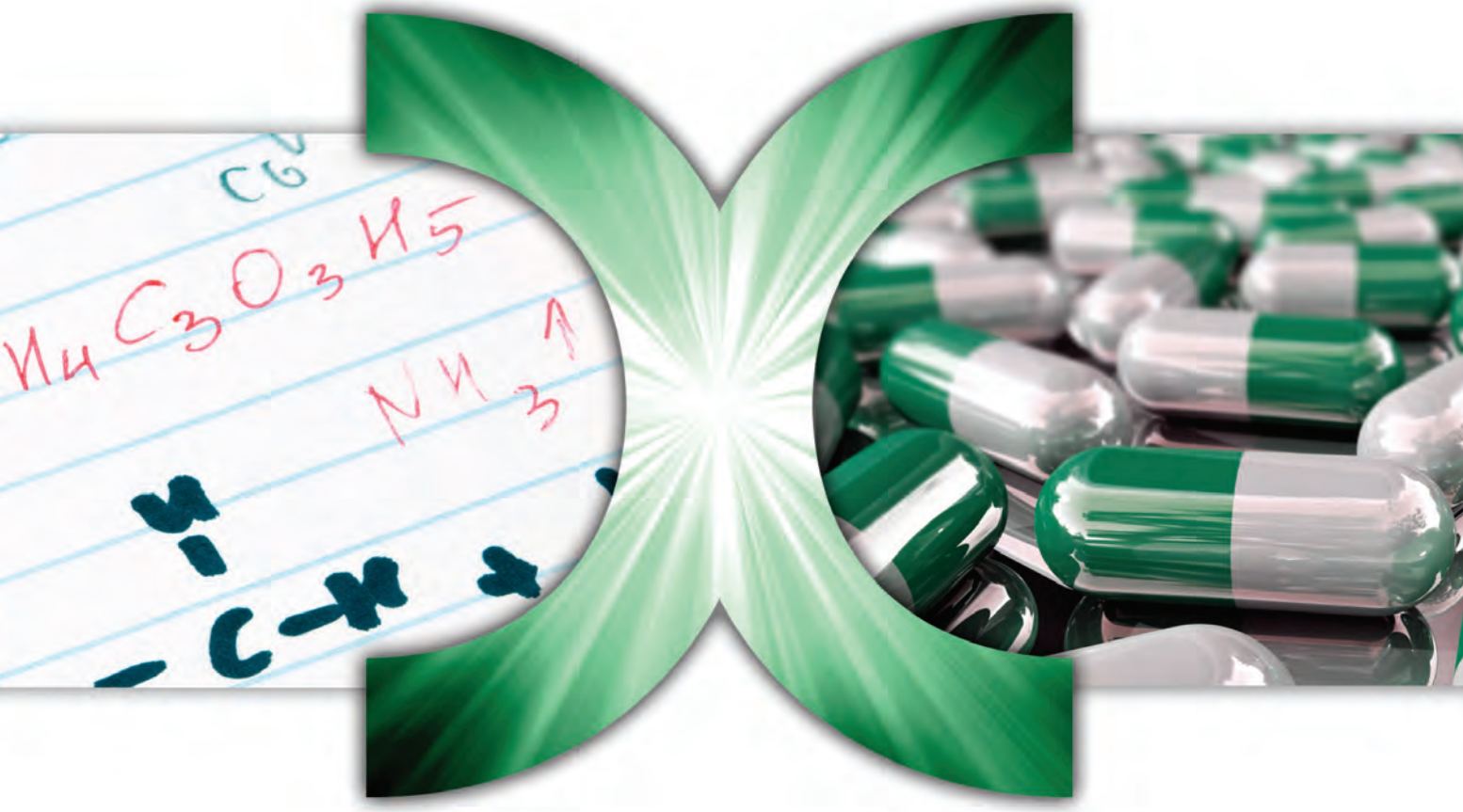

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Fast-Dissolving Systems

"Spurred by expanding use in existing indications and the anticipated introduction of new products, demand for transmucosal pharmaceuticals is forecast to increase over 11% annually to almost $1.3 billion in 2012. The penetration of low-cost generic fentanyl formulations into the marketplace will moderate even faster gains."

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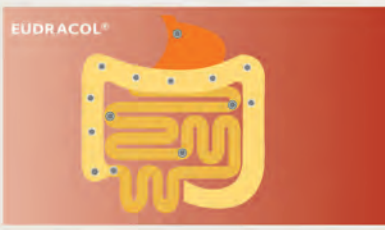

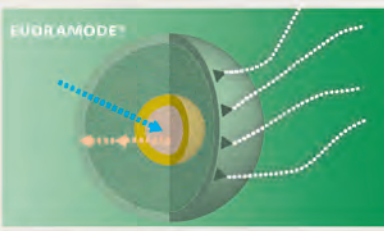

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CRO Trends & Drivers

"One of the most significant trends within the US, as well as global CRO markets, is the move from transactional to strategic outsourcing by sponsors. The fact that CRO market growth has consistently outpaced R&D spending growth is an indicator that outsourcing penetration is on the rise."

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Market News and Trends

Vertex Pharmaceuticals Buys 2 Hepatitis Drugs for $377 Million; Aquires ViroChem Pharma

Vertex Pharmaceuticals Incorporated, which is developing the hepatitis C virus (HCV) protease inhibitor telaprevir, will add two polymerase inhibitors to its HCV drug development portfolio through a definitive agreement to acquire privately held ViroChem Pharma Inc. in a stock and cash transaction. With the addition of these compounds, Vertex will advance its strategy to pursue novel combinations of Specifically Targeted Antiviral Therapies for hepatitis C (STAT-Cs) for the treatment of HCV infection.

Following completion of the transaction, Vertex will own worldwide rights to ViroChem's HCV drug development portfolio, including VCH-222 and VCH-759, which have demonstrated substantial reductions in plasma HCV RNA when dosed as single agents and have been well-tolerated in clinical studies to date. In particular, VCH-222 dosed as 750 mg twice daily resulted in a median 3.7 log10 decrease in HCV RNA at the end of dosing in a 3-day viral kinetic study, representing the most substantial reduction in viral load reported to date with an investigational HCV polymerase inhibitor dosed as a single agent. Vertex expects to begin clinical evaluation of novel combination regimens of its HCV protease inhibitor telaprevir, currently in Phase III clinical development, in the second half of 2009. The transaction is subject to customary pre-closing conditions.

VCH-222 is an oral non-nucleoside inhibitor of the HCV NS5B polymerase that recently completed a viral kinetic study in HCV patients. In this study involving five treatment-naïve genotype 1a and 1b HCV infected patients, VCH-222 dosed as 750 mg twice daily resulted in a median 3.7 log10 decrease in HCV RNA, equivalent to a 5,000-fold reduction in virus in the blood, at the end of 3 days of dosing. The results were consistent from patient to patient, and across HCV genotype 1 subtypes, and represent the most substantial reduction in viral load reported to date with an investigational HCV polymerase inhibitor dosed as a single agent. In clinical evaluations to date, VCH-222 has been well-tolerated, with no serious adverse events observed. VCH-222 has completed 28-day non-clinical toxicology studies in two species.

VCH-759 is an oral non-nucleoside inhibitor of the HCV NS5B polymerase that has completed Phase Ib clinical development. In a Phase Ib trial reported at a medical conference in 2007, VCH-759 dosed as 800 mg three times daily showed a mean maximal 2.5 log10 reduction in HCV RNA and a median 1.7 log10 reduction in HCV RNA at the end of 10 days. VCH-759 was also well-tolerated with no serious adverse events observed in clinical studies to date. VCH-759 has completed 28-day non-clinical toxicology studies.

Vertex plans to conduct additional dose-ranging studies of VCH-222 as a single agent and in combination with pegylated interferon and ribavirin. Vertex plans to initiate a first clinical study combining telaprevir with a ViroChem HCV polymerase inhibitor in the second half of 2009. Data from in vitro HCV replicon studies suggest that VCH-222 and VCH-759 may provide synergistic or additive antiviral activity to the HCV protease inhibitor telaprevir, thus creating the potential for a non-cross resistant, complementary profile in exploratory clinical studies.

Under the terms of the agreement, which have been approved by the Boards of Directors of both companies, ViroChem shareholders will receive $100 million in cash and 9.9 million shares of Vertex common stock. The stock portion of the consideration is subject to a collar, and the actual number of shares of Vertex stock to be issued will be based on an average Vertex share price prior to the acquisition closing, but per the agreement will not exceed 11 million shares. Vertex expects the shares issued in this transaction will be immediately tradeable under a resale registration statement, which Vertex plans to file at the time of closing. Goldman, Sachs & Co. is acting as exclusive financial advisor to Vertex.

Vertex is developing telaprevir, one of the most advanced investigational agents in development that specifically targets HCV. Telaprevir is being evaluated in a broad Phase III registration program, which has enrolled more than 2,200 genotype 1 HCV patients, including patients who have both failed prior treatment with pegylated interferon and ribavirin, as well as patients who are naïve to treatment. Vertex plans to file an NDA for telaprevir in the second half of 2010 assuming successful completion of its ongoing Phase III program. In addition, Vertex is developing two other novel HCV protease inhibitors, VX-813 and VX-985, currently in Phase I and preclinical development, respectively.

Vertex retains commercial rights to telaprevir in North America. Vertex and Tibotec are collaborating to develop and commercialize telaprevir in Europe, South America, Australia, the Middle East, and other countries. Vertex is collaborating with Mitsubishi Tanabe Pharma Corporation to develop and commercialize telaprevir in Japan and certain Far East countries. Vertex retains worldwide rights to VX-813 and VX-985.

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Market News and Trends

Teikoku Pharma USA & Eisai Announce Licensing Agreement for a 7-Day Transdermal Formulation

Teikoku Pharma USA Inc., an international specialty pharmaceutical company, recently announced it has signed an exclusive worldwide (excluding Japan) licensing agreement with Eisai Co., Ltd. to develop and commercialize a new 7-day transdermal formulation of donepezil, a leading compound for the treatment of Alzheimer's disease in the world.

The transdermal formulation is a once-a-week patch that continuously delivers donepezil through the skin into the bloodstream. It will enable the number of doses to be reduced, make it easier to be used for patients with Alzheimer's disease who have difficulty in swallowing, and also reduce the burden of caregivers or family members when administering to patients.

Teikoku Pharma USA Inc. is a wholly owned subsidiary of Teikoku Seiyaku Inc., a specialty pharmaceutical company that develops and manufactures enhanced pharmaceutical products based on its transdermal drug delivery technologies. Teikoku focuses its efforts in two therapeutic areas; chronic and acute pain and CNS. Teikoku's main product is Lidoderm (lidocaine 5% patch) for post-herpetic neuralgia in collaboration with Endo Pharmaceuticals in the US, Grunenthal GmBH in Europe, Mundipharma in South East Asia, and SK Pharma for Korea. Teikoku's commitment is to expand trandermal technologies for the benefit of patients and partners. For more information, visit www.teikokuusa.com.

Eisai Co., Ltd. is a research-based human health care company that discovers, develops, and markets products throughout the world. Eisai focuses its efforts in three therapeutic areas: integrative neuroscience, integrative oncology, and vascular/immunology reaction. Through a global network of research facilities, manufacturing sites, and marketing subsidiaries, Eisai actively participates in all aspects of the worldwide healthcare system. With operations in the US, Asia, Europe, and its domestic home market of Japan, Eisai employs more than 10,000 people worldwide.

Intranasal Therapeutics Changes Name to Ikano Therapeutics & Completes $9-Million Series B Financing

Intranasal Therapeutics, Inc. (ITI), a specialty pharmaceutical company, recently announced it has changed its name to Ikano Therapeutics Inc. (ITI) to better align with ITI's refocused corporate strategy.

ITI also said it had closed a second and final $9-million tranche in a Series B preferred stock financing with its current investor syndicate. This close followed ITI's announcement in December 2008 that it had completed a successful End-of-Phase II meeting with the FDA that would allow its midazolam nasal product, ITI-111, to begin Phase III trials for control of intermittent bouts of increased seizure activity in patients with epilepsy, as a practical alternative for outpatient use, within the next few months. As ITI-111 moves forward, the company has indicated that it is pursuing discussions with potential partners who can help leverage the product's commercialization.

The company further announced that Michael Ross, PhD, Managing Partner of SV Life Sciences, the company's largest investor, has also been elected Chairman of the ITI Board of Directors.

"ITI has refocused its corporate strategy from a narrow concentration on intranasally delivered medicines to a more diversified emphasis on high-impact specialty therapeutic products," said Peter Young, President and Chief Executive Officer. "The name Ikano is drawn loosely from the Greek for enable and aligns with our goal of applying our specialty pharmaceutical development expertise in areas where we can provide well differentiated, high-value products that improve patient care in meaningful ways, rather than limiting ourselves to being a nasal delivery platform company."

"ITI's investors believe the company has the makings of an important new specialty pharmaceutical enterprise and are pleased to underscore our support by completing our Series B funding commitment," added Dr. Ross. "These funds will complete ITI's transformation into a Phase III company and advance ITI-111's potential as an important new treatment for patients with epilepsy."

Ikano Therapeutics Inc. (ITI) is a specialty pharmaceutical company focused on developing innovative specialty therapeutics, with an emphasis on drugs in areas for which there is proven, unsatisfied medical and patient need. The company currently has additional products in its clinical development pipeline or in formulation and preclinical development. ITI's goal is to become a leader in the field of specialty pharmaceuticals by applying formulation and development expertise across selected therapeutic areas to create new and differentiated products that improve safety, efficacy, and clinical utility for patients, caregivers, and healthcare professionals.

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Market News and Trends

Bioject Enters Collaborative Agreement With IAVI for Delivery of HIV Vaccine Candidate

Bioject Medical Technologies Inc., a leading developer of needle-free injection therapy systems, recently announced it has entered into an agreement with the International AIDS Vaccine Initiative (IAVI) to supply its unique Needle-Free Injection Therapy (NFIT) system, the Biojector 2000, for the delivery of a DNA-based HIV vaccine candidate that is currently under development. The new agreement extends through December 2009.

IAVI and the St. Stephen's AIDS Trust at the Chelsea and Westminster Hospital have initiated a Phase I clinical trial in London to test a prime-boost combination of two HIV vaccine candidates. One of the vaccine candidates, a DNA-based vaccine called ADVAX, will be administered using the Biojector 2000.

"We welcome this collaboration with Bioject to assess the value of their needle-free device for the delivery of this DNA HIV vaccine candidate," said Dr. Pat Fast, Chief Medical Officer at IAVI. "It is essential that we enhance immune responses against HIV, which may be achieved by optimizing vaccine design, but also by evaluating alternative vaccine delivery methods."

The trial in London includes ADVAX to prime the immune system prior to the administration of an MVA-based HIV vaccine candidate called TBC-M4. In a previous Phase I trial, TBC-M4 generated modest immune responses in all volunteers who received the highest dose. The rationale for combining TBC-M4 with ADVAX is to improve immune activation. Previous Phase I studies with different DNA and MVA-based HIV vaccines in combination have shown that this prime-boost regimen was safe and well tolerated, and also able to generate enhanced immune responses when compared with the responses generated by either vaccine alone. Furthermore, DNA-based vaccine candidates, such as ADVAX, may offer value economically because these vaccines are relatively inexpensive and easy to manufacture, two characteristics that make them particularly appealing for use in the developing world. ADVAX will be administered with the Biojector 2000 needle-free injection system.

"Needle-free injection of a DNA vaccine can provide enhanced immune responses compared with administration by needle and syringe," said Dr. Richard Stout, Executive Vice President and Chief Medical Officer of Bioject. "We are quite pleased that IAVI has decided to utilize Bioject's B2000 system in order to explore the potential benefits over needle and syringe."

The development of a safe and effective AIDS vaccine is one of the greatest priorities in global health R&D. Today, 33 million people worldwide are living with HIV, and 7,500 are newly infected every day. It is vital to have both short-term and long-term solutions to this problem. Treatment must reach those who are infected, and proven prevention tools need to be made available to those who need it. At the same time, greater investment is needed to develop new and better tools to improve control and prevention of HIV infection. An AIDS vaccine offers the best hope for achieving this and to realize a world without AIDS.

TBC-M4 was designed by a biotech firm in the US in collaboration with Dr. Sekhar Chakrabarty from the National Institute of Cholera and Enteric Diseases (NICED) in Kolkata, India. ADVAX was designed by the Aaron Diamond Research Centre in New York, through collaboration with Rockefeller University in New York and IAVI. The Phase I trial in London is sponsored by IAVI and conducted in collaboration with the St. Stephen's AIDS Trust in London, UK.

Bioject Medical Technologies Inc., based in Portland, Oregon, is an innovative developer and manufacturer of needle-free injection therapy systems (NFITS). NFITS provide an empowering technology and works by forcing medication at high speed through a tiny orifice held against the skin. This creates a fine stream of high-pressure fluid penetrating the skin and depositing medication in the tissue beneath. The company is focused on developing mutually beneficial agreements with leading pharmaceutical, biotechnology, and veterinary companies.

Flamel Technologies to Receive $4-Million Milestone Payment From GlaxoSmithKline

Flamel Technologies recently announced it has earned an additional $4-million milestone from GlaxoSmithKline (GSK) pursuant to its Micropump license agreement for Coreg CR (carvedilol phosphate extended-release capsules). Coreg CR was launched by GSK in 2007 and is approved for use in treating three cardiovascular conditions: hypertension; post-myocardial infarction left ventricular dysfunction; mild-to-severe heart failure.

Coreg CR microparticles are produced by Flamel Technologies at its production facility in Pessac, France, using the company's MICROPUMP technology platform.

"These types of payments are an important driver for the financial strength and success of Flamel Technologies," said Stephen H. Willard, Flamel's Chief Executive Officer. "In addition to up-front fees, royalties, and payments for our research and development, these types of milestones play a significant role in the overall value we derive from licensing our technology. Flamel is engaged in 18 feasibility study programs with 7 of the top 20 pharmaceutical companies in the world."

Flamel Technologies is a drug delivery company with two intellectual property platforms: Micropump for the controlled release of drugs best absorbed in the small intestine; and Medusa for the controlled release of proteins, peptides, and other molecules injected subcutaneously. Both of these platforms offer potential advantages with respect to efficacy and the reduction of side-effects, in addition to the obvious benefits associated with more convenient dosing regimens.

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Market News and Trends

Eurand Announces International Agreements for Once-Daily Extended-Release Muscle Relaxant

Eurand N.V., a specialty pharmaceutical company that develops, manufactures, and commercializes enhanced pharmaceutical and biopharmaceutical products based on its proprietary pharmaceutical technologies, recently announced that Eurand Inc. has signed three new commercialization, license, and supply agreements for its novel extended-release (ER) formulation of the muscle relaxant cyclobenzaprine HCl. Financial terms were not disclosed. The respective pharmaceutical partners will be commercializing the product, subject to regulatory review and approval, in the following countries: Turkey (Nobel Ilac A.S.), Israel (PharmaSwiss SA), and South Africa (Adcock Ingram).

"These agreements represent important milestones in expanding Eurand's cyclobenzaprine ER franchise into new territories," said John Fraher, Eurand's Chief Commercial Officer.

As announced in August 2008, Eurand signed a license and supply agreement with Daewoong Pharmaceuticals Co. Ltd, a leading South Korean pharmaceutical company. Under terms of the agreement, Daewoong will commercialize cyclobenzaprine ER in South Korea, subject to regulatory approval. Developed using Eurand's innovative Diffucaps technology, cyclobenzaprine ER is a centrally acting muscle relaxant indicated as an adjunct to rest for the relief of muscle spasm associated with acute, painful musculoskeletal conditions. Cephalon markets the product in the US under the brand name Amrix. Cyclobenzaprine ER is available for licensing in certain other countries.

Nobel Ilac A.S. is one of the leading pharmaceutical companies in Turkey with successful marketing and sales strategies in the domestic and international market, supported by a vertical integration of developing and manufacturing API and pharmaceuticals. The product portfolio of Nobel comprises self-developed/manufactured pharmaceuticals, in-licensed pharmaceuticals, and OTC products.

Established in 2000 and based in Zug, Switzerland, PharmaSwiss offers full third-party representation of specified drugs or portfolios from research-based pharmaceutical and biotech companies, including drug registration, promotion, sales, compliance, and pharmacovigilance. It represents several blue chip clients, such as Amgen, Bristol-Myers Squibb, Wyeth Pharmaceuticals, Ipsen, Astellas Pharma, Eli Lilly, and Ferring. PharmaSwiss currently operates in Serbia, Croatia, Slovenia, Poland, Baltic countries, Czech Republic, Hungary, Romania, Bulgaria, Slovakia, Albania, Greece, Turkey, and Israel. During the course of 2008, PharmaSwiss has launched operations in Hungary, Romania, and Turkey and during 2009 in Poland. Development plans for the following years include also entering Russia and CIS.

Adcock Ingram is a leading South African pharmaceutical company with a history that spans 117 years of adding value to the lives of millions of South Africans. The company has an extensive range of prescription, generic, and OTC products and also provides life-saving hospital equipment, diagnostic products, and services. The extensive range of OTC and prescription products of original research and generic medicines was recently enhanced by the addition of a range of generic antiretroviral medicines. The company's in-house research and development facilities are approved by the South African Medicines Control Council and accredited by the World Health Organization. The company is extending its footprint in Sub-Saharan African and international markets.

Moberg Derma Enters License & Distribution Agreement With MedPharm

Moberg Derma AB and MedPharm Ltd recently announced a license and distribution agreement for the development, marketing, and sales of new dermatology products that will combine Moberg Derma's Kaprolac platform with MedPharm's MedSpray technology. According to the agreement, MedPharm will be eligible for royalty payments.

Moberg Derma obtains the exclusive rights to worldwide manufacturing, distribution, and sales and has the option to develop three products based on MedSpray. Moberg Derma will be responsible for the clinical development and registration of the new products.

"This collaboration with MedPharm enables us to broaden our pipeline with highly innovative and commercially attractive products. There are important synergies between MedPharm's formulation technology and Moberg's therapeutic concepts", explained Peter Wolpert, CEO of Moberg Derma AB.

"We have great expectations on this collaboration as MedPharm's know-how and experience add significant value to our development portfolio," added Andrew Muddle, CEO of MedPharm Ltd. "I am extremely pleased that we will be working with Moberg Derma to develop innovative dermatology products utilizing our MedSpray drug delivery system. This spray-on film technology will produce patient-friendly, elegant products. Combining our Patch in a Can technology with Moberg's Kaprolac platform should produce an exciting, novel product for the global dermatology market, which is greatly needed. It will be great to collaborate with an up and coming EU dermatology company."

Moberg Derma AB, Stockholm, Sweden, develops and commercializes patented medical products for the treatment of common skin disorders. The company focuses on innovative products based on proven compounds. Moberg Derma outlicenses product rights to partners and distributors while maintaining promotion rights for the Nordic region. Moberg Derma's Kaprolac technology is a composition of well-known and safe dermatological compounds that provides important therapeutic benefits. Kaprolac provides a unique combination of properties for dermatological products, a potent antimicrobial effect as well as keratolytic and moisturizing properties with an excellent safety profile. For more information, visit www.mobergderma.se.

