Drug Delivery Technology®

June 2009 Vol 9 No 6 www.drugdeliverytech.com

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Fiction or Reality?

"This article reviews one such interesting smart drug delivery system (thermoresponsive) in which the drug molecule is physically attached to or entrapped in a polymer that is capable of conformational or phase changes under different regimes of temperature. These are potential candidates for a targeted drug delivery system, especially for anti-cancer drugs. However, the concern here is the human body's capability to maintain a controlled body temperature unless there is a significant temperature change in the target organ."

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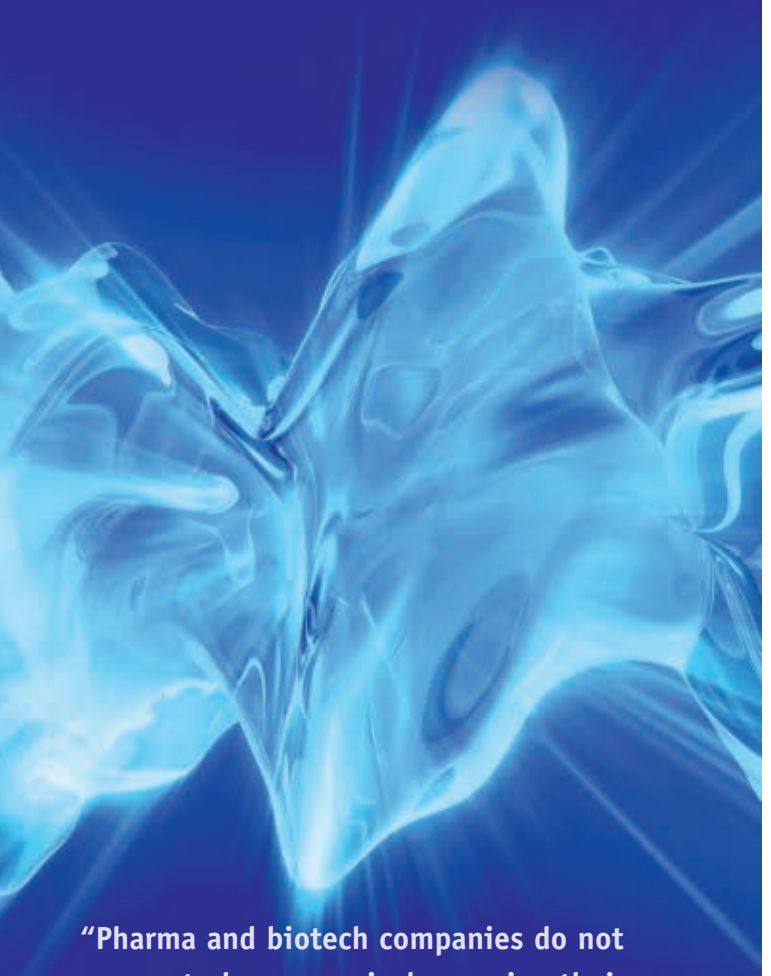
Changing Tides



"Pharma and biotech companies do not appear to be aggressively growing their pipelines or developing blockbuster drugs at the same pace they had in previous years. Thus, the business strategy of outsourcing formulation development has slowed a bit; it is more cost effective to keep this process in-house while pipelines get reconstructed to their previous strength. However, as the economy turns around, CROs are expected to see a revival."

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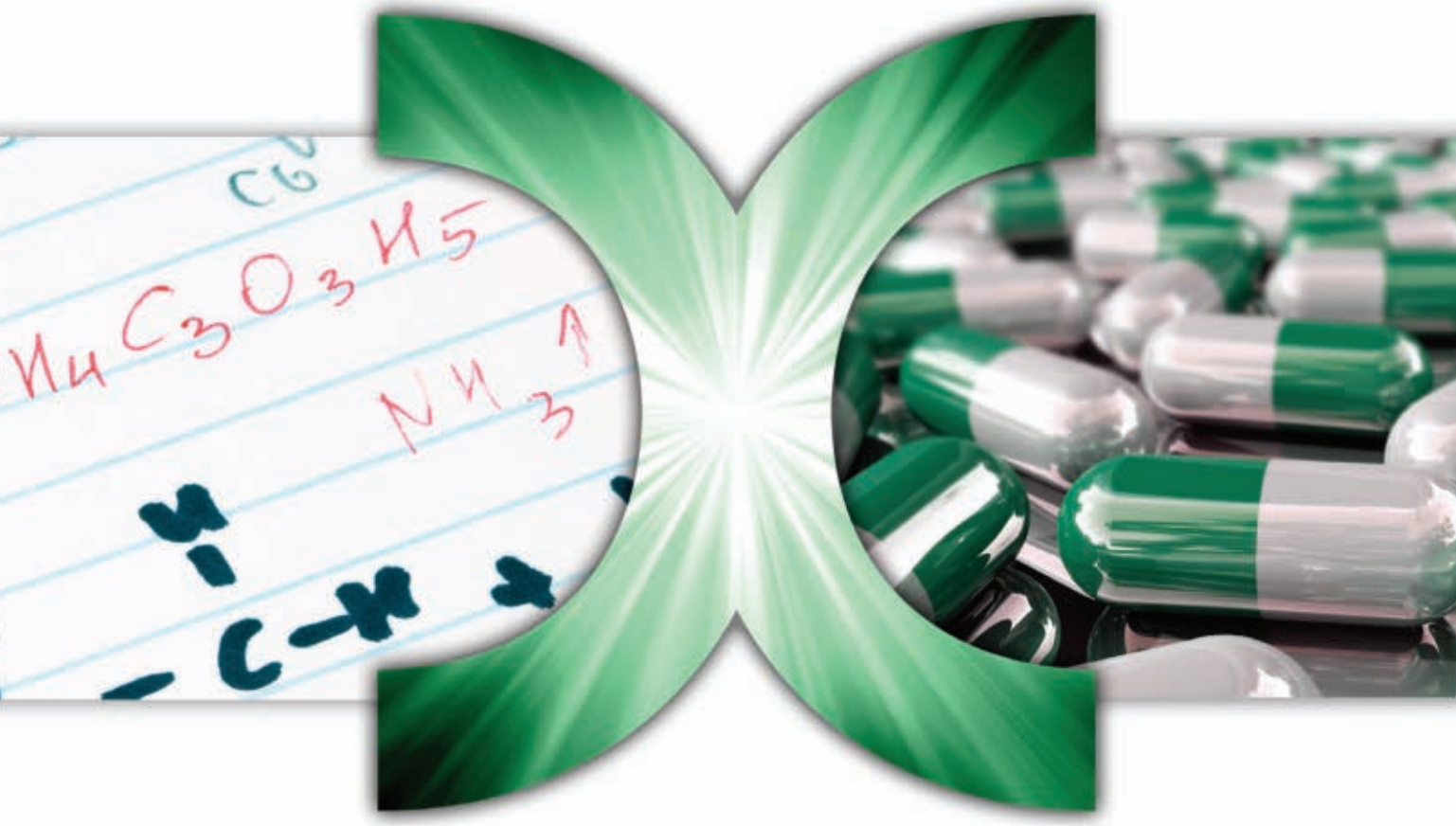

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MARKET NEWS AND TRENDS

Amylin Pharmaceuticals & Eli Lilly Announce Plans to Develop Pen Device; Companies to Share Development Costs

Amylin Pharmaceuticals, Inc. and Eli Lilly and Company recently announced the companies have agreed in principle to the terms of a joint supply agreement for an exenatide once-weekly pen device. Separately, the companies announced they have initiated a Phase I/II clinical study to examine a new exenatide once-weekly suspension formulation.

Exenatide once-weekly is an investigational diabetes therapy that is injected subcutaneously once a week and is currently in Phase III development. Exenatide is also the active ingredient in twice-daily BYETTA (exenatide) injection, currently available in the US and in many countries worldwide for people with type 2 diabetes who are unable to achieve good glycemic control with common oral therapies.

Amylin and Lilly have agreed in principle to cooperate in the development, manufacturing, and marketing of exenatide once-weekly in a dual-chamber cartridge pen configuration. This design will enable patients to mix and administer exenatide once-weekly from a prefilled pen device instead of the syringe and vial currently used in clinical trials. The companies will share the capital and development costs of the pen, including the initial capital investment of approximately $216 million over the next few years. Amylin and Lilly have agreed that the cost of the initial capital investment will be allocated 60% to Lilly and 40% to Amylin.

Amylin will be responsible for developing and manufacturing the final pen product for the US and for manufacturing unlabeled and unpackaged pens for the markets outside the US. Lilly will be responsible for labeling and final packaging of the pen product to support sales outside of the US. Amylin and Lilly will share sales and marketing rights in the US, while Lilly will be responsible for sales and marketing outside of the US.

"The agreement for an exenatide once-weekly pen device underscores our commitment to enhance the user experience for patients with type 2 diabetes," said Vince Mihalik, Senior Vice President, Sales and Marketing, and Chief Commercial Officer at Amylin Pharmaceuticals. "While our DURATION-1 patient questionnaire results showed that the delivery system used in clinical trials was well accepted by patients, we continue to look for ways to enhance delivery and offer patients a range of choices through alternative delivery possibilities."

Exenatide once-weekly suspension is an investigational formulation that eliminates the need to reconstitute the product prior to use. The companies have initiated a Phase I/II clinical trial designed to evaluate the pharmacokinetics, tolerability, and safety of this new exenatide once-weekly formulation in both healthy volunteers and people with type 2 diabetes. The study will also evaluate efficacy in the type 2 diabetes patients. The trial began this month and initial findings are expected by the end of 2009.

Exenatide once-weekly uses a proprietary technology for long-acting medications developed by Alkermes. The technology encapsulates active medication into polymer-based microspheres that are injected into the body where they degrade slowly, gradually releasing the drug in a controlled manner to provide continuous therapeutic exenatide levels in plasma.

Diabetes affects more than 23 million people in the US and an estimated 246 million adults worldwide. Approximately 90% to 95% of those affected have type 2 diabetes. Diabetes is the fifth leading cause of death by disease in the US and costs approximately $174 billion per year in direct and indirect medical expenses.

BYETTA is the first and only FDA-approved incretin mimetic for the treatment of type 2 diabetes. BYETTA exhibits many of the same effects as the human incretin hormone glucagon like peptide-1 (GLP-1). GLP-1 improves blood sugar after food intake through multiple effects that work in concert on the stomach, liver, pancreas, and brain. BYETTA is approved by the FDA for use by people with type 2 diabetes who are unsuccessful at controlling their blood sugar levels. BYETTA is an add-on therapy for people currently using metformin, a sulfonylurea, or a thiazolidinedione. BYETTA provides sustained A1C control and low incidence of hypoglycemia when used with metformin or a thiazolidinedione, with potential weight loss. BYETTA is not a weight loss product.

Amylin Pharmaceuticals is a biopharmaceutical company committed to improving lives through the discovery, development, and commercialization of innovative medicines. Amylin has developed and gained approval for two first-in-class medicines for diabetes, SYMLIN (pramlintide acetate) injection and BYETTA (exenatide) injection. Amylin's research and development activities leverage the company's expertise in metabolism to develop potential therapies to treat diabetes and obesity.

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Prefilled WFI Syringe Provides High-Quality Solution for Drug Reconstitution

West, the world's premier manufacturer of components and systems for injectable drug delivery, and Vetter, a worldwide leading independent specialist in the contract manufacturing of prefilled application systems, have introduced a ready-to-use, WFI prefilled syringe for reconstituting lyophilized drug products.

"The Vetter/West WFI syringe combines the best of pharmaceutical components in a drug administration system that we believe customers will embrace," said Mike Schaefers, Vice President, Marketing, Europe, West. "This system can be applied to our customers' high-value pharmaceutical and biopharmaceutical drug products."

"This system unites two of the world's leaders in drug administration systems and pharmaceutical processing," said Oskar Gold, Vice President, Key Account Management, Vetter. "We are pleased that we can offer customers a world-class prefilled syringe system."

The syringe features a plunger with West's FluroTec barrier film and Vetter's V-OVS tamper-evident closure, which includes a West tip cap. The film, developed by West's partner, Daikyo Seiko, Ltd., provides an effective barrier against organic and inorganic extractables, which helps maintain the purity of the diluent.

The V-OVS closure system is designed to give a prefilled syringe system effective protection features. It consists of a tip cap, a Vetter Luer Lock, and a tamper-evident seal. The components are pre-assembled as a single part, which is mounted on the syringe barrel with a Luer-cone and Luer-groove. The integrity of the syringe system is maintained if the seal has not been broken.

The syringes are available with fill volumes between 0.5 mL and 3.0mL. The glass syringe barrels are treated with baked silicone for lubricity and are 100% visually inspected to provide highest quality levels.

Customers will have packaging options, including individual blister packaging.

Vetter fills and terminally sterilizes the syringe at its facility in Langenargen, Germany. The syringes are supplied with regulatory documentation to meet requirements of markets in Europe, Japan, North America, and numerous other countries.

Encap Drug Delivery & Probac Collaborate to Develop an Oral Probiotic for AAD

Encap Drug Delivery and Probac AB recently announced they have entered into an exclusive collaboration agreement to develop an oral probiotic for the treatment of antibiotic associated diarrhoea (AAD). Both companies intend to build on their respective experience in this area to address the problem of hospital infections that can cause AADs, including Clostridium difficile (C difficile). A neutraceutical/pharmaceutical product will be developed using Probac's capabilities in probiotic development and Encap's expertise in drug delivery. The project will be part funded by both a Scottish Enterprise R&D grant and Sweden's Innovationsbron AB.

The use of probiotics in the treatment of C. diff and other AADs has been the subject of great interest lately. Recent studies have shown that by drinking probiotic yogurt drinks, the incidence of diarrhea symptoms can be reduced. However, concerns remain about the effectiveness of these products and the number of live bacteria that can survive passage through the stomach to recolonize the intestine. Encap and Probac intend to create a novel capsule product that will deliver specially selected probiotic strains to the small and large intestine. Approximately 20% of all hospital patients receiving antibiotic treatment will develop AAD, and it is hoped that this probiotic product will help reduce the incidence and severity of diarrhea, the length of stay in hospital, and ultimately the mortality rate from severe cases.

Under the terms of the agreement, Encap will perform all development and manufacturing of the product using their patented DuoCap technology. Probac will be responsible for the supply of selected microbial strains and for conducting a volunteer study to confirm the benefits of probiotic delivery to the lower intestinal tract using this technology.

Once the initial volunteer study has been completed, a partner will be sought to provide funding for a proof-of-principle clinical study in a hospital environment to demonstrate an acceptable level of efficacy and patient benefits. The partner will also help with subsequent commercialization of the product.

Solvay Licenses Exclusive Development & Commercial Rights to Lipocine's Oral Testosterone

Solvay Pharmaceuticals, Inc. recently announced a license agreement with Lipocine Inc. that provides Solvay Pharmaceuticals exclusive rights to develop and commercialize an oral formulation of testosterone.

Using its proprietary oral Lip'ral technology, Lipocine has developed an investigational oral testosterone product. Solvay Pharmaceuticals plans to initiate a development program to further study the investigational product as an oral treatment for male hypogonadism also known as low testosterone (low T).

"This agreement further demonstrates Solvay Pharmaceuticals' commitment to men suffering from low testosterone," said Dr. Stephen Hill, President, Solvay Pharmaceuticals, Inc. "As the market leader in the field, we will apply our expertise in the treatment of low testosterone to the development of an oral testosterone replacement therapy. This compound has the potential to be the next major innovation in the management of low testosterone."

"We are quite pleased to partner with Solvay Pharmaceuticals, a leader in testosterone replacement therapy, to bring this innovative treatment option to patients," said Dr. Mahesh Patel, President and CEO, Lipocine Inc.

Under the terms of the agreement, Solvay Pharmaceuticals will make an up-front payment, make future milestone payments, and pay royalties based upon product sales to Lipocine. Solvay Pharmaceuticals will also fund Lipocine development expenses associated with this program.

It is estimated that hypogonadism, also known as low testosterone, affects more than 13 million men in the US aged 45 and older. Because signs and symptoms of low testosterone are subtle and often overlap with other common medical conditions, low testosterone is frequently undiagnosed. Signs and symptoms of low testosterone may include low sex drive, erectile dysfunction, fatigue, depressed mood, reduced muscle mass and strength, increased fat body mass, and decreased bone mineral density.

Lipocine Inc. is a privately held pharmaceutical company leveraging its proprietary drug delivery technologies to commercialize innovative pharmaceutical products. Lipocine business objectives are to develop products with established drugs that have patient-friendly attributes, such as faster absorption, lower dose, fewer side effects, less frequent dosing, and no food effect.

Eurand Announces FDA Approval of EUR-1048 (Lamictal ODT), Co-Developed With GlaxoSmithKline

Eurand N.V., a specialty pharmaceutical company that develops enhanced pharmaceutical and biopharmaceutical products based on its proprietary pharmaceutical technologies, recently announced that the US FDA has approved EUR-1048, to be marketed as GlaxoSmithKline's Lamictal ODT (lamotrigine) Orally Disintegrating Tablets. Co-developed by Eurand and GSK, Lamictal ODT uses Eurand's AdvaTab orally disintegrating tablet (ODT) and Microcaps taste-masking technologies to provide Lamictal in a pleasant-tasting tablet that disintegrates on the tongue and that may be taken with or without liquid.

Lamictal ODT is indicated for the long-term treatment of Bipolar I Disorder to lengthen the time between mood episodes in people 18 years or older who have been treated for mood episodes with other medicine. It is not known if Lamictal ODT is safe or effective in children or teenagers under the age of 18 with mood disorders such as bipolar disorder or depression. Lamictal ODT is also used together with other medicines to treat certain types of seizures (partial seizures, primary generalized tonic-clonic seizures, generalized seizures of Lennox-Gastaut syndrome) in people 2 years or older or alone when changing from other medicines used to treat partial seizures in people 16 years or older. It is not known if Lamictal ODT is safe or effective when used alone as the first treatment of seizures in adults. Lamictal ODT will be available in 25-, 50-, 100-, and 200-mg strengths and is expected to be available in pharmacies in early July 2009.

"We were delighted to have the opportunity to use our AdvaTab and Microcaps proprietary technologies to co-develop Lamictal ODT with GSK, and we look forward to a successful launch," said Gearoid Faherty, Chairman and Chief Executive Officer of Eurand. "We see Lamictal ODT, Eurand's fifth FDA-approved drug since 2001, as another clear demonstration of the breadth of our drug formulation expertise and the depth of our pipeline."

Eurand will receive an undisclosed milestone payment upon launch, revenue for manufacturing Lamictal ODT tablets for GSK, royalties on net sales of the product, and milestone payments in connection with Lamictal ODT achieving predetermined sales levels in the US marketplace.

Net sales of Lamictal, one of the world's top 60 pharmaceutical products based on annual sales, were $1.3 billion in the US in 2008. Eurand retains exclusive worldwide manufacturing rights to Lamictal ODT and, subject to certain conditions, either Eurand or GSK may have certain rights to commercialize the product in a particular country outside the US.

Lamictal ODT uses a combination of two of Eurand's novel drug delivery technologies. AdvaTab orally disintegrating tablet technology uses Eurand's proprietary granulation and tabletting processes that allow the tablet to disintegrate rapidly in the mouth without chewing or the need for liquid. AdvaTab is distinct from conventional ODT technologies because it can be combined with Microcaps taste-masking technology. Microcaps taste-masking technology provides a coating that encapsulates drug particles, forming a barrier between the medication and the taste buds while still allowing the drug to dissolve in the stomach.

Roche Partners With Tekmira for its Delivery Technology to Advance RNAi Product Candidates

Tekmira Pharmaceuticals Corporation recently announced it has entered into a product development agreement with global healthcare company Roche to advance Roche's first two RNA interference (RNAi) product candidates into human clinical testing. Both of the product candidates will be based on Tekmira's stable nucleic acid-lipid particle (SNALP) technology.

Under the terms of the product development agreement, Roche will pay Tekmira up to $18.4 million to support the advancement of the product candidates to the filing of IND applications. Tekmira is also eligible to receive up to $32 million in milestones plus royalties on product sales as the first two products are advanced through development and commercialization based on Roche's access to Tekmira's intellectual property under previously announced agreements.

"We are extremely pleased to be working with Roche, a global pioneer in the development of important therapeutic products and a leader in the RNAi field," said Dr. Mark J. Murray, Tekmira's President and CEO. "This agreement is consistent with our strategy of working with leading pharmaceutical companies to help them advance products based on our SNALP technology, and to leverage this work in order to advance our own products. At the same time, the funding from Roche will further strengthen our balance sheet and extend our cash resources as we execute on our business plan of advancing novel RNAi products."

"We are enthusiastic about the potential of RNAi therapeutics for patients with hard-to-treat diseases," added Dr. Louis Renzetti, Head of RNA Therapeutics at Roche. "We believe Tekmira's SNALP is the leading lipid nanoparticle delivery technology, and we are confident that Tekmira's research and manufacturing capabilities will help us to meet our product development objectives."

Roche will use Tekmira's SNALP technology for two RNAi product candidates. Each of the product candidates will be comprised of Roche proprietary small interfering RNAs (siRNAs) encapsulated in a Tekmira proprietary SNALP formulation. Roche and Tekmira expect an IND for the first product candidate to be filed before the end of 2010. Tekmira will develop and manufacture the drug product for use in all preclinical studies, and both companies will collaborate on the preclinical testing. The agreement also provides that Tekmira will manufacture one batch of clinical product for a Phase I clinical trial.

RNAi drugs have the potential to treat human diseases by "switching-off" disease-causing genes. The technology, representing one of the most promising and rapidly advancing frontiers in biology and drug discovery, was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi drugs, such as siRNA, require delivery technology to be administered systemically. In preclinical studies, Tekmira's SNALP technology has been shown to be a safe and effective way to deliver RNAi drugs to disease sites. Tekmira believes it has a leading intellectual property position in the field of siRNA delivery.

Emisphere Announces SNAC Carrier Achieves Provisional GRAS Status, Strategic Alliance & Milestone Payment

Emisphere Technologies, Inc. recently announced the company has been informed by an independent expert panel of scientists that its Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate (SNAC) carrier has been provisionally designated as Generally Recognized as Safe (GRAS) for its intended application in combination with nutrients added to food and dietary supplements. Following a comprehensive evaluation of research and toxicology data, Emisphere's SNAC was found to be safe at a dosage up to 250 mg per day when used in combination with nutrients to improve their dietary availability. Achieving GRAS status will establish Emisphere's carrier as exempt from premarket approval.

Emisphere anticipates that the final step before achieving final GRAS status for SNAC will be the publication, currently scheduled for July/August, in the International Journal of Toxicology, of two peer reviewed papers describing the toxicology of SNAC.

The company also announced a strategic alliance intended to expand the application of Emisphere's Eligen Technology and AAIPharma's drug development services. AAIPharma Inc. is a global provider of pharmaceutical product development services that enhance the therapeutic performance of its clients' drugs. The company works with many pharmaceutical and biotech companies and currently provides drug product formulation development services to Emisphere.