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Molecular Responsibility

Growth or Recession: Selling Solutions is the Answer

Part I of a Six-Part Series

By: Derek G. Hennecke, MBA

Whenever I hear someone say it's a tough market out there, I am reminded of *Monty Python and the Holy Grail* in which the Black Knight gets both of his arms cut off and says, "It's just a flesh wound." It's nasty out there. Everyone is feeling it. Clients are having trouble finding funding. Competition is intense. This is the first of a six-part series on building a lasting competitive advantage. It's about gaining market share, even in a down economy.

I'm not going to dwell on the financial aspects of recessionary business. Most everyone who draws breath has learned those lessons already. A good conservative nest egg, not too much leverage - that message has been pounded home by the markets. In fact, the whole world has gotten that message, and I'd like to inform the markets that we're about done learning it now, thank you very much. What I want to talk to you about is the science of competitive advantage. At Xcelience, we are calling it molecular responsibility. The way we see it, our first responsibility is to the molecule. Everything flows from there.

Many in this market are tempted - and I've seen it happen numerous times already - to cut corners to offer a lower bid, to promise shorter time to market, or to design a less-than-optimal proposal, desperate to meet a client's not-so-reasonable request. These strategies will get you a paycheck and through the short-term, but your clients will not be happy with the result in the end, and ultimately, they will end up costing the client more when things begin to go wrong.

There are other, better ways to save client's money. It's about working smarter, not about cutting corners. Cutting corners *increases* risk. We need to be about *decreasing* risk because it's when things go wrong that costs begin to mount. The true cost saver is to focus on the molecule itself. Today's molecule is under pressure.

Faced with the pressures of burn rates, subsequent rounds of funding tied to product development milestones, and competition for internal resources, for many clients, it has become mission critical to do more with less. It's hard to find funds to produce more bulk active, which means clients need to work smarter and make the best choices right off the bat, with limited material.

But by working smart, it can be done. Ideally, a project should

begin at the API selection stage, as clients are getting ready for Phase I studies. They may already be aware of challenging molecular properties, such as poor aqueous solubility, or face constraints, such as limited API. Focusing on the molecule, Xcelience scientists meet with clients and work together to build tailored solutions that overcome challenging molecular properties and accelerate drug development.

Preformulation services can save money down the road as well, by helping clients understand the physical and chemical properties of their small molecule candidates. These services include salt screens that improve the aqueous solubility of the free-form candidate by identifying the optimal salt, polymorph screens to evaluate the potential for polymorphic forms and their effect on the molecular behavior, and drug substance characterization packages specifically designed to improve compound knowledge resulting in fewer drug development surprises.

Sometimes though, the preformulation step can be completely skipped. For some, API into capsule services provide an accelerated, cost-effective path to Phase I studies that enables clients to bypass traditional formulation development while retaining flexibility in dosing for the clinic, no loss in quality, and minimal stability requirements. And, if limited API is the obstacle, it's possible to work with clients to design a Phase I study custom designed to accommodate the amount of material available. All of these efforts will save money down the road.

Central to the concept of molecular responsibility is something called solutions selling. This means that we focus on where we want the molecule to be – the solution – rather than the current obstacle to getting there – the problem.

Sometimes our clients have a very good idea how to address their current obstacle, and that's great. But we have to be open to the idea that it may not be the optimal solution. Problems often arrive ill-defined, and the range of solutions may be constrained by unseen pressures and constraints within the client organization. We need to address those pressures and constraints, and build higher-order solutions accordingly.

Sure, it's easier and faster to just fix it the way the client tells you to, but your client won't thank you if the project fails. As experts in our tiny area of the drug development chain, we need to constantly remember that we can add value with solutions that not only address the technical and scientific challenges, but also speak to the broader business solutions of accelerating drug development or reducing the risk of quality issues, regulatory delay, or missed financial milestones.

Solutions selling is completely reliant on the quality of our people. There is just no substitute for top talent. Rote scientists come up with rote solutions. Pharmaceutical development is not an off-the-shelf business – one size does not fit all. We need to value personnel who think on their feet, who innovate, whose natural style is to look for ways to work smarter, and create a culture to motivate and reward those who consistently do so. We need project managers who listen effectively to clients, understand their goals, pressures, and priorities. A good project manager is part psychiatrist. He or she listens between the lines, too. Then we need to arm these people with the right equipment. Not just the basics, but also the right measure of cutting-edge innovations.

One of the best decisions Xcelience made was to put our money on Capsugel's Xcelodose® 600 and 600 S precision powder micro-dosing systems. We were the first CRO in North America to do so, and there were those who told me we were nuts to invest that kind of money. Today, the Xcelodose system is near constant demand, running full-time, and we've earned a reputation for being the most experienced service provider of API into capsule services, having processed more than 30 APIs and 70 batches.

Each of these elements makes a nice bullet point, but in combination, they empower us to provide a faster, cost-effective path to Phase I studies with greater dosing flexibility and no loss in quality.

Many firms can attract top talent. Still more can purchase the latest equipment or a new purpose-built facility. It's the unique combination of these elements, harnessed and directed for the cause of molecular responsibility that builds lasting competitive advantage. No matter where the market moves.

Next issue, I'm going to dive deeper into some of the specifics of molecular responsibility in the context of budgetary realities by focusing on preformulation services. In recessionary times, we have to work lean, mean, and accept that there's much less margin for error. We have to get it right the first time. Preformulation services are one strategy that every client should consider to make the formulation process smoother and less risky. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

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

ADVANCED DELIVERY DEVICES

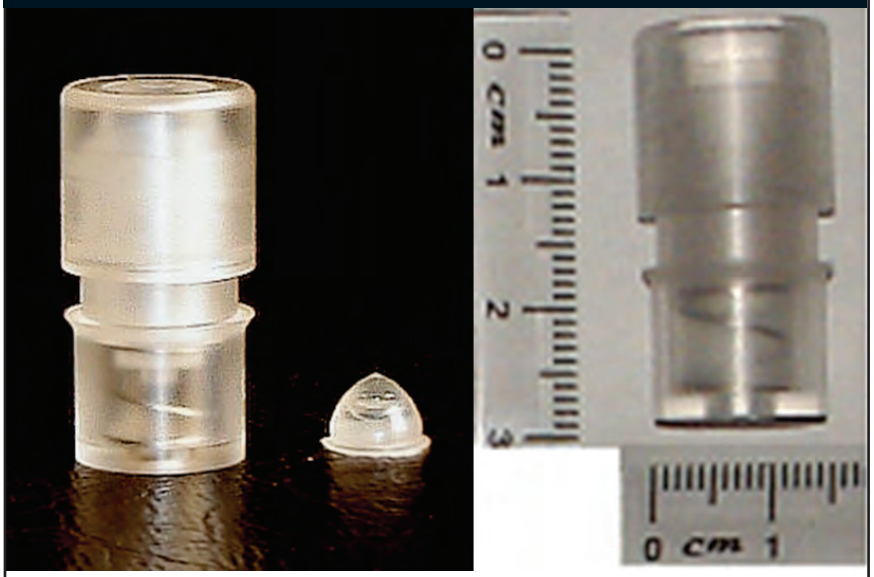
Painless Intradermal Delivery of Insulin: The Novel ClickSoft™ Microinjection Device

By: Maneesh Khanna, MEng; Marko Mihic, MD; Pankaj Modi, PhD, MD

Improving the convenience and ease of administration of parenteral therapeutics is becoming a common practice to augment the product marketability in the biotechnology and pharmaceutical industries. The growth of the injectable market, increased competition in the industries, and requirements of end-user safety has driven product improvements and ease of administrations. In addition to diabetes treatment, injection therapy use is widespread in treatment of cancers, anemia, fertility, thrombosis, hormone replacements, obesity, etc. There are a number of devices in use today to deliver a drug like insulin, including syringes, insulin pens, jet injectors, and insulin pumps. No single device or type of device works well for everyone. The decision of which device to use may be based on a person's insulin regimen, ability to manipulate or operate a particular device, visual ability, insurance coverage or ability to afford a particular device, related supplies, occupation, and daily schedule or leisure-time activities. This means the customer-specific injection device needs for improved convenience will continue to increase in the future.

Diabetes affects approximately 177 million people worldwide and is increasing, with the World Health Organization predicting 370 million diabetics by 2030. It is the sixth most common cause of death as recorded on US death certificates.

FIGURE 1



Device With Drug Chamber (L); Actual Device Size (R)

Therapy for diabetes mellitus has developed and changed extensively since Banting and Best isolated insulin in 1921. Many people consider an injection (at best) unpleasant and (at worst) a painful encounter. This is because most shots are given subcutaneously or intramuscularly, reaching deep enough into the skin to hit nerves and cause pain along the way. In the beginning, syringes were the sole method of delivery of insulin therapy and even today remain a mainstay around the globe.

Each improvement in an insulin delivery system strives for two common goals: patient convenience and better glycemic control. Patients are seeking flexibility and convenience beyond the traditional syringe and vial system. As practitioners and patients seek to normalize glycemic control, insulin delivery injection devices are being developed that can help achieve this goal with improved comfort, convenience, and safety. Today, many different types of insulin administration devices are available, eg, insulin pump, insulin pens, jet injectors, etc.[1-11]

While newer insulin pumps are easier to use, many patients still find the overall insulin pump experience to be very complicated as it requires good maintenance and understanding of the operation. Moreover, the pumps are very expensive and are not affordable for everyone.

Insulin pen devices have some of the same limitations as syringes. Patients with impaired visual acuity or manual dexterity,

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For more information on growth opportunities in the Drug Delivery market, please contact Johanna Haynes at johanna.haynes@frost.com.

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inability to cope with new technology, inability to manipulate the pen, or declining cognitive function will require the assistance and support of a caregiver. Pens, insulin cartridges, and pen needles are relatively much more expensive than the syringe and are not affordable by everyone.

The jet injectors have no needle, yet they can damage the skin if not adjusted properly. Many patients are bothered by the noise the injector makes upon delivery. Another deterrent for patients is the weekly maintenance and cleaning jet injectors require. Consequently, only a small percentage of patients use jet injectors.

Considering all of the aforementioned factors and in hope of improving the compliance and willingness for the exogenous insulin administration by diabetics around the world, PKA SoftTouch has developed a novel microneedle (ClickSoft™) with an ingenious mechanism for simple painless drug administration between the skin layers, ie, intradermal, painlessly insulin administration. The shallow delivery of drugs with this novel device actually causes no pain or much less pain and enhances the uptake.

This device (Figure 1) allows for the injection of drugs directly in between the epidermis and dermis (just under the stratum corneum), which avoids hitting nerves, and allows for rapid dispersal of the drug into the bloodstream via the interstitial fluid. Injection of the drug into the intradermal skin layers (between the epidermis and dermis) does not disturb the nerve junctions and thereby avoids the pain sensation. Thus, this device allows for the painless administration of insulin and many other therapeutics.

Furthermore, the proprietary technology is able to stabilize the insulin at room temperature. This is another milestone forward in the device as it will not require refrigeration for an extended period. It allows users to have a number of these devices in a pocket or purse and use them as required to control their insulin needs while they are away from their home or traveling. The different dosages will be indicated by various colored caps with large fonts on the devices. The following describes this novel ClickSoft device and its application in treatment of diabetes for a painless intradermal insulin administration.

FUNCTIONALITY, ATTRIBUTES & ADVANTAGES

ClickSoft is a spring-loaded microneedle intradermal injection system. Upon depressing the trigger, the device propels a fine stream of liquid medication from the drug chamber through an ultrafine needle in between the skin layers (intradermally). The pressure released on the trigger withdraws or retracts the needle completely into the device for a safe disposal (the device can be discarded without special handling). These steps are shown and explained in Figure 2. The attributes and advantages are listed in Table 1.

PROOF-OF-CONCEPT DOG STUDY

The device was tested on two separate occasions for its effectiveness, efficacy, and safety measures in two specific studies as outlined further.

OBJECTIVE: The purpose of this study was to establish that the novel ClickSoft delivery device effectively delivers Atropine into the systemic circulation via shallow intradermal

TABLE 1

Attributes & Advantages of the ClickSoft™ Microinjection Device

- The product is aimed squarely at the vast type 1 market and growing type 2 market. ClickSoft has the dose range capabilities going up to 100+ units in a single dose (in 150-microliter volume), greater than any pen on the market or insulin syringe.
- Most suitable for twice- or once-a-day fixed dose basal insulin or premixed insulin.
- Very suitable for fast-acting insulins, eg, Lispro, Apidra, Actrapid, etc.
- Faster onset of action (rapidly absorbed via interstitial fluid), which is faster than any rapid insulins available today (refer to the data shown below).
- Reduces the injection force by 60% or more in comparison to other leading disposable pens or injection syringes (no pain or much less pain).
- Beneficial for all people with diabetes and in particular, for those with lower grip strength. It is estimated that up to 60% of individuals have limited joint mobility of the hand, needing very gentle operation.
- Prefilled, fixed-dose chamber (color coded for different doses).
- Single-use, completely disposable device prevents contamination from patient to patient. No fear of needle sticks after disposal (needle is retracted back into the device completely after use), non-hazardous disposal.
- Cost effective and affordable, price is very comparable to standard injection syringe price.
- Quality of life: the small size of the device makes it convenient to carry anywhere and to use comfortably in public.
- The device user stabilized insulin formulation, which can be stored at room temperature, thus no refrigeration needed.
- Uses thin needle (30 or 31 gauge) that can penetrate the skin to within a depth of 1 to 2 mm.
- Broad applicability: the device and formulation are more versatile for many injectable therapeutic deliveries in addition to insulin, eg, heparin, GLP-1, Jenuvia, Symlin, Exnatide, and vaccines.
- Can be used anywhere on the body (all over arms, legs, and stomach).

injection. The biologic effects of Atropine can be quickly observed by increased heart beats if it is absorbed in the blood stream.

STUDY DESIGN: This study was a randomized cross-over study in 20 healthy Beagle dogs, divided into 2 groups of 10 dogs each. The dogs were acclimatized to the study condition and stabilized for 7 days. They were given their regular dog chow and water as needed along with 12 hours lights on and 12 hours lights off. On the day of the study, the dogs were fasted for at least 10 hours prior to the dosing with Atropine. The dogs were implanted with the Polar M52 Heart Rate Monitor device with triple LED displays and memory functions to store information, and also with the standard ECG device to monitor ECG and pulse rate and oxygen levels along with the blood pressure. All data are reported as means ± SE. Heart rate variability was obtained using a Delta-Biometrics vagal tone monitor triggering the ECG R-R interval (Urbana-Champaign, IL). This device employs the time-series signal processing techniques as developed by Porges to estimate the amplitude of respiratory sinus arrhythmia (ie, increase in heart rates).

TREATMENT 1: Five dogs received Atropine administered via the microneedle (ClickSoft) device (0.03 mL total volume or ~ 0.044 mg/kg), and 5 dogs received Atropine (0.03 mL or ~ 0.044 mg/kg SC) via conventional needle (22 g) and plastic syringe (1 cc). The dogs were given rest for 48 hours to ensure complete washout of the drug, and they were then crossed over for the treatments.

TREATMENT 2: Five dogs received Atropine administered via the microneedle (ClickSoft) device (0.03 mL total volume or ~ 0.044 mg/kg), and 5 dogs received Atropine (0.03 mL or ~ 0.044 mg/kg, SC) via conventional needle (22 g) and plastic syringe (1 cc).

Dogs were monitored continuously by a heart monitor and ECG equipment to assess their well being and general health. In the case of excessive heart beats, the antidote was kept near by to terminate the experiment immediately. The heart rates, pulse rates, and blood pressures were monitored continuously by online ECG equipment attached to their legs by a regular ECG equipment strap bend. Upon injection of Atropine, the heart rates increased within minutes. The increase in heart rates is shown in Figure 3. At the end of the study, all dogs were returned to their normal life and were found in good health.

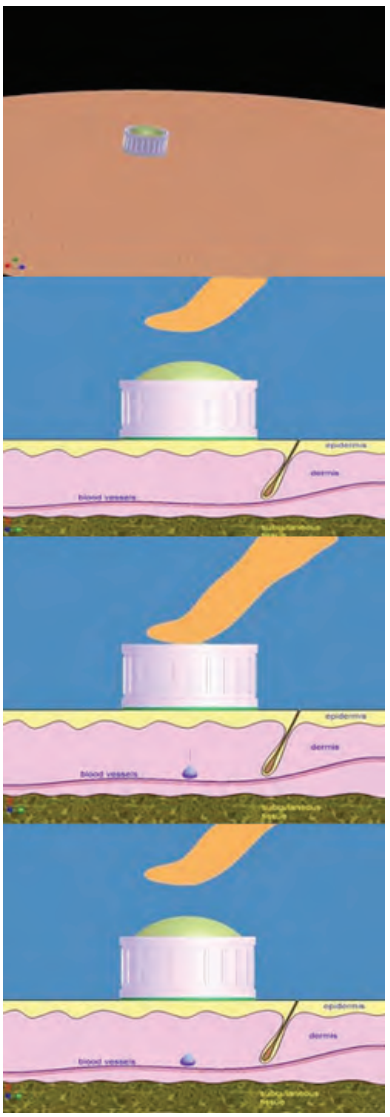
RESULTS & CONCLUSION

The heart rate and the heart rate variability responses to two dosing methods, ie, SC injection versus intradermal injection with the ClickSoft device before and after the dosing are shown in Figure 4. The injection with the microneedle device elicited a significant increase in heart rate (time effect, $t = 10$, Heart Rates = 276, $P < 0.0001$ compared with SC injection, $t = 20$ min, Heart Rates = 235) with larger increases noted when compared with the same animals injected with the regular SC injection of the same dose. The average rates of percent change in the heart rates were significantly higher with the microneedle (210% from the baseline versus 76% SC injection). The recovery rates of returning heart beats to normal value was the same for the ClickSoft device and the regular SC injection with syringe. The novel device was proven safe and almost painless as the dogs never felt pricks when the device was placed and activated as opposed to injection, of which the dogs felt pain as assessed from their withdrawal behavior and sound emitted.

PROOF-OF-CONCEPT HUMAN STUDY

OBJECTIVE: To compare the efficacy of the microneedle-based intradermal and epidermal drug delivery system with SC injection dose of human insulin after a standard meal at breakfast time in subjects with Type-1 diabetes.

FIGURE 2



Device is positioned or placed on the body (1); device is activated by finger pressure, ie, device dome is pushed downward (2); the internal needle punctures the drug chamber and simultaneously enters the skin and delivers the dose intradermally within 5 seconds (3); when the finger pressure is released, the needle retracts back completely into the device and is now safe for disposal in any container (4).

STUDY DESIGN: This was an open label, randomized, cross-over, comparative study of the microneedle device versus SC insulin injections involving 15 male or female volunteers with type 1 diabetes. All patients received the following two treatments in a randomized fashion on separate days.

TREATMENT 1: Subjects were given a bolus dose of insulin (Humalog, Lilly) 7 units at time 0 minutes.

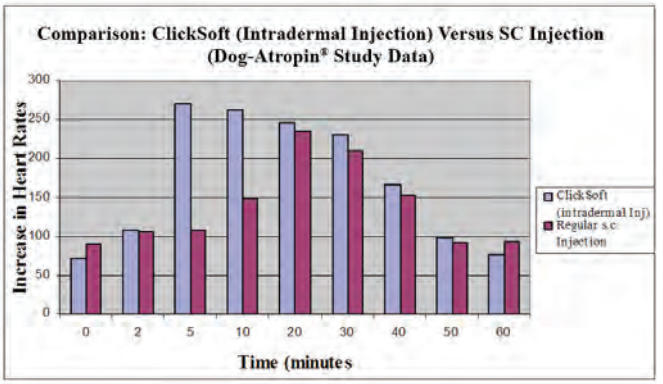
TREATMENT 2: Subjects were given an insulin dose (Humalog, Lilly) 7 units through the microneedle ClickSoft device at time 0 minutes.

Ten minutes after the dose, the subjects were asked to consume 360 calories from Boost or Ensure Plus liquid meals. Blood samples for plasma glucose and insulin were taken 30 minutes before the liquid meal (-30 minutes), just before the meal time (0 minutes), and after (15, 30, 60, 90, 120, 180, 240, and 300 minutes). At the end of the study period, the catheter was removed, and the subjects were permitted to leave the clinic after examination by a physician who declared them safe to leave the clinic.

RESULTS & CONCLUSIONS

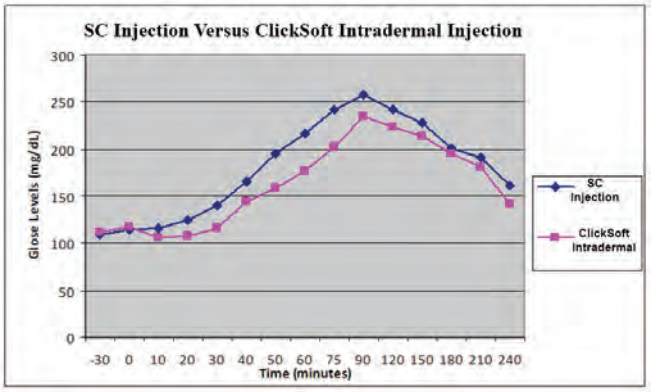
There was a significant difference in the glucose excursions at 30 and 60 minutes after a standard meal challenge as derived from the values of lower glucose levels in the microneedle device injection treatments when compared to the standard injection treatments. The 30 and 60 minutes post-prandial glucose levels were significantly lowered with the microneedle device versus the injection group (146 ± 5 mg/dL microneedle device versus 184 ± 7 mg/dL injection: 21% lower at 30 minutes and 192 ± 6 mg/dL microneedle device versus 236 ± 9 mg/dL injection: 19% lower at 60 minutes $p < 0.003$). The rises in serum insulin levels were significantly higher (Cmax = 93 ± 6 μU/ml for microneedle device at 20 minutes versus 78 ± 3 μU/ml injection treatment, 20% higher, $P < 0.001$). The absorption of insulin through the skin layers was significantly faster when compared to the SC-injected rapid-acting insulin (Humalog). The insulin delivered through the microneedle device was effective in lowering glucose when compared to the regular SC insulin injection. This was attributed to the much more rapid absorption of insulin through the skin layers (Tmax = 20 ± 3 minutes for microneedle device versus Tmax = 60 ± 10 minutes injection). There was no statistical difference in the variability of the absorption of insulin in the microneedle device versus SC

FIGURE 3



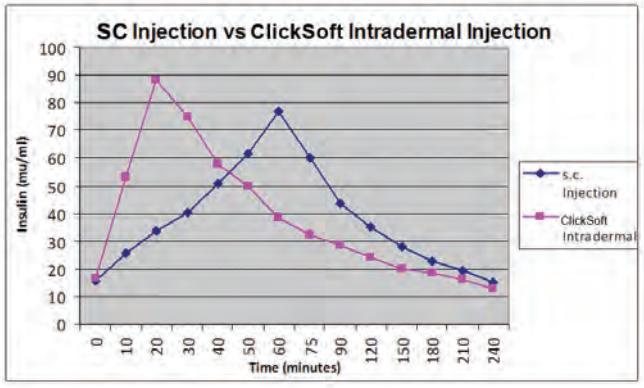
Comparison of ClickSoft (Intradermal Injection) Versus SC Injection (Dog-Atropin Study Data)

FIGURE 4



Average Blood Glucose Levels (ClickSoft Versus SC Injection)

FIGURE 5



Average Serum Insulin Level (ClickSoft Versus SC Injection)

injection as estimated from the individual data of each treatment, and both treatments were comparable to each other in absorption characteristics ($p > 0.751$). See Figures 4 and 5.