Emisphere's proprietary Eligen Technology is a unique and improved delivery method for therapeutic molecules and nutritional supplements. The key benefit of Eligen Technology is that it improves the ability of the body to absorb small and large molecules. These molecules with poor bioavailability may be currently delivered by injection. The Eligen Technology can be applied to oral administration or other routes of administration other than oral, such as buccal, rectal, inhalational, intravaginal, or transdermal.

Lastly, Emisphere announced it has received a $500,000 milestone payment from MannKind Corporation in connection with MannKind's recent filing and the US FDA's acceptance of MannKind's NDA for AFRESA®, an ultra rapid-acting insulin.

In February 2008, Emisphere sold to MannKind certain Emisphere patents and a patent application relating to diketopiperazine technology for a total purchase price of $2.5 million. An initial payment of $1.5 million was received in February 2008. An additional $500,000, now received, was to be paid no later than July 5, 2009. The remaining $500,000 is due to be paid to Emisphere no later than October 5, 2010. MannKind is seeking FDA approval of AFRESA for the treatment of adults with type 1 or type 2 diabetes mellitus for the control of hyperglycemia.

First-Ever 24-Hour Oral Liquid Sustained-Release Formulation Submitted to the FDA

Tris Pharma, a privately owned specialty pharmaceutical company that develops innovative drug delivery technologies, recently announced that the US FDA has accepted its first two NDAs for once-daily formulations of a cardiovascular drug. If approved, Tris Pharma's liquid and solid dosages will provide an alternative to the currently available immediate-release, twice-a-day tablet.

LiquiXR is the liquid dosage form of the company's proprietary OralXR platform. Only two extended-release liquid pharmaceuticals exist today. If the FDA approves Tris' liquid formulation, it will be the first sustained-release liquid commercialized in more than 25 years and the first-ever liquid dosage form available in a 24-hour extended-release formulation.

"LiquiXR offers the compliance and convenience benefits of other controlled-release dosage forms and allows physicians a limitless number of dose options because the dose can be customized through titration," said Dr. Yu-Hsing Tu, Head of R&D at Tris. "This will be particularly valuable as the technology is leveraged in the development of CNS, pain, and other narrow therapeutic window compounds."

The company's OralXR platform also includes other dosage forms, such as ODT, chewable tablets, and film strips. Using these technologies, Tris Pharma is developing products that are targeted toward pediatric and geriatric populations and other patients who have trouble swallowing a traditional pill.

"The FDA's acceptance of our two NDAs validates Tris' OralXR platform, and is an important milestone for the company," added Tris Pharma CEO and Founder Ketan Mehta. "We have an exciting future, with a robust pipeline of more than 20 extended-release products in different therapeutic categories currently in development."

Tris' drug delivery technology also offers other improvements over those used for the older products. To manufacture the cardiovascular drug, the company uses a safe water-based process, replacing the need for the toxic organic solvents used in the older products. This new aqueous solvent, coupled with Tris' patent-pending manufacturing process, also improves product stability and batch-to-batch uniformity.

Tris Pharma is a privately owned, product-focused, specialty pharmaceutical company engaged in the research and development of innovative drug delivery technologies. Through its OralXR platform, Tris has pioneered the delivery of sustained release in the liquid, chewable/ODT, and strip dosage forms, where by patients do not have to swallow a pill. Tris' Nobuse platform provides abuse-deterrence for opioids and other abuse-prone drugs. The company has more than 30 Rx and OTC products in development with pharmaceutical partners.

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

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The Curious Case of Thrifty Patent Procurement

By: Clifford M. Davidson, Esq.

Throughout the past few years, the pharma industry has steadily attempted to move toward less-costly patent procurement. This move is being made not only by strapped-for-cash drug delivery and specialty pharma concerns, but by big pharma as well. The author is often astounded by Pharma companies that are willing to spend millions of dollars to litigate a patent, but balk at the initial cost of obtaining the best patent possible where future litigation is possible or even inevitable. The following provides the benefits and pitfalls of such strategies from the viewpoint of the undersigned patent attorney.

OFFSHORE PATENT DRAFTING

A trend has emerged over the past few years based on the aggressive marketing of patent services by patent agencies based in India. Obviously, the pay scale is much lower in India. There is no shortage of highly educated scientists in India, however. These patent agencies have been offering their services to US law firms (for outsourcing overflow patent work) and directly to Pharma concerns. Any number of services is being offered, ranging from patent drafting to patentability and invalidity searches.

One issue that arises from the use of such services concerns the exportation of new technology across US borders without the permission of the US Government. Typically, a US patent application is awarded a foreign filing license during the preliminary stages of US patent prosecution (typically within 6 months of filing) as part of the completion of formalities. However, published in the Federal Register (73 Fed. Reg. 42781) this past summer, it was reiterated that the exportation of subject matter abroad pursuant to a USPTO-issued foreign filing license is limited to purposes related to the filing of foreign patent applications (see 37 C.F.R. § 5.15). The Notice states unequivocally that a foreign filing license from the USPTO does not authorize exporting of subject matter abroad for the preparation of patent applications to be filed in the US. Those who wish to export subject matter for the purpose of having a patent application prepared for US filing are advised to contact the Bureau of Industry and Security (BIS) at the Commerce Department in order to secure the appropriate clearances.

The advantage of offshore patent preparation in a low pay-scale country is clear - significantly lowered fees. But at what cost? The pharmaceutical field is littered with relatively worthless patents written by technicians who understood the technology but were not particularly patent savvy. There is a difference between one who is knowledgeable about a technology and one who is knowledgeable about the technology and understands how to write patent claims that maximize the value of that technology given the many forks in the patent-drafting road - Orange Book listability, capturing potential design-around strategies, covering all important aspects of the invention in a variety of different strategically designed claims, etc. The other factor to consider in offshore patent preparation is the relative hassle of obtaining Government permission to export the information, and the lack of a personal connection between the inventor(s) and patent draftsperson.

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FIXED-COST PATENT FILING

A number of companies are seeking to control patent costs by seeking "fixed" costs for the preparation of a patent application by outside patent firms, and further seeking to control the costs of the subsequent patent prosecution by seeking "price-fixed" patent amendments and related documents. Controlling costs in an abysmal economy is a necessity, without question. However, buyer beware. Outside counsel working on a fixed budget cannot possibly spend as much time on a fixed budget as they can on a less stringent budget, nor can they carefully consider all potentially important issues.

The fixed-cost model can easily lead to less interaction between inventor and patent counsel resulting in relevant information being left out of the patent filing. This can take the form of incomplete disclosures that do not meet the requirements of the USPTO regarding (a) written description (the application must adequately identify that subject matter that the inventor deems to be his/her invention), (b) best mode (the application must describe the "best mode" of carrying out the invention), and (c) enablement (the patent application must provide a disclosure that enables one of ordinary skill in the art to practice the invention). These problems, if present upon the filing of a patent application, cannot be cured later - new information is considered "new matter" by the patent offices of the world, and can only be added by filing a new patent application. Given the fact that most patent filings now publish within 18 months of original filing date, and most applications do not receive a first examination anywhere prior to publication, it is likely that the defective filing will become "prior art," affecting the ability of the inventor to patent an application with corrected and/or additional information, which is not entitled to the original filing date. Worse yet, such actions are unlikely to correct foreign filed applications, or if possible may lead to incurring huge costs for foreign filings anew.

This discussion leads to the problems one faces in obtaining European patents. The European Patent Office (EPO) has different standards for patentability than the USPTO. Moreover, and just as importantly, the EPO has different standards for making claim amendments. Claim amendments in the EPO must be literally supported by the specification - one cannot wordsmith to arrive at a description taking the general disclosure of an application to describe a feature in the European claims that is different than prior art relied upon by the European Examiner. While it is not possible for a patent practitioner to predict every issue that can arise during patent prosecution and include suitable descriptive language to address such issues, the less time and energy put into the drafting of a patent application, the more difficult and costly it becomes to overcome such issues later during prosecution of that application.

The fixed-cost model also does not lend itself well to the outside patent counsel being able to identify and cover potential third-party design-around strategies. Does this mean that I am steadfast against fixed patent costs in all situations? No. To say that would be ignoring the current economic climate and the needs of industry to control costs at a time when funding is difficult to obtain, at best. I do have a few suggestions for companies working under such financial constraints with respect to patent filings.

First, I would suggest that the inventor or another in-house person who understands the technology and has some basic understanding about patents draft as detailed a disclosure as possible - a few sentences and copies of lab notebook pages does not suffice. The more information provided to the outside patent attorney, the less time they need to spend identifying what is missing - and the more time they can spend on drafting suitable patent claims.

Second, I suggest the company have in-house patent searches performed, eg, on free on-line databases, such as the USPTO search engine or Google patents. The search strategy

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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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and results should be provided to the patent attorney as well. This enables the outside patent attorney to better identify the potential prior art and to better identify the proper claim scope.

Third, in my opinion, fixed-cost patent work should be limited to inventions that are not crucial to the success of the company. In addition to covering key aspects of new or developing proprietary technologies, patent applications are often filed and maintained for alternative processes of manufacturing, alternative formulations, compositions that are not going to be developed commercially, and the like. Those types of patent filings are more the candidate for limiting costs, in the author's opinion.

THE "I CAN DRAFT IT MYSELF" SYNDROME

I know many very smart people in Pharma who are patent savvy. Being patent savvy places one in a better position to contribute to the patent disclosure and the scope of the ultimate claims. Some inventors that I know are quite capable of writing a strong disclosure and claims. On the other hand, inventors should be careful about assuming that being patent savvy equates to being able to act as their own patent counsel. Some pitfalls that I have seen throughout the years includes choosing what to include and not include in the patent specification, not adequately explaining in useful language important differences between the new technology and the prior art, not providing adequate definitions of important parameters, lack of a clear understanding of how the prior art may be applied against a new invention, the devising of a successful strategy to obtain useful patent protection, and not adequately considering the full scope of the invention to ensure that possible alternatives are encompassed. Additionally, the drafting of claim language must be done carefully and with thought as to the use of each word and phrase and how they should be interpreted (or might be misinterpreted) by others. This is not just a problem for inventors - patent attorneys who are not familiar with the technology, the field, or are otherwise not savvy with respect to the invention or patent drafting suffer from the same problems.

Why is this important? One of the key moments during patent litigation is when the court determines what the claims mean, commonly referred to as "claim construction." The very words included in the specification to explain the invention (and the claims), or lack thereof, can have a profound effect on the scope of claim coverage. In *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), the Federal Circuit held among other things that the words and descriptions in the specification can be used to (narrowly) interpret the claims in certain situations.

That is not to say that patent attorneys do not welcome detailed reports or drafts of an invention disclosure. Certainly, this provides the patent attorney with the tools needed to draft a valuable application, and is a cost-cutting measure for the client. On the other hand, I have spent many hours "rehabilitating" patent drafts written by inventors - this can actually wind up being more costly than letting the patent attorney start working with the invention at an early stage.

The "I can draft it myself syndrome" can be just as dangerous during prosecution. In *Festo Corp. v. Shoketsu Kinzoku Co. Ltd.*, 535 U.S. 722 (2002), the Supreme Court held that there is a presumption that a claim amendment was made for a reason related to patentability, with limited avenues to rebut this presumption. *Festo* significantly expanded the doctrine of prosecution history estoppel, which in turn means that any changes made to the claims has the potential to turn into a reason why the alleged infringing product doesn't infringe the claim(s) under the Doctrine of Equivalents. Everything one writes in a document that goes to the patent office becomes a public record. Well-intentioned arguments and claim changes don't always play out well, even if a patent ultimately results: unnecessary estoppels to patent claim

coverage may be avoidable via the use of experienced patent counsel.

A well-drafted patent application is also crucial in view of the Supreme Court's decision concerning obviousness in *KSR v. Teleflex*, 550 U.S. 398 (2007). In *KSR*, the Supreme Court held that in order to demonstrate obviousness it was not necessary to satisfy the teaching/suggestion/motivation (TSM) test, and that an invention could indeed be found to be obvious in view of the "obvious to try" standard. Although the full impact of the *KSR* decision is still in its infancy, it is already quite clear to patent practitioners that there is a real need to develop a patentability strategy prior to filing.

IS HIGH COST ALWAYS BETTER?

High cost is certainly not always better, and the bigger the firm does not necessarily translate into a better product. It is important for the company that does not have in-house patent counsel to consider whether they have developed a useful patent strategy. Are filings being undertaken prior to publication of articles or disclosure to third parties without the benefit of confidentiality? Are decisions being made to control costs with respect to non-core technology? Is the patent strategy being vetted at an early stage, or is it reactionary to situations that arise when it may be too late?

SUMMARY

It is probably not the best time to argue that resources should be allocated to intellectual property during the midst of a deep recession. However, in the end, it is often the intellectual property that has a strong hand in determining the value of a new product, or even the company itself. Therefore, well-reasoned decisions should be made about how to allocate funds for patent filings, and when to cut corners… and when not to. If I have provoked thought about this topic via this article, then my purpose has been served. ◆

BIOGRAPHY

Clifford M. Davidson, Esq. is a founding partner at Davidson, Davidson & Kappel, LLC, an Intellectual Property law firm with offices in New York City and Frankfurt, Germany. He counsels pharmaceutical clients in pharmaceutical patent-related matters, including patent prosecution, freedom to operate and infringement opinions, due diligence and tech-transfer, and litigation (including ex parte and inter partes proceedings worldwide). He has assisted specialty pharma and drug development companies to create significant patent portfolios, and the patents he has written and the patent portfolios he has created have been recognized as creating significant value for his clients. He has written patents covering virtually all areas of drug development, and has pioneered strategic patent focus on the pharmacokinetic profiles and the pharmacologic activity of drug/drug formulations. Mr. Davidson earned his BS in Pharmacy and his JD from Rutgers University and is a member of the New York and New Jersey Intellectual Property Law Associations, the American Pharmaceutical Association, and The Controlled Release Society. His area of expertise includes new chemical entities; new pharmaceutical formulations (including controlled-release oral dosage forms, injectables, transdermals, ophthalmics, inhalation, intranasal, sublingual, suppository, and implantation administration); new combinations of previously known drugs; new modes of administration of previously known drugs; method of treatment; pharmaceutical excipients; and methods of preparation.

Molecular Responsibility

The SuperHero Complex

Part III of a Six-Part Series

By: Derek G. Hennecke, MBA

Lately I've been feeling a lot of pressure to make my company into a superhero. I see it everywhere. Society is pushing companies across numerous industries to unite into super organizations, like 3M or Berkshire Hathaway. In our industry, the drive is to create a one-stop shop to take a drug from cradle to market seamlessly.

It sounds great, doesn't it? Especially in today's market, where pharmaceutical companies of all sizes are under extraordinary pressure to survive and thrive. Who wouldn't want a superhero for their molecule? A single organization that would arrive in a flash, bravely rescue your molecule from obscurity, wrap it in its capable arms, and deliver to you a perfect, market-ready drug in an economic and efficient manner. It would be a single outsourcing partner with high-quality, timely execution, subject matter expertise, and the proven ability to not only advance your molecule through its current development stage, but take it seamlessly through to market. Let me tell you, if I thought this was the future, Xcelience would be well on its way to becoming that company by now.

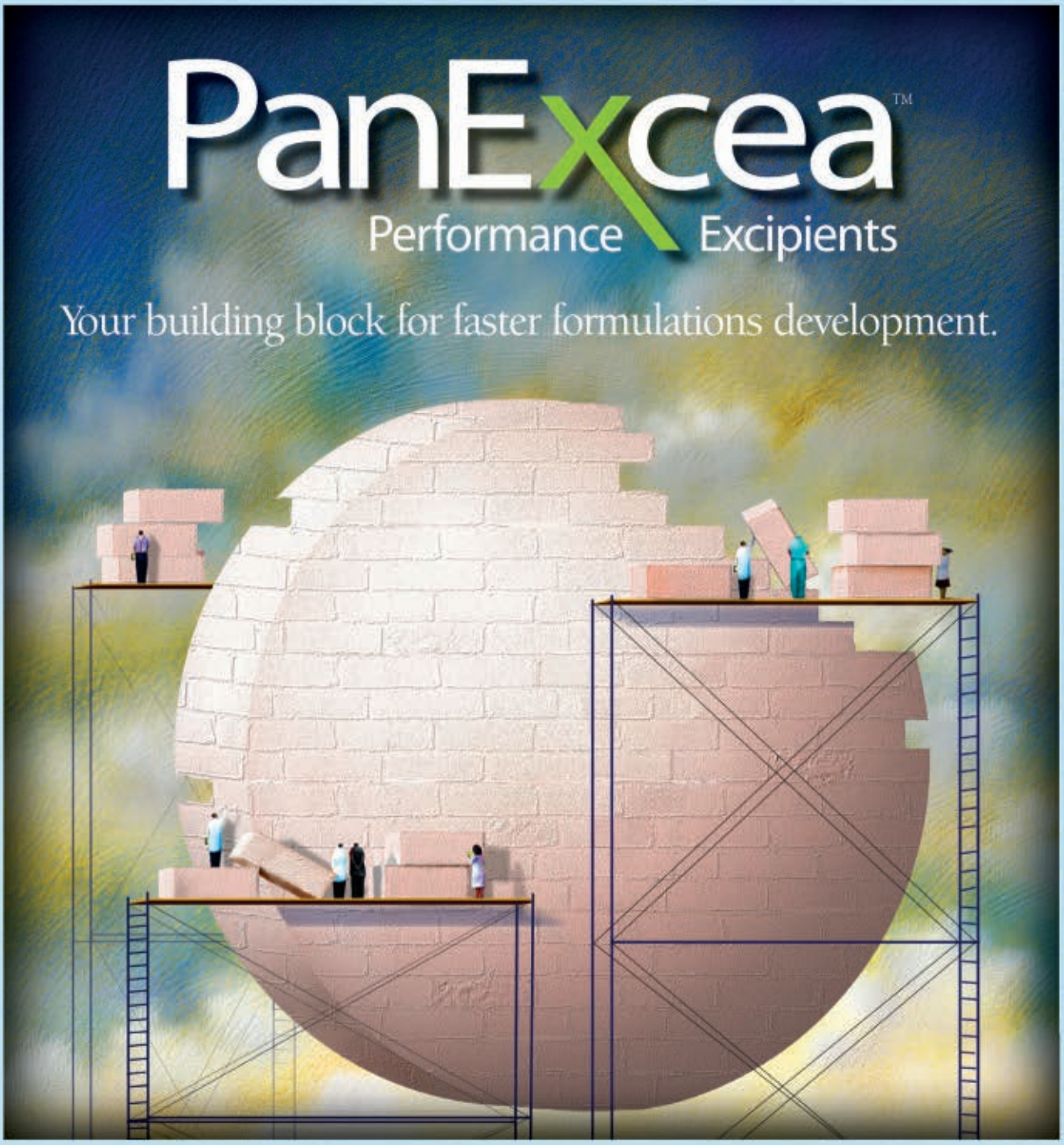
Now let me tell you why that will never, ever happen. It's the Peter Principle, applied to organizations. Do you remember this novel? About to celebrate its 40th anniversary, Peter and Hull's management book, The Peter Principle, is a harsh read. A wicked and witty treatise, the central tenet is that success drives individuals up the institutional hierarchy. But being good at one job doesn't necessarily prepare you to be good at the next job up the ladder. At some point, Peter and Hull argue, every individual reaches their own level of incompetence. Promotions end, and there they remain, clogging the flow of business, like little armies of Dilbert's pointy-haired boss.

Since their book was written, a lot has changed. The rate of merging, divesting, and conglomeration in the corporate world has skyrocketed. As a result, I would argue that Peter and Hull's logic can now also be applied to the organizational level.

Competent organizations are pushed by shareholders and general industry expectations to grow and achieve more and more. Why shouldn't a firm with a solid reputation and strong operational model for, say, toxicology acquire a clinical bed facility? Doesn't success in one arena predict success in another? Organizations that fail to maintain skyrocketing growth risk being left behind.

Our industry is extremely susceptible to the lure of superhero status. The notion of providing an A to Z service model that mimics the drug development continuum is so tempting to those of us one-step removed from the innovator bench.

At one point, our company was headed in that direction. In fact,



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10 years ago, there were a lot of companies attempting the superhero model of contract provider organizations. Xcelience itself is a divesture, born from a parent organization with that goal. The problem is this: to become an A to Z provider, it's simply impossible to do it all under one roof. There will be multiple locations. If there are multiple locations, it's no different than if they were separate companies. There will be hand-offs and communications gaps. And worse.

Here's how it goes. Service K and Service L have separate clients, service concerns and divisional goals. Let's assume, optimistically, that they offer an excellent level of attentiveness within the silo. Service K has finished its job and is on to the next. Service L might benefit from learning something from Service K, but their sales teams don't talk, and their scientists don't know each other more than in passing. So, how will the knowledge be transferred? And what happens when there's a conflict?

We all know what happens. There are endless internal meetings, finger-pointing, and in many cases, appeals to upper management for decisions. Now upper management, which is probably not an expert in either Service K or Service L, makes the decision.

When your molecule is mired in this conflict between Service K and Service L, will you be able to get your molecule out of the muck, or will you be contractually or otherwise too far committed and end up sitting tight through it all? Is this what's best for your molecule? It's hardly the superhero you dreamed of.

I could go on and on. Service K is paying three times what the regional market would offer it for photocopying and accounting services because head office wants synergies. It passes these costs on to clients. Both services are using an antiquated computer system because it would be hugely costly to change to a newer more effective system throughout the whole organization, and besides, the ideal system for K is not the same system that would best serve L. Managers of both plants spend roughly 50% of their time meeting head office reporting requirements and lobbying within the organization for resources. Time that would otherwise be spent servicing customers, cutting costs, and innovating.

You may be thinking that many of these are matters of business, not of science, but the two are inextricable. Inefficiencies anywhere in the company ultimately take time and resources away from scientists.

Drug development is both an arduous and nimble act, with each step requiring an agile, expert, customer-driven contract provider. Everyone talks about partnership, but the point I want to emphasize is shared concern. Shared concern means that you and your outsourcing team both feel a sense of urgency and responsibility. The CRO should make you feel like its lab is an extension of your own facility through close project communication, access to scientists, dedicated equipment, or FTE programs. Your people should be allowed in their plant, or transfers should be coordinated.

Shared concern means the CRO understands that you have limited funding, and so you need the right technology at the right place at the right time. It understands that you might need to get your compound into an animal model in less than 30 days so your product can be evaluated. Similarly, a company with a poorly soluble compound in early drug development will experience an immediate benefit from an outsourcing firm capable of providing alternatives to traditional formulation, such as API into capsule or liquid-filled capsule services that can accelerate their path to Phase I studies.

Shared concern means that your outsourcing firm will measure performance in the context of your goals, not its own. The CRO will pick the right people with the right expertise. It takes focused expertise and focused customer service to be the best.

The era of the superhero organization is declining. Remember when the big companies were stalwarts in economic storms? How can it be that GE shares traded in March for the less than the cost of a pack of light bulbs? At Halloween, my wife suggested giving out GM shares instead of candy - the cost worked about the same. Citigroup and Bank of America have fallen a long way from their iconic pedestals.