The absorption of insulin through the intradermal route was significantly faster when compared to the subcutaneously injected rapid-acting insulin (Humalog). The 30 minutes and 60 minutes post-prandial glucose levels were rapidly lowered with the microneedle device versus the injection group. The Humalog peaked faster (approximately 50%) within 20 minutes of intradermal injection (Tmax = 20 minutes) as opposed to regular SC-injected Humalog (Tmax = 60 minutes). This was attributed to the much more rapid absorption of insulin through the intradermal interstitial fluid with microneedle injection. There was no pain associated with the microneedle device injection as patients never felt the pricking pain that is associated with the SC injection.

Experts agree that interest and developments in novel insulin injectors are needed, especially toward the ease of administration and reduction in pain during the injection process. The pain reduction and the ease of administration will add substantial value to injectable products. Pharma partners now strongly recognize that the development and selection of the optimal injection device can have a significant impact on product success, and view single-dose, disposable technology as an interesting and rapidly changing market segment. In conclusion, based on its simplicity, cost-effectiveness, and its ability to reduce or eliminate pain in most cases, the Microneedle (ClickSoft) device will help initiate early insulin therapy to prevent dreadful future complications of diabetes and may help increase patient compliance to take insulin doses when needed. ◆

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BIOGRAPHIES

Mr. Maneesh Khanna is Partner and Director at PKA. He has over 21 years of industrial experience with key exposure in the field of product development leading from an initial concept to the final product development. His vast international experience and technical skills for the design and manufacturing of precision products and assemblies have provided him a strong background for the innovative development of microneedle devices. His contributions in the field of medical devices include the development of IV Cannula, the Blood Collection Bag system, an Endotracheal Tube, and other IV therapy products for a medical company in India. Mr. Khanna earned his MEng in Design and Manufacturing and Micro Machining from McMaster University in Canada.

Dr. Marko Mihic is a Physician and Surgeon at the Diabetes Research Institute, St. Joseph Hospital in Toronto, Canada. Dr. Mihic is also Co-Founder of the Institute (Center, University Clinic) of Diabetes in Zagreb as a central institution for the organization of healthcare, education, and research in the field of diabetology in Croatia. He has authored several key publications in the field of Diabetes and Metabolic Syndromes. Dr. Mihic earned his MD from the University of Toronto with specialization in Diabetes.

Dr. Pankaj Modi is the Founder and President of PKA. He has over 23 years of experience in developing novel drug delivery systems and non-invasive medical devices for various therapeutics. Dr Modi is author of 30 US and 175 worldwide patents on various drug delivery systems. He has published over 35 papers and book chapters in leading medical and biotechnology journals. Dr. Modi is an Editorial Board Member for many drug delivery and medical journals. Dr. Modi earned his PhD in Biomedical Sciences from the University of Toronto, Postdoctoral Fellowship from McMaster University, and Doctorate in Internal Medicine with specialization in Endocrinology and Diabetes.

Silicified Microcrystalline Cellulose as a Multifunctional Pharmaceutical Excipient

By: Jignyasha A. Raval, Jayvadan K. Patel, PhD

ABSTRACT

Today is the age of competition and challenge for the scientist to develop solid dosage formulations quickly and cost effectively. The important fact that can impact the success of this pursuit is the choice of excipients and its relation with the process to be adopted for manufacturing, ie, wet granulation, roller compaction, and direct compression. Excipient technology advancements have led to a new class of multifunctional excipients, which simplify formulation. Silicified microcrystalline cellulose (SMCC) as Prosolv® is one such multifunctional pharmaceutical excipient that has changed the face of the manufacturing process. The characteristics offered by Prosolv are high compactibility, high intrinsic flow, enhanced lubrication efficiency, and improved blending properties. These characteristics provide tremendous benefits throughout the product lifecycle in formulation, manufacturing, and marketing. It can ease the formulation scientists' burdens by decreasing many of the challenges they face today. The number of successes Prosolv SMCC offers is limited only by the imagination of the formulator.

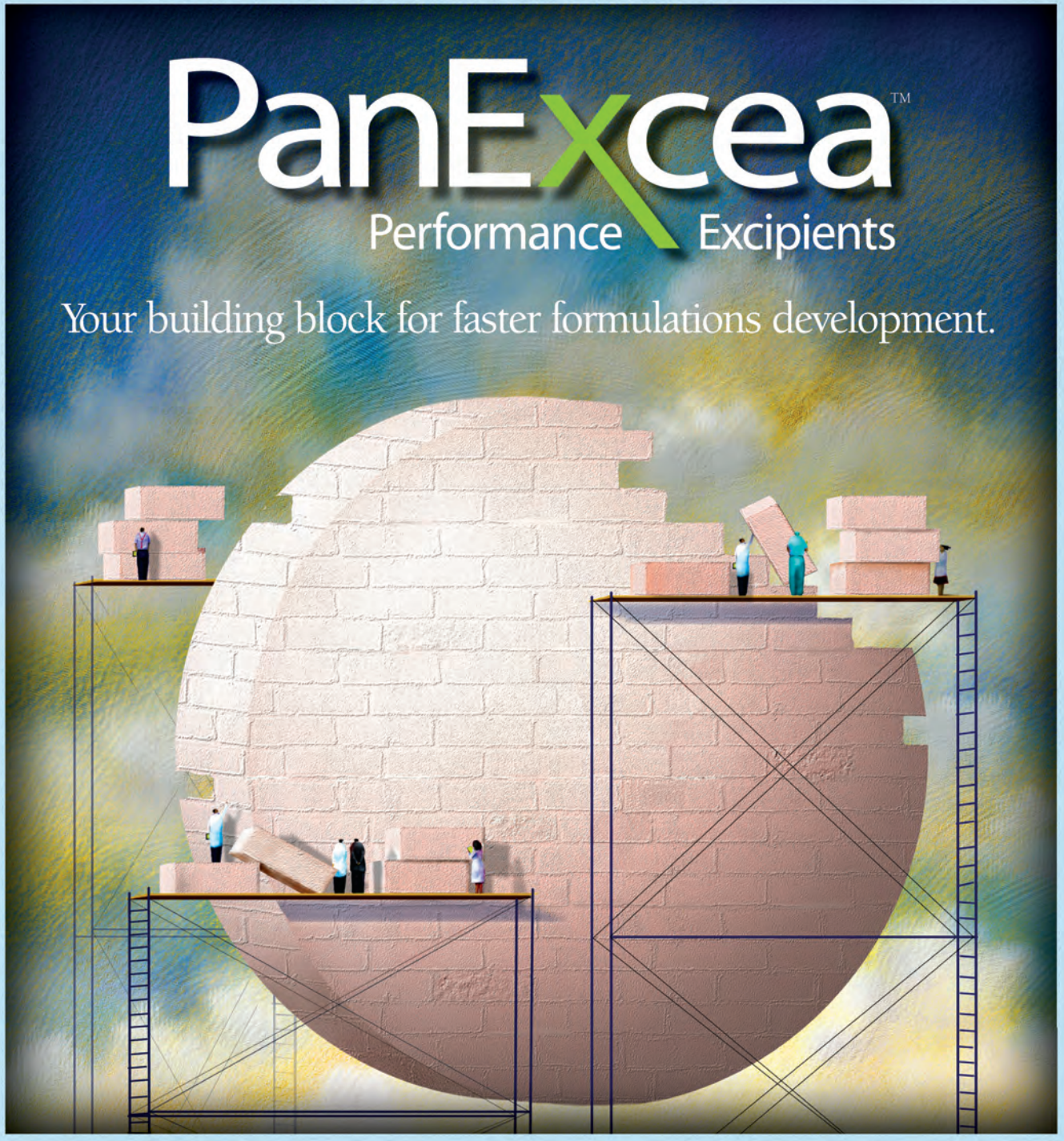
INTRODUCTION

The pharmaceutical industry is in the era of dynamic competition with an ever-increasing challenge for scientists to develop solid dosage formulations quickly and cost effectively. This concept emphasizes the optimal use of the potent and costly newer active pharmaceutical ingredients (API) and other excipients. The rush for capturing market share with the introduction of generic drugs is equally important. Simplified formulations and processes provide the most effective route to accomplishing such goals, while conventional formulation ingredients and approaches may limit the opportunities.[1,2]

One important fact that can impact the success of this pursuit is the choice of excipients. Experts in the art of tableting are aware of the basic art of tableting via three well-known methods, ie, wet granulation, roller compaction, and direct compression. The pros and cons of wet granulation and roller compaction are well documented in the literature.[3-5] The processing of direct compression has been found in the literature for quite some time, but experienced a wave of consideration since the 1960s. However, a formulation made using this method requires several conventional excipients. Good formulation flow, compaction, powder blending, content uniformity and carrying capacity, enhanced stability, lubricity, and dosage form disintegration all rely on formulation scientists choosing ingredients that best provide those attributes necessary for successful formulations. Identifying excipient combinations in optimum concentrations to achieve adequate solid dosage forms often requires significant time and expensive processes, which vary with API characteristics.

Excipient technology advancements have led to a new class of high-functionality excipients (HFE), which simplify formulation. It is very obvious the use of high-functionality excipients that perform multiple functions or are combinations of the required functions shall have a preference to that of the use traditional excipients.[2] With the introduction of high-functionality excipients, formulation scientists in the generic pharmaceutical industry have access to unique materials in providing simplified formulations both in terms of ingredients and processes, while maintaining overall economic value. HFEs provide several functions to a drug formulation (eg, high-intrinsic flow, compactibility, and disintegration attributes), using fewer ingredients, simplifying final dosage forms and the manufacturing process.

Conventional excipients may be processed to get an effective functional formula, but these are



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costly to process and often result in compromising some other characteristic. With microcrystalline cellulose, in which density and/or particle size have been altered to improve flow or compaction, it was found that the improvement of flow was at the expense of compaction and vice versa. As another example, co-processed cellulose and lactose is no more than a special lactose grade with improved compaction properties.[2] Dr. Arvind K. Bansal et al were the first to correlate formulation performance differences with modifications in inherent excipients functionality.[6] HFEs have been successful in making a big change in the scenario by effectively enhancing and simplifying pharmaceutical and nutritional formulations.[7,8]

Prosolv SMCC is an example of a multifunctional excipient meeting the HFE definition criteria. Silicified microcrystalline cellulose was introduced in 1996, initially produced by Penwest Pharmaceuticals Co. as Prosolv SMCC, and is recently marketed under the same trademark by J. Rettenmaier and Sohne.[9-12] It is co-processed silicified microcrystalline cellulose. It consists of 98% microcrystalline cellulose and 2% fumed colloidal silicone dioxide.[13,14] Although co-processed, the two excipients maintain their independent chemical properties while synergistically providing increased functional performance and imparting high multifunctionality to API formulations. The CSD is uniformly and highly dispersed across the cellulose surface, which provides a five-fold surface area increase compared with traditional MCC.[15] It has been documented that the co-processed material demonstrates enhanced multifunctionality regarding compactibility, flow, blending properties, lubricant insensitivity, and tablet disintegration.[16] Ever since its introduction, Prosolv SMCC has been applied to a number of pharmaceutical formulations and has gained worldwide acceptance and approval. It is an accepted ingredient by the US FDA and is listed on the FDA's website in the Inactive Ingredients Guide (IIG). It has also been used and accepted in several European applications and is now accepted for use in Japan. A drug master file (DMF) has been created and filed with the FDA.

Prosolv SMCC is such an HFE that it has provided formulators a means to develop unique dosage forms for the generic market segment in a much shorter time (which may be a non-infringing formulation), and at the same time, substantial economic benefits. One direct result is the reduction in the amount of API consumed; this in turn has less impact of the side effects. Exicipient-release testing is decreased and the in-process testing is eliminated for complex processing.

PROPERTIES/BENEFITS OF PROSOLV TECHNOLOGY[17]

Prosolv is a high-functionality ingredient that offers significant benefits in terms of tablet size, production yield, and overall cost. Early use in formulation development can result in early market entry, direct compression formulas, and smaller tablets that consumers prefer. Its characteristics include high compactibility, high intrinsic flow, enhanced lubrication efficiency, and improved blending properties. These characteristics of provide tremendous benefits throughout the product lifecycle in formulation, manufacturing, and marketing.

Enables Direct Compression

Tablets made with Prosolv may eliminate the need for costly wet granulation because it is the most compactible ingredient available, is up to 50% more compactible than microcrystalline cellulose, demonstrates superior flow, and provides drug dispersion and content uniformity in direct compression. The use of direct compression means that the cost of wet granulation can be avoided and unstable drugs can be handled without water or heat. Thus, the benefits are reduced processing costs and a simplified formulation solution for unstable actives.

Enhances Flow

Formulations made with Prosolv demonstrate superior flow versus formulations made with traditional ingredients because of the reduced inter-particulate friction. Superior flow means that Prosolv formulations demonstrate reduced tablet weight variation, impart flowability to all formulation ingredients, and meet the demanding material flow requirements of high-speed presses. The benefit is Prosolv formulations can be run at increased press speeds.

Enhances Mixing Characteristics

Content uniformity of low dose drugs is enhanced by Prosolv because of the unique physical properties of high-surface area and roughness and reduced inter-particulate friction. These unique

physical properties mean that powder flows into the die quickly and evenly, blending is efficient and uniform, de-blending is eliminated, powder-bed expansion and aeration is prevented, percolation is reduced, and ordered mixing is enhanced. The benefit is that content uniformity challenges that are typically solved by wet granulation can be overcome with Prosolv and direct compression.

Improves Compactibility

Tablets made with Prosolv are more robust due to the high compaction it imparts on the formulation. Prosolv is 30% more compactible than microcrystalline cellulose in placebo formulations; and in actual formulations, it has shown to be 50% more compactible than the microcrystalline cellulose formulation. This means Prosolv formulations can result in more robust tablets that will stand the rigors of film coating, packaging, and general handling. The benefit is increased cost savings from higher manufacturing yields.

Increases Production Capacity

Formulations with Prosolv can increase production capacity because it is the most compactible ingredient that results in smaller tablet size; therefore, more tablets per batch; has superior flow that results in accelerated press speeds and thus higher tablet output; and has higher density (Prosolv HD90) that results in larger batch sizes in the same equipment. This means Prosolv formulations can use the same production equipment for larger batch sizes. The benefits are cost savings from production efficiency and reduced quality control analysis.

Less Excipients Needed

Tablets made with Prosolv require fewer and reduced levels of excipients. This is because it is 30% to 50% more compactible and flows at two times the rate of microcrystalline cellulose, eliminating the need for ingredients, such as microcrystalline cellulose, dibasic calcium phosphate, lactose, and colloidal silicon dioxide. Higher compactibility and superior flow mean less binder is required, glidant and anti-adherent requirements are reduced or eliminated, disintegrant requirement is reduced due to smaller tablet size, and lubricant levels are reduced due to smaller tablet size and more efficient lubricant utilization. The benefit is the savings from the reduction in the number and amount of ingredients required in a Prosolv formula.

Rapid Formulation Development

Formulations developed with Prosolv are simpler and more robust because of its multifunctional attributes that result in shorter development time. Rapid formulation development means the design of experiments are significantly reduced, the quantity of active required is minimized, and the benefit of shorter development time is speed to market.

Smaller Tablets

Tablets made with Prosolv are smaller because it imparts flow and compaction to the formulation. This results in fewer and less excipients needed in the formulation. In one formulation, 7% Prosolv replaced 20% microcrystalline cellulose and 20% dibasic calcium phosphate, resulting in smaller, easier-to-swallow tablets. Smaller tablets mean that Prosolv can be used for combining products that were previously difficult to formulate; adding more active in each tablet to reduce dose regimens; and penetrating key high-dose market segments, such as anti-virals and analgesics. Smaller tablets are easier to swallow, allowing for greater patient compliance.

The applications of Prosolv SMCCs have been varied and many. A number of examples have been established in which the technology has provided formulation scientists with the means to simplify formulations by replacing several traditional excipients with one, eliminating costly and complex processes. Traditional excipients used in combination still do not perform as well as Prosolv SMCC (due to the synergistic performance enhancement) and require increased levels to match the performance of Prosolv SMCCs.[1]

Prosolv is multifunctional, meaning it does not perform just a single function like glidants, lubricants, anti-adherents, binders, or disintegrants. It is a high functionality excipient that combines two or more functions through a single ingredient. It has high inherent functional performance, allowing for increased batch sizes and higher drug-loading, even at low usage levels. Prosolv requires no complex processing, making it ideal for direct compression processes. Lastly, it imparts its high inherent performance characteristics to the overall formulation. This last

criterion is critical and separates this HFE from other multifunctional excipients or conventional specialty excipients. The highest level of functionality can be imparted to a pharmaceutical active by coprocessing with the Prosolv advanced ingredient technology. This was first demonstrated with RediRun DC Herbal Ingredients.[18] Active herbal extracts were greatly enhanced in functionality and stability when co-processed with Prosolv SMCC. Performance improvements were significant for flow, compactibility uniformity, and hygroscopic stability.[2]

SUMMARY

The benefits and value of using advanced ingredients in modified-release systems has been demonstrated. In matrix hydrogel systems, SMCC provides better uniformity of flow, content, weight, hardness, and drug release.[19] Ultimately, pharmaceutical active co-processing using Prosolv technology will be used to achieve optimal effectiveness and cost in immediate-release and modified-release dosage forms. High functionality excipients are a reality and have gained wide acceptance across multiple industries and industry segments. They are particularly important to the generic pharmaceutical industry because development and production can be streamlined, saving time and money. A competitive advantage can be realized, which will advance market share and increase revenue. Prosolv SMCC is one such HFE.[1] It can ease the formulation scientists' burden by decreasing many of the challenges formulators face today. The number of successes it offers is limited only by the formulator's imagination. Overall, with the advent of advanced ingredients, pharmaceutical companies can look forward to achieving higher product quality bringing products to market faster, reducing development and production costs, and enjoying longer product lifecycles. ◆

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BIOGRAPHIES

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OCULAR OPPORTUNITIES

Ocular Drug Delivery: Expanding the Field of Vision

By: Misty Hughes, Frost & Sullivan

INTRODUCTION

Developing therapies to effectively treat ocular diseases is often more complex than discovering drugs for treating other areas of the body. While sensitive and delicate, the eye's seemingly unassailable natural defense systems present researchers with a considerable obstacle to overcome when trying to achieve optimal therapy levels in targeted tissues. Currently, the pharmacologic management of most ocular diseases is done with topical applications of solutions, ointments, and suspensions to the front of the eye (FOTE). While roughly 95% of all FOTE products are delivered via traditional eye drop bottles, the protective anatomy and physiology of the eye blocks a significant amount of topically applied drugs from ever effectively penetrating the cornea. This area of opportunity has piqued the interest of several pharmaceutical and drug delivery companies, enticing them to broaden their research into improving the delivery of drugs to the eye.

The same mechanisms that protect the eye and block foreign substances greatly limit the usefulness of topical treatments when they are distressed or diseased. When the volume of fluid in the eye exceeds about 7 to 10 microliters, the nasolacrymal system works quickly to flush the excess out. As the size of a drop from a conventional eye dropper is nearly 8 to 10 times the size of a normal tear, the majority of the dose administered is rapidly eliminated. It is estimated that as little as 5% of a topically applied drug ever reaches the intraocular tissues due to drug loss resulting from tearing, lacrimal fluid-eye barriers, and blood-ocular barriers.

In spite of their shortcomings, topically applied therapeutics will undoubtedly remain a mainstay in the treatment of most disorders in the eye. However, achieving the optimum therapeutic drug levels required to more effectively treat many ocular conditions will necessitate improvements in drug delivery. Researchers are working to enhance ocular drug bioavailability with innovative controlled delivery technologies, such as ocular implants, absorption enhancers, and iontophoresis, to name a few, which can be adapted to deliver a broad spectrum of ophthalmics. Companies wishing to generate new avenues for revenue growth or extend the patent life of their products are partnering with drug delivery companies to reformulate existing products, or develop new chemical or biologic entities that utilize some of these novel technologies.

OCULAR IMPLANTS

For the sane majority of us, the thought of a physician piercing our eyes with a needle tip large enough to pass a grain of rice through holds absolutely zero appeal. Faced with a sight-stealing disease; however, each of us would certainly stop at nothing to prevent loss of vision. Bypassing the physiological barriers of the eye, ocular implants release a constant amount of medication in a highly localized fashion with minimal systemic effects. Additionally, ocular implants are designed to release medication over pre-set treatment periods ranging from months to years. This technology not only holds promise for treating serious anterior diseases like glaucoma, where frequent daily dosing limits patient compliance, but could also put an end to the multiple invasive procedures typically required to treat retinal diseases.

One company leading the way in ocular implant technology is SurModics, a drug delivery and surface modification company working to develop advanced solutions to improve therapeutics. SurModics' I-vation™ Implant and I-vation™ Sustained Drug Delivery System are an intravitreal implant and drug delivery system designed to provide controlled and sustained release of a variety of drug compounds. While most ocular implants are designed in the shape of rods, plugs, discs, or sheets, the I-vation Implant system leverages a helical design that maximizes the drug delivery surface area, while providing a secure anchor of the implant to the sclera. The implant itself is coated in SurModics' proprietary drug delivery polymer matrix, which can be fine-tuned and customized for the controlled diffusion of the drug into the eye.

ABSORPTION ENHANCERS

As 40% to 60% of new chemical entities are lipophilic, researchers are investigating ways to improve solubility

and absorption. Novagali Pharma's proprietary emulsion technology, Novasorb®, is a cationic emulsion technology platform being investigated to treat dry eye, glaucoma, allergies, and anterior uveitis. The effective treatment of surface ocular conditions is often limited by dispersion and lubrication. Novasorb technology increases the absorption and efficacy of drugs in ocular tissues through electrostatic attraction between the positive charge of the therapeutic emulsion and the eye's negatively charged mucous, cornea, and conjunctiva. By increasing the drug's residence time on the eye, more of the drug is able to diffuse into the eye, which increases therapeutic drug levels. It also means the patient will require fewer instillations, which will undoubtedly increase patient compliance and decrease side effects.

IONTOPHORESIS

Iontophoresis, while on the brink of becoming a breakthrough in treating ocular diseases, has long been in transdermal use for purposes such as the active transport of the drug pilocarpine when testing for cystic fibrosis, for the detection of blood glucose levels in diabetics, and even to deliver certain pain medications. When used in the eye, iontophoresis works by overcoming the eye's natural protective barriers to deliver drugs non-invasively via the application of low-voltage electrical current to actively transport charged substances through ocular cells and tissues. When an electrode and a drug have like charges, either positive or negative, the repulsion between the two propels the charged drug across the cell membrane.

EyeGate Pharma is a specialty pharmaceutical company researching iontophoresis technology to safely and more effectively deliver therapeutics to the eye. The company's EyeGate® II Delivery System works by applying a low-level electrical current to the eye to hydrolyze water and increase cellular permeability so that the charged drug is delivered in greater concentrations across the sclera. Alongside its potentially broad applicability in treating numerous eye diseases, such as uveitis, AMD, glaucoma, and diabetic retinopathy, EyeGate's novel utilization of iontophoresis technology provides many notable benefits over standard modes of treatment. Virtually painless and requiring only topical anesthesia in the form of eye-drops, EyeGate II's non-invasive, needle-free administration decreases many complications, such as retinal damage, infection, and other serious visual disturbances associated with other invasive treatments without sacrificing efficacy. Most importantly, the EyeGate II achieves high therapeutic concentrations at both the front and back of the eye with minimal systemic uptake or toxicity.

INSIGHT INTO OPPORTUNITY

As the baby boomer population in the US ages, there will be a significant increase in demand for ophthalmics that improve, restore, and preserve sight. Therapy ease-of-use is also expected to be of considerable importance among this growing elderly patient base. Herein lays a huge area of opportunity for pharmaceutical and drug delivery companies to boost revenues. By cleverly managing product life cycles via reformulating marketed drugs or applying cutting-edge delivery techniques to compounds in clinical trials, industry participants can create remarkable new sources for revenue generation. At a time when drug developers are seeking areas of opportunity for product development, the ophthalmic disease area presents many avenues for companies to provide new solutions to patients and positive returns for themselves.

BIOGRAPHY

Misty Hughes is a Research Analyst with the Frost & Sullivan North American Healthcare team. She focuses on monitoring and analyzing emerging trends, technologies, and market behavior in the Pharmaceutical and Biotechnology industries. Since joining Frost & Sullivan in April 2007, Mrs. Hughes has completed several research studies and consulting projects in Oncology (Breast Cancer), Vaccines, and Ophthalmic diseases/drug delivery. Prior to joining Frost & Sullivan, Mrs. Hughes worked as a pharmaceutical sales representative for Schering-Plough, Synthon Pharmaceuticals, and JDS Pharmaceuticals, where she covered the cardiovascular, allergy, and central nervous system markets.

MARKET BRIEF

A Look at Fast-Dissolving Drug Delivery Systems

By: Bill Martineau, MBA

INTRODUCTION

Two major types of drug delivery systems incorporate fast-dissolving properties that speed up the onset of therapeutic actions imparted by oral pharmaceutical formulations. The first, known as orally disintegrating systems, dissolve or disperse active medicinal ingredients in a polymer or alternative carrier. The combination is then solidified through lyophilization or other method to create an amorphous porous structure suitable for tablet molding.

The second fast-dissolving oral formulation is referred to as transmucosal or buccal. Transmucosal drug delivery systems enclose active pharmaceutical ingredients in an adhesive patch or reservoir. Inside the mouth, the active pharmaceutical ingredients are separated from the carrier by saliva and mucus and flow through the buccal cavity.

ORALLY DISINTEGRATING TABLETS

Orally disintegrating tablets (ODTs) are evolving into an important delivery system for drugs for treating medical conditions vulnerable to a sudden onset of symptoms. Such conditions include allergies, nausea, migraine headaches, and schizophrenia. ODTs are also used widely for medicines prescribed to elderly and other patients who have trouble swallowing conventional dosage formulations. Based on expanding indications, demand for ODT-adapted drugs is forecast to increase 8.9% annually to nearly $2.6 billion in 2012.

ODTs are formulated to dissolve rapidly, usually in a matter of seconds, in the oral cavity after placement on the tongue. Because they are taken orally without water, most drugs based on this technology incorporate excipients that mask unpleasant tastes. ODTs can be produced as compression-molded tablets or lyophilized wafers. Although more expensive to manufacture than conventional dosage formulations, medicines adapted to ODT delivery systems are expected to expand significantly in number over the next decade and beyond. Pharmaceutical companies are employing these systems to introduce product line extensions eligible for patent protection and differentiable from generic versions of conventional formulations. Aripiprazole, risperidone, and olanzapine for schizophrenia; fexofenadine HCl for allergies; donepezil HCl for Alzheimer's disease; rizatriptan benzoate and zolmitriptan for migraine headaches; and ondanestron HCl for chemotherapy-induced nausea and vomiting are among the widely prescribed drugs available in ODT dosages.

Among the available ODT technologies are Catalent Pharma Solutions' ZYDIS, CIMA LABS' DURASOLV and ORASOLV, Eurand's ADVATAB, and SPI Pharma's PHARMAFREEZE systems. Catalent's ZYDIS technology employs a proprietary freeze-drying process in which an aqueous drug solution or suspension is dispensed directly into pre-formed blister packaging. The filled blister packaging is then passed through a specially designed cryogenic process to control the ultimate size of the ice crystals, thereby ensuring that the tablets have a porous matrix capable of facilitating rapid disintegration. Large-scale freeze-driers complete the sublimation process, which removes the majority of the remaining moisture from the tablets. ZYDIS tablets dissolve on the tongue in less than 3 seconds. Olanzapine for bipolar disorders is among the widely prescribed drugs that have been adapted to the delivery system.

The DURASOLV and ORASOLV ODT delivery systems commercialized by CIMA LABS are based on compression-molded tablets that dissolve in the oral cavity in 30 to 40 seconds. Both are compatible with a wide range of water-soluble and water-insoluble drugs, including analgesics, antidepressants, cough and cold preparations, and migraine therapies. The DURASOLV system is intended for low dosage concentrations and provides a compact structure. ORASOLV

formulations contain larger drug concentrations and can be adapted to both immediate- and controlled-release delivery.

Eurand's ADVATAB is an ODT technology used in combination with encapsulated drug particle formulations. The system is based on a coated tablet that dissolves rapidly and releases the encapsulated particles which, in turn, dissolve in a controlled-release manner in the bloodstream. Eurand licenses commercial rights to ADVATAB technology from its developer Kyowa Hakko (Japan). The system has been adapted to risperidone for schizophrenia, among other therapies. In addition, Eurand and Johnson & Johnson are developing an ADVATAB formulation of the over-the-counter antihistamine BENADRYL.

SPI Pharma's PHARMAFREEZE ODT technology is a lyophilized, wafer-based system that accommodates high drug loadings. The wafers dissolve within 5 seconds, which is much faster than ODT formulations based on compressible-molded tablets. SPI is seeking to adapt the PHARMAFREEZE system to therapeutic peptides and herbal extracts, among other medicines.

ORAL TRANSMUCOSAL SYSTEMS

Oral transmucosal (or buccal) drug delivery systems facilitate the transfer of medication across the mucous membrane. Interest in these systems is increasing among pharmaceutical manufacturers due to advantages related to faster onset of action and adaptability to self-treatment. Transmucosal-based drugs on the US market include two formulations of fentanyl for breakthrough pain and a hormone for testosterone replacement. Potential therapies extend to anti-migraine agents, asthma medication, and insulin, among other medicines. Spurred by expanding use in existing indications and the anticipated introduction of new products, demand for transmucosal pharmaceuticals is forecast to increase over 11% annually to almost $1.3 billion in 2012. The penetration of low-cost generic fentanyl formulations into the marketplace will moderate even faster gains.

The mucous membrane is highly

FIGURE 1

ORALLY DISINTEGRATING TABLET DEMAND BY THERAPEUTIC CLASS (million dollars)

Item	1997	2002	2007	2012	2017
Chronic Conditions (million)	869	935	1012	1100	1195
$ ODT/condition	0.7	1.2	1.7	2.3	3.3
Orally Disintegrating Tablet Demand	620	1110	1670	2560	3900
Central Nervous System Agents	450	840	1280	2030	3200
Respiratory Agents	90	150	220	300	400
Gastrointestinal Agents	80	120	170	230	300
% orally disintegrating tablets	3.9	4.1	4.2	4.5	4.9
Oral Drug Delivery Systems	15700	26800	40200	56700	79800

Source: The Freedonia Group, Inc.

FIGURE 2

ORAL TRANSMUCOSAL DRUG DELIVERY SYSTEM DEMAND BY THERAPEUTIC CLASS (million dollars)

Item	1997	2002	2007	2012	2017
Patients w/Cancer History (million)	7.0	10.5	14.6	19.2	25.0
$ transmucosal drugs/patient	15.7	17.3	50.7	65.6	80.0
Oral Transmucosal DDS Demand	110	182	740	1260	2000
Central Nervous System Agents	95	140	660	1080	1700
Hormones & Related Agents	15	42	80	180	300
% transmucosal	0.7	0.7	1.8	2.2	2.5
Oral Drug Delivery Systems	15700	26800	40200	56700	79800

Source: The Freedonia Group, Inc.

MARKET BRIEF

permeable and provides an effective route for delivering drugs to the lungs. Drugs penetrate the lungs at a much greater rate than alternative oral administration routes. The first large-selling medicine to be adapted to transmucosal delivery was a lozenge formulation of fentanyl citrate known as ACTIQ. Produced and marketed by Cephalon, ACTIQ gained FDA approval for US marketing in November 1998. The patent on the original formulation expired in February 2007, opening up the market for generic competition. Cephalon produces a generic version of ACTIQ that is distributed by Barr Laboratories. In 2007, the two transmucosal fentanyl citrate preparations recorded sales of approximately $400 million.

ACTIQ and its generic equivalent are produced as a flavored lozenge attached to a plastic stick. This system resembles a lollipop. Patients receive the medication by sucking on the lozenge, which begins to provide pain relief in approximately 15 minutes. ACTIQ was developed by Anesta in collaboration with the University of Utah. Anesta was acquired by Cephalon in October 2000. The potential US patient base for transmucosal fentanyl citrate includes upward of 800,000 sufferers of chronic and breakthrough pain.

The second transmucosal drug commercialized by Cephalon is a tableted form of fentanyl citrate based on CIMA LABS' ORAVESCENT technology. This formulation, which was approved by the FDA in September 2006, is sold under the FENTORA tradename and is indicated for the management of breakthrough pain in opioid-tolerant cancer patients. FENTORA tablets are placed between the upper cheek and gum and dissolve upon contact with saliva, delivering medication through the buccal mucosa. In late 2007, Cephalon filed applications with the FDA, petitioning for approval of the drug for additional breakthrough pain management indications.

The only other transmucosal drug approved for US sale is a testosterone replacement therapy sold by Columbia Laboratories under the STRIANT tradename. STRIANT is a tablet designed to adhere to the gum or inner cheek. The tablet dissolves upon contact with saliva and delivers testosterone through the buccal mucosa in a sustained-release manner.

In addition to CIMA LABS, other developers of transmucosal drug delivery systems include BioDelivery Systems International (BDSI), Generex Biotechnology, CP Kelco, and Lipocine. BDSI is commercializing a technology based on a dissolvable, dime-sized polymer disc designed to deliver a rapid dose of medication across mucous membranes for time-critical conditions, such as breakthrough cancer pain. Generex Biotechnology is developing buccal spray formulations of fentanyl, insulin, and morphine, which will be administered into the mucosa through a hand-held applicator. CP Kelco is seeking to adapt xanthan gum excipients to a wide range of transmucosal drugs. Lipocine is pursuing buccal formulations as part of a broader effort to introduce pain control and other drugs with enhanced absorption properties.

An in-depth report on this and other related topics can be obtained by contacting the Freedonia Group at www.freedoniagroup.com.

BIOGRAPHY

Mr. Bill Martineau is an authority on the healthcare industry. He has performed in-depth research in biotechnology, pharmaceuticals, medical packaging, and related areas, producing titles such as *U.S. Pharmaceutical Packaging, Cardiac Implants, Nanotechnology in Healthcare, Drug Delivery Systems, and Biochips*. Prior to joining Freedonia, he was Manager of Market Development at American Sterilizer Company, where he gained experience in healthcare research and strategic planning. At Invenex Laboratories, he served as Product Manager, responsible for the administration of a line of injectable pharmaceuticals. He also served as Senior Health Care Analyst at Predicasts Inc. and Manager of Market Research at Life Technologies Inc. (a division of The Dexter Corporation). Mr. Martineau earned his BA in Management and his MBA in Marketing and Finance from Kent State University.

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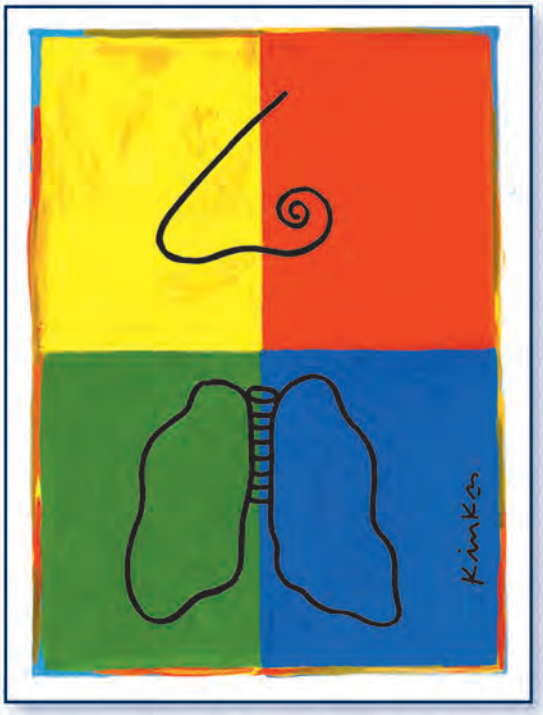

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ADHESIVES TECHNOLOGY

The Evolution of Adhesives: From Transdermal Drug Delivery to Other Novel Delivery Formats

By: William G. Meathrel, PhD

ABSTRACT

As transdermal product designs and capabilities continue to evolve, adhesive manufacturers are embracing opportunities to formulate highly specialized pressure-sensitive adhesives, coatings, and related polymer technologies to meet the requirements of these delivery systems. The following reviews the evolution and formulation challenges of adhesive technologies from their use in passive transdermal drug delivery systems to their use in cutting-edge active delivery devices and novel forms for alternative site delivery.

INTRODUCTION

The transdermal drug delivery system (TDDS), or patch, is a proven and widely accepted form for predictable and reproducible drug delivery. Because the drug is absorbed through the skin for delivery to the blood or lymphatic systems, the TDDS bypasses the hepatic first-pass effect and potential gastrointestinal side effects. Treatment is easily terminated if toxicities, such as drug allergies, occur simply by removing the patch for immediate discontinuance of drug delivery. The TDDS has improved patient compliance for chronic or maintenance treatments, such as hormone replacement, which was previously available only in an oral dosage format, by virtue of its ease of use, fewer side effects, relatively low cost in comparison to alternative devices, and minimal risk of trauma or infection.[1]

Since the introduction of the scopolamine transdermal patch in the late 1970s for motion sickness, pharmaceutical-grade pressure-sensitive adhesives (PSAs) have played a critical role in the function and accurate delivery of TDDS.[2] An adhesive development project may begin with an existing base technology; however, the result is typically a customized adhesive based on design input for each application, which also considers the requirements of the customer's manufacturing process. Base adhesive chemistries for passive systems may include polyisobutylene, acrylics, and silicone formulations in several types of the following passive transdermal patch constructions:

Single-Layer Drug-in-Adhesive - The adhesive layer of this system contains the active pharmaceutical ingredient (API) and performs two functions: bonding multiple

FIGURE 1

Pressure-sensitive adhesives play a critical role in the function and accurate delivery of TDDS.

component layers of the patch together while affixing the device to the skin.

Drug Matrix-in-Adhesive - A semi-solid matrix drug layer is surrounded by an adhesive overlay that affixes the patch to the skin.

Drug Reservior - A liquid drug compartment containing a drug solution or suspension is separated from the adhesive layer by a diffusion-controlling membrane.

While transdermal patches offer many advantages, passive systems are restricted to low-dosage lipophilic and low molecular-weight molecules (< 500 Daltons).[3] To extend the application of diffusion systems, pharmaceutical companies developed chemical enhancers that alter the permeability of the stratum corneum layer of the skin for the delivery of higher weight molecules. Penetration enhancers may include chemicals, such as ethanol, propylene glycol, oleic acid, azone, terpenes, and bile acids.[4] Adhesive manufacturers responded by developing "enhancer-tolerant" adhesive formulations that maintain their PSA properties when exposed to chemical enhancers. What this means is that the use of enhancers slightly broadens the range of drugs that can be delivered through passive systems.

Much of the current growth for transdermal drug delivery is focused on active systems to deliver a wider range of drug molecules, including proteins such as vaccines. Targeted drug delivery applications for sites beyond traditional skin delivery, such as ocular treatments, are another exciting area of development that can further benefit from TDDS adhesive technology and polymer coatings.

CHALLENGES OF FORMULATING ADHESIVES FOR TDDS

As the scope for transdermal drug delivery capability widens, the performance expectations of related materials are also raised. Pharmaceutical-grade PSAs offer functionality in addition to simply good skin adhesion. Some examples of PSAs with added functionality are evident in electrically conductive and porous PSAs, hydrogels, and molecularly imprinted polymers. The science of formulating adhesives for transdermals is a careful balance of delivering functionality in a safe, compatible format to the device's other components. Today's adhesives are highly specialized chemistries that overcome a number of specific challenges to deliver precise performance for each application. A number of these challenges are discussed in detail below.

Drug Compatibility

Compatibility of the API or compound with the adhesive chemistry is one of the most significant obstacles to be overcome in formulating adhesives for TDDS. For example, acrylate-based adhesives are widely used in TDDS for their skin-friendly bonding characteristics but may absorb up to 5% moisture from skin, which could potentially affect drug bioavailability. Because pH changes can affect iontophoretic drug delivery[5], acrylate-based adhesives must be free of residual acrylic acid monomer to avoid reaction with the active drug or device components. To address challenges like these, adhesive manufacturers must consider formulations that are free of acrylic acid monomer while taking precautions to ensure that the adhesive's pH is neutral. Also, any residual monomers or leachable components must be removed. Compatibility can change as components age, so accelerated and real-time aging studies are needed to ensure that the adhesive properties and drug bioavailability are maintained during the shelf-life of the drug delivery device. If the delivery device requires sterilization, it is necessary to ensure that the adhesive will withstand the sterilization dosage and procedure while maintaining its adhesive properties and compatibility with the API.

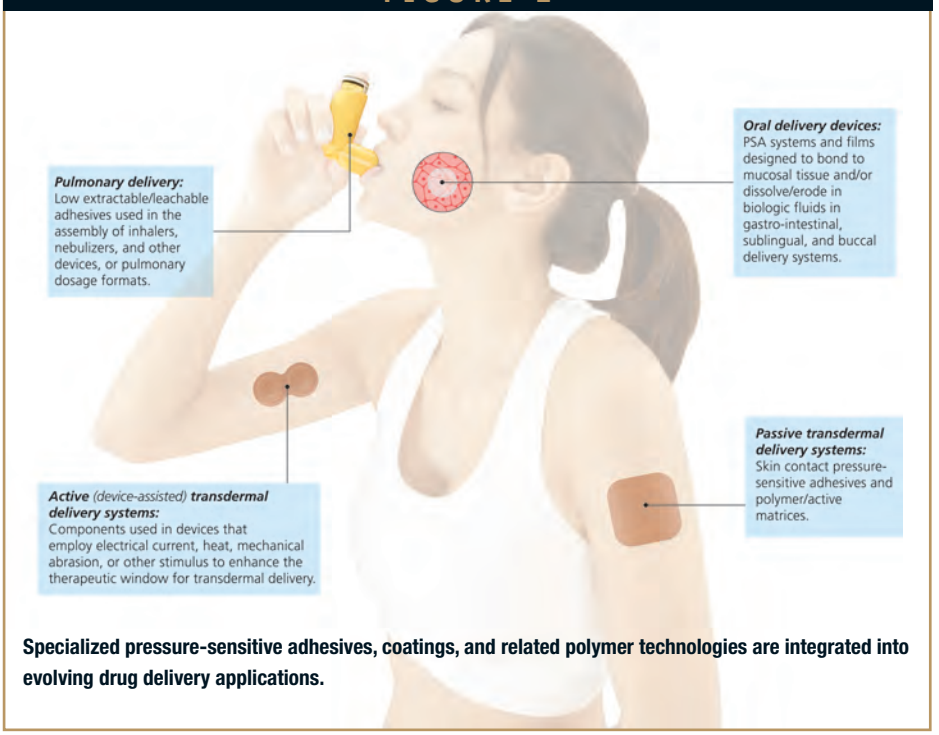
Moisture Maintenance

The majority of transdermal patches available today are removed within 24 hours; however, extended-wear patches can be envisioned for time periods of 7 to 10 days. To ensure a healthy skin environment for proper dosing, it is important that the adhesives selected for longer-term wear enable the skin to breathe to prevent over-hydration or skin maceration, which can potentially affect drug bioavailability.

Adhesion & Sealing

Good adhesion performance is paramount

FIGURE 2



Specialized pressure-sensitive adhesives, coatings, and related polymer technologies are integrated into evolving drug delivery applications.

for preventing patch movement or shifting during the dosing period and even more so for treatments requiring a skin preparation step prior to applying the patch. A number of factors can impact adhesive performance, so the formulation must ensure the following:

- the patch comfortably conforms to a number of application sites, so all component materials must be flexible to prevent pulling the patch away from the skin;
- the correct product geometry is used; because shape can potentially contribute to uplifting patch edges, rounded shapes are preferred;
- the product maintains proper adhesion during movement and exposure to moisture from sweating, showering, or swimming as most patches are worn by active, ambulatory patients; and
- the protective adhesive film overlays used to seal active compounds or highly sensitive electronic components prevent any moisture exposure that could potentially affect bioavailability and device performance.

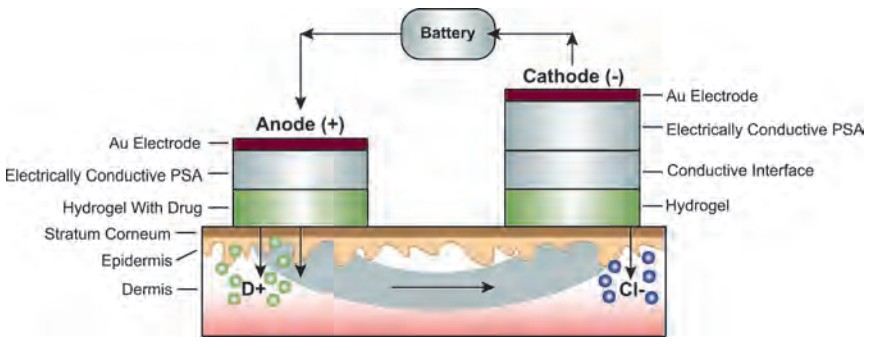
Adhesion Versus Removability

One of the primary uses of adhesives in TDDS is to effectively hold the patch or device securely in place on the patient's skin so the patch that conveys the drug makes constant contact for the desired dosing timeframe. Ease of removal following treatment is typically a secondary concern, but is gaining attention as TDDS developers consider the special needs of different skin types. Adhesives that are designed for ease of removal are formulated to be softer, or more gel-like, than other forms. This is accomplished by forming polymer chains that are mobile and can stretch. The challenge then becomes maintaining a balance between secure skin adhesion and low-trauma removal while eliminating any possible negative impact upon drug flux through the adhesive.