What is the right size for an organization? It's the size at which you can continue to be nimble and competent, without compromising or over-extending. Any organization simply needs to be the best at what it does and not take any action to compromise that position. It needs to pick the right people with the right expertise for the job and make sure they have the resources to do it to the best of their ability. That's it.

It's the philosophy attributed to US Airways Captain Sully Sullenberger, who after his dramatic landing on the Hudson River, said, "I know I speak for the entire crew when I tell you we were simply doing the job that we were trained to do." Captain Sullenberger and his crew did what they were trained to do and did it superbly. They were trained to fly the plane and to handle emergency scenarios. US Airways didn't try to also train them to maintain the aircraft, de-ice the wings, and fuel the plane. Only to fly it!

Xcelience trains scientists to deliver molecules safely and economically through the formulation process. Our people have the necessary expertise to deal with things when they go as expected, and to find effective and often creative solutions for more complicated compounds. I guess that's our version of landing your molecule on the Hudson River. That's all we do. And we leave the superheroes to the comics' page. ◆

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).

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MIMETIC DELIVERY SYSTEMS

Mimetic Drug Delivery Systems for Release With Specific Molecular Triggers

By: Lisa Brannon-Peppas, PhD

ABSTRACT

Although the field of controlled delivery in pharmaceutical and consumer products has grown exponentially throughout the past decade, most classical controlled-release systems provide only passive release. Some may release due to a change in temperature, and some may rupture due to applied pressure, but few if any can actually respond to the presence of one specific molecule in its environment and release its contents in response to that molecule and that molecule alone. The unique use of molecular imprinting in the Affinimer™ delivery systems allows that sensitivity to become reality.

INTRODUCTION

Recognition in nature is a complex orchestration of numerous interactions between individual atoms and cumulative interactions between secondary structures. For example, the active sites of enzymes are composed of several amino acid residues, which covalently bind ligand molecules in a very specific manner. However, the activity of the site is dependent on the stabilization of the three-dimensional structure by the interactions of hundreds of other residues within the structure of secondary and tertiary domains. The term configurational biomimesis refers to the three-dimensional arrangement of chemical groups that can specifically bind a biomolecule via non-covalent forces. This designed recognition involves analyzing the molecular basis of recognition in biological systems and attempts to mimic similar interactions on a molecular level. Molecularly imprinted polymers (MIPs) are polymers that are formed in the presence of an imprinted compound or targeting chemical, biological, or other molecule such that the imprinted compound may later be removed, leaving an MIP that is able to recognize and bind to the imprinted compound via a binding cavity, perhaps even able to differentiate with isomeric specificity.[1-5]

The design of a precise macromolecular chemical architecture that can recognize target molecules from an ensemble of closely related molecules has a large number of potential applications. The main thrust of research in this field has included separation processes (chromatography, capillary electrophoresis, solid-phase extraction, membrane separations), immunoassays and antibody mimics, biosensor recognition elements, and catalysis and artificial enzymes. However, relatively little attention has been paid to controlled delivery.[6-11]

Configurational biomimesis and nanoimprinting create stereo-specific three-dimensional binding cavities based on the template of interest. Configurational biomimetic imprinting techniques involve forming a pre-polymerization complex between the template molecule and functional monomers or functional oligomers (or polymers) with specific chemical structures designed to interact with the template either by covalent, non-covalent chemistry (self-assembly) or both (Figure 1).

Proper tuning of non-covalent interactions, such as increasing macromolecular chain hydrophobicity, including strong ionic directed recognition sites with hydrophobic domains, or including stronger hydrogen bond donors and acceptors, has been shown to enhance binding and achieve selective recognition in aqueous solutions. Thermodynamic analysis regarding energy contributions of ligand-receptor binding outlines the importance of directed tuning of these parameters in non-covalent recognition.

CONCEPTUAL APPROACH

The Affinimer system is a molecularly imprinted polymer coupled with an active agent that responds in a

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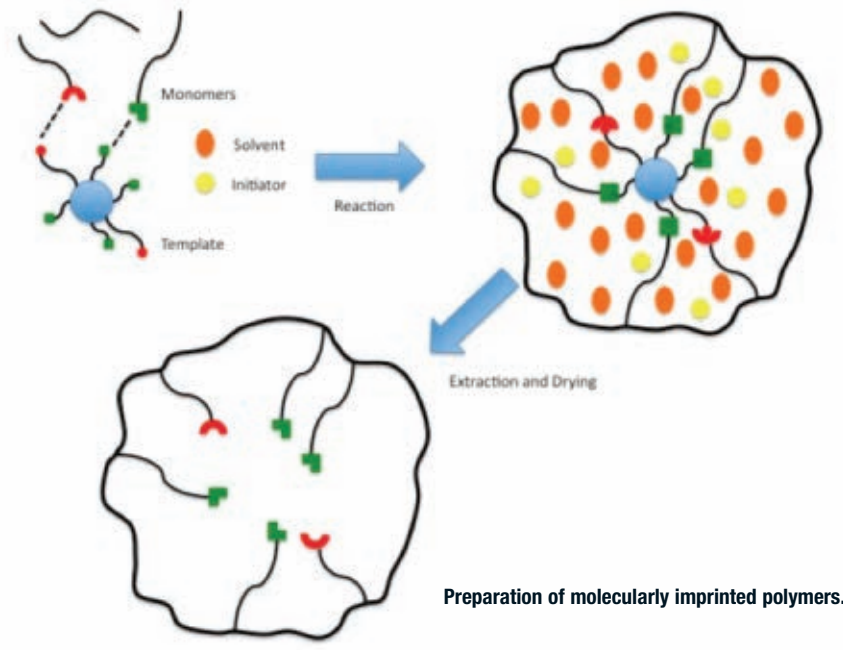
unique way to the presence of the analyte to which it has been imprinted. It does not simply bind and sequester the analyte, but the polymer itself swells and can be made to rupture due to the presence of the analyte. This creates a system that not only recognizes, but recognizes and releases.

This system gives the flexibility to provide release upon not one, but many different possible triggers. For example, one of these intelligently designed systems is currently being used to selectively recognize and respond to variations in analyte concentrations and trigger a controlled, dose-appropriate, level of active determined by this recognition event. Therefore, the primary advantage of this system is that potential Affinimer technology components can be evaluated against numerous analytes and environmental triggers to determine which combination of analyte and Affinimer system components will have the most desirable protection and release characteristics. It is our belief that this range of triggering opportunities will allow utilization of this technology to enhance release performance in a number of products and applications.

Utilization of environmentally relevant analytes, biomarkers, and conditions (ie, the use of a specific molecule or environmental trigger) will allow for selective activated release only at the desired point of use or application. Furthermore, this approach, coupled with the use of a robust intelligent material, will provide the necessary level of protection of active during storage and controlled rate of release upon activation.

These systems allow reversible or non-reversible release, depending on the design of the system, of incorporated active agents. The release will happen selectively due to the presence of the imprinted active agent and can be made to be proportional to the amount of agent present or can be an "all-or-nothing" release when the concentration of the active agent reaches a desired or critical amount. Again, these different formulation types can be prepared using the same basic imprinted polymer structure, then utilizing a variety of controlled-release designs and techniques to give reversible, non-reversible, proportional or complete release of the desired agent. The results that will be presented in this paper confirmed the sensitivity and selectivity of the triggering mechanism as well as quantitative and qualitative release profiles with dose-response curves.

FIGURE 1

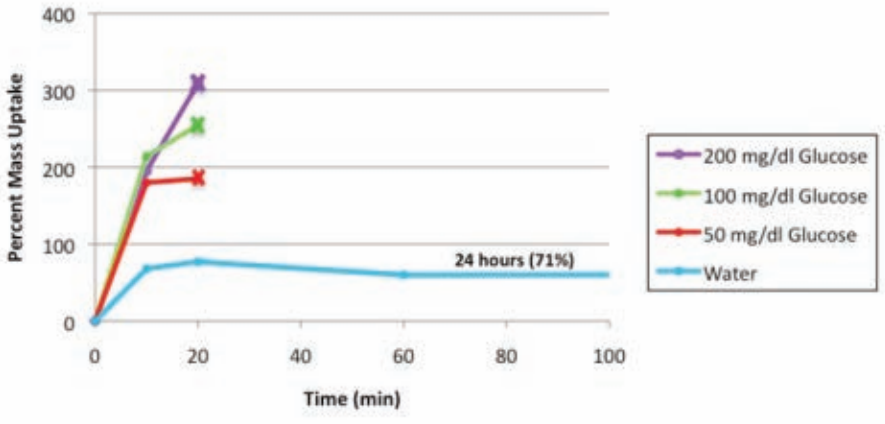


Preparation of molecularly imprinted polymers.

MATERIALS & METHODS

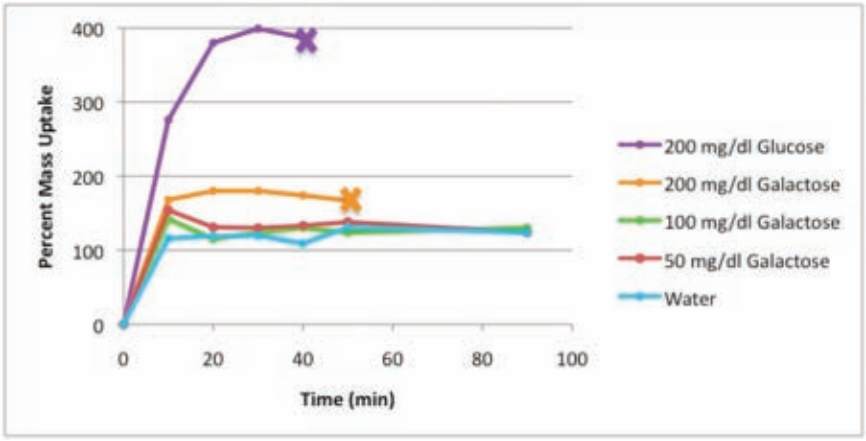
Affinimer films are based on copolymers of methacrylic acid (MAA) cross-linked with triethyleneglycol dimethacrylate (TEGDMA). We have evaluated a number of different monomers as well as cross-linking agents and the combination described here has proven to yield the best balance of imprinted sensitivity,

FIGURE 2



Mass uptake and rupture of molecularly imprinted films due to presence of glucose. Rupture of films is denoted by X.

FIGURE 3



Mass uptake and rupture of molecularly imprinted films due to presence of glucose or galactose. Rupture of films is denoted by X.

selectivity, and physical strength. Many research groups utilize ethyleneglycol dimethacrylate (EGDMA) for the cross-linking agent for MIP systems, but we found TEGDMA cross-linked films to have a much better physical integrity. The concentrations of glucose and lactic acid to which we have exposed these films to evaluate their mimetic nature are concentrations that are physiologically relevant. The high concentration of 200 µg/dl is, oddly enough, a high concentration for both glucose in the blood and lactic acid in human sweat. We present release studies representing our analyte-triggered systems. Nile Blue was chosen as an active surrogate for its hydrophobic nature (similar to essential oils, fragrances, and Vitamin E) and the ability to capture visible results in the laboratory. Geraniol is a potential active agent with a number of applications. More hydrophilic agents have been studied but are not presented here because of space limitations.

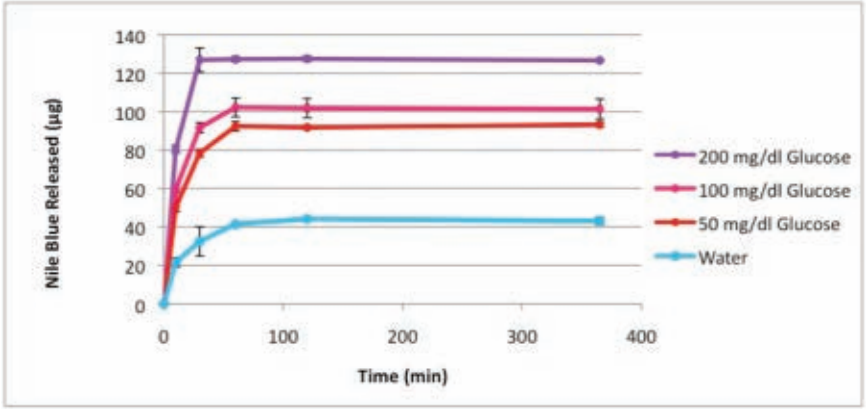
Preparation of Films

Water (4 ml) and ethanol (4.5 ml) were pipetted into a 25-ml glass container. Lactic acid (60 mg) was added, and the mixture was sonicated for 5 minutes, followed by the addition of 0.39 g of methacrylic acid. The mixture was again sonicated for 5 minutes and left at room temperature for an additional 5 minutes. TEGDMA (3.1 g) was added, and the mixture was vortexed. Initiator (DMPA, 50 mg) was added, and the mixture was degassed with nitrogen for 3 minutes.

Thin films were prepared in molds consisting of glass slides with appropriate spacers. When the polymer solution was degassed, the molds were filled with the solution using a 100-ml pipettor, making a note of volume introduced. This was done quickly and with minimum light exposure to avoid undesired early polymerization. When filled, the molds were immediately placed under the UV lamp. The lamp position was calibrated to irradiate the slides at 15,000 mwatts/cm^2. The films were irradiated for 5 minutes at which time they were opaque and solid.

The slides were carefully separated, and the slide containing the film was washed gently in a beaker containing 10% methanol/water. When washed, the films were rinsed with distilled water, placed in plastic containers, and covered with water. Films were washed at room temperature for 5 days with the water being changed twice daily. At the end of the 5 days, the films were carefully removed and allowed to dry. When dry, 7-mm discs were carefully cut out using a standard stainless steel cork borer.

FIGURE 4



Release of Nile Blue from MIP polymers in glucose solutions.

Loading of Films With Nile Blue for Release Studies

For dye loading, 50 mg of Nile Blue was weighed out and dissolved in 100 ml of distilled water, resulting in a final concentration of 0.5 mg/ml. The mixture was vigorously mixed and sonicated for 5 minutes. In the meantime, discs were arranged in a segmented plastic container, and the Nile Blue solution was gently pipetted onto the discs until they were fully covered. The container was covered and left at room temperature overnight.

The following day, the Nile Blue was gently removed by pipettes until the discs were visible. The discs were carefully removed and washed three times with water and then placed in a clean container and covered in water. The container was then placed on a hot plate set to 55°C and left for 3 hours. The water was removed, and the process repeated. At the end of 6 hours, the discs were removed and placed on a clean foil and dried overnight at room temperature. The following day, the discs were ready for study.

Loading of Films With Geraniol for Release Studies

When dry, 7-mm discs were carefully cut out using a standard stainless steel cork borer. The discs were lifted out and placed on a clean dish. For the loading, 100 mg of Geraniol was weighed out and dissolved in 100 ml of 50% ethanol:distilled water, resulting in a final concentration of 1.0 mg/ml.

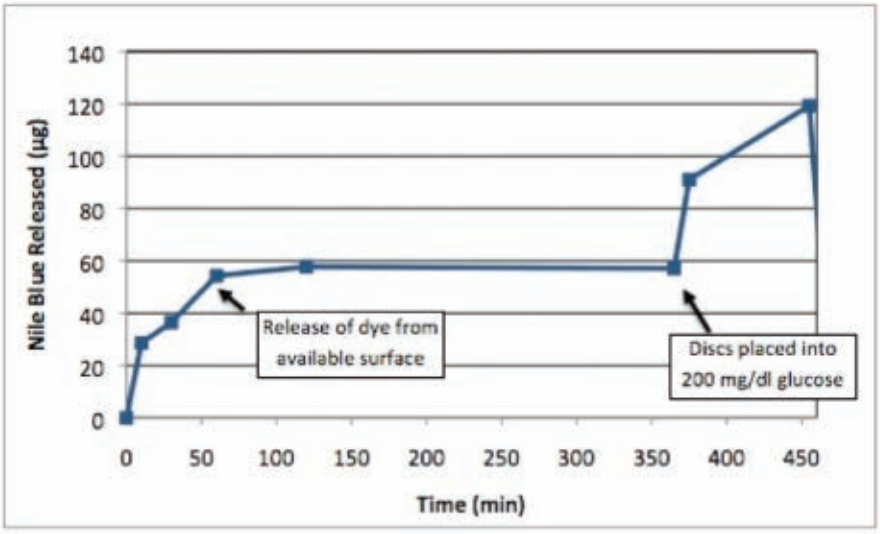
The mixture was vigorously mixed and sonicated for 5 minutes. In the meantime, discs were arranged in a segmented plastic container, and the Geraniol solution was gently pipetted onto the discs until they were fully covered. The container was tightly covered and left at room temperature overnight.

The following day, the Geraniol solution was gently removed by pipettes until the discs were visible. The discs were washed three times with water and placed on a clean foil and left to dry overnight.

Preparation of Lactic Acid Solutions

Lactic acid (200 mg) was weighed out and dissolved in 100 ml of water, resulting in a final concentration of 200 mg/dl. Serial dilutions in water resulted in concentrations of 100 mg/dl, 50 mg/dl, 25 mg/dl, 12.5 mg/dl, and 0 mg/dl. The pH of all lactic acid dilutions was adjusted to a pH of 5.0 by the addition of sodium hydroxide.

FIGURE 5



Release of Nile Blue from MIP polymers in water followed by 200 mg/dl glucose solution.

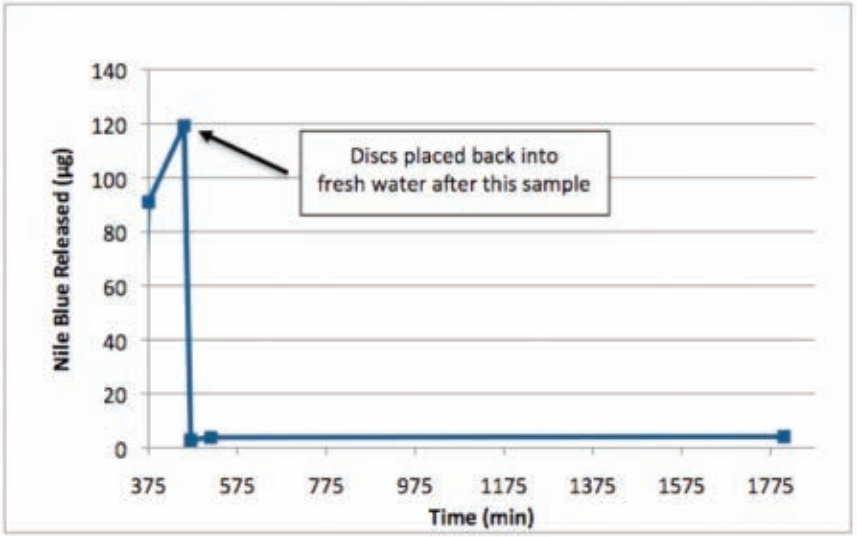
Preparation of Glucose Solutions

Glucose (200 mg) was weighed out and dissolved in 100 ml of water, resulting in a final concentration of 200 mg/dl. Serial dilutions in water resulted in concentrations of 100 mg/dl, 50 mg/dl, and 0 mg/dl.

Incubation Study - Nile Blue

The aforementioned solutions of glucose or lactic acid were used as triggers

FIGURE 6



Release of Nile Blue from MIP polymers in 200 mg/dl glucose solution followed by water.

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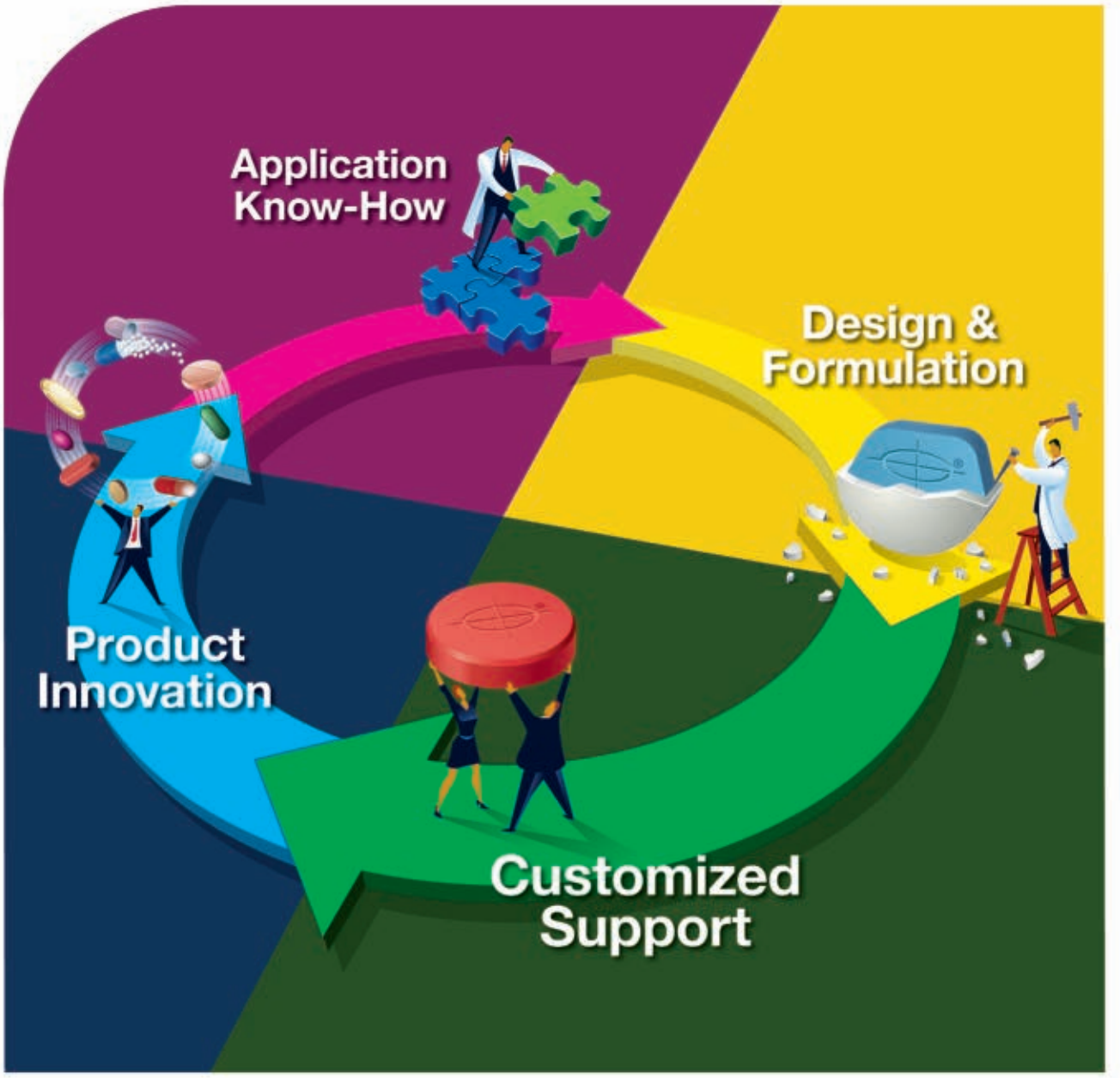

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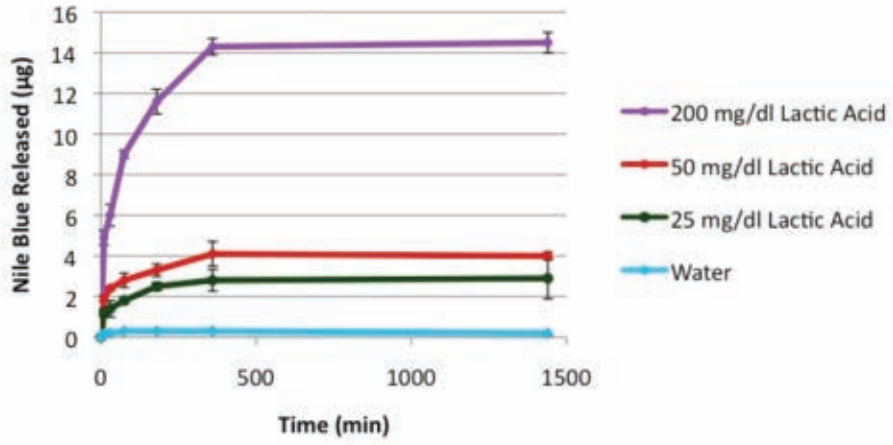
FIGURE 7



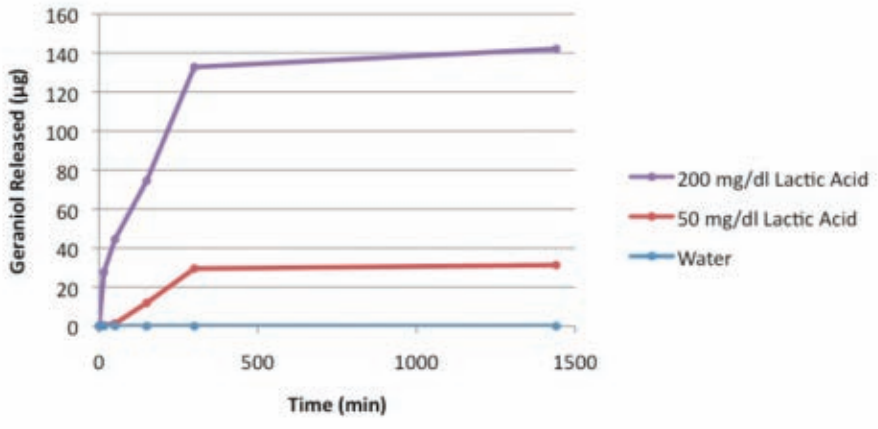
Release of Nile Blue from MIP polymers in lactic acid solutions.

for Nile Blue release. Exactly 4 ml of each solution was placed into three petri dishes kept at room temperature. Stained discs were placed into each dish and the dish covered. Samples were taken (400 µl) into micro-cuvettes at specific time points, and the concentration of Nile Blue present was determined by measuring the absorbance of the Nile Blue solutions at 625 nm.