Thickness Control

Adhesive and substrate thickness control from lot to lot is crucial for applications in which any thickness variations can negatively impact dosing. For example, some microprojection designs involve an array of drug-treated microneedles (solid metal, hollow metal, or polymer needles) that are adhered to the skin with a PSA. The combined thickness of the device's components controls how deeply the microneedles penetrate the skin to release the drug into the bloodstream or lymphatic system. If penetration is too shallow, the user may not receive the proper dose; alternatively, if the needles penetrate too deeply, the user could experience some discomfort or pain.

FIGURE 3



In iontophoretic patches, electrically conductive pressure-sensitive adhesives transmit an electric current through layers of the device while bonding electrical components within the patch.

EVOLUTION OF TDDS TECHNOLOGY IN FORM & FUNCTION

As transdermal product designs and capabilities continue to evolve, adhesive manufacturers are embracing opportunities to formulate highly specialized PSAs, coatings, and related polymer technologies to meet the requirements of these delivery systems.

Needle-Free Delivery of Vaccines

Needle-free delivery of therapeutics and vaccines can potentially address the growing global issues associated with diseases that are passed intravenously through the improper use and disposal of needles. Patch-based needle-free immunization systems for the safe and convenient delivery of vaccines are currently in clinical trials.[6] The construction of the vaccine patch is similar to that of a transdermal patch, but contains an antigen and an immune-boosting adjuvant to stimulate the body's immune system. The patch works by delivering the vaccine to a group of antigen-presenting cells in the skin called Langerhans cells, which transport the vaccine to nearby lymph nodes to produce a sustained immune response.

When considering adhesive and component materials for this type of delivery system, formulators must assure the proper chemical compatibility of these materials with the device's proteins and active ingredients. Device component materials cannot contain any biocides or toxic leachables that could potentially denature proteins or interfere with biological activities or targeted immunization response. Skin-contact adhesives should demonstrate good wear properties and moisture control to prevent lateral movement of the vaccine, which could alter dosage and decrease device efficacy.

Iontophoretic Drug Delivery

PSAs perform multiple functions in iontophoretic drug delivery systems, such as bonding to the skin, creating a protective seal, and forming conductive bonds for internal electronic component assemblies.

Iontophoretic devices offer a non-invasive alternative for delivering therapeutic substances

via the electro-transport of molecules that would not normally diffuse across the skin. A small electric current passes through the patient's skin, between positively and negatively charged electrodes. The drug or active substance is located at one of the electrode sites, depending upon the drug's polarity. The active electrode repels the charged drug, forcing it into the skin by electro-repulsion, where it is picked up by the blood or lymphatic system. Charged drug molecules are attracted to electrodes of the opposite polarity. The rate of drug delivery is controlled by the strength of the electrical current to transport the drug rapidly and accurately, via on-demand dosing or patterned/modulated drug delivery.[7]

Iontophoretic patches benefit from customized electrically conductive and skin-contact adhesive components. Electrically conductive PSAs transmit the current through layers of the device while bonding electrical components within the patch. In some versions of these devices, the electrically conductive layer may contain conductive fillers to lower the resistance of the interface and to form electrical connections. A PSA membrane overlay may be used to adhere the patch to the user's skin while bonding and protecting components within the device's housing. It is important to ensure that this PSA is compatible with the drug, bonds without interfering with the electrical charge of the drug compounds, and facilitates bioavailability.

Novel Coating Technologies for Drug Delivery

A number of the technologies that have been perfected for TDDS throughout the past 20 years form the basis of a natural evolution into other novel forms for delivering APIs. ARx, LLC is one company leveraging the polymer chemistry and coating techniques used in TDDS in the form of custom-developed dissolvable films and adhesive platforms for oral drug delivery, transdermal drug delivery, and biopharmaceuticals.

Dissolvable oral thin films (OTFs) are a proven technology for the systematic delivery of APIs to patients for OTC medications and are in the clinical stages for prescription drugs. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices.[8]

A number of the film's physical formats can be customized, including dissolution rates, thickness, material composition, taste-masking, and API absorption rates to broaden its potential for application into other areas, including the following:[9]

Topical Applications - Films can deliver active agents, such as analgesics or antimicrobial ingredients for wound care or other applications.

Binding Agents - Dissolvable films are being considered in applications for enveloping active particles in multi-layer or combination systems to enable controlled release.

Buccal, Sublingual & Mucosal Delivery Systems - Layers of dissolvable films with tailored dissolution rates may be combined with bioadhesives for the controlled release of APIs over a period of minutes or hours.

Gastro-Retentive Dosage Systems - Water-soluble and poorly soluble molecules of different molecular weights can be contained in a film format to disintegrate at a specific pH or enzyme exposure within the gastrointestinal tract to treat GI disorders.[10]

ALTERNATIVE TREATMENT SITES

This is an exciting time for adhesive manufacturers as we leverage our knowledge of polymer chemistry and coating technologies for emerging formats for drug delivery. A number of novel systemic and topical delivery forms are in the research stage or clinical trials for targeted treatments to alternative delivery sites. Some examples follow.

The respiratory tract and nasal passages hold promise as alternative sites for drug delivery due to fast absorption and rapid onset of drug action. The inhalers and other devices for these drug delivery forms require inert, non-reactive components. Pharmaceutical-grade adhesives demonstrating low-extractable, low-leachable properties are ideally suited for assembling the drug cartridges tailored for pulmonary and nasal delivery formats.

Ocular treatments can potentially benefit from dissolvable film and TDDS adhesive technology. Ocular disease or wound

TABLE 1

ADHESIVE DESCRIPTION	CHEMISTRY	FUNCTIONAL PROPERTIES FOR DRUG DELIVERY
Skin-friendly PSAs	Acrylic, polyisobutylene, silicone, and hybrid chemistries	Tailored to bond in various skin types and environments for wear times ranging from minutes to days
Electrically & ionically conductive coatings	Acrylic and polyisobutylene chemistries	Polymer formulations that overcome traditional insulative properties of an adhesive to allow current or ion transport
Dissolvable films & erodable PSAs	Natural and synthetic polysaccharides, hydrophilic copolymers	Polymer coatings designed to erode at predetermined rates when in contact with biological fluids
Ethanol- & enhancer-tolerant coatings	Acrylate chemistry	PSAs that can withstand exposure to enhancer chemicals found in drug delivery systems
Ultra-clean & non-reactive adhesives	Acrylate chemistry	Chemically inert coatings that are compatible with APIs and excipients
Porous adhesives	Acrylic, rubber, polyurethane chemistries	Coated polymer systems with tailored pore size to allow controlled fluid transfer. Doping used to create biphasic formulations
Hydrogels & organogels	Hydrophilic polymers and copolymers	High-fluid content coatings that form an interface between the skin and sensing element in device-assisted delivery
Hybrid PSAs	Rubber/acrylic graft	Polymer matrix that offers high tack and chemical stability
Molecularly imprinted polymers	Acrylate chemistry	Synthetic polymers for the capture and release of target APIs or other chemical moieties

Advanced Adhesives & Polymer Coatings for Drug Delivery Systems

treatments many times require an API to be maintained at the treatment site for a period of time to ensure good bioavailability. Given the eye's natural tendency to wash away foreign substances and the low impermeability of the cornea to hydrophilic molecules, the effectiveness of ocular treatments can be challenging.[11] Surface-contact films or tacky polymer "patches," similar to the adhesive and polymer technology used in transmucosal or buccal drug delivery systems, can be considered for sustained delivery of ocular drugs. One example might be a dissolvable film loaded with APIs that is formulated to also demonstrate PSA characteristics that safely adhere to the eye surface. Following the treatment duration, the film would dissipate completely or be gently removed.

Another example of a localized alternative site for drug delivery can be found in developmental nail patches, which would be used to treat chronic, highly resistant fungal infections of human nails. Topical delivery is preferred over systemic treatments because it doesn't cause adverse effects; however, topical treatments are limited in their ability to penetrate the nail to also treat the underlying perionychium.[12] A medicated nail patch with an API- and enhancer-loaded PSA matrix layer that would cover the entire nail and treatment site for an extended period of time may offer an improved treatment regimen.[13] The concept of a nail patch can be applied to other treatments, such as strengthening agents or novel consumer applications of cosmetics for nails or skin.

SUMMARY

It is clear that pharmaceutical-grade adhesive technologies that were originally formulated for passive TDDS have evolved into highly specialized adhesives and coated polymers that add functionality to the next generation of drug delivery platforms. Versatile in their chemistry and form, PSAs are a critical component in achieving intended outcomes, such as sustained skin adhesion, component bonding, electrical component bonding and assembly, moisture seals, and drug envelopment. To overcome a number of technical challenges, base adhesive technologies are customized to each unique application to ensure accurate and sustained drug delivery. As pharmaceutical product developers explore new methods for delivering a wider range of drugs and biopharmaceuticals, PSA manufacturers like Adhesives Research will continue to push the capabilities of our technology to meet the unique challenges of new and emerging applications.

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BIOGRAPHY

Dr. William Meathrel is a Senior Research Scientist at Adhesives Research. With over 30 years of experience in Product Development and Applied Research, his career has focused on Polymers, Adhesives, and Coatings, and he has secured numerous patents for his work. He holds three degrees form the University of Toronto, including a PhD in Organic Chemistry, an MS in Biological Chemistry, and a BS in Chemistry. He also has a diploma in Chemical Engineering from the Ryerson Polytechnic University. He can be reached at bmeathrel@arglobal.com or (717) 227-3460.

OSMOTIC TABLETS

Design & Development of Novel Osmotic Tablets for Glipizide Controlled Delivery

By: Jayvadan Patel, PhD; Mukesh Patel, PhD; and Jayant Chavda, PhD

ABSTRACT

The purpose of this study was to develop a new squeeze-type osmotic tablet (SQT) to completely deliver glipizide, a Biopharmaceutics Classification System (BCS) Class II drug, in a zero-order manner over an extended period. Osmotic delivery systems are based on an osmotic-deriving force. Glucotrol XL®, the tablet dosage form of glipizide, was commercialized with an elemental push-pull osmotic pump (PPOP) drug delivery system that operates successfully in delivering water-insoluble drugs. To improve the release pattern and solubility of the drug, an SQT was developed for glipizide. The SQT was composed of one or more ring-type of squeeze-push layers (squeeze-discs) and a centered drug core. Squeeze-discs were characterized by different physicochemical properties. With the objective of delivering water-insoluble glipizide at an approximate zero-order rate and step-function rate for 24 hours, SQTs were successfully prepared with significantly improved release rates, and in vitro release patterns were compared with Glucotrol XL's push-pull system. Linear and reproducible release similar to that of Glucotrol XL was achieved for the optimized SQT formulation with $f_2 > 50$.

INTRODUCTION

Osmotic delivery systems for the administration of drugs in a fluid environment release drug by utilizing osmotic pressure as the driving force. Such osmotic delivery systems are based on osmosis, the diffusion of water through a semi-permeable membrane from a medium with low osmotic pressure to a medium with high osmotic pressure. Osmotic drug delivery formulations have been used as inserted systems as well as oral tablet formulations.[1-6] Drug release from these systems is not influenced by pH and vermicular movement within the gut lumen; and the release characteristics by optimizing the properties of drug and system can be predicted easily from the known properties of the drug and the dosage form.[7] There have been widespread descriptions of osmotic delivery systems, such as the elemental osmotic pump (EOP), the two-layer push-pull osmotic tablet system, the monolithic osmotic tablet system, and the sandwiched osmotic tablet system.[8-12] In addition, numerous patents on and examples of osmotic tablet systems have been reviewed.[13,14]

The EOP consists of an osmotic core incorporating the drug, which is surrounded by a semi-permeable membrane with a delivery orifice. In operation, the osmotic core imbibes water from the surrounding medium via the semi-permeable membrane. Subsequently, a drug solution is generated within the device and delivered out of the device via the orifice. This system is very simple in preparation and can deliver water-soluble drugs at a zero-order release rate.[5,8] However, this system is incompatible for delivering water-insoluble drugs.

The two-layer push-pull osmotic tablet system consists of two layers: the upper layer containing the drug and the lower layer containing an osmotic agent and an expandable agent. The drug compartment is linked to the outside environment via a delivery orifice. A semi-permeable membrane that regulates water influx into both layers surrounds the system. After the fluid imbibes into the

FIGURE 1

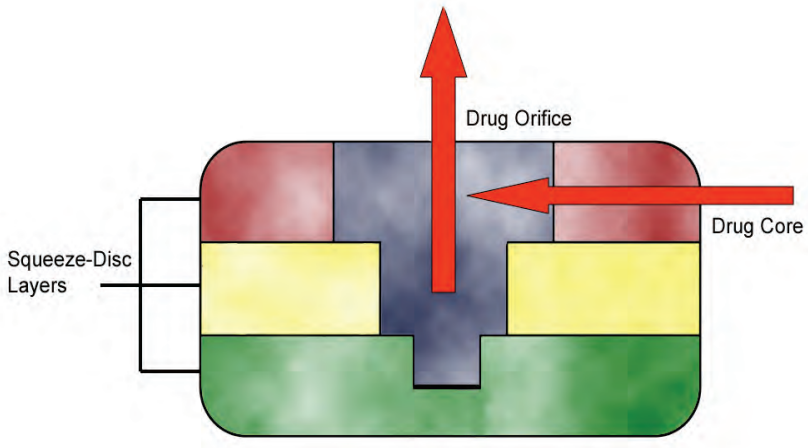


Illustration of Squeeze-Type Osmotic Tablet

device, the layer with the expandable agent swells and pushes the drug core.

Glipizide is a second-generation sulfonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat type II diabetes (non-insulin-dependent diabetes mellitus). Its short biological half-life (3.4 ± 0.7 hours) necessitates that it be administered in 2 or 3 doses of 2.5 to 10 mg per day.[15] Thus, the development of controlled-release dosage forms would clearly be advantageous. Researchers have formulated oral controlled-release products of glipizide using various techniques.[16-17] As stated previously, the tablet dosage form of glipizide (Glucotrol XL) is commercialized with an elemental PPOP drug delivery system that operates successfully in delivering water-insoluble drugs.[18]

Thus, the purpose of this work was to prepare and characterize novel squeeze-type osmotic tablets of glipizide, evaluate in vitro release rates of SQT and compare them with those of Glucotrol XL tablets, and investigate the effect of different preparation factors.

MATERIALS

Glipizide was obtained as a gift sample from (USV Ltd., Daman, India). Polyethyleneoxide (PEO, Aldrich Chem. Co., Inc., US), microcrystalline cellulose (Zydus Research Center, Ahmedabad, India), potassium chloride (S.D. Fine Chemicals Ltd., Mumbai, India), cellulose acetate (S.D. Fine Chemicals Ltd., Mumbai, India,), polyethylene glycol (Zydus Cadila, Ahmedabad, India), polyvinylpyrrolidone (Zydus Cadila, Ahmedabad, India), and polyvinylalcohol (Zydus Cadila, Ahmedabad, India) were used. The Glucotrol XL tablets (Pfizer) were purchased from the market.

METHODS

Tablet Preparation

The basic formulation of the SQTs' cores and the ratios of various excipients are listed in Table 1. The loading of glipizide was 10 mg, which is the same amount as the Glucotrol XL tablet. Each tablet core consisted of 175 mg of drug core and 180 mg of squeeze layers formulated as listed in Table 1. The influence of microcrystalline cellulose (MCC) was assumed to be minor; therefore, its amount was changeable to balance the weight of the squeeze-layer or drug core, which was fixed to 175 mg when the formulation was varied in trial, to maintain a relatively constant volume and surface area. The SQT was prepared via a lab press (Cadmach Csi 670, India) under a pressure of 25 or 50 kg/cm^2 using two concave punches with a 7.9-mm diameter (Figure 1). First, the powder of each squeeze layer formulation was pressed into a ring-type die cavity of the first punch using a pressure of 25 kg/cm^2 for 10 seconds. Second, the three layers of squeeze-discs were stacked in the die cavity of the second punch, and the powder of the drug core formulations was loaded in the remaining cavity among the squeeze-discs. Finally, the entire composition was pressed using a pressure of 50 kg/cm^2 for 10 seconds.

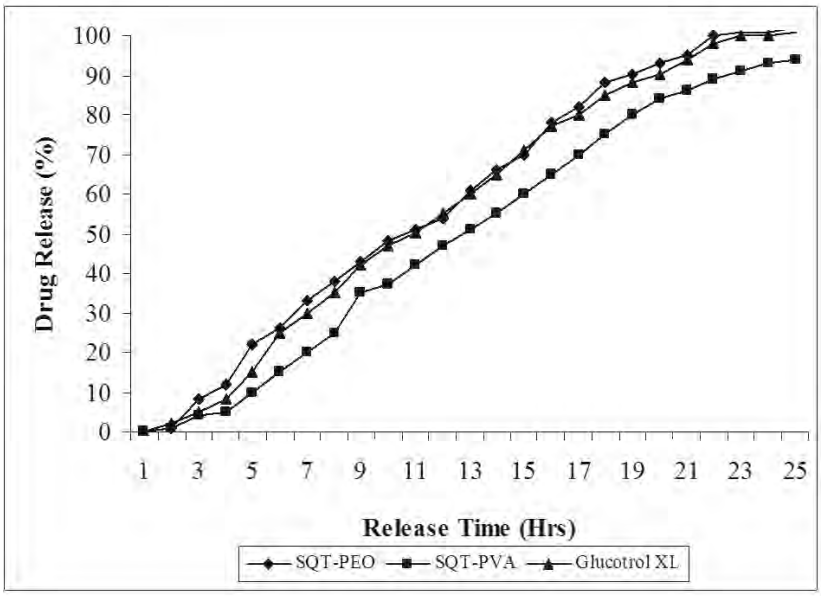
Coating of Tablets

Tablets were coated in a pan coater with a spray gun. The coating solution was composed of cellulose acetate (CA), polyethylene glycol, triacetin, and acetone. The coating conditions included (a) pan specification: stainless steel, spherical, and 150 mm in diameter; (b) pan rotating rate: 50 rpm; (c) spray rate: 2 ml/min; and (d) drying by a heat spray gun. After coating, the tablets were dried overnight in a vacuum oven of 50°C to remove residual solvent. One delivery orifice on the drug-layer surface of the tablet was drilled using a sharp needle (0.4 mm in diameter) for drug release.

Drug-Release Study

The drug-release study was carried out using a USP XXIV basket apparatus (Electrolab, TDT-06T, India) at 37°C ± 0.5°C and at 50 rpm using 250 ml of phosphate buffer (pH 7.4) as a dissolution medium (n = 5) as per the USP XXVI dissolution test prescribed for glipizide extended-release tablets.[19] SQTs of glipizide (10 mg) were used for the test. A 5-ml sample solution was withdrawn at predetermined time intervals, filtered through a 0.45-micrometer membrane filter, diluted suitably, and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately following withdrawal of the test sample. The percentage of drug dissolved at different time intervals was calculated using the Lambert-Beer's equation ($y = 0.1619x + 0.0139$, $R^2 = 0.993$). The percentage of drug release of SQT glipizide tablets and Glucotrol XL are shown in Figure 2.

FIGURE 2



Drug Release Profiles of SQT-PEO (-◆-), SQT-PVA (-■-), and Reference Product, Glucotrol XL (-▲-).

Comparison of Dissolution Profiles

The dissolution profiles of products were compared using a similarity factor (f_2). This similarity factor (see equation below) is a logarithmic reciprocal square root transformation of one plus the average mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products over all time points.

$$f_2 = 50 \times \log\{[\,1 + (1/n)\Sigma_t = \text{in } (R_t\text{-}T_t)2\,]\text{-}0.5 \times 100\}$$

Where n is the number of dissolution time points and R_t and T_t are the reference and test dissolution values at time t. Two dissolution profiles are considered similar when the f_2 value is 50 to 100. Comparison of drug release from the SQTs of glipizide and Glucotrol XL are shown in Figure 2.

RESULTS & DISCUSSION

Preparation & Formulation Design of SQTs

The SQTs were composed of a body having a ring-like configuration with one or more squeeze-push layers (squeeze-discs) and a centered drug core. The core material squeeze-disc was composed of three layers of mixtures of drug, osmotic agent, hydrophilic polymers, and excipients. The SQT core was composed of an equal weight ratio of drug core/squeeze layer at 175/180 mg. The basic formulation of SQT core and ratios of various chemicals are listed in Table 1. The SQTs were coated with the coating solution in a pan coater with specific coating conditions. The coating solution was composed of CA (a hydrophobic, water-insoluble material), polyethylene glycol (water-soluble materials), triacetin (plasticizer), and acetone (solvent). Finally, one orifice for drug release was drilled on a side surface of the drug core with the coated system. When the SQT came in contact with the aqueous environment, the drug core and the squeeze-push layer were imbibing water across the CA membrane, resulting in osmosis as the osmotic agents dissolves and increases the pressure inside the system. At the same time, the squeeze-push layer was squeezing, resulting in pushing the drug core and thereby delivering the drug via the delivery orifice on the drug core, depicting the total mechanism of drug delivery from this system. The squeeze-disc gradually acted on step function from the bottom disc to the top disc (Figure 1). Therefore, this system allows for the delivery of a water-insoluble drug, such as glipizide.

To investigate the influence of the amount and types of excipients on glipizide release, SQT systems with various formulations were prepared, subsequently coated with the basic formulation of coating solution and featuring a drilled orifice (0.4 mm in diameter).

TABLE 1

		Hydrophilic Polymer		KCl	MCC	Glipizide	Total
Squeeze-Disc Layer	Top	PEO (Mw: 8000 kg/mol)	30	20	10	-	60
	Middle	PEO (Mw: 900 kg/mol)	30	20	10	-	60
	Bottom	PEO (Mw: 100 kg/mol)	30	20	10	-	60
Drug Core		PEO (Mw: 900 kg/mol)	100	60	5	10	175
Total							355

Tablet formulation variables with various excipients (mg).

Effects of PEO-PVA Squeeze-Disc on Drug Release

To investigate the types of hydrophilic polymers of squeeze-discs on drug release, PEO and PVA were used. Squeeze-discs, according to the swelling efficiency of polymers in the order of PEO and PVA, were stacked from the bottom layer to the upper layer with a ratio of 1:1, 2:1, and 1:2. The results show that an increased amount of hydrophilic polymers induced more swelling and squeezing in the earlier stages, resulting in an increased initial release. It can be concluded that the designed release pattern for specific drug varied with hydrophilic polymers of squeeze-discs.

Effects of KCl Amount in PEO-PVA Squeeze-Disc on Drug Release

To investigate the effect of KCl on the glipizide-release profile, a varying amount of KCl was incorporated with the PEO and PVA hydrophilic polymer squeeze-discs. KCl formulated the higher concentration from the bottom layer to the upper layer with a ratio of 20:15:5 mg in each hydrophilic polymer squeeze-disc. The hypothesis was that higher concentrations of KCl would result in stronger expressions of osmotic power. This exhibited a zero-order release pattern.