Incubation Study - Geraniol

The aforementioned solutions of glucose were used as triggers to assess the concentration profile of Geraniol release. Exactly 4 ml of each solution was placed into three petri dishes kept at room temperature. Stained discs were placed into each dish and the dish covered. The stop clock started and samples were taken (100 µl) into HPLC autosampler vials, and the concentration of Geraniol present was determined by injecting onto a C18 HPLC column and monitoring at a wavelength of 195 nm.

FIGURE 8



Release of Geraniol from MIP polymers in lactic acid solutions.

Assay for Geraniol

Geraniol concentration was quantified using an HPLC Diode array detector (DAD) at 195 nm. After blanking with water, samples were injected, and the peak area of the geraniol peak was recorded. Intermixed with the samples were standards of Geraniol of known concentration made from the staining solution. This allowed for the construction of a standard curve to determine the concentration of Geraniol in the incubation samples.

RESULTS & DISCUSSION

Our initial studies were conducted on mimetic polymer films that have been shown to rupture due to the presence of the trigger molecule for which they were prepared. These studies evaluated the swelling of the polymer films in desired solutions of glucose at various concentrations as well as in solutions of extremely similar molecules, such as galactose, which differs from glucose in the -OH and -H bonding at only one carbon atom. We were able to show (Figure 2) that our MIP films swelled at progressively higher levels when in higher concentrations of glucose. Rupture occurred at the earliest times for films in concentrations of 200 µg/dl glucose (high but possible physiological level) with no rupture being seen in water even after 24 hours.

Studies were repeated in the same concentrations of galactose and showed rupture with the glucose solutions, and only the 200-mg/dl galactose solution caused rupture of the polymer film and with a much lower degree of swelling than the film showed in a similar glucose solution. In fact, the swelling in all solutions of

galactose at less than 200 mg/dl showed swelling indistinguishable from that in water with no rupture as shown in Figure 3.

Although the swelling tests showed the structural changes that result when the mimetic polymer films are exposed to their target analyte, the true test of performance would be release of an unrelated compound from those films. This performance was tested with release of Nile Blue as described previously. Figure 4 shows some early release data in which there is still some release into the water as the washing steps had not yet been optimized, but it forms the basis of another reversibility study to follow. Even with some release of Nile Blue in the water, it is clear that the Nile Blue is released in increasing amounts as the concentration of glucose in the solution increases.

The films that had been in water, and that had not showed any significant release for about 5 hours, at 365 minutes were removed from the water and placed in a solution of 200 mg/dl glucose. The release of Nile Blue from these films began almost immediately even though their release in water alone had stopped as shown in Figure 5. To evaluate the true reversibility of these systems, at 450 minutes the films were removed from the glucose solution and placed in fresh water. The release stopped almost immediately as shown in Figure 6.

Imprinted films have also been prepared that are sensitive to the presence of lactic acid, and release of Nile Blue from those films is shown in Figure 7.

Following methods described previously, Geraniol was loaded into MIP films prepared that are triggered by lactic acid. The loading in these films was approximately 145 µg per disc. Figure 8 shows the release of Geraniol as triggered by lactic acid, with nearly 100% release of Geraniol at 200 mg/dl of lactic acid at 24 hours.

SUMMARY

The validity of polymer systems that display analyte-specific recognition has been established over the past several years. Opportunities utilizing this technology have been focused primarily on chromatography. With the work presented here, we show that molecular recognition may be expanded to combine recognition and release, reversible and non-reversible. Further work will show how these intelligent systems can be used for drug delivery, consumer products, biosensors, and other applications.

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BIOGRAPHY

Dr. Lisa Brannon-Peppas is Vice-President of Scientific Operations of Mimetic Solutions. She is known for her research contributions in nanoparticle research, biomaterials, controlled drug delivery, drug targeting, as well as structure-property relationships of polymers. She has published three books and more than 75 research and technical publications. She has received several awards, including the 2008 Award in Chemical Engineering Practice from AIChE.

SUBCUTANEOUS DELIVERY

Subcutaneous Delivery of Small Molecule Formulations: An Insight Into Biopharmaceutics & Formulation Strategies

By: Viral Kansara, PhD; Amitava Mitra, PhD; and Yunhui Wu, PhD

ABSTRACT

Subcutaneous (SC) drug delivery systems are becoming increasingly important injectable techniques to administer a wide range of therapeutic formulations. This review provides an insight into biopharmaceutical and formulation aspects of systemic delivery of small molecules upon SC administrations. The review also provides an overview of the factors that govern SC absorption and describes research and technologies focused on utilizing or modifying SC absorption mechanisms. General guidance on conducting pharmacokinetics and tolerability studies has been briefly covered. Various SC formulation strategies and marketed and in-pipeline SC formulations for delivering small molecules have been thoroughly reviewed. It was summarized that even though SC administration continues to be the main route for the delivery of protein and polypeptide formulations, successful application of SC formulations for the delivery of small molecules with poor aqueous solubility is somewhat limited. Integration of various biopharmaceutical and formulation factors into the overall SC formulation strategies should be carefully considered in designing safe and effective SC drug delivery systems.

INTRODUCTION

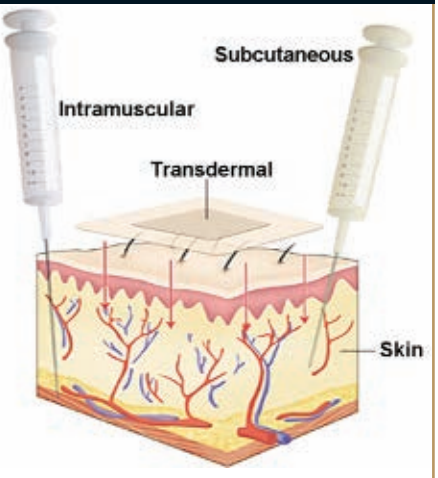
SC injections are usually administered in small volumes (0.5 to 1 mL; upto 2 mL) into the outer surface of the upper arm, anterior surface of the thigh, abdomen, or buttock, and can be self-administered. As shown in Figure 1, during SC administration, a needle is inserted through the epidermal and dermal layers of the skin and into the fatty subcutaneous tissue.[1] Following SC administration, drug molecules enter the systemic circulation by direct absorption into SC blood capillaries or indirectly via absorption into the lymphatic capillaries, which are present within the interstitial space. Therefore, characterization of the SC absorption process is crucial to the design of improved SC drug delivery systems and the interpretation and development of useful pharmacokinetic-pharmacodynamic relationships.

OPPORTUNITIES & LIMITATIONS

SC injections have several immediate advantages over intramuscular (IM) or intravenous (IV) administrations. In contrast to the skilled personnel required for the administration of IV and IM injections, SC injections can be administered by the patient.[2] Slower absorption of subcutaneously administered drug, as compare to IV administration, may avoid the risks of bolus administration. A small needle is required (length of ⅜ to ⅝ of an inch), and the injections are not generally painful and carry a reduced risk of infection and other complications. For infectious agent delivery, SC injection may prove beneficial by restricting the infection to local site of injection. For patients requiring multiple doses, SC injections offer a broader range of alternative sites.[3]

From many perspectives, including reduced pain, improved patient quality of life, reduced cost of patient care, and reduced risk of infection, SC represents a

FIGURE 1



Comparative sites of injection for subcutaneous, intramuscular, and transdermal administration. (http://publications.nigms.nih.gov/medbydesign/chapter1.html)

TABLE 1

Species	Dosing Volumes (mL/kg)
Mouse	10 (40)
Rat	5 (10)
Rabbit	1 (2)
Dog	1 (2)
Macaque	2 (5)
Minipig	1 (2)

Recommended dosing volumes for SC administration routes. Values in parenthesis represent maximum dosing volume per day.

preferred route for administering a drug by self-injection. Many drugs, including insulin and heparin, have been delivered subcutaneously for many years with excellent outcomes. Compared with IV drugs, SC drugs are considered clinically safer and more cost-effective, resulting in higher patient satisfaction.[4]

Despite the aforementioned advantages, there are limited marketed formulations available as SC injection as compare to oral formulations. This may be explained by well-known disadvantages/limitations associated with SC drug delivery. Limited injection volume (not more than 1 to 2 mL) is a major disadvantage of this route of administration.[5] Degradation of the drug at the site of injection may result in poor plasma bioavailability and can be a challenging issue. Moreover, based on the physicochemical properties, potent active compounds may get trapped into the interstitial SC fluid, which may lead to the irritation, precipitation, and concentration-dependant adverse effects. These limitations need to be carefully considered in assessing feasibility of SC formulation development.

PHYSIOLOGY OF SC INJECTION SITE & EFFECT ON ABSOPRTION

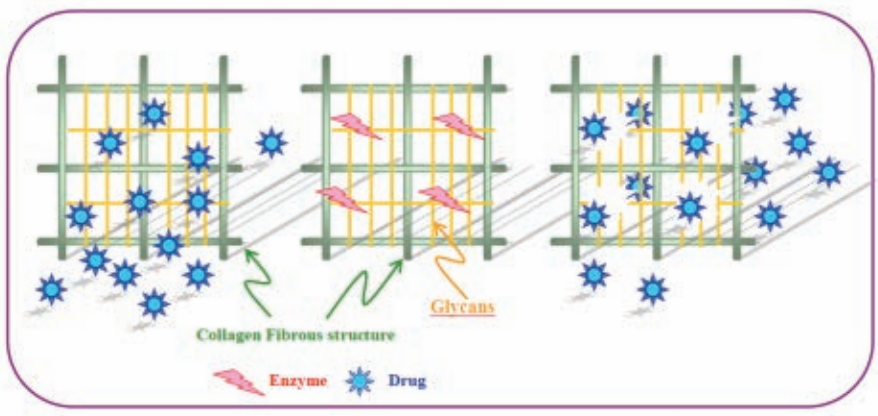
Drug administration by SC injection results in delivery to the interstitial area underlying the dermis of the skin. The interstitium consists of a fibrous collagen network supporting a gel-phase comprising negatively charged glycosaminoglycans (largely hyaluronan), salts, and plasma-derived proteins.[6] The proteins present within the interstitial space are essentially the same as those in plasma, although they are thought to be present at a much lower concentration. The physiology of the SC environment likely dictates the patterns of absorption of both typical small drug molecules as well as macromolecular and particulate systems after SC administration. In general, small drug molecules are thought to be preferentially absorbed by the blood capillaries due to their largely unrestricted permeability across the vascular endothelium together with the high rate of filtration and reabsorption of fluid across the vascular capillaries. By contrast, the absorption of small particulates (generally less than about 100 nm) and macromolecules into the blood is restricted by their limited permeability across the vascular endothelia, and in this case, the lymphatics provide an alternative absorption pathway from the interstitial space.[7,8]

The influence of different SC injection sites on the rate and extent of protein absorption has been shown for several different proteins in humans.[9] Although the extent of absorption is typically consistent for different injection sites, variability in the rate of absorption could be a result of differences between SC blood and lymph flow in different anatomical regions. Passage through the interstitium to the vascular or lymphatic capillaries can also present a barrier to efficient drug absorption after SC administration. Interstitial diffusion of drug molecules is likely to be influenced by their physiochemical characteristics, including size, charge, and hydrophilicity, and their interactions with endogenous components present within the interstitium. Transient enzymatic breakdown of glycosaminoglycans in the extracellular matrix, particularly hyaluranon, have been used to increase the injection volume and bioavailability after SC injection.[10] Simple formulation characteristics, such as drug concentration, injection volume, ionic strength, viscosity, and pH, together with the presence of formulation excipients can also influence the rate of diffusion from the SC injection site.[11] Other factors that can limit the extent of absorption of drugs from the interstitial space include susceptibility to enzymatic degradation at the injection site, cellular uptake by endocytic and phagocytic mechanisms, and simple precipitation, aggregation, or poor resolubilization.[12]

PHARMACOKINETICS FOLLOWING SC ADMINISTRATION

The rate of drug absorption from SC injection site into the blood is proportional to the amount of drug at the site. The penetration coefficient from the site of injection depends on the diffusion coefficient of the drug, the area of membrane exposed to the solution, the distance of diffusion, and the concentration gradient of drug across the absorption membranes. The primary absorption membrane in SC connective tissue is the blood capillary wall. Drug absorption might also be influenced by the buffer capacity of the surrounding tissue and fluids. For example, the rate of absorption

FIGURE 2



A cartoon illustrating a mechanism of enzyme-based SC delivery. Interstitial matrix, primarily composed of collagen fibrils and glycosaminoaglycans, may act as a barrier to drug diffusion following SC administration. Enzyme (Hyuronidase)-based degradation of aminoglycans results in faster diffusion of drug molecules (blue) through the SC space. Basic structure of collagen fibrils remains intact.

TABLE 2

Product/Drug Molecule	Indication/ Therapy	Admin. Mode/ Dose	Formulation Technology	Formulation Characteristics	PK Characteristics
Marketed Formulations					
Imitrex I® Stat Dose Pen Injection (Sumatriptan succinate)	Migraine/Acute	SC: solution (12 mg/mL)	Imigran Injection (Pen Injector) containing 2 prefilled single-dose syringe cartridges, 1 IMITREX STATdose Pen®	Clear, colorless to pale yellow, sterile, non-pyrogenic solution Each 0.5 mL of solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP in water for injection, USP pH: 4.2 to 5.3. Osmolality: 291 mOsmol	Clearance: 1.02 ± 0.13 L/h/kg Distribution $T_{1/2}$: 15 ± 2 min Terminal $T_{1/2}$: 115 ± 19 min V_d (plasma): 0.71 ± 0.11 L/kg Protein Binding: 14% to 21%
Brethine Injectable (Terbutaline sulfate)	Bronchospasm	SC: solution (1 mg/mL)	Injectable solution Dosage strength: 0.25 mg	Each mL of solution contains 1 mg of terbutaline sulfate USP (0.82 mg of the free base), sodium chloride for isotonicity, and hydrochloric acid for adjustment to a target pH of 4	First-pass metabolism in the liver and the gut wall ~60% excreted unchanged in the urine CL: 311 (112) mL/min $T_{1/2}$: 2.9 hr
Opana® Injection (Oxymorphone hydrochloride)	Pain, dyspnea, obstetrical analgesia	Solution: SC/IM/IV (1 mg/mL 1.5 mg/mL)	Injectable solution 1 mg/mL (1 mL) ampoules (paraben /sodium dithionite-free) and 1.5 mg/mL (10 mL) multiple dose vials (sodium dithionite-free)	Each 1 mg/mL ampoule contains 8.0 mg/mL sodium chloride Each 1.5 mg/mL vial contains 8 mg/mL sodium chloride, 1.8 mg/mL methylparaben, and 0.2 mg/mL propylparaben pH adjusted with hydrochloric acid	After an IV dose: Vd_{ss}: 3.08 ± 1.14 L/kg Extensive hepatic metabolism Mean terminal $T_{1/2}$: 1.3 ± 0.7 h Mean systemic clearance: 2.0 ± 0.5 L/min
APO-go PEN (Apomorphine HCl)	Parkinson's Disease/ Chronic	SC: solution (10 mg/mL)	Disposable multiple dose pen injector system incorporating a clear glass (type I) cartridge Each pen contains 3 ml of solution for injection Packs containing 1, 5, or 10 x 3ml pens in a moulded plastic tray	A solution formulation in a single use cartridge contains sodium bisulphite, hydrochloric acid to adjust pH to 3 to 4 and water for injection uses	T_{max}: 10 to 60 min Linear pharmacokinetics over a dose range of 2 to 8 mg Mean terminal $T_{1/2}$: 30 to 60 min V_d: 123 to 404 L Mean apparent CL: 125 to 401 L/hr
Apokyn Pen (Apomorphine HCl)	Parkinson's Disease/ Chronic	SC: solution (10 mg/mL)	Disposable multiple dose pen injector Manual; reusable The pen can deliver doses up to 1.0 mL in 0.02 mL increments	Clear, colorless, sterile solution for subcutaneous injection and is available in 3-mL cartridges Each mL of solution contains 10 mg of apo morphine hydrochloride, USP as apomorphine hydrochloride hemihydrate and 1 mg of sodium metabisulfite, NF in water for injection, USP, sodium hydroxide, NF and/or hydrochloric acid, NF to adjust the pH of the solution and 5 mg/mL of benzyl alcohol, NF as a preservative	T_{max}: 10 to 60 min Linear pharmacokinetics over a dose range of 2 to 8 mg Mean terminal $t_{1/2}$: 30 to 60 min Vd: 123 to 404 L Mean apparent CL: 125 to 401 L/hr
Metoject® (Methotrexate disodium)	Rheumatoid-, Juvenile-, Psoratic-Arthritis/Chronic	Solution: SC, IV, IM (10 mg/mL)	Injectable solution prefilled syringe Dosage strengths: 10, 15, 20, 25 mg	Clear, yellow solution Excipients: Sodium chloride, sodium hydroxide for pH adjustment, water for injections	$T_{1/2}$: 3 to 17 hr Plasma protein binding :50% Liver metabolism: 10%;excreted unchanged in the liver Caution: Once a week only
Remodulin Injection (Treprostinil Na)	Pulmonary artery hypertension	Solution: SC/IV infusion (1, 2.5, 5 & 10 mg/mL)	Injectable solution Infusion rate is initiated at 1.25 ng/kg/min	Each mL contains 5.3 mg sodium chloride (except for the 10 mg/mL strength that contains 4 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6 and 7.2	Rapid and complete absorption $T_{1/2}$: 2-4 h Hepatic metabolism Absolute BA: ~100% V_d: 0.2 L/kg. PPB: ~91% CL: 0.43 L/h/kg
Dilaudid-HP Injection (Hydromorphone hydrochloride)	Moderate-to-severe pain	Solution: IV/SC/IM (10 mg/mL)	Injectable solution, Lyophilized powder Dosage strength: 1-14 mg	Inactive ingredients: 0.2% sodium citrate, and 0.2% citric acid solution Available in amber ampoules or single-dose vials	$T_{1/2}$: 2.3 hr V_d: 302.9 L (4.33 L/kg) CL: 1.96 L/min (1.68 L/h/kg) PPB: 8% to 19% Extensive liver metabolism, small amount is excreted unchanged in the urine.
Prolixin Decanoate (Fluphenazine decanoate)	Psychiatric disorders	SC/IM (25 mg/mL)	Injectable solution	Each mL of injectable solution contains Fluphenazine decanoate 25 mg (5-ml vial) or 100 mg (1-ml vial) in sesame oil with	Very slowly absorbed from the site of SC or IM injection. They both gradually release Fluphenazine into the body and are therefore suitable for use as depot injections

Marketed SC formulations for small molecule drug delivery. (Source: PharmaCircle)

(after SC administration) of lidocaine HCl is affected by pH changes at the injection site. Absorption of drugs administered SC is generally slower than that of drugs administered IM because of the less efficient regional blood circulation of the former. Coadministration of vasodilators generally increases rate of drug absorption after SC administration whereas vasoconstrictors have been shown to lower the rate of absorption.[13]

Drug absorption can be increased at the SC site by rubbing the skin around the injection site and by exercise. This net effect could be due to changes in the interstitial fluid pressure of SC tissue owing to contractions of underlying musculature or movements of the injected limb. Drug action of SC-administered drugs may be prolonged by making deeper SC injection, by co-administering drugs that prolong absorption, or by cooling the injection site, which can cause local vasoconstriction. The bioavailability might also differ between administration sites, eg, thigh, abdomen; therefore, in the exploratory in vivo studies, the injection site should be consistent throughout the study to evaluate the relative bioavailability in a specific animal species.

TOLERABILITY & PK STUDIES IN PRECLINICAL SPECIES

General Guidance

The tolerance studies should be performed to elicit any potential risk of local irritation associated with the formulation (both active and excipients) upon SC administration.[14,15] Tolerance testing should be determined at sites that come into contact with the formulations as a result of the method of administration, and also at the sites that might come into contact through accidental or unavoidable exposure of the formulations. The testing strategy should be such that any mechanical effects of administration or purely physicochemical actions of the formulations can be distinguished from toxicological or pharmacodynamic ones. The tolerance testing for long-acting formulations (after SC dosing) should cover the entire period for which the formulation is expected to remain at the site of injection.[16] It is recommended to have appropriate positive and negative controls for all tolerance tests.