Effects of Molecular Weights of PEO Squeeze-Disc on Drug Release

On the basis of the release behavior of the hydrophilic polymer squeeze-disc layers, the effect of molecular weights of hydrophilic polymer squeeze-discs had been investigated. Squeeze-disc layers were stacked 8000/900/100 kg/mole for PEO from the bottom disc to top disc (Figure 1). Release profiles of PEO with 8000/900/100 kg/mole improved the initial release rate and total release amount. Furthermore, it was found that the zero-order release pattern was similar to that Glucotrol XL.

In this work, it was found that the water permeability and viscosity of the formulation depends upon the molecular weight of PEO. As a consequence, the release rate increased as the

amount of PEO increased. Higher molecular weight PEO acted predominantly as a swelling and viscosity-increasing agent, maintaining the integrity of the dosage form. Several studies have been reported on this efficiency of PEO with respect to its molecular weight.[3] The optimal formulation for squeeze-disc was demonstrated by formulating squeeze layers composed of PEO of different molecular weights.

Optimal Tablet Formulation for PEO SQT

The SQT core consisted of an outer and midpoint drug core containing glipizide, KCl as the osmotic agent, MCC as a binder, and PEO as a thickening agent with a molecular weight of 900 kg/mole, and a squeeze-disc containing KC1 as an osmotic agent, MCC as a binder, and the expandable hydrogel PEO with a molecular weight of 8000, 900, and 100 kg/mole from the bottom disc to top disc, respectively.

Comparison of Dissolution Profiles

SQT formulation-release profiles and dissolution profiles obtained from the dissolution test of Glucotrol XL were compared using a model-independent, pair-wise approach of similarity factor f_2 and was found to be 75.84, which indicates a close similarity between the two dissolution profiles. Comparison of drug release from the SQT formulation and Glucotrol XL are shown in Figure 2.

CONCLUSIONS

Release patterns were affected by the selection of polymers, molecular weights of polymers, amount of polymer and KC1, coating process, and orifice size. It was observed that the SQTs' optimal hydrophilic polymer for each squeeze-disc layer was composed of different molecular weights of PEO and drug core. It has been found that PEO with a molecular weight of 900 kg/mole is suitable to be a thickening agent in the drug core, while PEO with a molecular weight of 8000, 900, and 100 kg/mole is suitable to be an expanding hydrogel in squeeze-disc layers from bottom layer to top layer, respectively. The weight ratio of drug core/squeeze-disc might be suitable at 175/180. It has been observed that the amount of PEO in the drug core and the amount of KCl in the squeeze-discs have a significantly positive effect on glipizide release. The drug release of this system was co-controlled by the squeeze-disc layer and drug core. With the purpose of delivering water-insoluble glipizide at an approximate zero-order rate and step-function rate for 24 hours, SQTs have been successfully prepared and compared with Glucotrol XL.

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BIOGRAPHIES

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Technology *Showcase*

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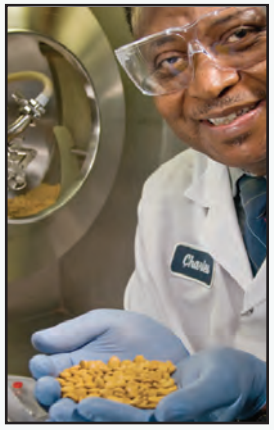

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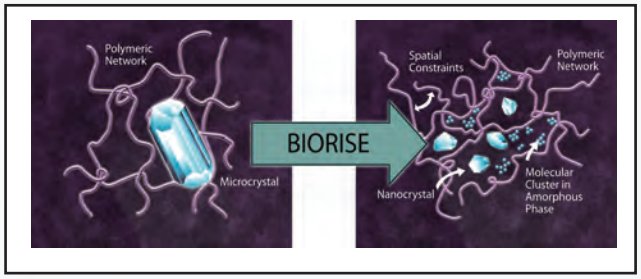
Technology *Showcase*

Bioavailability Enhancement



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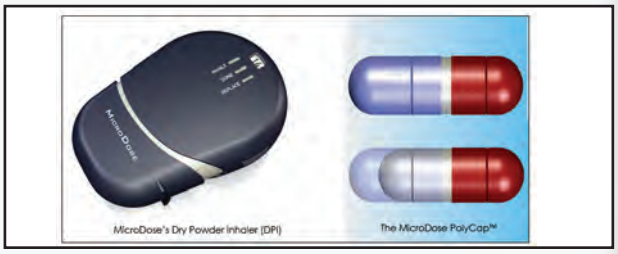

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Technology *Showcase*

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DRUG DELIVERY Executive

inovio BIOMEDICAL CORPORATION

INOVIO BIOMEDICAL: DELIVERING THE POTENTIAL OF DNA VACCINES

Avtar Dhillon, MD
President & CEO
Inovio Biomedical

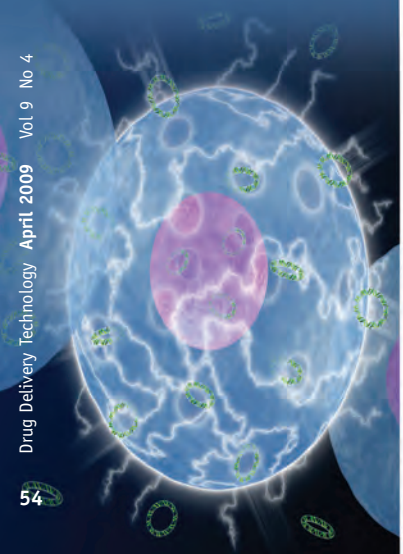
"I believe it is a matter of when (not if) electroporation-delivered DNA vaccines achieve clinically relevant breakthroughs and that Inovio and its partners have strong potential to be associated with such breakthroughs."

Inovio Biomedical (NYSE Alternext: INO) is focused on developing a new generation of preventive and therapeutic vaccines - DNA vaccines - with the potential to address cancers and chronic infectious diseases, such as HIV and hepatitis C virus. Using its novel electroporation-based delivery technology, which uses brief, controlled electrical pulses to significantly increase cellular uptake of useful biopharmaceuticals, initial human data has shown safety, tolerability, and significantly increased gene expression and immune responses from DNA vaccines. Inovio is working with organizations such as Merck, University of Southampton, US Army, National Cancer Institute, and International Aids Vaccine Initiative, and has recently entered into a definitive merger agreement with VGX Pharmaceuticals, a leader in DNA vaccine development with a pipeline that includes candidates for HIV, HPV, and influenza. Drug Delivery Technology interviewed Avtar Dhillon, MD, President and CEO of Inovio Biomedical, to discuss his company's unique technology and its role in the next generation of vaccines.

Q: You mention cancers and infectious diseases as potential targets of your technology, which is a broad focus. Tell us about DNA vaccines.

A: To provide some background, conventional vaccines have been among the most important medical advancements ever developed, protecting millions of people from debilitating disease effects and significantly improving human survival. The concept of enhancing the body's immune system to fight diseases remains a powerful one, and today, scientists are working to develop a new generation of vaccines with the potential to provide not only preventive but also therapeutic benefits against cancers and chronic infectious diseases, such as HIV and hepatitis C virus. This next generation of vaccines is DNA vaccines.

DNA vaccines offer a number of potential



safety and efficacy advantages over conventional vaccines that may enable them to address the challenges of cancers and chronic infectious diseases without good treatments. While conventional vaccines primarily induce an antibody response, which can be effective for eliminating viruses or bacteria that have just entered the body, DNA vaccines are also able to induce a T-cell response, which is required to kill infected cells. In addition, DNA vaccines cannot replicate and infect the patient with the disease they are intended to protect against, which can be an issue with certain conventional vaccines. They are also readily designed and manufactured, and may potentially move from design to market approval in a much shorter time frame.

Q: What is the status of DNA vaccine development?

A: Under the broad umbrella of immunotherapies, there have been many recent breakthroughs that provide validation of the potential to develop powerful new ways of stimulating the immune system. Gardasil, for cervical cancer, is one example.

With respect to DNA vaccine development, significant resources applied by many companies and academic or governmental organizations throughout the past decade and a half have achieved compelling preclinical data. Yet, the advancement of promising candidates into the clinic has been met with repeated failures. One of the roadblocks appears to be an unwavering commitment by many scientists to the use of viral vectors, which uses a genetically modified virus to carry the vaccine into cells of the body. These vectors have been recognized as inducing unwanted immune responses and in some cases, toxicity that has led to patient death. Repeated failures or weak results from virus-based DNA vaccines have motivated some scientists to seek alternative methods of delivering DNA vaccines into humans, and this is where Inovio has made tremendous progress.

Q: Tell us a little more about Inovio and its current focus.

A: Inovio has for over 25 years been focused on the use of electroporation to enable the delivery of genes and useful biopharmaceuticals. The phenomenon of electroporation, which was discovered in the 70s, enables drug delivery by locally applying brief, controlled electrical fields to tissue such as muscle or skin, and in doing so, creating temporary, reversible permeability in the membrane of cells in that local area, enabling significantly increased uptake of an injected biologic material without unwanted immune responses found with viral vectors.

In the past decade, Inovio and its partners have made significant strides in validating the utility of electroporation to enable DNA vaccines. Interim human results from studies led by University of Southampton (prostate cancer), Moffitt Cancer Center (metastatic melanoma), Vical (metastatic melanoma), and Tripep (hepatitis C virus) have indicated safety, tolerability, and heightened immune responses. In the studies that have already reported clinical responses, we have observed partial and complete responses of both treated and untreated melanoma lesions, suggesting a systemic effect, as well as a viral load reduction of up to 99% for hepatitis C virus. A detailed description of our electroporation technology and results was published in *Drug Delivery Technology's*

January 2009 issue.

We are enthusiastic about the results and potential of our technology. DNA vaccines are an elegant approach - rather than using a killed or attenuated form of a virus, bacteria, or a subunit of these organisms to place a particular antigen into the body, you are using a readily manufactured fragment of DNA that is coded to produce only the desired antigenic protein. From what we have observed to date, the use of electroporation to deliver a DNA vaccine does not create unwanted immune responses nor does it leave residual material that might create toxicity.

What it does accomplish, based on preclinical results in large animals, is to produce substantially heightened antibody AND T-cell responses that have been capable of providing protection against multiple diseases. These results justified the initiation of multiple human studies, and we are optimistic that encouraging interim clinical results we have already obtained will be expanded with additional positive data that can guide us in tweaking the antigens and other aspects of the therapy we use against each respective disease. I believe it is a matter of when (not if) electroporation-delivered DNA vaccines achieve clinically relevant breakthroughs and that Inovio and its partners have strong potential to be associated with such breakthroughs.

Q: What sort of intellectual property is it possible to secure in this field and what IP does Inovio possess?

A: Many important gene sequences useful for vaccine development are in the public domain or will be in the next few years, thus product protection/monopolization based just on native gene sequences is limited. However, patents can be granted and product protection obtained for public domain gene sequences used in combination with a proprietary delivery method, such as electroporation, or for unique, synthetically derived gene sequences, a new area of focus that we expect to become involved in shortly (see reference to VGX merger and SynCon™ technology further on).

Inovio is a leader in the advancement of electroporation-based DNA delivery and has built a patent estate that has been subjected to intense due diligence by companies such as Merck and Wyeth, which both subsequently concluded license agreements with us. Our patents provide comprehensive coverage for electroporation methods and conditions used to deliver DNA vaccines and other biopharmaceuticals in humans and animals.

Fundamental to the use of electroporation is a device to deliver the electrical pulses. We have excellent engineering capabilities and have designed and manufactured multiple generations of devices to deliver the vaccine and electrical fields, with each generation further enhancing utility of the devices.

Q: What type of business strategy/model are you employing?

A: Inovio's growth plan has consisted of collaborations, in-house development, and expansion of IP and opportunities through licenses and acquisitions. Inovio has been able to secure partnerships and collaborations with leaders in DNA vaccine research, including Merck, Wyeth, Vical, Tripep, University of Southampton, Moffitt Cancer Center, the US Army, National Cancer Institute, and International Aids Vaccine Initiative. These

partners have covered nearly all the costs of preclinical research and clinical development relating to their agents in combination with our electroporation technology.

More recently, we embarked on the development of proprietary vaccines and, to advance this process, also announced last year a proposed merger with VGX Pharmaceuticals. VGX was co-founded by MIT and Wharton grad, Dr. Joseph Kim, and Dr. David Weiner, a University of Pennsylvania professor widely considered to be a pioneer of DNA vaccines. VGX has a proprietary development platform, called SynCon, which enables the identification and creation of synthetic "consensus genes" among multiple strains of a virus, providing the potential to develop a single vaccine against viruses that evolve, such as HIV, and creating the prospect for a universal influenza vaccine that can address shifting seasonal AND pandemic flu viruses without having to develop new vaccines on a yearly basis. VGX currently has in the clinic vaccine candidates for HIV and cervical cancer (therapeutic, as opposed to preventive, which is Gardasil's focus), and has an IND for an avian influenza candidate under review. Last fall, the NIAID division of the NIH granted VGX $23.5 million to advance research for a proprietary HIV DNA vaccine candidate.

We believe this merger, which we expect to be completed by mid-year, will position Inovio Biomedical as a strong force in DNA vaccine development and are optimistic that we may be involved in vital breakthroughs for the field. We anticipate new data from multiple studies before the end of 2009 and expect that this data may provide important new validating results.

Because our Phase I studies are treating patients with disease, we obtain pertinent data beyond just safety data. With immunogenicity and preliminary clinical response data from some of these studies, some of these programs may be licensable after Phase I. Our preference is to advance promising agents through Phase II. There are examples of compelling DNA vaccine data from just 20 patients facilitating multi-hundred million dollar license agreements with double-digit royalties. Our goal is to achieve similar types of deals.

Q: Looking ahead 5 to 10 years, what impact do you see your technology having in medicine?

A: We are focused on what is clearly a broad set of challenging diseases. If we can achieve the final validation of electroporation-delivered DNA vaccines that is suggested by preclinical data and preliminary human data, then the development and delivery platforms via the combination of Inovio with VGX (presuming that the merger is consummated) will place the company in an enviable position to target multiple multi-billion dollar markets and potentially create tremendous incremental shareholder value with the application of a relatively nominal amount of capital. If we can achieve this outcome, we would we able to provide significant treatment benefits for millions of people with a range of cancers or chronic infectious diseases, such as HIV, HPV, HCV, HSV, and influenza. To achieve breakthroughs for any one of these diseases would be a profound accomplishment. ◆

COLON-SPECIFIC DELIVERY

Colon-Specific Delivery: Histomorphological Analysis & Targeted Prodrug Approach

By: Anil K. Philip, PhD

ABSTRACT

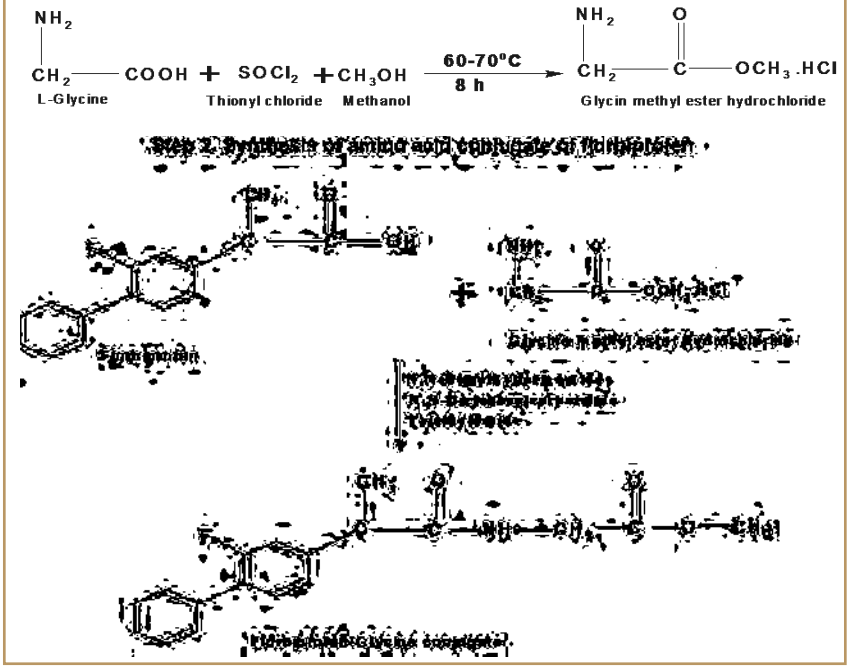
In the present study, a carboxylic group of propionic acid derivative (flurbiprofen/FLU), responsible for gastric side effects, was masked temporarily to not only overcome the side effects but also accomplish colon-specific delivery for the drug. Amide prodrug (FLU-GLY) was synthesized by coupling FLU with L-glycine. The synthesized prodrug's structure confirmation and characterization included elemental analysis, FT-NMR, Mass (FAB) spectroscopy, and Rt and RM value determination. In vitro reversion of FLU-GLY to FLU was done at different pH and in colonic environment. In vivo evaluation for acute toxicity and ulceration potential was done in albino rats. In vitro reversion suggested prodrug to remain intact until colonic pH was attained, where the colonic microfloral enzymes hydrolyzed FLU-GLY amide linkage, releasing the free drug. In vivo evaluation, indicated prodrug to have much lower toxicity and ulcerogenic activity as compared to the parent drug. By forming the prodrug of FLU, the adverse effects of the drug can be overcome and targeted delivery to the colon can be achieved. Thus, selective drug delivery to the colon can be more therapeutically effective in terms of reduced dose and reduced undesirable side effects.

INTRODUCTION

Inflammatory bowel disease (IBD), which comprises Crohn's disease and ulcerative colitis, is characterized by relapsing and remitting episodes of active inflammation and chronic mucosal injury.[1] Currently, no curative therapeutic agents are available, and IBD treatment relies heavily on nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, and immunomodulators. The primary goal of the drug therapy for IBD is to reduce inflammation in the colon that requires frequent intake of anti-inflammatory drugs at higher doses, which may lead to gastric ulceration, bleeding, and other gastric complications.[2] One study suggests that the direct tissue contact of NSAIDS plays an important role in the production of gastrointestinal tract (GIT) lesions, confirming that gastric side effects are due to the presence of carboxylic group in the parent drug moiety.[3] NSAIDs containing carboxylic group gets poorly absorbed from GIT due to unfavorable physiochemical properties. Therefore, out of the need to overcome this barrier of GIT, colon-specific drug delivery (CSDD) has evolved as an

FIGURE 1

Step 1. Synthesis of L-glycine methyl ester hydrochloride



ideal delivery system for the topical treatment of disease of colon-like IBD, colorectal cancer, and amebiosis. To achieve successful colonic drug delivery, a drug needs to be chemically and biochemically stable and non absorbable in the upper intestine and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs.[4] A CSDD system through colon-specific prodrug activation may be accomplished by the utilization of high activity of certain enzymes at the target site, relative to non-target tissues for prodrug to drug conversion. The amino acid glycine was chosen as the promoiety because it has broad spectrum anti-inflammatory, cytoprotective, and immunomodulatory properties, so it is also expected to potentiate FLU activity.[5] Being a natural component in the body, it would be non-toxic and free from side effects. To reduce the gastric side effects of FLU, structural modification with an amide or ester has to be carried out to mask carboxylic group temporarily. A strategic group attached to mask carboxylic group will protect the vulnerable group and stabilize the molecule as well as direct the drug to its target site.

The aim of this study was to synthesize a prodrug of propionic acid derivative (NSAID FLU), using glycine as a promoiety. The FLU-GLY conjugate was synthesized, characterized, and evaluated for in vitro kinetic studies. The synthesized compound was also evaluated for its ulcerogenic and acute toxicity effects in albino rats and compared with FLU.

MATERIALS

FLU was obtained as a gift sample from Elcon Drugs Pvt. Ltd., Gurgaon, Hariyana, India. L-glycine was commercially obtained from Merck (India) Ltd., Bombay, India. Thionylchloride and N,N-dicyclohexylcarbodiimide were commercially obtained from Spectrochem Pvt. Ltd., Mumbai, India. Diethylether, methanol, N,N-dimethylformamide were obtained from Qualikems Fine Chemicals Pvt. Ltd., New Delhi, India. Triethylamine and n-butanol were purchased from Qualigens Fine Chemicals, Mumbai, India. HPLC-grade acetonitrile, methanol and water, sodium sulphate (anhydrous), sodium bicarbonate, and chloroform were commercially obtained from Ranbaxy Fine Chemicals Ltd., New Delhi, India. Distilled water was used throughout the study. All other materials used were of analytical grade, and those of synthetic grade were purified prior to use. Albino rats were purchased from Central Drug Research Institute, Lucknow, Uttar Pradesh, India, and housed in the animal house, Department of Pharmacology, Rajiv Academy for Pharmacy, Mathura, Uttar Pradesh, India.

METHODS

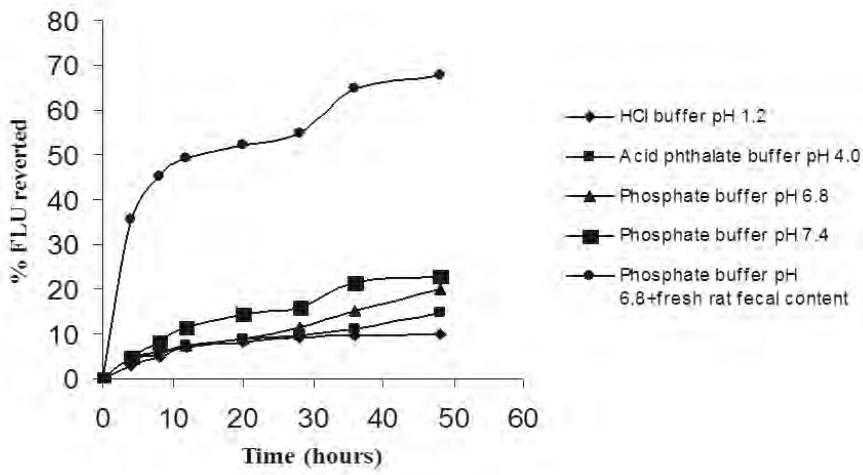
Synthesis of Amino Acid Conjugate of Flurbiprofen

FLU-GLY was synthesized via the following two-step reaction (Figure1):

1. SYNTHESIS OF L-GLYCINE METHYL ESTER HYDROCHLORIDE - Freshly distilled thionylchloride (0.1 mole) was slowly added to methanol (300 ml) with cooling, and L- Glycine (0.2 mole) was added to it. The mixture was refluxed for 10 hours at 60°C to 70°C with continuous stirring on a magnetic stirrer. The solvent was distilled at 64°C to 65°C, and the resulting product was collected and triturated with cold diethyl ether (50 ml), to remove the excess amount of dimethyl sulphite. The obtained crude product was recrystallized with hot methanol by adding diethyl ether (20 to 25 ml) followed by cooling at 0°C.[6]

2. SYNTHESIS OF AMINO ACID CONJUGATES OF FLURBIPROFEN - 20-mmole drug was dissolved in 60 ml N,N-dimethylformamide (DMF) in a conical A-flask, and 20-mmole N-N-diclohexylcorbodiimide (DCC) was added with continuous stirring. 20 mmole of methyl ester hydrochloride of L-Glycine was dissolved in 60-ml DMF in a conical B-flask, and 42 mmole triethylamine was added at 0°C. The contents of the A-flask were added into flask B, and after stirring for 15 minutes

FIGURE 2



In Vitro Reversion Profile of FLU-GLY at Different pH and in the Colonic Environment

on a magnetic stirrer, the mixture was filtered, and an equal volume of distilled water was added to the filtrate followed by extraction of the drug with ether. In the ether layer, 10 to 15 g of sodium sulphate (anhydrous) was added, and the crude product was recrystallized with methanol.

Elemental Analysis & MASS FAB Spectroscopy of FLU & FLU-GLY

The elemental analysis and mass spectrum of FLU (C,H,O) and FLU-GLY (C,H,N,O) to prove the exact mass or m/z ratio were carried out on elemental analyzer Elementer Vario ELIII, Carlo Erba 1108, and Jeol SX 102/DA-6000 mass spectrometer, respectively, at Central Drug Research Institute (CDRI), Lucknow, Uttar Pradesh, India.

FT-NMR Spectroscopy

To determine the nature of proton or protonated group in the FLU and FLU-GLY, the ^{1}H NMR spectrum in $CDCl_3$ were recorded on a Jeol AL 300, FT-NMR spectrometer, 300 MHz, using TMS as the internal standard. Chemical shifts (δ) were recorded in ppm.

High Performance Liquid Chromatographic (HPLC)

HPLC analysis was carried out on an Adept CECIL (CE-4201). The chromatographic column used was a C_{18} reverse phase column (dimension = 250 x 4.6, particle size = 5 microns). Acetonitrile:methanol:water (2:1:2) was used as the mobile phase. Sampling was done by microliter syringe. The flow rate was monitored at 1 ml/min and was detected by a UV detector set at 247 nm.[7]

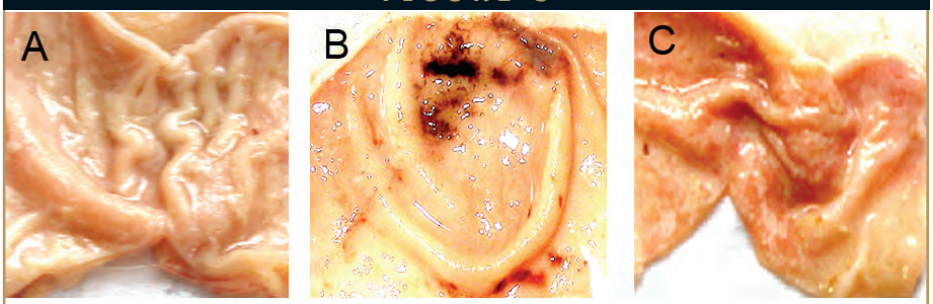
R_M Value Determination

R_M value was determined by reversed phase TLC. Silica gel GF_{254} TLC plates were soaked for 5 hours in acetone containing 3% n-octanol and left to dry overnight.[8] Sample spots of 5 microliters of compound solution were loaded at 1.5-cm intervals. The compounds were allowed to develop via an ascending technique in a chromatographic chamber under conditions of equilibrium using a mobile phase of methanol:water:chloroform (14:5:1 v/v). The plates were dried, and the developed spots were localized under ultraviolet fluorescence cabinet at a short wave length (254 nm). The R_f values were determined for the compound as the average of three readings, and the corresponding R_M values were calculated using the following equation: $R_M = \log (1/R_f - 1)$.[1]

In Vitro Reversion Study of FLU-GLY to FLU at Different pH in Colonic Environment

The reversion of the FLU-GLY was studied in HCl buffer pH 1.2, phthalate buffer pH 4.0, phosphate buffer pH 6.8 and 7.4, and phosphate buffer pH 6.8 containing fresh rat fecal content (20% w/v) to mimic the colonic environment at 37°C ± 0.5°C. The ionic strength (0.5 microns) was maintained constant for each buffer by adjusting with a calculated amount of potassium chloride.[9] The FLU-GLY conjugate was dissolved in sufficient volume of buffer so that final concentration of the solution was 1000 micrograms/ml; one ml of the prodrug solution was taken into glass vials and diluted to 10 ml with the buffer to have a concentration of 100 micrograms/ml. The vials were kept in a water bath at 37°C ± 0.5°C for different time intervals. For

FIGURE 3



Stomach of Albino Rats for Ulcerogenic Activity
A: Control Group (1% w/v CMC)
B: Drug Group (1000 mg/kg)
C: Prodrug Group (1000 mg/kg)

TABLE 1

Animal Group	*Ulcer Index ± SD*
Control	2 ± 1
FLU	65.2 ± 4.6
FLU-GLY	15 ± 1.3

Ulcerogenic activity of control, FLU, and FLU-GLY

analysis, 5 ml of solution was withdrawn from the vials at different time intervals and shaken with equal amount of n-butanol to extract free FLU reverted from FLU-GLY. The concentration of FLU was directly estimated from the n-butanol layer on a Cecil 4200® HPLC system.

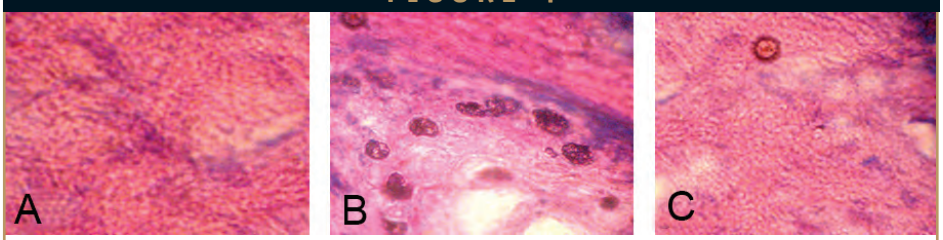
Ulcerogenicity Study

The ulcerogenic activity was determined via the Rainsford cold stress method, which is an acute study model and is used to determine ulcerogenic potency of a drug at 10 times higher dose.[10] Albino rats weighing 150 to 200 g were taken after prior approval by the institutional animal ethical committee (IAEC/RAP/1433/2007) and fasted overnight prior to administration of the compounds. Water was given at libitum. The animals were randomly distributed in control, drug, and prodrug groups of six animals each. The controlled group received 1% w/v Carboxy methyl cellulose (CMC) orally. The drug (FLU) and prodrug (FLU-GLY) were administered orally as fine particles suspended in 1% w/v CMC by continuous stirring. Following oral administration of 5 ml of the aqueous drug suspensions, the animals were stressed by exposure to cold (-15°C for 1 hour). The animals were placed in separate polypropylene cages to ensure equal cold exposure. Following 2 hours of drug administration, the animals were scarified by cervical dislocation. The stomach and duodenal parts were opened along the greater curvature, and the number of lesions were examined using a magnifying lens. Ulcer size was measured via Microimage process software (DA1-180M v 2.01) using an Olympus SP 350 camera. Scoring for the ulcers was allocated as 0 for normal-colored stomach, 0.5 for red coloration, 1 for spot ulcers, 1.5 for hemorrhagic streaks, 2 for ulcers ≥ 3 but ≤ 5, and 3 for ulcers ≥ 5.[11]

Acute Toxicity

Single-dose acute toxicity studies were carried out following OECD guidelines No. 401.[12] Prior to the experiment, the animals were fasted overnight but with free access to water. Three groups of six animals (control, drug, and prodrug group) each containing equal number of males and females were formed. Just before the experiment, the animals were weighed. A dose limit of 2000 mg/kg body weight of drug and prodrug suspended in demineralized water using 1% w/v CMC as a suspending agent was administered orally to the pre-weighed rats. The animals in the control group received 1% w/v CMC in demineralized water. In each case, the volume administered was 5 ml. Any toxicity or mortalities was observed at 0.5, 1, 2, 4, and 6 hours following dosing and thereafter twice a day for 14 days, respectively. All observations were systematically recorded, with individual records being maintained for each animal. Cage-side observations included evaluation of skin and fur; eyes; respiratory effects; autonomic effects (salivation, diarrhea, urination); and central nervous system effects, including tremors and convulsions, changes in the level of activity, gait and posture, reactivity to handling or sensory stimuli, and altered strength. Individual body weight was measured and recorded on day 14. Weight changes were also calculated

FIGURE 4



Histopathology of Albino Rat Stomachs for Ulcerogenic Activity
A: Control Group (1% w/v CMC)
B: Drug Group (1000 mg/kg)
C: Prodrug Group (1000 mg/kg)

TABLE 2

Animal Group	Weight in Grams ± S.D.			*% Weight Increase*
	On Day 0	On Day 14	Weight Increased	
Control	160 ± 11.21	171 ± 12.69	10 ± 1.56	6.99
Drug	169.5 ± 16.13	188 ± 18.41	10.9 ± 2.23	6.15
Prodrug	170.1 ± 14.22	184 ± 16.12	10.5 ± 2.12	6.71

Weight of the albino rats during the study

and recorded. Weighed animals were sacrificed by cervical dislocation on day 14. Gross pathologic evaluations were performed, and the weight of heart, liver, kidney, stomach, and spleen were measured and recorded immediately afterward. Relative organ weight (organ-to-body weight ratio) was also calculated and recorded for the organs. Histopathological examination was performed on routinely prepared sections of stomach tissues; the tissues were fixed in 10% v/v formalin immediately following removal and weighing to avoid autolysis.

RESULTS & DISCUSSION

Characterization of FLU & FLU-GLY Conjugate

Characterization of FLU and FLU-GLY involved RM and Rt value determination, and the results (0.476, 0.254, 4.56, 2.17 minutes, respectively) differentiated the drug and prodrug. The synthesized prodrug was further characterized via analytical techniques. Theoretical elemental analysis calculated for FLU-GLY ($C_{18}H_{18}FNO_3$) was C: 68.55, H: 5.78, N: 4.42, O: 15.19. Practical values were C: 68.53, H: 5.73, N: 4.44, and O: 15.17.

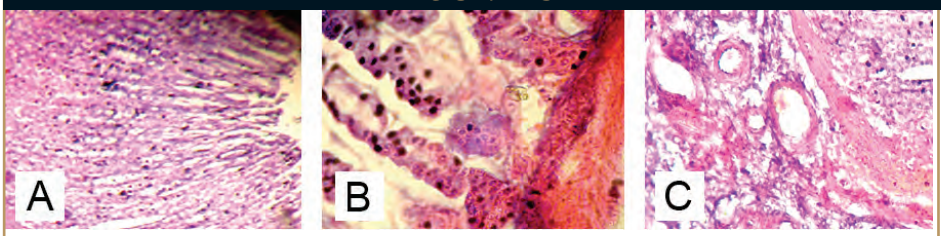
The results of the NMR studies also helped in indicating the formation of a newer compound: (1H NMR ($CDCl_3$), 7.6 ppm (Benzene, 3H,m), 7.48 ppm (Benzene, 5H,m), 3.9 ppm (CH,1H,q), 1.6 ppm (CH_3,3H,d), 7.27-7.42 ppm (CONH 1H,m), 3.7 ppm (CH_3 of ester 3H,s),1.48 ppm (GH_2, 2H,d).

High resolution FAB-MS theoretical calculation of M+ for $C_{18}H_{18}FNO_3$ resulted in a value of 315.15, whereas the observed value was found to be 316. All the studies confirmed the synthesis of a new compound.

In Vitro Reversion Study

In vitro kinetics (Figure 2), monitored by determining the reverted amount of FLU, confirmed negligible prodrug reversion in the gastric environment (HCl buffer pH 1.2) and cecal environment (acid phthalate buffer pH 4.0), with only 5.94% and 7.56% prodrug getting reverted to FLU in the intestinal environment (phosphate buffer pH 6.8 and 7.4), respectively, over an 8-hour period. Reversion was further studied in phosphate buffer pH 6.8 in the presence of 20% w/v fresh rat fecal matter to confirm the colonic breakdown of the prodrug. In colonic conditions, over a period of 48 hours, 69.13% of the prodrug reverted to FLU with first-order kinetics. The increased reversion in the presence of the colonic environment was due to catalyzed hydrolysis of prodrug in the presence of amidase enzyme released by colonic microflora. In vitro reversion suggested that the prodrug might bypass the GIT and revert to FLU as colonic miroflora release amidase enzyme in the colon.

FIGURE 5



Histopathology of Albino Rat Stomachs, Isolated on Day 14 of Acute Toxicity Study A: Control Group (2% w/v CMC)

TABLE 3

Organ	*Weight in Grams ± S.D.*		
	Control	**Drug**	**Prodrug**
Heart	0.63 ± 0.12	0.81 ± 0.86	0.67 ± 0.12
Liver	8.12 ± 0.22	7.65 ± 0.53	7.31 ± 0.23
Kidney	1.43 ± 0.21	1.89 ± 0.21	1.09 ± 0.09
Stomach	1.54 ± 0.43	1.77 ± 0.33	1.79 ± 0.21

Weight of different organs

Ulcerogenic Study

Ulcerogenic activity of FLU and FLU-GLY was determined via the cold stress (Rainsford) method, and the results are summarized in Table 1. The stomach walls of the rats in the drug group showed severe congestion, numerous haemorrhagic spots, streaks, corrosion in gastric mucosa, deep ulceration, and necrotic cells (Figure 3). In the prodrug group, there were hemorrhagic and red spots but not necrosis of the cells. No haemorrhagic or red spots were found on the stomach walls of the rats in the control group. Upon comparing the histopathology of the stomachs of the rats in the drug and prodrug groups, there was significant and severe haemorrhage, ulcers, and necrosis in the drug group as compared to the prodrug group (Figure 4).

Acute Toxicity

Following single-dose administration, there were no overt signs and symptoms of toxicity (except weakness) in all dosed groups on the first day. One rat in the drug group was found dead on the first day. The anomalies waned over time, and all surviving animals became overtly normal until termination of the study. There was no significant difference in the activities observed and no significant difference (one way ANOVA, $P < 0.05$) in body weight gain at the termination of study (Table 2).

Measurement of organ weight (Table 3) on necropsy of control, prodrug, and treated groups did not show any significant change (one way ANOVA, $P < 0.05$). Gross pathological observation of the animals at autopsy following single-dose administration of drug showed cysts in the stomachs and haemorrhagic abdomen, while no changes were observed on gross pathologic evaluation of organs of terminally sacrificed animals. Upon histopathological evaluations of stomach tissue of the drug group revealed a number of lesions, such as eosinophilic reaction in the junction of the stomach and esophagus, severe haemorrhage, glandular destruction, and severe necrosis. The prodrug group exhibited oedema, haemorrhage, and some glandular destruction. In the control group, normal glandular arrangement was observed. The microscopic examinations of the liver, kidney, heart, spleen, stomach, and intestine were essentially similar in all the animals.

Results obtained in the albino rats showed that FLU-GLY exhibited a moderate acute toxicity compared to FLU, and the 50% lethal dose (LD_{50}) had been estimated to be higher than 2000 mg/kg body weight for both FLU-GLY and FLU. The marked reduction in the ulcerogenic activity and lower toxic effects in albino rats in the prodrug group (FLU-GLY) compared to FLU (one way ANOVA, $P < 0.05$) may be due to the temporary masking of the carboxylic group of FLU, making the prodrug safe for oral use. These results coupled with the higher estimation of LD_{50} (> 2000 mg/kg body weight) indicate the prodrug is safe even with the higher dose.

CONCLUSION

The synthesized prodrug of FLU had much lower toxicity and ulcerogenic activity than the parent FLU. Thus, a prodrug approach not only significantly reduces the adverse effects of the drug, but also achieves targeted drug delivery to the colon. And, targeted drug delivery to the colon is more effective in therapy in terms of reduced dose and reduced undesirable side effects.

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BIOGRAPHY

Dr. Anil K. Philip is presently working as a Reader in the Department of Pharmaceutics, Mathura, Uttar Pradesh, India. He earned his BPharm from Rajasthan University, his MPharm from Dr. M.G.R. Medical University, and his PhD in Pharmaceutics form U.P. Technical University. He has several national and international original research publications to his credit. Dr. Philip's research primarily focuses on osmotic, buccal, and prodrug delivery systems. He is also an editorial member and reviewer of various reputed international journals.

SPECIALTY PHARMA
Strategies For Business Development

CRO Trends & Drivers

Specialty Pharma & Biotech Driving Current CRO Growth & Trends

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Chief Medical Officer
WorldCare Clinical

Andrew MacGarvey
President of US Operations
Quanticate

David Kwok, PhD
President / CEO
Biopharmaceutical Research Inc.

Biotechnology remains the strongest driver of incremental Contract Research Organization (CRO) revenue growth, followed by Specialty Pharmaceuticals and niche/start-up pharmaceuticals, according to Frost & Sullivan. The Texas-based Growth Partnership company also finds that the US CRO market earned revenues of $9.77 billion in 2008 and estimates this to reach $23.78 billion in 2015. The US CRO market has witnessed strong double-digit growth since 2003 and expects strong growth through the forecast period. Before 2003, the market witnessed a sharp drop in growth rates between 1998 and 2002 due to several mergers and acquisitions that led to a decrease in outsourcing relationships of the newly merged entities. There was also a significant slow-down in biotechnology funding from the meltdown of global markets. The markets, however, have since recovered strongly and consistently added over $1.50 billion in incremental revenues each year. This increase in incremental revenue is primarily driven by growth in R&D spending and the subsequent increase in outsourcing penetration.

There is a strong demand for early stage services from the supply side (R&D spending) that could translate to higher business for CROs if their services are positioned to meet the demand and requirements of sponsors. According to Frost & Sullivan, greater growth potential exists for CROs in early stage work with increased potential for outsourcing, especially in areas such as toxicology studies in which outsourcing penetration is lower. Several CROs are adding early stage capabilities to garner a greater share of outsourcing within this market segment. Companies looking to expand and capitalize on these opportunities, however, expect to increase capital expenditure and build new facilities or acquire them.

As CROs continue to expand their global presence, they must coordinate closer with IT vendors to ensure the systems are in-line with the rapidly changing requirements of the market. Also, moving forward, we are likely to witness a greater role for CROs in deciding on the IT systems and platforms to invest in as the decision-making moves away from sponsors.

One of the most significant trends within the US, as well as global CRO markets, is the move from transactional to strategic outsourcing by sponsors. The fact that CRO market growth has consistently outpaced R&D spending growth is an indicator that outsourcing penetration is on the rise. It is also interesting to note there have been several preferred partner announcements; the Covance-Eli Lilly partnership being the most recent and interesting one. More deals are expected to be announced, signifying a move toward this trend. These types of partnerships are driven by the fact that despite significant increases in R&D spending, the number of new drug approvals is at a historic low.

Specialty Pharma magazine recently asked some leading CROs to respond to some of the current trends Frost & Sullivan has identified. Participants include John C. Ho, MD, Senior Vice President, Corporate Strategy, Charles River; Andrew MacGarvey, President of US Operations, Quanticate; Richard Walovitch, PhD, Chief Medical Officer, WorldCare Clinical; and Dr. David Kwok, President and CEO, Biopharmaceutical Research Inc.

Q: ***Specialty Pharma and Biotech have been identified as the strongest drivers of the CRO market. Please describe the type of work you are doing for these types of companies.***

Dr. Walovitch: We provide core imaging services to a mix of Fortune 500, Specialty Pharma, and Biotech companies. In 2004, the FDA indicated there had been slow-downs in innovative medical therapy and that imaging could help make the drug development process less costly and more predictable. This resulted in an explosion in the use of imaging as a surrogate marker/direct marker of disease progression in the drug development process. We fit in very well because high-quality reads that we can offer through our strategic relationships become more cost effective over the length of the trial, as the study requires less adjudication and the imaging data better correlate with efficacy endpoints. WCC's 17-year heritage and close relationship with Massachusetts General Hospital (MGH) also means we can read the imaging data that is not yet in full clinical practice. In addition, our in-house radiology team ensures our scalability for processing large volumes of reads.

Dr. Kwok: For the past 11 years, we have been engaged in the development of drug candidates performing a large variety of in vitro/in vivo DM/PK/TK/ADME studies. We also routinely perform bioanalytical LC/MS/MS assay development and validation studies supporting clinical sample assay. Our laboratory is also equipped and routinely performing analytical chemistry CMC studies relating to drug substance and drug product specification assays and stability evaluations.

Mr. MacGarvey: Quanticate is a specialist biometrics company. Our model allows us to offer a range of statistical, programming, clinical data management, and medical communications services. In working with our customer base, we have worked on contracts in which the requirement is a few hours consultancy right through to full-blown support where we might be brought in to get involved with the design of the Clinical Development Program. I find as I meet this type of customer that many of them run with a minimal infrastructure as they seek to slow down the burn rate of their funding. We can help because we are used to plugging into the sponsor's team and becoming an extension of that team while the demand requires it. These customers are very exciting to work alongside as the products tend be at the leading edge, and so our work needs to be the same.

Dr. Ho: We collaborate with Specialty Pharma and Biotech clients to help bring therapeutic candidates from late discovery through preclinical and into clinical development. Specialty Pharma and Biotech face challenges in both designing and efficiently and cost effectively executing the drug development process. As technology, regulatory requirements, and the biopharma industry continue to evolve, so does the drug development process. We see sponsors exhibiting a stronger desire to migrate/outsource services that support development, planning, and project design. This is similar to the demand for CRO support services in the early 90s compared to today's environment, and is substantiated further by our primary industry research conducted by the Tufts Center for the Study of Drug Development. Essentially, the center found that contract research already accounts for more than 17% of total drug development spending, and this number is likely to increase. Specialty Pharma and Biotech expect to work with a CRO to help determine what is essential to accelerate drug development during the critical transition from preclinical to clinical. This is particularly true as smaller biotech and pharma companies carry the responsibility to bring candidate products through clinical proof-of-concept. Continued and increased expertise is required of preclinical and early phase teams to offer tangible value to sponsors. The value offered by our expert teams helps identify appropriate go/no-go decisions earlier in the development process and provides information to optimize subsequent development. At the preclinical-clinical transition, for example, one specific problem is determining starting doses and escalation multiples, and anticipating key IND review issues. These decisions may not be entirely straightforward, even with the *Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* in hand. An experienced CRO with integrated teams can contribute substantially to the discussion. In the current life sciences environment, it is critical to demand and expect more from your CRO.

Q: ***Early stage work, such as toxicology studies, have traditionally not been outsourced. How are you attracting Specialty Pharma and Biotech companies to reach out to you earlier in the drug development process?***

Dr. Kwok: Non-GLP tox studies may not be outsourced traditionally, but GLP tox is commonly outsourced from Biotech and Big Pharma alike. We are able to attract non-GLP tox studies by having developed proven study protocols and best practice procedures for each of the DM/PK/ADME and bioanalytical areas. Another added value is our ability to delivery data more timely and at lower cost than our internal pharma counterparts. One of the strongest drivers for Biotech and Specialty Pharma to work with BRI is their confidence on our scientific ability and their understanding that we deeply care about the success of their projects. This trust is established at an individual level scientist to scientist.