Animal Model Selection

The species selection is not restricted by any official guidelines as long as the species is considered to be scientifically appropriate. Ideally, a species of selection is both "most sensitive" and "most relevant" with regard to dosing routes and dose levels.[17] Rats are the preferred species for the preliminary PK and local tolerance testing of SC dosing, due to ease of dosing and accessibility of the samples for histological examination after euthanasia. To assess local tolerability, rabbits are the most sensitive species that often react to tissue irritation with purulent inflammation. With average body weight of 2 to 3 kg, clinically relevant doses could be tested in rabbits without exceeding the maximum tolerated dose (MTD). However, rabbits are considerably more expensive than rats, and handling of rabbits require special training. Monkeys and/or dogs could be dosed with clinically equivalent doses without exceeding the MTD. However, studies in non-rodent species are typically not terminal, and samples would require a biopsy for histological assessment.

Recommended SC Dosing Volume

Table 1 presents recommended SC administration volumes in the most frequently used species. These are consensus figures based on published literature and internal guidelines. If maximal values are exceeded, animal welfare or scientific implications may result and reference to the responsible veterinary surgeon should be made. The scientific validity of PK studies could be compromised by physiological reaction to high-dose volumes or repeated SC injections. Therefore, it is essential to fully consider these issues before protocols are finalized and work commences. It is also strongly recommended for ethical as well as scientific reasons that in vitro physicochemical compatibility studies and small-scale pilot studies are carried out on any new formulation before conducting larger-scale studies. Dose volumes should be the minimum compatible with SC formulation and accuracy of administration.

Sample Collection

Biological sample collection for PK studies generally includes plasma at predefined time points. In addition, tissue samples from the injection site can be collected at the end of the PK study for preliminary irritation assessment, or a separate tolerability/irritation study can be designed according to the program needs. Sampling collection should follow the general good practice for animal studies according to protocol(s) approved by the Institutional Animal Care and Usage Committee. The maximum volume of blood that can be withdrawn during a PK study is dependent on the species, body weight, animal health, frequency of blood collection, as well as method of blood collection. It is of utmost importance to remain within the blood sampling limits as removal of excessive blood will result in hypovolemia, cardiovascular collapse, anemia, excessive morbidity, and unexpected mortality, which might lead to data invalidation and compromise of the study. It is generally recommended that blood withdrawal be limited to 1% of circulating blood volume per 24 hours, not to exceed 10% of circulating blood volume per 2 to 3 weeks. The recommended sites for repeated blood sampling and circulating blood volumes of commonly used preclinical species are summarized somewhere.[18] For terminal blood sampling in mice and rats, cardiac puncture can be used after euthanasia.

TABLE 3

Product/Drug Molecule	Indication/ Therapy	Admin. Mode/ Dose	Formulation Technology	Formulation Characteristics	PK Characteristics
Products in Development					
Sumitriptan Dose Pro (Sumitriptan)	Registration/ Migraine/ Acute	SC: Solution	Intraject (Needle free SC injection)	Single use, sterile, disposable injector; clear, colorless to pale yellow, sterile, non-pyrogenic solution	Bioavailability: ~96% T_{max}: ~ 25 min Intraject PK bioequivalent to marketed SC injection product.
Ceflatonin® (CGX-635) (Omacetaxine mepesuccinate)	Phase II/ Cancer, (CML & MDS)	SC	Injectable solution Dosage strength: 2.5, 1.25 mg/m^2	-	-
Tetrodin™ (Tetrodotoxin)	Phase II/Drug addiction	SC	SC Injectable A 4-day pre-treatment regimen of 30 micrograms of SC Tetrodin should be administered 2 times a day	-	-
Bimosiamose	Phase I / Psoriasis	SC	SC Injectable	-	The Phase I study demonstrated safety and tolerability of Bimosiamose after single and multiple administrations of 3 escalating doses, PK results support once-daily dosing

SC Products inDevelopement for small molecule drug delivery. (Source: PharmaCircle)

MARKETED & IN-DEVELOPMENT SC FORMULATIONS FOR DELIVERING SMALL MOLECULES

Although SC administration continues to be the main route for the delivery of protein and polypeptide drugs due to their poor stability and bioavailability by most non-parenteral routes, application of subcutaneous formulations for the delivery of small molecules with poor aqueous solubility is somewhat limited.[19-21] Various SC formulation strategies (eg, aqueous solutions, implant, microspehres, liposomes, PLGA-based depot systems) have been reported in the literature.[22-26] However, focus of this review is limited to systemic delivery of small molecules using the SC administration route. Systemic delivery of large molecules (proteins, polypeptides, and growth hormones) following SC administration and control/delayed-release formulations are topics of separate discussion. Tables 2, 3, and 4 provide a summary of currently marketed and in-development small molecule SC formulations.

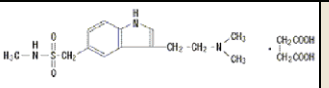
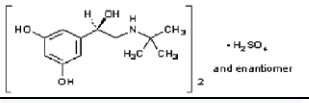
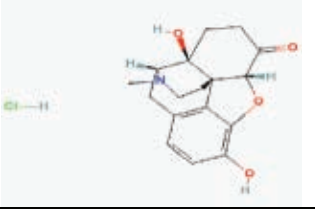
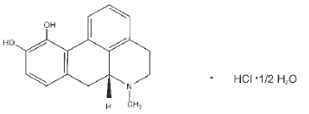
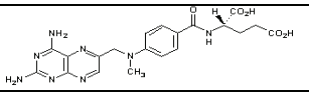
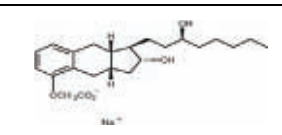
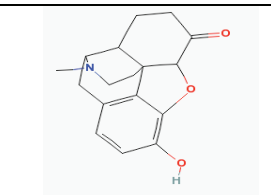
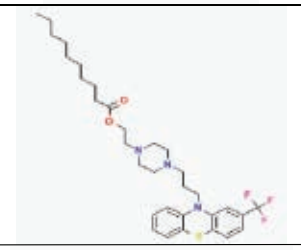
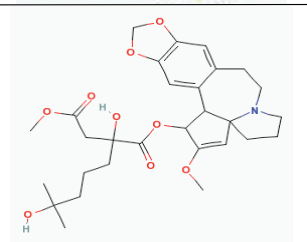
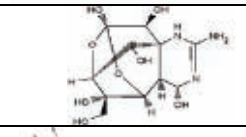
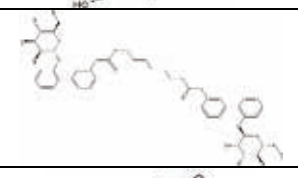
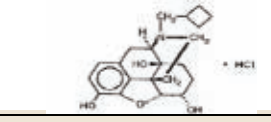
FORMULATION STRATEGIES: GOALS, CHALLENGES & OPPORTUNITIES

Development of SC formulations of poorly soluble small molecules is a challenging task. Unlike IV formulations, a streamlined formulation strategy for SC formulation remains to be established. In general, a target product profile (TPP) essentially drives the SC formulation strategies. For example, the need for immediate-release/fast onset requirements will eliminate oil- or polymer-based particulate delivery systems, while these strategies could be of high priority for controlled-release formulation development in which maintenance of plasma therapeutic levels for a prolong period of time is a must. Additionally, development of an SC injectable device might be an integral part of the overall SC formulation strategy. Various SC injectable devices have been discussed in great detail elsewhere and beyond the scope of this current article.

Solubilization Approach

Dissolution of drug, following SC administration, depends on the availability of fluid at the site of injection and solubility of the drug in SC space. The majority of small molecules reviewed in Tables 2 and 3 have adequate aqueous solubility and therefore resulted in aqueous solution formulations. However, SC formulations of compounds with poor aqueous solubility eliminate the possibility of utilizing conventional aqueous formulation approaches. In that case, application of various solubilization techniques becomes evident to formulate unconventional formulations. Solubility of drug in oils (approved for parenteral use) and physical stability of emulsion formulations are two critical parameters for emulsion formulations and thus must be thoroughly investigated. Micronized suspensions are suitable for SC administration; however, utmost care should be taken to avoid tissue irritation and local tolerability issues by controlling particle size of the suspension. Although preferred by the IV route, emulsions and microemulsion formulations can be considered for the SC route. A number of different formulations strategies, such as depot formulations, encapsulations, and drug modifications, can be employed to modify release rate and

TABLE 4

Compound	Properties	Structure	Mol. Wt.	Aq. Solubility
Sumatriptan succinate	Weak base, salt		413.5	Freely soluble
Terbutaline sulfate	Weak base, salt		548.65	Soluble
Oxymorphone hydrochloride	Single enantiomer		337.8	Freely soluble
Apomorphine hydrochloride	Crystalline, Single enantiomer		312	Sparingly soluble
Methotrexate	Crystalline		454.45	Practically insoluble
Treprostinil sodium	Weak acid salt, Single enantiomer		412	Soluble
Hydromorphoe hydrochloride	Crystalline, single enantiomer		321.8	Freely soluble
Fluphenazine decanoate	Weak base salt		591.8	Practically insoluble
Omacetaxine mepesuccinate	Weak base salt		545.6	NA
Tetrodotoxin	Weak base, Single enantiomer		319.3	NA
Bimosiamose	Weak base, Enantiomer		862.9	NA
Nalbuphine hydrochloride	Weak base salt, Single enantiomer		393.9	Soluble

Physicochemical properties of small molecules used in marketed/in development formulations (Table 1). (Source: Wikipedia, PharmaCircle)

pharmacokinetics of a drug upon SC injection. SC administration of particulate formulations can be an interesting strategy to maintain plasma levels for a prolong period of time (days/months); however, it may fail to achieve fast onset action due to slower dissolution. Chemical modifications of an active moiety (analogues/prodrugs) may also serve as a viable approach to achieve desired physicochemical properties (enhanced aqueous solubility and adequeate in vitro/in vivo stability) and may therefore aid benefit to the SC delivery of small lipophilic molecules. Use of organic cosolvents for SC administration must be carefully assessed by safety and tolerability studies.

Enzyme (Hyaluronidase)-Mediated SC Delivery Approach

Rapid systemic absorption of drug from SC space depends on the permeability/diffusivity of drug molecules into surrounding tissues. The extracellular matrix in SC space may act as a major barrier by limiting diffusivity/permeability of drug and injection volumes. As shown in Figure 2, the transient digestion of hyaluronic acid containing extracellular matrix using hyaluronidase enzyme represents a unique strategy to overcome the volume barrier of SC injection. This strategy has been proven highly efficient in developing SC formulations of large molecules (protein and polypeptides), where volume of SC injection can be a major constraint.

Recent discovery of the molecular engineering of a purified soluble human rDNA-derived PH-20 hyaluronidase enzyme (rHuPH20) has led the clinical development of an enzyme-mediated drug delivery system.[27,28] A higher C_{max} and earlier T_{max} have been achieved using this approach. Thus, SC co-administration of rHuPH20 represents a broad platform technology for large molecules. However, application of this strategy remains to be evaluated for the delivery of small and poorly water-soluble molecules in which solubility rather than diffusivity of drug molecule can be a major constraint.

SUMMARY

Despite the fact that SC administration continues to be the main route for the delivery of protein and polypeptide drugs due to their poor stability and bioavailability by most non-parenteral routes, application of SC formulations for the delivery of small molecules with poor aqueous solubility is somewhat limited. Integration of various biopharmaceutical and formulations factors into the overall SC formulation strategies are highly recommended and should be carefully considered in designing SC drug delivery systems.

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BIODEGRADABLE IMPLANTS

Antibiotic Drug Delivery for Post-Surgical Infections

By: Mayur Bafna and Ganga Srinivasan, PhD

ABSTRACT

Local antibiotics therapy has become an accepted and common adjunct to systemic antibiotics for surgical prophylaxis and existing infections. However post-surgical antibiotic therapy by conventional oral and/or intravenous routes is sub-optimal for various reasons. Hence, a number of delivery systems have been proposed and researched for maximum efficacy and minimum side effects for prolonged time. Because of the high dose of antibiotics, designing a delivery system is all the more challenging. This review encompasses treatment of post-surgical infections using biodegradable implants of antibiotics that will be able to overcome a number of concerns. In addition, these types of delivery systems offer precise spatial (site control) and temporal (rate control) placement within the body, thereby reducing both the size and number of doses, hence lesser side effects. Thus, post-surgical implants result in a possible reduction in cost of therapy because of reduced patient care and also enhance the efficiency of treatment as it destroys the residual cause of ailment that remains even after surgery. Currently, biodegradable implants actually constitute 10% of the total marketed drug delivery systems.

INTRODUCTION

Post-surgical infection is a major source of illness yet a less-frequent cause of death in patients.[1,2] It results in longer hospitalization and higher therapy costs. The currently followed treatment for such infection involves antibiotic prophylaxis by conventional oral and/or intravenous routes before surgery. However, in some cases, this antibiotic treatment is recommended to continue for at least 48 hours following surgery.[3,4]

Conventional antibiotics therapy using the intravenous and/or oral route is usually given in bolus form with periods of rest in between or as continuous infusion. Thus, patients are restricted by intravenous administration and/or oral administration of antibiotics and are frequently exposed to peak drug concentrations, which are well above the toxic levels. The fluctuations in the plasma levels can prove fatal to the patient or may result in severe adverse effects.

Local antibiotics therapy has become an accepted and common adjunct to systemic antibiotics for surgical prophylaxis and existing infections because post-surgical antibiotic therapy by conventional oral and/or intravenous routes is sub-optimal for the following reasons[5]:

- The blood supply to the affected tissue is already poor, hence the distribution and delivery of antibiotic is less in these areas.
- The high dose of antibiotic required to achieve effective levels in the target tissue may result in various systemic side effects.
- Moreover, the drug concentration at the desired site must be sustained for a prolonged period of time for maximum efficacy.

Post-surgical biodegradable implants of antibiotic will be able to overcome these concerns. Moreover, they do not require a special surgery for their administration, thus eliminating the problem of patient compatibility associated with solid implants. An implant at the site of

action releases the drug locally for a prolonged period of time and provides high local concentration while minimizing the potential for side effects and toxicity.

Implants can be defined as sterile polymer-drug matrices, capsules, discs, cylinders, pellets, films, or mechanical devices containing one or more medicaments for the introduction into body tissues such that the medicaments are released gradually over an extended period of time.[6]

Different polymeric systems have been used for implant fabrication, such as biodegradable, bioerodable, and non-degradable systems. Of these, biodegradable polymers are the most

TABLE 1

Surgical Procedure	Predominant Infecting Microorganism	Recommended Agent	Dose	Route	Comment
CARDIO-THORACIC & VASCULAR SURGERY -Reconstruction of the abdominal aorta -Procedure on the leg involving a groin incision -Any vascular procedure with insertion of a prosthesis/foreign body -Lower extremity amputation for ischaemia -Cardiac surgery, prosthetic valve insertion -Coronary artery bypass graft -Other open-heart surgery -Pacemaker implant -Median sternotomy -Non-cardiac vascular surgery -Aortic resection, prosthesis, groin incision, lower extremity amputation	Staphylococci	First-generation cephalosporin eg, Cefazoline or Second- generation cephalosporin (if resistant to Cefazoline), eg, Cefuroxime or Vancomycin only if there is a high rate of documented MRSA infections unit	1 -2 g 1.5 g	IV IV	Some authors recommend continuing the antibiotic for up to 48 hrs. During prolonged operations, additional intraoperative doses every 4-8 hrs are indicated. The value of antibiotics in carotid or brachial artery surgery has not been established unless prosthetic material is used.
ORTHOPEDIC SURGERY -Arthroplasty of joints, joint replacement -Open reduction of fractures -Lower limb amputation	Staphylococci	First-generation cephalosporin, eg, Cefazoline or Second- generation cephalosporin (if resistant to Cefazoline) cefoxitin	1-2 g 2 g	IV IV	Some authors recommend continuing the antibiotic for up to 48 hrs.
GASTRO-DUODENAL SURGERY -Bleeding ulcer, obstructive duodenal ulcer, gastric ulcer, low gastric acidity, decreased GI motility, malignancy, or morbid obesity	Streptococci, coliforms, anaerobic bacteria (including Bacteroides spp)	Cefazolin Gentamicin + Clindamicin (for beta lactam allergy)	1g 120 mg + 600 mg	IV IV	------
BILIARY TRACT For high risk only: > 70 years Obstructive jaundice Acute cholecystits Acute cholangitis Common duct stone	Coliforms, enterococci, anaerobic bacteria (including Bacteroides, clostridia)	Cefazolin or Cefoxitin	2 g 2 g	IV IV	Cephalosporins are not active against the enterococci, yet are clinically effective as prophylaxis in biliary surgery.
INGUINAL HERNIA REPAIR	----------	First-generation Cephalosporin	----	----	Limited data available
COLON/SMALL BOWEL -Elective colon surgery, terminal ileal surgery -Non-elective colorectal surgery	Coliforms, anaerobic bacteria (including Bacteroides fragilis)	Cefoxitin Metronidazole, or ampicillin + metronidazole + aminoglycoside, or third-generation cephalosporin + metronidazole, or metronidazole + gentamicin for alteratives cefoxitin	2 g & every 6 hrs for 3 doses 500mg 500 mg + 3 mg/kg 1 g + 1 g, 3 doses over 8 hrs	IV IV IV IV	------
APPENDECTOMY	Coliforms, anaerobic bacteria (including Bacteroides fragilis)	Cefoxitin Metronidazole for beta lactam allergy	2 g For up to 3 doses 500 mg	IV IV or suppository	If perforated, continue for 3-5 days.
PENETRATING ABDOMINAL TRAUMA	Coliforms, anaerobic bacteria (including Clostridia, Bacteroides fragilis)	Cefoxitin Metronidazole + Gentamicin	2 g 500mg, 1.7 mg/kg	IV IV IV	Continue qid for 2-5 days for intestinal perforation.
OBSTETRICS & GYNECOLOGY -Vaginal hysterectomy & emergency caesarian section -Abdominal hysterectomy -Caesarian section with high-risk, eg, premature rupture of membranes -Abortion	Coliforms, enterococci group B streptococci	Cefazoline Cefazolin or Cefoxitin Cefazolin	1-2 g 1 g 2 g 1 g	IV IV IV IV	-----
UROLOGICAL SURGERY -Prostatectomy -Transrectal prostate biopsy	Coliforms	Ciprofloxacin or Gentamicin	500 mg 1-5 mg/kg	PO IV	-----
CNS SHUNTS	Staphylococci	Cefazolin	1 g	IV	-----
HEAD & NECK SURGERY Major head, neck, and oral surgery	----------	Cefazolin or Amoxycillin Clavulanate or Gentamicin + Clindamycin	2 g 1-2 g 80 mg, 600 mg	IV IV IV	-----

Infecting microorganisms usually associated with certain operative procedures and the prophylactic antibiotic recommendation.[13-15]

preferred polymers, as they are biocompatible and degrade into non-toxic byproducts, eliminating the need of second surgery after the purpose is served.

Biodegradable controlled-release systems offer the advantage of gradual biological elimination without a residual implant structure remaining. Biodegradable implants play a major role in this field, though implants actually constitute just 10% of total currently marketed drug delivery systems. In addition to acting as a mode for sustained-release dosage forms, biodegradable polymers can control the rate and amount of drug release as well as the duration for which the drug delivery system remains in the body, and thus contribute to the therapeutic efficacy of biodegradable drug delivery systems.[7]

Of the different types of biodegradable polymers, polyesters polymers are the best-suited polymers for the formulation of implants as they have proven their biocompatibility and safety from their uses in surgical grafts, implants, and various prosthetic devices.[8] They have largely available toxicological and clinical data, predictable biodegradation kinetics, are sterilizable, and are with good mechanical strength.[9] They also have a well-accepted safety profile and have received regulatory approval.[10]

FUNDAMENTAL PRINCIPLES OF PREVENTION OF POST-SURGICAL INFECTIONS

The antibiotic must be in the tissue before the bacteria are introduced, ie, antibiotic must be given intravenously shortly before surgery to ensure high blood/tissue levels. Prophylaxis failure may be due to antibiotics given too late or more often, given too early. The half-life of the particular antibiotic is therefore important. The chosen antibiotics must be active against the most common expected pathogens. Deviations from these guidelines may be warranted in certain situations, eg, MRSA outbreak in an individual hospital. High risk patients, such as patients with jaundice or diabetics, or patients who have undergone any procedures to insert prosthetic devices, generally warrant antibiotic prophylaxis. There are no convincing statistical differences in efficacy between the first-, second-, and third-generation cephalosporins.

MICROBIOLOGY OF SURGICAL SITE INFECTIONS

The pathogens isolated from infections differ primarily depending on the type of surgical procedure. In clean surgical procedures, in which the gastrointestinal, gynecologic, and respiratory tracts have not been entered, Staphylococcus aureus from the exogenous environment or the patient's skin flora is the usual cause of infection. In other categories of surgical procedures, including clean-contaminated, contaminated, and dirty, the polymicrobial aerobic and anaerobic flora closely resembling the normal endogenous microflora of the surgically resected organ are the most frequently isolated pathogens. However, more of these pathogens show antimicrobial drug resistance, especially methicillin-resistant Staphylococcus aureus.

ROUTE OF ADMINISTRATION OF PROPHYLACTIC ANTIBIOTICS

Intravenous administration of the prophylactic antibiotic is preferred for most patients undergoing an operative procedure. Oral antibiotics currently play a major role only in the preparation of patients before elective colon surgery.

CURRENTLY FOLLOWED TREATMENT

Esposito et al reported that preoperative administration of antibiotics to prevent possible post-surgical infections represents a cornerstone of modern medicine.[11] Advances in surgical techniques, the changes in bacterial ecology in the hospital, the spread of bacterial resistance, and the substantial increase in the surgical population at risk suggest that several aspects of surgical prophylaxis should be reviewed, and new controlled studies should be carried on.

Pea et al reported that only clean-contaminated and prosthetic clean operations are eligible for antimicrobial prophylaxis, whereas contaminated or dirty operations are eligible for early therapy.[12] First- or second-generation cephalosporins or aminopenicillin/beta-lactamase inhibitors are optimal choices for surgical prophylaxis, depending on location of the surgical wound.

The highest licensed dosage of the chosen antimicrobial agent should be administered at induction of anesthesia, and re-dosing should be considered when the intervention lasts more than two antibiotic half-lives. This allows maintenance of optimal drug exposure against the potential pathogens in plasma and in the extracellular environment of the potentially contaminated tissues for the entire procedure and for some hours following wound closure. Post-surgical doses are not recommended in most cases, whereas ultra-short prophylaxis is preferred.

PROBLEMS WITH CURRENT TREATMENT & PROPOSED SOLUTION

Local delivery of antibiotics is desired in conditions such as osteomyelitis, soft tissue infections, and for the prevention of post-surgical infections. In osteomyelitis, soft tissue infections, after the surgical debridement of the dead, infected tissue, oral and/or intravenous antibiotic therapy is required to prevent infections contracted during surgery.

However, this currently used therapy has the following drawbacks:[5,16]

- High plasma concentrations of drugs may lead to toxicity or low drug levels that cause sub-therapeutic drug levels.
- May lead to drug resistance in some instances.

TABLE 2

Drug	Polymer Used	Implant Form	Purpose	Reference (Year)
Gentamicin, Cefazoline	Poly (d, l-lactide)	Cylindrical implants	Treatment of post-surgical infections, osteomyelitis	17 (1984)
Gentamicin Implant	Biodegradable lactic acid polymers & copolymers	Implants	Acute & chronic bone & tissue infection	18 (1995)
Gentamicin	Collagen	Implants	Wound infection	19 (1996)
Ciprofloxacin Implants	Poly(lactides-co-glycolides) [PLGA][50:50]	Implants	Treatment of osteomyelitis	20 (1997)
Cefazoline & Ciprofloxacin	Glyceryl monostearate	-----	Prevention of post-surgical infections	21 (1998)
Gentamicin	Poly (d, l-lactide)	Implantable beads	Treatment of osteomyelitis	22 (1998)
Gentamicin	Calcium phosphates/poly (d, l-lactide)	Matrix	Treatment of osteomyelitis	23 (2000)
Gentamicin Sulphate	Poly (d, l-lactide)	Microparticulates	Treatment of osteomyelitis	24 (2001)
Gentamicin	PLA &/or PLA / PEG copolymer	Discs by compression of microspheres	Prevention of post-surgical infections	25 (2001)
Ceftriaxone	Polymethyl-methacrylate	Beads	Treatment of osteomyelitis	27 (2002)
Ciprofloxacin	The cross-linked high amylose starch	Matrix	Treatment of osteomyelitis	27 (2002)
Teicoplanin	Sodium alginate	Implantable beads	Treatment of osteomyelitis, bone infections	28 (2002)
Gentamicin Sulfate Containing Microspheres	Poly(lactide); Poly(lactide-co-glycolide) Biodegradable microspheres; Targeted drug delivery	Microspheres	Treatment of soft tissue infections	29 (2002)
Gentamicin	Collagen, collagen sponge, collagen/PLGA composite	Matrix	Wound healing	30 (2003)
Vancomycin	Poly (ε-caprolactone)	Microparticulates	Bone implantation	31 (2003)
Tobramycin	Poly (ε-caprolactone)	Matrix	Treatment of osteomyelitis	32 (2003)
Cefadroxil	Polyurethane	Matrix	Post-surgical infections	33 (2003)
Cefoxitin Sodium	Poly (lactide-co-glycolide)	Nanofibrous membranes	Prevention of post-surgery-induced abdominal adhesions	34 (2004)
Gentamicin Sulphate	Polyanhydrides	Implantable beads	Treatment of osteomyelitis	35 (2004)
Mefoxin, Cefoxitin Sodium	Amphiphilic block copolymer (PEG-β-PLA)	Nanofibrous biodegradable scaffolds	Antimicrobial effects on Staphylococcus aureus	36 (2004)
Doxorubicin	Block copolymers poly(ethylene oxide)-block-poly(allyl glycidyl ether) (PEO-PAGE)	As polymeric micelles	For high antitumor activity	37 (2004)
Gentamicin, Cefazoline	Biodegradable PLA/PGA beads Polylactide-polyglycolide	Biodegradable beads	Post-surgical infection	38 (2004)
Gentamycin Sulphate or Vancomycin Hydrochloride	Poly (acrylic acid) & gelatin	Interpenetrating network (IPNs) hydrogel	Treatment of osteomyelitis	39 (2005)
Tobramycin	Calcium sulphate	Bone matrix	Prevention of bone infections	40 (2005)
Ampicillin	Chitosan-alginate	Multilayered beads	For gastric and intestinal infection	41 (2005)
Vancomycin	Trehalosehydroxyethylcellulose Microspheres, Gamma radiation	Microspheres + gamma radiation	Treatment of wound infections	42 (2005)
Tetracycline HCl & Chloramphenicol	Three-dimensional cultured human skin	Dermal patches	Serious skin defects, such as severe burns.	43 (2005)
Vancomycin	Poly-lactic-glycolic acid (PLGA)	PLGA capsules	Post-operative treatment on osteomylities	44 (2006)

Some of the research work on antibiotic implants.

- The only way to eliminate peak and trough plasma levels of drug therapy was to continuously intravenously infuse a patient at a constant rate based on the pharmacokinetic of the drug. This type of therapy, however, required constant monitoring of plasma concentration of drug by healthcare professionals, and thus usually cannot be performed at home.

- Results in a generalized non-specific site of action of drug.

- When drug is administered systemically, it is distributed in the body to various organs and tissues perfused with blood, and a relatively small amount reaches its target tissue.

These drawbacks can be overcome by formulating post-surgical implants of antibiotics. As previously stated, post-surgical implants are locally implanted controlled-release systems, which are administered immediately following surgery, but before suturing. This obviates the need of special surgery for implant administration. They are normally fabricated using biodegradable polymers and can overcome many challenges as they:[5]

- Provide high-sustained concentrations locally in the bone or other tissues;

- Reduce hospitalization-related costs as they require no monitoring, and the biodegradable implant will degrade completely, obviating the need for further surgery;

- Do not need a special surgery for their administration, eliminating the issue of patient incompatibility associated with solid implants;

- Eliminate the need of subsequent administration of drugs required following surgery to prevent post-surgical manifestations, thus improving patient compatibility;

- Are formulated using biodegradable polymers, eliminating the need of surgical removal of implants after the purpose is served;

- Offer precise spatial (site control) and temporal (rate control) placement within the body, reducing both size and number of doses (hence lesser side effects);

- Result in possible reduction in therapy cost because of reduced patient care; and

- Enhance the efficiency of treatment as they destroy the residual cause of ailment even after surgery.

It is important to note, however, that once implanted, the drug delivery rate is fixed, unless the device is removed.

PATENTS AVAILABLE FOR ANTIBIOTIC DRUG DELIVERY[45,46]

Antibiotic Drug Delivery System: European Patent No. EP1404397. An antibiotic drug delivery system for controlled infusion of an antibiotic drug to a patient, in which system comprises (i) a delivery device for providing an infusion of the antibiotic at a controlled rate, together with (ii) a control system for varying the infusion rate and time of dosing of the antibiotic according to one or more parameters of the drug so as to maintain antibiotic levels in the patient of a desired percentage above the accepted MIC for that antibiotic.

Bioerodible Polymers for Drug Delivery in Bone: United States Patent No. 5286763. Bioerodible polymers which degrade completely into non-toxic residues over a clinically useful period of time, including polyanhydrides, polyorthoesters, polyglycolic acid, polylactic acid, and copolymers thereof, are used for the delivery of bioactive agents, including antibiotics, chemotherapeutic agents, inhibitors of angiogenesis, and simulators of bone growth, directly into bone.

FUTURE ASPECTS OF POST-SURGICAL BIODEGRADABLE IMPLANTS AS A DRUG DELIVERY SYSTEM[5]

Post-surgical biodegradable implants find their major areas of application in post-surgical infections, cancer treatment, and pain management.

Cancer Therapy: Conventionally, solid tumors are removed by surgical resection, followed by irradiation and/or systemic chemotherapy to kill the residual malignant cells that may have survived the surgery, and prevent metastasis and regrowth of tumors. A biodegradable implant containing an antineoplastic agent when placed at the site of tumor resection delivers high local concentration of drug, thus eradicates the tissue from the residual malignant cells and prevents the systemic side effects of chemotherapy normally associated with intravenous administration.

Pain Management: Prolonged reversible nerve blockade is required in a number of clinical situations involving acute or chronic pain, such as post-surgical pain following herniorrhapy and thoracotomy. It requires analgesic medications for 3 to 5 days following surgery. For this purpose, clinicians must use local anesthetic infusions via an indwelling catheter, repeated blocks, or neurolytic agents. Hence, a biodegradable implant loaded with a local anesthetic drug will release the drug slowly at the surgical site for an extended period.

Antibiotics: Parenteral antibiotic therapy for acute bone infections, soft tissue infections, and osteomyelitis may result in high serum concentrations associated with nephrotoxic, ototoxic, and allergic complications. Therefore, recent investigations have explored the use of antibiotic-loaded biodegradable implants, as mentioned earlier.

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THERMORESPONSIVE DELIVERY

Thermoresponsive Drug Delivery Systems: Fiction or Reality?

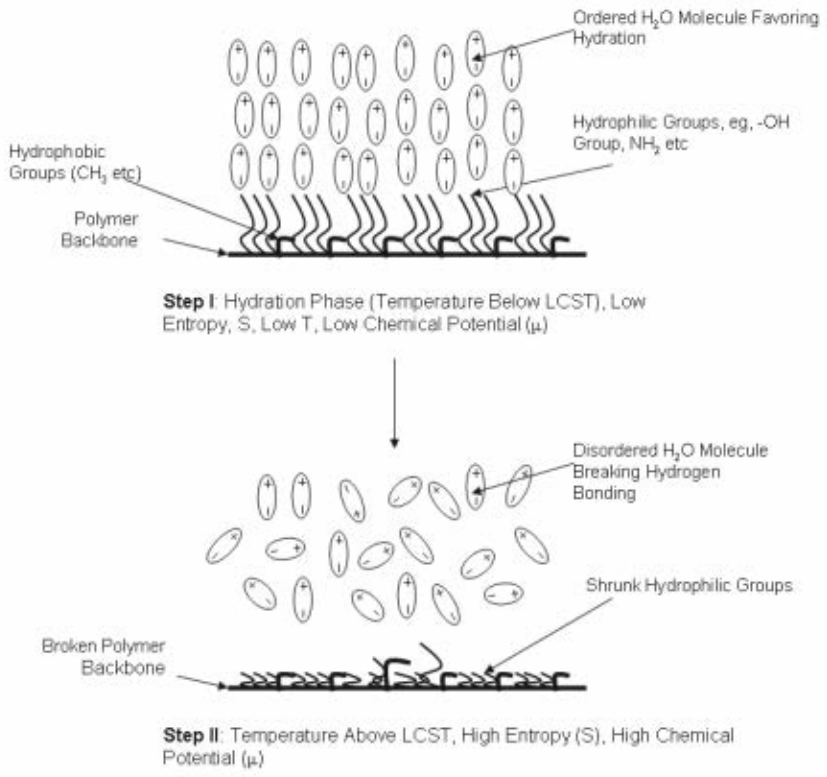
By: Akm Khairuzzaman, PhD

INTRODUCTION

The pharmaceutical world is getting more complicated, diversified, and expensive in modern times. Successful efforts have been made with commercially available controlled-release devices to deliver drugs to a specific site, but there still exists insufficiencies in certain clinical situations, such as the delivery of insulin, arrhythmia, chemotherapy, hormonal therapy, and many others.[1-4] Therefore, diseases are now very often looked at from a genetic perspective, and a molecular level of treatment is increasingly being considered as the therapeutic future. To achieve such an objective, several environmentally responsive polymers have been used that are commonly known as *Smart Materials*.[5] They react to an external applied force, ie, electrical, chemical, stress/strain, light, and magnetic field. Using these concepts, some researchers actually have been able to control drug release in connection with several physiological stimuli. Prof. Robert Langer at the Massachusetts Institute of Technology is the pioneer who has successfully designed numerous smart materials for drug and DNA/RNA delivery platforms for many therapeutic areas.[6] He has used almost all sorts of stimuli, such as oscillating magnetic fields, thermal, chemical, ultrasound, light, and electrical, to modulate the drug release from such smart materials. Similarly, many other research articles have been published in the past decade, but yet the possibility of commercialization of these concept-based dosage forms is indeed fiction.

This article reviews one such interesting smart drug delivery system (thermoresponsive) in which the drug molecule is physically attached to or entrapped in a polymer that is capable of conformational or phase changes under different regimes of temperature.[7] Such polymers are called thermosensitive polymers. These are potential candidates for a targeted drug delivery system, especially for anti-cancer drugs. However, the concern here is the human body's capability to maintain a controlled body temperature (except in the case of fever) unless there is a significant temperature change in the target organ. One such clinical situation is very common in cancer treatment, where there is a bimodality approach of combining localized

FIGURE 1



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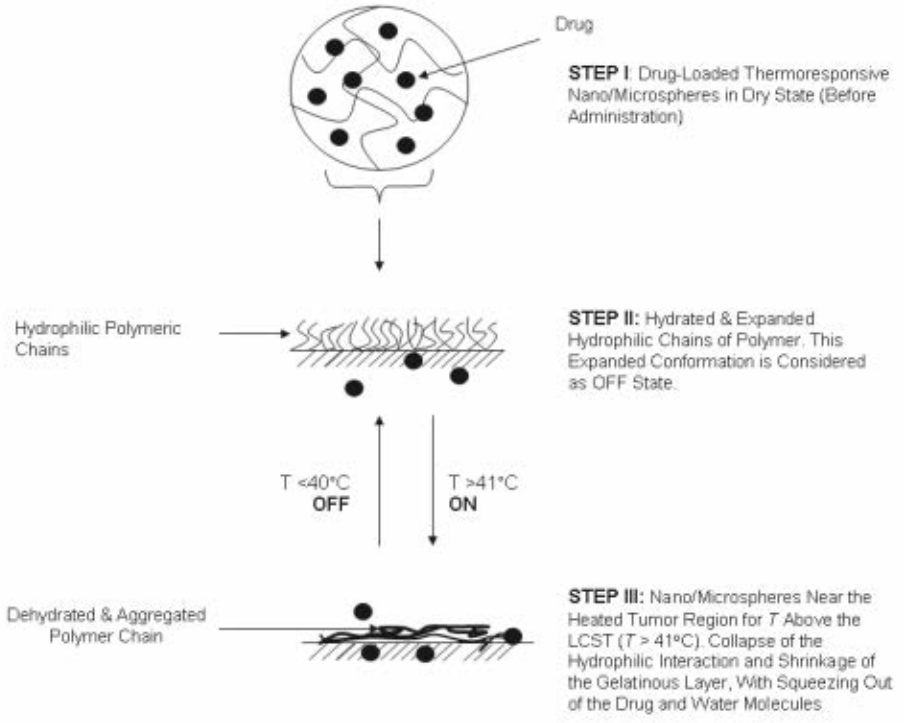
hyperthermia (42°C to 44°C) and chemotherapeutic agents (systemically). This combinition frequently results in increased cytotoxicity due to a lack of target-specific drug release from the systemically administered dosage form.[8,9] But the efficacy of this bimodality approach could be increased significantly if the chemotherapeutic agents are delivered selectively to tumor cells along with a thermoresponsive micro/nanocarier followed by the application of localized hyperthermia. Attempts have already been made to coat anti-cancer drugs into thermosensetive nanoparticulate polymers.[10] The main hypothesis behind such an attempt is that if the thermoresponsive nanoparticles carrying anticancer drugs are stable and soluble in the blood at a normal physiologic temperature, but releases the drug content at elevated temperature (around 40°C to 45°C) because of localized hyperthermia, then such a system can improve the specificity of the drug delivery, while reducing or minimizing systemic side effects. So the question remains: do we have any such smart thermosensetive carriers that can respond to a thermal stimulus and show an ideal phase inversion in such a temperature range and deliver the therapeutic moiety at the target site only?

HOW THERMORESPONSIVE DRUG DELIVERY SYSTEMS WORK

The key feature of thermosensetive polymers is that they exhibit a conformational or phase transition at certain temperatures that result in the polymer transitioning from a soluble to insoluble form in a given solvent. The temperature at which the transition occurs is referred to as the critical solution temperature. Polymers that exhibit this behavior fall into two categories. The first exhibits lower critical solution temperature (LCST), in which the polymer is in solution below the LCST and insoluble above it.[11] The second type exhibits upper critical solution temperature (UCST), in which the polymer is soluble above and insoluble below the UCST in a given solvent. A thermosensetive polymer that is designed for human use should have an LCST temperature at around 41°C to 45°C because it is near the heated tumor's temperature. Therefore, when a thermosensetive polymeric carrier containing anticancer drug passing through a heated tumor region precipitates and shows a phase inversion, it results in drug release at the tumor region.

FIGURE 2



Schematic Illustration of the Novel Thermoresponsive Drug Delivery System to Give a Drug Release Modulated by External Temperature at the Heated Tumor Region

THERMODYNAMIC CONSEQUENCES OF PHASE TRANSITION AT LCST FOR A POLYMER IN SOLUTION

LCST is the temperature below which a polymer is in a solution state and above which becomes insoluble in a given solvent. The principles of this phenomenon can be explained stepwise by the following:

- Generally, thermoresponsive polymers have a hydrophilic and hydrophobic group in their structure.
- Below the LCST, hydrophilic groups of the polymer are hydrated due to hydrogen bonding between the water and polymer to form a gelatinous structure. The hydration results in a negative energy term (the H of hydration). It also results in a loss of entropy due to the ordered arrangement of the hydrating water molecules (S of hydration).
- The aforementioned hydrated gelatinous structure is hydrophilic. However, for some polymers, if the water leaves the structure (dehydration) for any reason, the polymer will undergo configuration changes in which the hydrophobic groups predominate. For these

polymers, dehydration will result in a transition from a hydrophilic to hydrophobic nature, which can result in precipitation or aggregation. If the stimulus for this transition is the temperature, then an LCST or UCST will result.

- The previously mentioned transition can be described in terms of a competition between the changes in enthalpy and the entropy associated with that transition. This is reflected in Gibbs energy in the following equation: $\Delta G = \Delta H - T\Delta S$. For this case, heat must be added to dehydrate the polymer (positive ΔH required to separate water and the hydrophilic groups of the polymer), which will result in a positive addition to ΔG. At the same time, this dehydration will result in a positive ΔS (previously associated water molecules are free to spread out), which will result in a negative contribution to ΔG through the - $T\Delta S$ term. It should also be noted that what is important are the net (ie, total of all positive and negative) changes in enthalpy and entropy. For instance, if a polymer folds onto itself somewhat due to dehydration, then the loss of entropy by the polymer folding could be smaller than the gain in entropy due to the water freedom.

- When the temperature is increased and it is above the LCST, the hydrogen bonding is overcome by the entropic tendency of the water to spread out (change in chemical potential of the water, $\Delta\mu$). As a result, the hydrophilic groups of the polymer become dehydrated and convert to hydrophobic in nature. This results in a phase separation. Such movement is promoted by a gain in the entropy.

Figures 1 and 2 schematically illustrate the drug-release mechanism from a thermoresponsive drug reservoir. When the drug-loaded nano/microspheres are injected into blood, they are exposed to a temperature of 37°C to 38°C. If this is below the LCST, the hydrophilic part of the polymer becomes hydrated and swells, so the volume of the particles becomes enlarged. This leads to a formation of a gel-like structure surrounding the particles that act as a barrier for the drug release below the LCST temperature (especially for hydrophobic drugs). This swollen state of the nanoparticles is considered the "off" state for drug release.

On the other hand, when these particles are close to a heated region that is above the LCST, the chemical potential of the water molecule is changed, and the water molecules move away from the polymer chain (dehydration). This reduces the hydrophilic interaction between the water molecule and the polymer's hydrophilic part, resulting in de-swelling and shrinkage of the gelatinous structure that leads to a mechanical squeezing of drug and water molecule out of the core.[12,13] This shrunken state is considered the "on" state for the drug release. Because of such surface property changes (from hydrophilic to hydrophobic) above the LCST, the nano/microparticles would adhere to the heated tumor and provide specificity for that location. In contrast, below the LCST, a complete off state may not be possible because drug is released by diffusion through the gel at the swollen state.[14]

The importance of this is that the solubility of entrapped drugs may play a major role in their release at the site of the heated tumor when they are above the LCST temperature and also during their travel before reaching the tumor site. Because these coated particles will develop a gelatinous-like barrier below LCST during their travel after injection, hydrophilic drugs may show comparatively a higher diffusion than that of hydrophobic drugs. However, poorly soluble drugs entrapped into such polymeric particles may show improved dissolution at the site of precipitation provided that the particles are at nano/micro sizes.

RECENT INNOVATIONS/ IDENTIFICATION OF POLYMERIC MATERIALS WITH THERMOSENSITIVE CHARACTERISTICS

Various thermally reversible polymers and hydrogels applied in therapeutics and diagnostics were reviewed by Hoffman and Okano et al.[15,16] However, the most studied polymers are of N-isopropylacrylamide, commonly known as pNIPA and its copolymers.[17,18] It exhibits a sharp phase transition, with an LCST at about 32°C in pure water.19 Copolymerization of pNIPA with a more hydrophilic monomer increases the overall hydrophilicity of the polymer, and the stronger polymer-water interactions lead to an increase in the LCST. Likewise, copolymerization with a more hydrophobic monomer results in a lower LCST than pNIPA.[20] But this material is non-biodegradable and that rules out the possibility of its use in developing this kind of drug delivery system, unless used as an external drug delivery device. Only a few alternative biodegradable polymers with thermosensetive characteristics are currently receiving a great deal of interest. A recent review article summarizes the applications of thermosensitive materials in fields of interest for pharmaceutical and biomedical scientists and engineers.[21] Some of the potential examples are discussed further.

CHITOSAN-BASED HYDROGEL: It is a biocompatible and biodegradable pH-dependent cationic polymer obtained by alkaline deacetylation of chitin.[22] They can be divided into two classes: chemical and physical hydrogels.[23] Chemical hydrogels formed through covalent cross-linking exhibit enhanced mechanical properties thorough the formation of gels. However, such cross-linking agents can potentially interact with loaded bioactive compounds leading to significant toxicity. But physically cross-linked hydrogels have similar mechanical integrity with no possible interaction with the active drug

component. Several chitosan-based hydrogels were derived using both kinds of cross-linking. A majority of these utilize cross-linking agents, such as pNIPA and ethylene glycol, which can be a potential threat in terms of toxicity. A cross-linking agent with low cytotoxicity helps in quasi-linear drug release for up to 40 days; however, the hydrogel loses its thermoreversibility at 37°C.[24] Other polysaccharide-based hydrogels, such as Xyloglucan, Dextran, and Cellulose derivatives, have also been extensively studied due to their thermosensetive characteristics.

Gelatin: This is a bovine (usually) origin biopolymer with thermoreversible properties. At temperatures below 25°C, an aqueous gelatin solution solidifies due to the formation of triple helices and a rigid three-dimensional network. When the temperature is raised above approximately 30°C, the conformation changes from a helix to the more flexible coil, rendering the gel liquid again. It is by far the safest thermosensetive biopolymer besides chitosan. However, the challenge is to increase the gel-sol transition temperature above the physiological temperature to use it as a potential carrier for drug molecules.