Mr. MacGarvey: This is a very pertinent question for a company that specializes in biometrics, as customers will tend to consider the clinical aspects of the study or program first. We found that there was a demand for consultancy at the early stage and in 2007 established a consultancy arm. This group brings together industry experts, and they are able to provide knowledge around program and trial design early in the process. The main benefit of this is that it leads to efficiencies downstream - critical in a climate in which reducing the cost of the development program is very important.

Dr. Ho: It is important to define early stage work and toxicology. In general, early stage is the series of studies performed to identify the appropriate drug candidate to advance into preclinical development, leading to IND submission and Phase I clinical trials. Usually, these IND-enabling preclinical studies are referred to as toxicology studies and traditionally form a major portion of the work performed by a CRO on behalf of clients. Toxicology studies are regulated and comply with GLP guidelines and, over the past few years, we have seen increasing volumes of these studies outsourced as our clients reduce their internal capacity and staffing. Attracting Specialty Pharma and Biotech companies is key to our growth plans and is driven by continual investment in the technologies required to evaluate the safety of these often novel therapeutic drug classes. Recent technology investments have enabled us to address specific questions regarding biologics, particularly monoclonal antibodies, stem cells, sIRNAs, and a wide range of immunomodulators. It is also important for CROs to hire industry-respected experts who are not only technically and scientifically knowledgeable, but also well-versed in the current regulatory expectations and issues for these types of drugs. True early stage development involves supporting drug discovery and lead candidate selection prior to the start of the preclinical toxicology evaluation. This is a sector of the business that has traditionally been conducted in-house or in small, niched, boutique-type CROs. However, we are seeing an increasing interest in having this work done externally with large CROs and to the same degree of rigor, as is expected for clients conducting the work themselves. Feedback indicates that this is seen as a key area that can help reduce later-stage attrition of drug candidates, the primary cause of the escalating cost of bringing a drug to

market. Large integrated broad portfolio providers like us can simplify the transactional complexities and substantially accelerate drug timelines versus using a set of smaller, niche providers. We are working to engage this market through our emphasis on transgenic rodents, surgical preparation of research models, small and large model pharmacokinetic and ADME (absorption, distribution, metabolism and excretion) studies, expanding portfolio of disease and in vivo pharmacology models, and selective acquisitions in areas such as preclinical imaging and oncology specialty providers. We believe that as we continue to build and extend these capabilities, and gain more experience with specific drug classes, it will become an increasingly attractive and cost-effective option for many small-to-medium-size Specialty Pharma and Biotech companies. The impartiality and range of complementary capabilities a CRO can bring to this critical area (that often defines the development and spend portfolio of a company for many years to come) seems to be generating a lot of discussion at senior management levels between the Specialty (and large pharma) companies and CROs.

Dr. Walovitch: In collaboration with current Pharma and Biotech clients, WCC developed a unique new service offering designed to help those that are still in the early stages of the drug development process. The service, called Collect, Ready Hold,™ gives study sponsors a way to cost effectively collect, QC, and store images in a central database until it is determined if a central review of the imaging data is required. This approach greatly reduces time and cost associated with a retrospective image collection should the need arise for a central review at the end of a study. We have also received positive feedback on our image library creation and archival service, which allows sponsors to protect important corporate assets by creating a long-term library of image data collected from your pre-trial research, clinical trials, or post-approval activity. All imaging data is archived in the industry-standard DICOM format, enabling immediate access to images and trial data for potential use in future research, marketing, and physician or employee training. Both of these services are unique to our company and are based on our patent-pending WorldPro technology platform. In addition, our strategic relationship with the MGH Radiology team allows us to provide protocol consultation and design services to sponsors in the development stages of their imaging trials.

Q: ***What moves have you made to expand your global presence, and how has this affected business with your Specialty Pharma and Biotech customers?***

Dr. Ho: We are seeing the difficult economic climate, increasing market consolidation, and looming patent expirations drive significant industry changes. Pharmaceutical and biotech organizations are realigning their therapeutic focus areas and taking steps to improve R&D productivity. These organizations recognize the benefits of strategic outsourcing, which enables faster, more efficient drug development; reduced need for infrastructure investment; and the provision of expertise, which would be cost prohibitive and inefficient to duplicate or sustain in-house. As a result, we are see increasing collaboration as a key strategic partner. By partnering with us on a broader, more strategic basis, our clients are reducing their R&D costs and improving efficiency. To meet our client's needs, we provide drug discovery and development expertise in North America, Europe, Japan, and China. This global network supports our clients' outsourcing model and reduces their need to further invest in infrastructure. In fact, between 2007 and 2009, we opened approximately 1 million square feet of new, customized space globally. In October 2008, to support the growing demand from multinational pharmaceutical clients for outsourced drug development services, we opened a 60,000-square-foot preclinical facility in Shanghai. The new China facility positions us as the strategic partner of choice to fully support clients' global drug development needs. With this facility, we expect to be the first global preclinical provider offering both discovery and GLP-compliant services in China. In addition, this spring, the company will open the first phase of a new preclinical facility in Sherbrooke, Canada. The new facility will be approximately 300,000 square feet. An estimated 25% will be constructed in the first phase and dedicated to only one or two clients. Through its flexible design, the construction for the remaining phases is timed and designed to accommodate changing market demands. The Sherbrooke facility is ultimately expected to employ 1,000 people, who will work collaboratively with the 1,600 staff currently located at the company's Montreal facility.

Mr. MacGarvey: Our company has its headquarters in the UK, but in response to a demand from our customers, decided to expand into the US. We chose Cambridge, MA, as our base, and as such, have been able to serve the many Biotech and Specialty Pharma companies who are right on our doorstep. To maintain a competitive edge, we have operations in Poland and more recently expanded into South Africa. This global expansion has allowed us to gain the critical mass to support our customers as they progress to bigger studies.

Dr. Walovitch: Through our parent company, ProScan Imaging, we have the ability to use radiologists in Eastern Europe, Asia, India, and the Middle East. And because WorldPro supports readers remotely, we are able to work with the best assessment talent, regardless of the location. To date, we have serviced over 4,000 investigator sites in 50 countries. We can also perform assessment reads for patient enrollment in clinical trials within 24 hours, using our HIPAA-compliant ProScan InteleGRID image upload application. Not only does this expedite the patient enrollment process, but it also ensures that reads can be processed regardless of the location or time zone.

Dr. Kwok: We have provided preclinical development services to biotech and pharma companies overseas in Europe and in Asia. The CRO market outside of North America is largely built on personal contacts with individual outsourcing scientists and business managers who recognize BRI as a CRO with both regulatory experience and scientific expertise in delivering the studies in support of an IND filing. The traditional mass marketing and advertising to overseas markets can be cost intensive and time consuming.

Q: ***Frost & Sullivan stated that IT system decision-making is moving away from the client sponsor and into the hands of the CRO. Is this the situation with your clients, and how is that working out?***

Dr. Walovitch: We believe WCC (as the imaging CRO) is responsible for meeting or exceeding all trial-specific needs identified by our client sponsors, and for anticipating future technical trends within the marketplace. Because we strive to do this every day, we take on the role of market monitor, and assume some of the IT decision-making right from the outset. For imaging trials, IT revolves around the image management system, and we addressed many of the typical issues that challenge sponsors with our WorldPro platform, which centralizes image submission, radiology review, and program management in a single system. Unlike many other systems in the imaging trial world, sponsors can control every aspect of transmission and review, including quality control and compliance checks – a huge bonus for reducing IT expenses and streamlining the entire trial. We have received a great response from sites using the system, as well as from sponsors leveraging the flexibility of the tool to support independent panels assessing the blinded radiology

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Dr. Kwok: To a large extent, IT system design and LIMS implementation in support of clinical data management is driven by a few large clinical CROs/CRAs that perform the majority of clinical phase development. Some of the dedicated purpose-built LIMS in support of clinical development in Big Pharma and large CROs can be narrowly focused and lacks the boarder scope of IT infrastructure to support a small company's project management needs, such as financial and scheduling information. However, for a small CRO that wants the LIMS or IT system becomes a prerequisite to become qualified to do business, rather than a decision based on the merits and suitability of the IT system matching the operating requirements of a CRO.

Dr. Ho: As sponsors increase wholesale outsourcing of clinical development services, they are less concerned with integrating their IT systems and platforms that collect and manage clinical data with those of their CRO partners. Instead, CROs are stepping forward to wholly manage this responsibility. As CROs broaden service offerings, it is less important to our clients which eCRF, data management, and/or analytics systems we use as long as the data and reports measure up with expected quality and standards. Particular consideration is given to systems that exceed CDISC standards, provide a user-friendly interface, and expedite data management activities. Additionally, when clients consider which IT systems to use, they often request and consider input from the CRO. Our clients are, more often than in the past, looking to us as a service provider to supply more data management solutions and base their decisions on the capabilities and robustness of the electronic system(s) we choose. We have also seen with the establishment of the electronic regulatory submission process that there is an expectation to provide data in a format and structure that allows easy and rapid integration into the required format. This has resulted in major CROs to play a key role in these regulatory submission initiatives.

Mr. MacGarvey: I believe CROs have always driven the adoption of technology in our sector, they have been willing to take the risks associated with new technologies as they have moved to improve efficiencies and deliver better service. This makes sense as these providers are always looking to deliver the best product to the customer. What's interesting now is that a lot of the experience with these technologies lies within CROs - people working in CROs have had exposure to multiple systems whilst completing studies for various customers. This gives them a great perspective and allows them to learn the pros and cons of each system. In terms of our customers, we are seeing demand for assistance in vendor selection, system validation, and system implementation. Another big area is integration of technologies and data mapping between systems, we have seen a very large demand for CDISC mapping for example.

Q: ***Rising competition and fragmentation in the CRO industry has affected revenue. However, it seems that more preferred-partner relationships vs. transactional relationships have been one of the outcomes of that trend. Are you generating more of these strategic-based relationships with your Specialty Pharma and biotech clients?***

Dr. Kwok: A preferred-CRO relationship is always desirable, and a preferred relationship is always justified by a client sponsor company receiving some form of competitive advantages within that preferred relationship. For instance, access to exclusive technology or know-how, guaranteed delivery timelines, preferential pricing, etc. In addition to these preferred advantages, the relationship must continue to be built on the CRO's scientific reputation and earned from performing on the job above and beyond the sponsor client's expectations.

Mr. MacGarvey: We have well-established relationships with some long-standing customers, and this has allowed us as a company to learn the very best ways to work at the strategic level. We know what the problems are when a CRO and a sponsor are establishing a strategic relationship and as such can plan accordingly. There is a definite skill to getting the preparation right, not just in terms of contracts but looking at information systems, training, and SOPs. Our experience in these areas, coupled with our critical mass has allowed us to foster more of these relationships. I believe the key word is relationship too. A big driver in a successful partnership is the relationships between the players and that runs from the contracts group right through to operations. Speciality Pharma and Biotech look for a good fit before they will work for you. They don't have the funds or the time to get the decision wrong.

Dr. Ho: As discussed, the economic and patent challenges, as well as market consolidation, are driving significant industry changes. As a result, we are seeing the dynamics of our clients relationships evolve toward broad-based partnerships that help accelerate their drug development programs and drive enhanced productivity and flexibility. At this time, clients are re-examining their core competencies and defining what can be externalized, to focus on what they do best. This focus on shedding non-core activities and assets is shifting the CRO/sponsor dynamics. For example, in our Research Models business, we have a 10-year, $111.6-million contract with the National Cancer Institute (NCI). In July, we announced the opening of this state-of-the art 52,000-square-foot facility to support our relationship with NCI while expanding our presence in the Frederick, MD, area. In the new facility, we are working side-by-side with NCI in a seamless partnership to produce the highest quality research models available. The new facility provides genetically defined, pathogen-free mice to support NCI/NIH (National Institutes of Health) funded research targeting metabolic diseases and cancer. In addition, in response to individual customer needs, we have also been flexible in entering into broad based multi-year partnering arrangements, generally involving financial commitments from the customer, which tap into the broad array of physical and/or service resources that we provide, such as reserving dedicated space within existing facilities, building out space to a particular specification, working within our clients' infrastructure, or even establishing a new facility. By partnering with us, our clients realize that working with us can help to lower staff and operating costs while better accommodating changing biomedical research and drug pipeline priorities and demands. We also offer facilities and services providing specialized product and services that are often too prohibitive to clients to maintain in-house. We also are working across the industry on a range of strategic partnerships. By leveraging our extensive portfolio and global footprint, we create substantial impact on our clients' overall R&D and manufacturing productivity. ◆

Executive Summary

Gary Cupit
CEO
Somnus Therapeutics

Somnus Therapeutics: Taking On the Top Unmet Need in the Blockbuster Insomnia Market

Early in 2007, venture capitalists at Care Capital found a new controlled-release formulation of a successful insomnia drug that was nearing patent expiry. Somnus Therapeutics, based in Bedminster, New Jersey, was formed to exploit this opportunity, and is developing an improved therapeutic to address the top need of insomnia patients: preventing mid-night awakenings without next-day hangovers. In June 2007, Somnus licensed the SKP-1041 formulation of zaleplon (Sonata, Starnoc) from SkyePharma, PLC, a company that applies drug delivery to improve and extend the life-cycle of existing drugs. Gary Cupit, CEO, tells *Specialty Pharma* magazine that while the company's focus is on the insomnia market, these economic times call for a broader view of product development.

Q: ***What makes Somnus unique as a specialty pharmaceutical developer?***

A: From the beginning, our business model was designed to emphasize efficiency, accelerate product development, and reduce costs to increase return on investment. We had in-licensed an off-patent entity from the most successful class of current insomnia drugs, and intended to use technical advances in formulation, controlled-release, and clinical testing to develop a better product faster and less expensively to address a big underserved market segment. Our business model is to develop through Phase II and partner the drug for commercialization.

So we recruited a virtual team of 20-year experienced pharmaceutical executives, and leveraged their abilities with outsourced capabilities from our scientific advisory board, contract research organizations, and consultants. Indeed, we have been able to move quickly, and since establishing our development team in October 2007, we have designed, conducted, and completed the first SKP-1041 Phase I trial in 14 months. In keeping with this nimble approach, we plan to commercialize the product through an established pharmaceutical partner.

Q: *Why has Somnus Therapeutics chosen the insomnia market?*

A: Insomnia is a huge market, estimated to total $3.5 billion within the United States and $4.6 billion worldwide. It's a growing market with sales estimated to be $7 billion in 2012. Growth is driven by an aging population, travel across time zones, ubiquitous artificial light at night, and shift work. Around the world, sleep disturbances are prevalent: with estimates ranging from a low of 7% in Japan, to more than 30% in some European countries, depending on methodology and definitions.

Remarkably, market research indicates that fewer than 12% of people with insomnia make use of prescription medications. Because it's such an underpenetrated market, we believe better therapeutics will not only capture market share but also drive market penetration. In particular, we believe improvements in drug delivery, dosing, and development can produce a more effective product faster with a lower cost to market.

We also focused on the biggest unmet need in the insomnia market: middle-of-the-night (MOTN) awakening. Our market research confirms that some two-thirds of insomnia sufferers find staying asleep a major problem, making it the most frequent complaint of insomnia patients. MOTN insomnia is strongly associated with daytime fatigue and cognitive impairment and thus with reduced job productivity and safety. Mid-night awakenings are more prevalent in women and increase with age for both sexes. A recent study showed a significant association with comorbidities, including obesity, mood disorders, and chronic pain, which may be exacerbated by nocturnal awakenings. All in all, it's a big unmet need.

Because the developers of earlier generations of insomnia therapeutics generally focused on falling asleep, this sector is less competitively crowded. However, as an indication, sleep maintenance calls for a differentiated approach to product design. Avoiding next-day hangover side effects is one challenge when treating nocturnal awakenings, but one amenable to a controlled-release approach. Furthermore, our market research found that medical practitioners and patients prefer a single dose at bedtime to maintain restful sleep. Thus, a delayed-release formulation of a short-acting drug struck us as a product design with great market potential. An independent third-party forecast has determined the market potential to be greater than $600 million on the low end.

Q: *What advantages does reformulating an approved drug have over the new chemical classes of drugs in development?*

A: Zaleplon is a chemical entity from a successful, established chemical class with a big safety database and an excellent track-record over many years. All that knowledge mitigates our development risk going forward compared to developing a drug from a novel chemical class. New chemical entities have a longer path to market and entail higher risk, as less is known about real-world safety and patient response.

Non-benzodiazepine GABA agonists have been one of the most successful classes of insomnia drugs. Zaleplon, and two other so-called Z-drugs, were the first of this class to reach the market, and in their patented forms (Sonata®, Ambien®, Lunesta®) were blockbusters among the most successful insomnia product introductions. The zaleplon patent expired in 2008, dovetailing nicely with our clinical timeline.

Interestingly, the biggest shortcoming of zaleplon (its 1.5-hour half-life) makes it a superior candidate for a controlled-release version with improved pharmacokinetics and pharmacodynamics as well as for fine-tuning the dosing specifically for the MOTN awakening market. All in all, zaleplon is an ideal candidate for use with the Geoclock™ controlled-release technology.

Q: *How does controlled-release technology work in this product?*

A: The SKP-1041 tablet uses two of SkyePharma's controlled-release technologies, Geoclock and Geomatrix™. The Geoclock layer combines a hydrophobic wax with a material that enables a pH-independent (important in the high-acid environment of the stomach) drug delivery at a predetermined release rate. The inner payload uses the Geomatrix technology, a multilayered tablet of hydrophilic polymers with surface-controlling barrier layers. These barrier layers control the active loaded-core surface that releases when exposed to fluid.

The tablet opens like a clamshell to deliver the inner payload with a precisely calibrated delay before delivery. That makes possible the single bedtime dosing we are aiming for, allows the patient to experience normal deep levels of delta sleep before the drug is delivered, and the drug metabolizing completely before the sleeper awakens for the morning.

So, the patient will swallow one tablet at bedtime, fall asleep normally, and then 3 to 5 hours into the sleep period, the tablet releases the zaleplon, which will prevent mid-night awakening but be out of the patient's system by morning. This approach is user-friendly for patients, consistent with providers' preferences, and should minimize next-day cognitive impairment and fatigue.

Q: *What is your clinical strategy?*

A: There are three major elements to our clinical strategy aimed at speeding product development while keeping costs down to increase return on investment. First, we licensed in a molecule with an excellent performance, safety, and sales record that went off patent as we completed Phase I. This means we can pursue accelerated development through the 505(b)2 pathway for known chemical entities. Furthermore, we are taking advantage of SkyePharma's superior formulation and proven controlled-release technology to rapidly develop an improved product.

Second, as discussed previously, we targeted an underserved indication, sleep maintenance, in a large market (insomnia), in which we thought an improved product would capture share and may increase the market.

Third, we took advantage of the growing body of biochemical and pharmacological knowledge about sleep, building particularly on the clinical expertise of our SAB, who are guiding the clinical study design. A key aspect of the clinical strategy is leveraging advanced technology. In Phase I, our international CRO, FORENAP Pharma in Rouffach, France, used their state-of-the-art sleep-monitoring instrumentation and cognitive testing capabilities to provide high-tech evaluation of sleep patterns and next-day alertness that improved the efficiency of our clinical trials.

We plan to add US clinical sites in 2009 for Phase II, and to that end have filed an IND with the FDA. Both in Europe and the US, we will be using the MSLT (Multiple Sleep Latency Test) to screen clinical subjects to reduce statistical "noise" in the data sets. We will also pursue studies in specific sub-populations, like the elderly and shift-workers, to keep the data clean and allow us to fine-tune the dosing if that produces better outcomes.

Q: *What's next for the company?*

A: Beyond SK-1041, our strategic focus is on CNS indications. Especially in this financial environment, our accelerated development model is attractive to both investors and licensors, so we are looking at a number of opportunities to pursue next. ■

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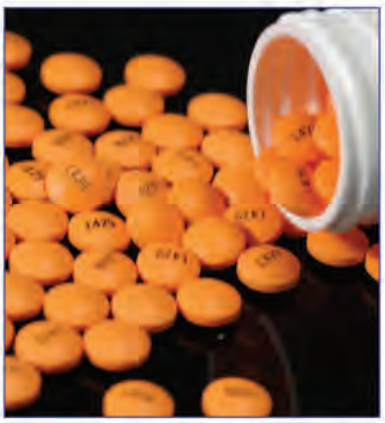

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The Fallacy of Retention Bonuses

By: John A. Bermingham

I have been reading with great interest the excuses AIG has been offering to the American people as to why they had to pay out millions of dollars in retention bonuses to keep valued employees from quitting. Specifically, AIG paid out $165 million in bonuses to employees regardless of performance with 73 employees receiving over $1 million, including 11 people who have since left the company. How about we call it what it really is…. a bribe!

Several turnarounds ago, I joined a company that was in deep trouble. The private equity firm that owned the company asked me to attend this company's Board meeting as a prospective director. The company had no borrowing ability but did have $6 million in cash. The plan was to move one of their manufacturing facilities to Canada at a $4.5-million dollar cost, leaving $1.5 million in cash. The CEO and CFO presented a bonus plan to the Board calling for $500,000 of the remaining cash to be given to executives as bonuses. The reason for this? To keep the executives from leaving the company. Yes, those same executives who took the company from a strong healthy position to one in which the financial losses were so great that the accounts payable obligations could not be met.

Following the Board meeting, I told the private equity sponsor they should not approve the bonus plan. I told them they were being held hostage by the executives and they were paying for failure, not successful performance. The private equity firm approved this plan anyway. Big mistake!

Five months after joining this company as CEO, I was approached by the CFO who informed me that 7 employees who reported to him had demanded they all be paid a bonus for their efforts during the first half of the year. These 7 employees told the CFO they were going out to lunch and would be back in 1 hour. If I refused to pay them this unplanned bonus, they would walk out of the company that day. The combined bonus amount for these 7 people was nearly $500,000.

I told the CFO to do the following: 1) Go to the mail room and find 7 bankers boxes and put one on each person's desk; 2) Place a sign on each box informing the person he/she was now unemployed and had 60 minutes to clear the building; and 3) Update his (CFO) resume because I was replacing him with a new CFO within 30 days.

When the 7 people returned from lunch and realized what was happening, they all came to my office on bended knee asking for another chance. I told them I was appalled by their demand and threat and would not tolerate this type of conduct, particularly because the company was in financial distress. All apologized and asked for their jobs back. I allowed them to stay due to the key positions they held in the company, but throughout the next couple of months, I replaced every one of them, including the CFO.

Guess what? The new management team I brought in turned the company around, and we sold it for twice what the secured lenders had anticipated. Each of these people received a sizable bonus for their successful efforts.

I recommend the captains of industry on Wall Street consider this. No bonus should be contractually guaranteed regardless of performance. Any bonus plan must have a provision that the Board has the discretion to modify or cancel all bonuses due to poor performance. If any person ever approaches management demanding a bonus and threatens to leave if the answer is no, especially when the company is in distress, the answer has to be, see ya! ◆

BIOGRAPHY

John A. Bermingham is the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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