PEO/PPO-Based Systems: Triblock copolymers poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PEO-PPO-PEO), known also as Pluronic® or Poloxamers, are another important group of synthetic polymers with a thermoreversible behavior in aqueous solutions. It works through a gelation mechanism, which has been extensively investigated. This reversible gelation can occur at physiological temperature and pH through an adjustment of its composition, molecular weight, and concentration.[25] However, it has been reported that Pluronic gel has an inadequate mechanical integrity that makes it inappropriate for certain biomedical applications.[26] Moreover, carboplatin toxicity has been reported with the use of three different kinds of Pluronic triblock copolymers, such as F127, P85, and L61.[27]

Others: Several other synthetic, nonsynthetic polymers or combination of synthetic/nonsynthetic polymers have been used as possible candidates for this kind of drug delivery platform. Examples are PEG/biodegradable polyester copolymers, poly(ethylene glycol)-b-poly(d,l-lactic acid-co-glycolic acid)-b-poly(ethylene glycol) (PEG-PLGA-PEG) triblock copolymers, PLGA-PEG-PLGA-based systems, poly(ethylene glycol)/poly(l-lactic acid) (PEG/PLLA), methoxy poly(ethylene glycol) (mPEG) with poly(propylene fumarate) (PPF), and poly(organophosphazenes) grafted with amino acids. However, in all cases, the fundamental challenges are to modulate these polymer/polymer combinations to get a desirable LCST value close to a physiological temperature.

MODIFICATION OF THE LCST & ITS APPLICATION TO DRUG DELIVERY

Once a possible thermoresponsive polymeric candidate is identified, there are several chemical ways to modulate its LCST. Usually, the introduction of monomer units of stronger amphiphilic character results in a systematic decrease of the LCST. The LCST modulation can be controlled by the choice of the co-monomer as well as the co-monomer ratio and can be tuned in the temperature range from 46°C to 49°C.[28] However, in drug delivery, the physical situation differs from a pure polymer in solution because the polymer is used as a coating (eg, drug coated nano/micro spheres) or as a matrix to form what is sometimes referred to as a Thermoresponsive Drug Reservoir. Because the formation of the gelatinous structure associated with the hydration effects (as discussed in the previous section) can still occur, the potential for displaying thermosensitive behavior still exists. However, because of drug loading, there will be less configurational freedom for the polymer, and thus less ability to coil and/or uncoil. Therefore, the actual transition temperatures for coated/loaded nano/microparticles may differ from the actual LCST of the free polymer.

Drug-loaded nano/microparticles cannot form a true solution. Therefore, the actual behavior change associated with the temperature may appear to be different for these particles than for free polymer molecules. Still, the effects will be associated with a hydrophilic/hydrophobic transition, which could result in aggregation or sticking to local tissues (in vivo), either of which would be expected to result in some type of localization effect in vivo.

Another transition effect could be differences in the release of drugs from the coated nanoparticles. For hydrophobic drugs, the hydrated gelatinous structure would likely act as an effect barrier to drug release. In that case, the release of drugs would be increased above the LCST. For hydrophilic drugs, this layer might also act to slow down release, although perhaps not as effectively as would be the case for hydrophobic drugs. For either effect, the factor controlling the transitions in surface properties and drug release from a thermoresponsive drug reservoir is the critical solution temperature.[29]

CONCLUSION

Based on the above discussion, mechanism, and citation of some examples, it is indeed very promising that we do have some successful thermosensetive platform that can be further evaluated/developed as a possible drug-reservior candidate. They may also serve as a potential carrier for oral use whereby swelling/de-swelling kinetics can be utilized for the control of drug release. However, the ultimate folllowing three questions remain:

- What is the safety of such material and what is the LCST?
- Can it be possible to modulate the LCST safely at aroung 40°C to 45°C ?
- Would the drug-loaded dosage form be stable and manufacturable and deliver the therapeutic moiety at the targeted region?

Answers to these questions could be the key to take this noble concept to commerce and benefit some particular therapeutic class like anti-cancer drugs.

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I would like to thank my PhD degree mentor Dr. Robert Bellnatone, Associate Professor of Division of Pharmaceutics, Long Island University, for his critiques on this topic. Without his encouragement, this article would not have been possible.

DISCLAIMER

This article was written by the author in his private capacity. No official support or endorsement by the United States Food and Drug Administration is intended or should be inferred.

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BIOGRAPHY

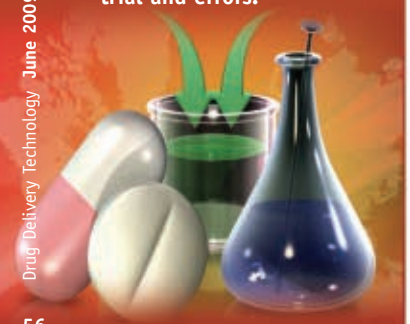
Dr. Akm Khairuzzaman is a Senior Staff Fellow at the FDA's Office of New Drug Quality Assessment, Office of Pharmaceutical Science, CDER, where he resumes responsibility of risk-based assessment of chemistry, manufacturing, and controls for NDAs and INDs seeking approval in the US. Prior joining to the FDA, Dr. Khairuzzaman worked for Barr Pharmaceuticals Inc. for 7 years as a Scientist and Research Investigator in its research and development department, where he earned his expertise in the field of preformulation and formulation science of solid dosage form development. His research contributed publications in the area of sustained-release matrix dosage forms using chemically modified polymers and thermodynamic consequences of micro/nanoporosity of excipients on loaded drug materials. Dr. Khairuzzaman earned his BS in Pharmacy from Bangladesh, his MS in Industrial Pharmacy, and his PhD in Pharmaceutics from Long Island University, New York.

DRUG DELIVERY Executive
SPI Pharma™

SPI PHARMA: FORMULATING SUCCESS WITH PATIENT-FRIENDLY DOSAGES

Sarath Chandar
VP, Excipients & Drug Delivery Systems
SPI Pharma

"Speed to market is primarily achieved through our Pharmasolutions service, which is an in vitro dossier development in CTD Module 3 format. SPI has developed several drug formulations using its proprietary platforms in combination with different APIs, creating a large excipient compatibility database to draw from; thus streamlining the drug development process and avoiding formulation trial and errors."



SPI Pharma is a global company focused on delivering unique, value-added solutions to the pharmaceutical industry. A US company owned by Associated British Foods, an $11 billion public company headquartered in the UK, SPI offers functionally superior and proprietary excipients, antacid actives, and drug delivery platforms. All of SPI's manufacturing plants conform to strict pharmaceutical cGMP standards. The company's charter is to develop innovative and unique ingredients that offer functional benefits to their customers' products. In addition, its experienced scientific staff develops and tests finished drug formulations in several patient-friendly dosage forms. Drug Delivery Technology recently interviewed Sarath Chandar, Vice President of Excipients and Drug Delivery Systems, to discuss SPI Pharma's path forward in patient-friendly formats.

Q: Can you discuss for our readers SPI's market presence and global reach?

A: We sell in more than 50 countries around the world, providing technical and commercial service to our global customers from our sites located in the US, Peru, France, India, Australia, and China. SPI has a wide network of multilingual sales and distribution professionals to assist our customers in finding the right solutions to their challenging issues. Our major customers are global multinationals, including Sanofi-Aventis, Bayer, J&J, Novartis, and GSK as well as generic giants and regional pharmaceutical companies. Our sales are an estimated 40% in the Americas, 40% in Europe/Middle East/Africa (EMEA), and 20% in Asia-Pacific.

Q: Please describe the current excipient line SPI offers the pharmaceutical industry.

A: We offer a broad line of excipients that are used in various dosage forms, such as swallow

tablets, chewables, ODT, lozenges, softgels, effervescent tablets/sachets, chewing gums, dry/wet suspensions, and injectables. Our excipients, like Mannitol, Maltose, Effer-Soda™, and Sorbitol Special™, can deliver functional benefits to finished drug formulations, such as improved dissolution, higher permeation rates, better stability, and a longer shelf-life. We back our products with good technical support strategically located around the world.

Q: On a more specific note, what can you tell us about your antacids business?

A: SPI is the global leader in the traditional antacid API segment made up of aluminum and magnesium hydroxides and calcium carbonates. Driven primarily by our superior product quality and functionality, we have a global market share exceeding 55% of the antacid market. SPI offers unique spray-dried APIs and co-processed liquid blends that are easy to formulate and deliver exceptional organoleptic properties. We have multiple production sites and technical service centers to support our global customers.

Q: Provide some background on SPI's expertise in the drug delivery systems business.

A: SPI has developed, over the past 75 years, a great understanding of the link between pharmaceutical material chemistry and their functionalities. Using this expertise along with our co-processing know-how, we have developed and patented easy-to-use drug delivery systems like the Pharmaburst™ platform for ODT applications, Pharmagum™ platform for chewing gum applications, and Pharmasperse™ platform for dry powder suspensions and sachets. We plan to introduce soon a new and functionally superior swallow tablet platform called Pharmatab™.

Q: What is the latest on SPI's Pharmaburst platform, which we hear a lot about in the market?

A: Pharmaburst was the first off-the-shelf, co-processed ODT excipient system introduced in the pharmaceutical market. I believe it is still the only off-the-shelf excipient system that is patent protected. Several generic and new Fast-Melt drugs have been launched, and several are in the regulatory pipeline in the US, EMEA and Asia.

Pharmaburst is the only ODT excipient system included in the US FDA's Inactive Ingredient Guide (IIG List). In Quick-Dissolve formulation comparisons, especially with high-dose actives, Pharmaburst has consistently outperformed all the competitive off-the-shelf copycats. SPI invests and supports continuous improvement of its ODT platform, and it is still the most cost-effective system. Mouth dispersing tablets made with Pharmaburst can be packaged in blisters or bottles. The Pharmaburst ODT system has been able to deliver "speed to market" in several successful product launches.

Q: How does SPI help its customers achieve speed to market?

A: Speed to market is primarily achieved through our Pharmasolutions service, which is an in vitro dossier development in CTD Module 3 format. SPI has developed several drug formulations using its proprietary platforms in combination with different APIs,

creating a large excipient compatibility database to draw from; thus streamlining the drug development process and avoiding formulation trial and errors. We work with our customers to develop a detailed project scope and key milestones. The development fee is based on SPI achieving these critical milestones: Pay for Success. SPI has a strong track-record of successfully completing dossiers for several pharmaceutical companies around the world.

Q: Can you expand on your statement about developing patient-friendly drugs?

A: While there are several pharma-ingredient companies that focus on supplying me-too ingredients, our charter has been to offer our customers excipients and drug delivery systems that are geared to making patient-friendly dosage forms, such as chewables, ODT, lozenges, effervescent tablets, and dry powder sachets/suspensions. Our scientists focus on convenience, compliance, and efficacy features in these patient-friendly formats. For example, we own a joint-patent application for an insomnia drug in which the ODT formulation has been able to achieve the same therapeutic effectiveness at reduced API dosing, thus offering efficacy improvement.

Q: Please explain some of the dosage forms SPI offers through its drug development service.

A: One of the most popular and often requested dosage forms are ODT, where we are the only company that offers both a direct-compression tablet system and lyophilized wafer system with the patent-protected Pharmaburst and Pharmafreeze™ platforms, respectively. In addition, we develop formulations in chewing gum, lozenge, dry powder, and wet suspension dosage forms.

Q: What is SPI's track-record in product approvals?

A: Finished dosage forms developed by SPI using its proprietary platforms have successfully gone through approval in the US, Europe, and other parts of the world. In Rx, for example, products used to treat Parkinson's, migraine, nausea, allergies, depression, and schizophrenia have been approved. In OTC, we have had success with formulations made for analgesics, GI, and respiratory ailments.

Q: What's on the horizon for SPI?

A: While we have several strategic initiatives in the pipeline, I can only comment on a few of them due to the confidential nature of the projects. We are partnering with companies specializing in pediatric formulations to develop and test child-friendly dosages. Also, we have a strong initiative in API enhancement and efficacy improvement. ◆

Technology Showcase

MDI Components

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

PSL Nanotechnology

Azaya Therapeutic's Protein Stabilized Liposome (PSL™) nanotechnology utilizes a new, next-generation nanotechnology to produce liposome-encapsulated drug products. The company's interest in these agents is based on the potential for improved delivery of poorly soluble drugs, reduction in chemical and enzymatic degradation, and improvement in the toxicity profile of an agent. This technology is a key advancement in liposomal delivery, utilizing a proprietary single-step manufacturing process that produces uniform particles less than 200 nanometers while stabilizing drug encapsulations. Enhanced delivery of cytotoxic agents using PSL nanotechnology provides a safer, less expensive, and more convenient use to preferentially target tumors through an enhanced permeation retention (EPR) effect. In addition, Azaya's PSL nanotechnology offers an active targeting mechanism that utilizes protein identification of up-regulated tumor biomarkers. For more information, contact Azaya Therapeutics at (210) 341-6600 or visit **www.azayatherapeutics.com**.

Development Services

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

Technology Showcase

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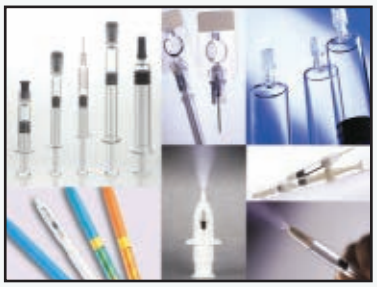
Prefillable Delivery Systems



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

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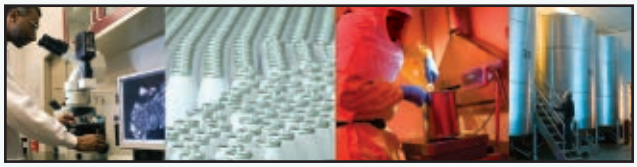
Colorcon has developed HyperStart® oral solid dose formulation service, a unique formulation start-up service specifically for hydrophilic matrix tablets. This predictive formulation model uses mathematical relationships supported and validated by extensive experimental data. The model generates an initial extended-release formulation based on inputs such as drug dose and solubility, dosage weight, and target-release profile. HyperStart can accelerate the development process for a wide range of oral solid doses and a variety of release rates. Use HyperStart at the concept test stage or with programs partnered through ongoing project support. This resource offered by Colorcon can simplify your development process and reduce time and costs for initial formulation. To access this free service, simply complete the HyperStart Formulation Questionnaire at **www.Colorcon.com**.

Specialty Pharma

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

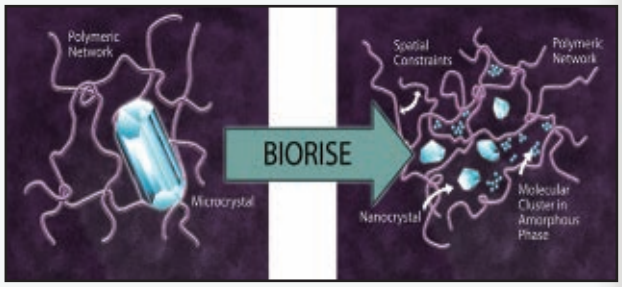
Technology Showcase

Development & Manufacturing



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

Bioavailability Enhancement



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

Pharma Polymers

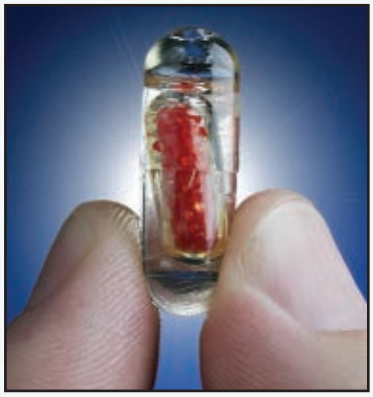
Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products and services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers manufactures EUDRAGIT® acrylic polymers used for enteric, sustained-release, and protective formulations. The unique functionality of EUDRAGIT polymers can also meet high sophisticated drug delivery requirements (eg, pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. For more information, contact Evonik Degussa Corp., Pharma Polymers at (732) 981-5383 or visit **www.eudragit.com**.

Manufacturer & API Specialist

Hovione is an international group dedicated to the cGMP development and manufacture of APIs, serving exclusively the pharmaceutical industry. With FDA-inspected plants in Europe, the Far East, and the US, Hovione is committed to the highest levels of service and quality. With a 50-year track-record, Hovione offers advanced technologies as well as APIs for all drug delivery systems, from oral to injectable and from inhalation to topical applications. Specializing in complex chemistry and particle engineering, Hovione offers all services related to the development, manufacture, and preformulation of both NCEs and existing APIs for off-patent products. Our aim is to do well what is difficult, to give our customers what they cannot find elsewhere. For more information, visit Hovione at **www.hovione.com**.

Technology Showcase

Combination Capsule Technology

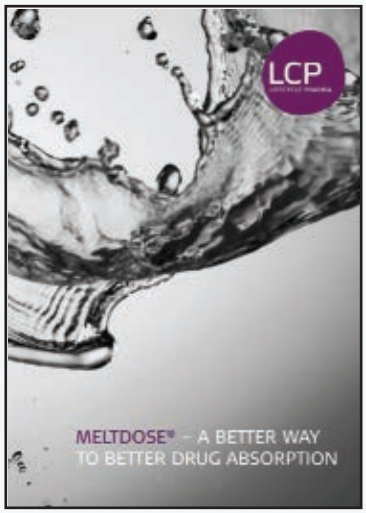


InnerCap offers an advanced patent-pending multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions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

Ultra-Pure Chitosan

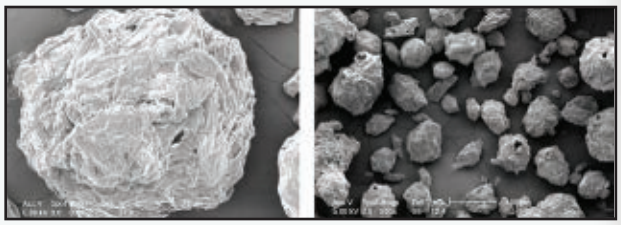
KitoZyme offers KiOmedine, the first range of non-animal ultra-pure chitosan and services for medical devices and drug delivery systems. Manufactured from vegetal source and in accordance with cGMP, KiOmedine ultra-pure chitosan exhibits excellent reproducibility, constant quality totally independent of seasonal variations, traceability, no risk of allergenicity, along with competitive price. KitoZyme's product development team (7-person staff of PhDs and engineers) provides expertise in functionalization, processing, and formulation of biopolymers applied to health sciences. KitoZyme also offers contract services, co-development opportunities, and capabilities to support customers in bringing innovative products to the market in the fields of wound care, haemostatics, surgical aids, ophtalmics, tissue engineering, drug delivery systems, adjuvants for vaccination, or cell encapsulating material. For more information, contact KitoZyme at info@kitozyme.com or visit **www.kitozyme.com**.

Absorption Enhancement



LCP is an emerging specialty pharmaceutical company focused on certain cardiovascular indications and organ transplantation. It currently has one product on the market, seven clinical development programs covering five product candidates, and three product candidates in preclinical development. Its first commercialized product, LCP-FenoChol, has received FDA approval for sale in the US under the brand name Fenoglide™ and is marketed in the US by Sciele Pharma. Fenoglide and its other development compounds are based upon its unique drug delivery technologies. The proprietary MeltDose® platform enhances the absorption of poorly soluble drugs. Applying MeltDose technology creates new versions of existing drugs with improved oral bioavailability, improving efficacy, allowing for lower dose, and in some cases, reducing food effect and/or potential side effects. For more information, visit LCP at **www.meltdose.com**.

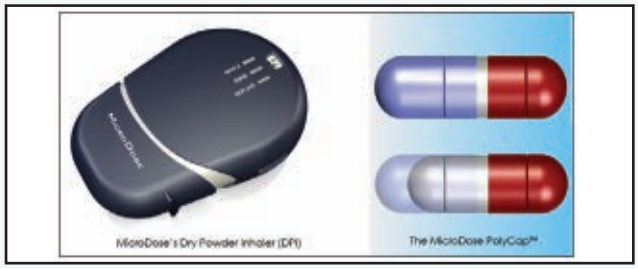
Performance Excipients



Mallinckrodt Baker recently launched PanExcea™ MHC300G performance excipient, a homogeneous particle that serves as a filler, binder, and disintegrant for immediate-release applications. Manufactured using novel particle engineering technology, the granular spherical excipient provides multifunctional performance capabilities that enable efficient and cost-effective drug development and manufacturing. PanExcea MHC300G lowers the total cost of ownership for the drug formulator by facilitating direct compression of even the most difficult APIs. It offers extensive API compatibility and variable API load capability to increase formulation flexibility. PanExcea MHC300G, which can be used as a building block or as a complete excipient, provides formulation development flexibilities and efficiencies, and enables implementation of Quality by Design (QbD) initiatives. For more information, contact Mallinckrodt Baker at (800) 943-4747 or visit **www.MallBaker.com/PanExcea**.

Technology Showcase

Next-Generation Products



MicroDose Therapeutx is pioneering the creation of next-generation products utilizing its proprietary technologies. MicroDose's Dry Powder Inhaler (DPI) and PolyCap™ combination oral dose capsule system promise to dramatically improve efficacy and compliance. MicroDose's next-generation DPI is a state-of-the-art electronic inhaler providing superior delivery for both small and large molecules to the lungs. It provides a platform technology that is low cost, reusable, and environmentally friendly, which can support a full pipeline of products. MicroDose's PolyCap System is a proprietary approach that enables the rapid development of FDC therapies in a single dose, but separated by a physical barrier. Utilizing the proven strengths of capsules and the advantages of a barrier system, it allows for more rapid development timelines and lower regulatory requirements. For more information, contact MicroDose Therapeutx at (732) 355-2100 or visit **www.mdtx.com**.

Delivery & Specialty Pharma

Penwest has a family of patented drug delivery technologies with a proven track-record (TIMERx®, Geminex®, SyncroDose™, and GastroDose®), all of which are available for product development. Products based on these technologies have been approved and marketed around the world. Our most recent success is Opana® ER, a pain product with $100 million+ sales in its first year of launch. Our technologies are well-suited for drugs with solubility, bioavailability, or site-specific delivery issues. The formulation flexibility and range of potential delivery profiles, coupled with a successful track-record of product approvals, is what attracts companies to TIMERx technologies for reinvigorating their products and extending exclusivity. For more information, please e-mail bizdev@penwest.com or visit **www.penwest.com**.

Knowledge Management

PharmaCircle™

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

Contract Service Provider

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

Technology Showcase

Nanotechnology Platform

SoluBest has developed a proprietary nanotechnology platform (Solumer™) for significantly improving the bioperformance of poorly soluble and insoluble. The versatile solubilization technology is widely applicable to numerous off-patent (or soon to be off-patent) drugs and NCEs. Rapid screening times allow the identification of suitable candidates in a few short weeks. Feasibility studies to clinical batch preparation can proceed in under 6 months. A significant advantage of the technology stems from its use of readily available equipment for a process consisting of a few simple steps, making scale-up safe, robust, rapid, and inexpensive. The company's strategy focuses on the development of novel drug formulations that can be performed in collaboration with API manufacturers, generic and brand pharmaceutical companies, biotechs, and drug delivery firms. For more information, visit SoluBest at **www.solubest.com.**

Excipient System

Pharmaburst™ is the first and ONLY patented off-the-shelf co-processed excipient system for fast-dissolving ODT applications in the pharmaceutical market. It is now being used in a wide variety of new and generic drug applications by many leading multi-nationals and several top generic companies. Pharmaburst is the only ODT platform included in the USFDA's Inactive Ingredient Guide (IIG List). Since its inception, several grades of Pharmaburst have been introduced to meet specific formulation needs. A brand new version with superior performance and cost effectiveness will be launched. Oral dispersible drugs containing Pharmaburst have been successfully launched in regulated and developing markets around the world for indications such as migraine, allergy, analgesics, anxiety, oncology, schizophrenia, depression, Parkinson's, etc. SPI Pharma has a fully integrated drug development program that utilizes its functionally superior excipients, proprietary delivery platforms, and enhanced APIs. For more information, visit SPI Pharma at **www.spipharma.com**.

Drug Development

Xcelience is the premier source for unsurpassed quality in drug development services. The company brings together the industry's most experienced and talented scientists, consistently and efficiently moving compounds through the research and development continuum to regulatory approval. Since 1997, the Tampa-based laboratory has been developing formulations for clients throughout the pharmaceutical industry. Xcelience's unique corporate structure creates project teams that work intensively with each client, bringing an extension of their own organization into the Xcelience lab. The lab uses only state-of-the-art equipment, highlighted by the patented Xcelodose®, which fills API directly to capsules (Xcelodose is a registered trademark of Capsugel BVBA). This and other technologies give Xcelience unparalleled speed to market without compromising its absolute commitment to quality. For more information, contact Xcelience at (608) 643-4444 or visit **www.xcelience.com**.

Solubilization Platform

Gateway BioPharma's solubilization platform offers a compelling approach to overcome solubility challenges, accelerate drug development, and improve patient outcomes. Our platform will advance the way a wide array of compounds are manufactured and administered to patients. At the core is a suite of novel particle engineering technologies that produce superior nanostructured particles with high surface area, providing rapid dissolution, improved physical stability, and exceptional bioavailability when compared to conventional formulation technologies. We take a portfolio approach to solving solubilization issues, based on well-characterized and scalable controlled particle growth technologies, regardless of the delivery objectives for a particular drug. Both Controlled Precipitation and Ultra-Rapid Freezing are used in order to optimize compound solubility and long-term stability. For more information, contact Gateway BioPharma at (512) 891-1216 or visit **www.gatewaybio.com**.

SPECIALTY PHARMA
Strategies For Business Development

Formulation Development

Changing Tides in Formulation Outsourcing

By: Cindy H. Dubin, Contributor

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Catalent Pharma Solutions

Derek G. Hennecke, MBA
President & CEO
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Michael Ruff, PharmD CPIP
VP, Pharmaceutical Development
Metrics, Inc.

Paul F. Skultety, PhD
Director, Pharmaceutical Development Services
Xcelience, LLC.

There appears to be a shift in the outsourcing industry, particularly as it relates to formulation development. CROs really saw increased usage from the early to late 1990s up until just recently. Many of the leading CROs are seeing revenues below $25 million, according to a May 2009 report from PharmaFocus.com. Pharma and biotech companies do not appear to be aggressively growing their pipelines or developing "blockbuster" drugs at the same pace they had in previous years. Thus, the business strategy of outsourcing formulation development has slowed a bit; it is more cost effective to keep this process in-house while pipelines get reconstructed to their previous strength. However, as the economy turns around, CROs are expected to see a revival.

Specialty Pharma magazine recently asked some formulation development contractors how they are setting themselves apart from their competition during these trying times and how their clients can benefit. Participants include Jeffrey E. Browne, PhD, Technical Director, Pharmaceutical Softgel Sales, Catalent Pharma Solutions; Derek G. Hennecke, MBA, President & CEO, Xcelience, LLC; Michael (Mike) Ruff, PharmD, CPIP, VP, Pharmaceutical Development, Metrics, Inc.; and Paul F. Skultety, PhD, Director, Pharmaceutical Development Services, Xcelience, LLC. Research Inc.

Q: ***Talk about the importance of being able to deliver fast-into-human formulations.***

Dr. Browne: The rapid delivery of FIH formulations is extremely important to virtual-small pharma and Big Pharma alike. Often, the ability of virtual-small pharma to obtain funding is predicated on the timely completion of milestones such as FIH studies. Tremendous product pipeline pressure exists for pharma companies of all sizes to identify viable drug candidates through FIH studies, and to weed-out those that are not. The focus of our FIH formulation approach is delivery of a formulation using the simplest approach possible, which minimizes the formulation and analytical efforts required, and achieves adequate drug exposure in a limited number of healthy subjects.

Recognizing this need, we now offer and promote "fast-track" FIH formulation programs. Catalent's approach yields FIH supplies in 4 to 6 months from first receipt of the client's API. This program builds on the client's available API data, and runs many formulation and analytical activities in parallel. In addition to our extensive multi-dose form preformulation and formulation expertise, one of the greatest time-savings we provide Catalent clients is the streamlined turnkey ability to develop, manufacture, and package FIH supplies within our network of facilities. In addition, Catalent offers a range of FIH formulation options to best match up with the specific requirements of the client's API. This means our clients only have to deal with one outsourcing partner instead of two or three, thereby simplifying the whole process.

Mr. Ruff: At Metrics, we understand that most proposed clinical programs are under significant time pressure for both public health and business reasons. More effective and safer drugs are urgently needed to treat a variety of diseases currently not adequately treated, such as cancer and hepatitis. Likewise, the viability of a client company may be entirely dependent on how quickly they can demonstrate an encouraging result from early human trials. Therefore, time to dosing in the clinic is frequently the most important concern to the client. Metrics prides itself in being able to deliver FIH formulations, in part because it has a 4 to 1 ratio of analytical chemists to formulators. This high ratio helps ensure that analytical method development, typically the critical path, can keep pace with formulation development.

Mr. Hennecke: It is absolutely vital that a contract developer provide solutions that enable clients to move quickly into first-in-human studies. Now, more than ever, pharmaceutical companies of all sizes are under pressure to reach critical milestones faster despite challenging molecular properties associated with their candidate, and with limited API. Subsequent rounds of funding often depend upon it.

As financing is tight and pharmaceutical companies struggle to do more with less, Xcelience delivers solutions that help clients work smarter in order to move drug development candidates forward faster and to maximize the chance for success. We offer a number of formulation development approaches specifically tailored to enable speed to first-in-human studies while conserving API and other resources. Though not all are relevant for commercial scale, API-in-bottle, powder-in-bottle, API-into-capsule, and traditional formulations are all approaches worthy of consideration as possible formulation options for clinical supplies for a Phase I clinical trial.

Q: ***Once a proof-of-concept has been established, how rapidly can the drug development program advance through to Phase II and III studies?***

Mr. Ruff: It depends on the definition of proof-of-concept, which is different for different clients and different disease indications. For some clients, this means getting through Phase I studies examining pharmacokinetics and side effects from dose-escalating studies in healthy volunteers. For others, it may also mean completing a small Phase II study to demonstrate some proof of efficacy. Regardless, it is always important to be able to move quickly into subsequent Phase II and III studies.

At Metrics, the transition from Phase I to manufacturing larger, Phase II supplies is typically rapid and seamless if the client has adopted our recommendation of developing a formulation for Phase I trials. Unfortunately, if the client has adopted a non-formulated dosing approach for Phase I (API alone in either a bottle or a capsule), Phase II studies cannot proceed until the formulation and analytical methods are developed, along with the necessary stability data. At Metrics, this can usually be achieved in about 12 weeks, including a month of stability data. The client must weigh the likelihood of success in Phase I and subsequent need for quick entry into Phase II trials against any possible time savings by starting clinical trials with a non-formulated product.

Early Phase III studies can commence as soon as the client feels confident about the Phase II results. Formulation and process optimization and scale-up will be performed before large, pivotal Phase III efficacy studies commence to ensure that clinical material is identical to the proposed commercial product, an FDA requirement. The optimization and scale-up typically is completed in 12 weeks, depending on the complexity of the formulation and process.

Dr. Skultety: On average, the total timing from start of Phase II through filing an NDA can range anywhere from 18 months up to years, depending on the approach used to establish clinical proof-of-concept, the intended therapeutic indication, and considerations for scale-up to commercial formulation. For example, if a powder-in-capsule approach was used for Phase I, then a formulated product will need to be developed for Phase II. A typical traditional formulation development would include dosage formulation, time to gather sufficient stability data, and the manufacture of clinical supplies, which may take between 4 to 6 months. The therapeutic indication may greatly impact product development timelines. Some indications require larger and longer clinical trials than others. For example, it is much easier to find patients with high blood pressure for an anti-hypertensive indication that it is to find people with certain cancers. This applies to both Phase II and Phase III studies. Lastly, the Phase III dosage form should be quantitatively and qualitatively close to the formulation that will be commercialized.

Dr. Browne: The length of time from proof-of-concept to Phase II and III depends on a number of factors, some within the control of outsourcing providers, while others are not. Often, the availability of API or the time for completion of the Phase I study is rate-limiting factors, over which the outsourcing provider has little control. When these are not at issue, the time it takes to develop an acceptable formulation, select the right drug delivery technology, and perform the related analytical support can often determine the length of time it takes to advance to Phase II studies. Where feasible, some clients run their early Phase II (IIa) studies using the same formulation used for their Phase I studies, allowing the quicker initiation of Phase II studies, while a more optimized formulation and advanced dose form is developed for later stage Phase II (IIb) and III studies.

Development cycle times depend on choosing the right formulation approach from the start, taking into consideration the known API properties, as well as any formulation work that might have been undertaken to date. For example, trying to formulate a poorly water-soluble (BCS II) API into a conventional tablet, using the one-size-fits-all approach can lead to excessively long development times, when a lipid-based formulation approach could have been more rapidly and successfully employed, allowing for the more timely initiation of Phase II studies. Challenging API properties and formulation complexity can add to the formulation development cycle times, and these are areas to which Catalent brings a wealth of problem-solving experience.

We have 75 years of experience as a company in developing formulations for oral dose forms, and we've learned to be practical and pragmatic. We believe in using the simplest formulation approach possible to meet the desired formulation attributes, such as manufacturability, stability, drug release, etc. Because we have formulation experience across so many dose forms and routes of administration, we have a great deal of practical know-how, which frequently gives us an edge to get to a stable formulation very quickly.

We work hard to effectively manage those factors within our control to provide our clients with a quality formulation for Phase II and III studies in the shortest time possible.

The last thing we want to do is to delay our client's development programs. To achieve this, we have built state-of-the-art development and manufacturing facilities around the world, and staffed these facilities with experienced formulation and analytical personnel. Being able to apply the right type and level of scientific expertise is important to ensuring the timely completion of development programs. We have found, for example, that it is important to maintain a ratio of 2.5 to 3 analysts to every formulator, recognizing that inadequate analytical support can often lead to project timeline delays. Typically, our project plans call for 6 to 12 months to complete the activities needed for progress into Phase II studies.

Q: ***How knowledgeable is your team with regard to dosage forms, formulation requirements, and commercialization?***

Dr. Browne: Given that Catalent is a world's leading provider of advanced dosage forms and outsourced dose form manufacturing, we have proven experience in bringing products from preformulation or the clinic to the market. We are also very fortunate to have a team of scientists with considerable knowledge and expertise in formulation development and commercial manufacturing. Investment in highly talented, experienced people has always been a priority for us, and we have experts in every major route of administration, dose form, and package. The technical personnel in each of these capabilities are experts in their field. Most also have significant pharma industry experience. Just as importantly, we have invested heavily in our other development and commercial support functions, such as quality, regulatory, and project management. Globally, we have more than 1,000 scientists supporting formulation, analytical, and other client-focused activities. We also offer commercial manufacture and packaging services and regulatory consulting, and call on all of these disciplines to help our clients bring their products to market faster and more successfully.

Mr. Hennecke: The Xcelience team is very experienced in the area of oral, solid, and semi-solid dosage formulation. Our team consists of a number of individuals with greater than 10 years industry experience taking products from preclinical development through commercialization. In July 2008, Xcelience was fortunate to attract top industry talent in Paul Skultety, PhD, who has served as Director, Pharmaceutical Development Services at Xcelience, LLC. Dr. Skultety has a unique background in pharmaceutical development combining extensive experience with contract development and pharmaceutical companies. He has a successful track-record of developing NCEs from pre-IND to commercialization.

Mr. Ruff: We have a seasoned pharmaceutical development team of 10 formulation scientists with an average of 12 years of experience in formulation development, scale-up/optimization, and commercial manufacture. Some of the senior scientists and scientific management have more than 20 years of experience. All scientists have earned degrees ranging from BA to PhD. They are supported by 15 pharmaceutical technicians with an average of 14 years experience in the same disciplines.

Metrics has successfully developed dosage forms, including tablets (uncoated and coated), capsules (powder, bead-filled, and liquid-filled), and topical and oral powders. To meet the dosing requirements for each drug, we have developed the following drug delivery characteristics: instant release, sustained release, controlled release, delayed release, enteric-coated, and zero-order release. The Metrics facility is fully equipped with modern GMP assets to support all typical solid dose manufacturing processes. Our equally experienced commercial manufacturing group, working with the pharmaceutical and analytical development teams and regulatory affairs, has successfully scaled-up, validated, filed, and launched six commercial products during the past 5 years. This is demonstrated proof of not only our excellent technical ability but also our understanding of the sometimes complicated regulatory requirements.

Q: *Talk about the financial and schedule benefits of outsourcing formulation development activities.*

Mr. Hennecke: A Specialty Pharma company can save a great deal of time, infrastructure costs, and capital expenditure by outsourcing formulation development activities. Outsourcing enables Specialty Pharma companies to remain virtual or avoid increased headcount throughout periods of fluctuation, all the while ensuring that their project remains on track. In addition, outsourcing enables companies to avoid wasteful spending upward of $500,000 on a new piece of equipment that may be project dependent and therefore used only once or twice.

At Xcelience, we can use the same piece of equipment multiple times and spread that capital cost over several additional projects that year alone. Our experience with a broad range of formulation and manufacturing equipment translates into time savings by reducing the learning curve that would have been associated with operationalizing a new piece of equipment. Experience with encapsulators is a good example. Each new model has novel features or quirks that require experience to master. Xcelience provides immediate access to scientific and instrument expertise and custom-tailored solutions designed to accelerate drug development and reduce risk for Specialty Pharma companies.

Xcelience API-into-capsule services are a great example of how much time and money can be saved by outsourcing formulation development activities. We have earned a reputation for being an experienced provider of API-into-capsule services, having processed more than 30 APIs and 90 batches using Capsugel's Xcelodose® 600 and 600 S precision powder micro-dosing systems. Our defined API-into-capsule program enables clients to shave an average of 17 weeks from a traditional formulation program, and our confidence in filling such a variety of APIs enables us to offer a guarantee.

Mr. Ruff: There are two types of savings Specialty Pharma can achieve using an outsourcing plan. The first is time, both to proof-of-concept and to NDA filing. With significant experience executing first-time-in-man and subsequent Phase II and III plans, the client can be assured of meeting aggressive delivery dates for clinical materials, method validation, development reports, and regulatory documents. Metrics has completed well over 100 first-time-in-man plans for clients, which provides a significant level of confidence for our clients in our plans for their new chemicals. Each week that we can shorten the timeline to completion of proof-of-concept is a week of savings and an earlier arrival to the next level of development and ultimately, the NDA filing.

The second type of savings is in actual dollars. By outsourcing, the client does not need to invest in the significant staff and capital expenditures associated with development and clinical manufacture. Whereas most Specialty Pharma are focused on just a few projects, an experienced contract development company has proven expertise in a variety of dosage forms and can apply that experience to each unique project. This means the Specialty Pharma company can keep its focus on research and key knowledge of its molecules.

Dr. Browne: The time and money saved by outsourcing can be significant. If outsourcing reduces the development cycle time, the product can be potentially launched earlier. The potential to start generating revenues weeks or months ahead of schedule can be huge for a large-volume product. Clients can reduce development cycle time by outsourcing if they have limited or no in-house resources that can be applied toward the program. Often, with specialized dosage forms, the client does not have the capability to develop or manufacture the dosage form in-house even though it represents the preferred dosage form for their API. In this case, the client can add significant time to the development cycle by choosing instead to "force-fit" the API into an existing in-house dosage form technology. Bringing specialized dosage form technologies in-house for a given product just doesn't make good business sense given the money and resources necessary to do so.

Outsourcing results in time and money savings, and the magnitude of these savings does depend on the competency of the outsourcing provider. Having knowledgeable and experienced people can make a world of difference. Not only does it increase the probability of first-time success, but when problems do arise, experienced partners know how to deal with them - quickly and effectively. As mentioned previously, it is equally important to have strong staffing in the development and manufacturing support areas, such as quality, regulatory, and project management. If a client has to spend significant in-house resource to babysit a contract developer, it kind of defeats the purpose of outsourcing.

Q: ***One outsourcing consultancy is claiming that the contracting sector is "ripe for consolidation," and many have revenues below $25 million, particularly in formulation development. How are you competing in this market to ensure long-term support?***

Mr. Ruff: Metrics management has a serious commitment to the local community, which is reflected in the extremely low turnover of employees. Consequently, Metrics is not as prone to consolidation as other contractors in these volatile times. However, it does recognize the need to stay competitive in a market where consolidation may take place and so will maintain a marketplace watch on these issues and how they might affect our organization.

The key competitive tool that Metrics utilizes is quality. We use quality people to deliver quality results to quality clients. We try to do this time and time again as this is what allows the client to be confident in our plans, results, and working relationships.

Finally, while we focus on meeting our current clients' needs, we work with each new lead as if they are already a client, so that they can get a feel for the way our teams work with each project. Each client or potential client knows that we look at their project as if it is the only project in our system.

Mr. Hennecke: Consolidation in an industry happens when clients are better served by fewer companies. If the industry is better served by more vendors, then that's what will prevail in the long run. Formulation development has diseconomies of scale. The larger you are, the slower you get. Xcelience knows that better than anyone - we were once part of a larger company that was trying to consolidate the drug development chain. It was too wieldy and slow. Once we were separated off from the company, we were able to become lean and mean and more client-oriented, rather than mother-company-oriented. Our bottom line exploded upward. I guess that means we were doing something right. Formulation services have been affected as pharma companies put their limited resources into late-stage drugs, hoping for quicker payoffs. This has been particularly damaging to smaller companies with only a few clients. Xcelience is fortunate to have a range of client companies of varying sizes from all over the world. We have been able to weather this storm solidly, and remain in an excellent cash position. Privately owned and debt-free, we look forward to the next stage, when we expect companies to resume pipeline development for early stage drugs.

Dr. Browne: Catalent is currently the largest outsourcing service provider of advanced technologies and outsourced development, manufacturing, and packaging services serving the global pharma and biotech industry. We have a strong business, with fiscal 2008 revenues of approximately $1.8 billion, 9,500 employees, and a strong and stable financial position. We have built this business by understanding the needs of our customers and deploying our experience and expertise to solve the challenges our customers face. Simply put, we ensure our long-term viability by doing each day what we've done for 75 years: combining the talent of our people, our extensive intellectual property, and our world-class scientific and manufacturing network to solve our customers hardest challenges, and to act as a catalyst to their products' success. ◆

Stem Cell-Based Therapies

Embryonic Stem Cells: Moving Ahead in 2009

By: Kathryn Symank, Research Analyst II, Frost & Sullivan

Introduction

This year has been a momentous one for human embryonic stem cell research with two significant announcements: the clearance by the FDA to start the first human clinical trials, and the ban lift on federal funding for stem cell research. Both of these announcements signify key turning points in the history of these controversial cells and represent the clearance of significant roadblocks. Moreover, it makes the promise of embryonic stem cell-based therapies a closer reality. However, the moral and ethical debate over the R&D of human embryonic stem cells continues.

Embryonic Stem Cells

Often dubbed miracle cells, embryonic stem cells exhibit several attractive characteristics that are unique and set them apart from other cells. Specifically, these pluripotent cells are essentially blank and can become any of the 220 types of cells in the body that are derived from the three germ layers. In addition, they are easily cultured and can self-renew for long periods of time without differentiating or losing pluripotency, resulting in an unlimited supply of almost any specific cell type.

The unique attributes of embryonic stem cells give them high potential as therapies for a range of diseases, particularly ones that result from damaged cells or tissues. Evidence indicates that these cells may be transplanted to replace the damaged cells with healthy ones. This replacement gives great hope for diseases that result from tissue degeneration, such as Parkinson's disease or spinal cord injury.

Immersed in Controversy

Since their discovery, the research and use of embryonic stem cells has been immersed in a heated political and ethical debate. While being hailed for their potential as research tools and therapies for the treatment of diseases, embryonic stem cells are also the subject of great controversy because they are harvested from human embryos. Additionally, there is concern over safety risks associated with their use in humans.

One of the main points of contention with the research and use of embryonic stem cells is the involvement and destruction of human embryos. Specifically, they are derived from surplus embryos (typically 4 to 5 days old) that have been donated from *in vitro* fertilization clinics. Those who are opposed to the use of these cells believe that human life begins once fertilization has occurred. Because the embryo must be destroyed in order to harvest stem cells, this results in the loss of human life. Those who support embryonic stem cell research postulate that because embryos are not viable outside of the human body, they should not be considered human life. In addition, considering the embryos used to harvest stem cells are slated for destruction and were never implanted into a human, using them as a source of embryonic stem cells is more practical and benevolent than mere destruction.

Another key disputation is safety, including issues such as the risk of passing viruses, uncontrolled or misdirected growth, and immune

rejection. As a result of these concerns, an FDA advisory committee was held in April 2008 to determine the safety of developing cellular therapies from human embryonic stem cells and whether these products could be safely tested in humans. A main concern raised was the ability of embryonic stem cells to generate teratomas — tumor formations containing tissue from all three germ layers. Evidence indicates that teratomas may arise from the administration of embryonic stem cells that have not been fully differentiated. Furthermore, some experts have stated that because some embryonic stem cell therapies may contain a heterogenous mixture of cells with different degrees of differentiation, there is a possibility that these cells may migrate and differentiate into inappropriate cells.

Adult Stem Cells: A Good Alternative?

Critics against embryonic stem cell research claim that adult stem cells may offer the same potential. Although less flexible then their embryonic counterpart, adult stem cells are multipotent. This means that they can produce different types of related cells. In the body, adult stem cells primarily help maintain homeostasis and assist in the repair of damaged tissues. This less controversial option is closer to the market than embryonic stem cells, with several late-stage adult stem cell products in development.

Although used therapeutically for the past 30 years in the form of bone marrow transplants, adult stem cells have some limitations that complicate their comparison to their embryonic counterpart. Despite the fact that they are found in many different tissues, including adipose tissue, liver, and blood, adult stem cells are relatively rare and hard to isolate in large amounts. Historically, they have been difficult to culture because they stop dividing and lose potency over time. As a result of these challenges, adult stem cell therapies were thought of as products that could only be produced in limited quantities using cells obtained from one or more donors for each patient needing treatment.

New innovations in adult stem cell culture have allowed some companies to develop adult stem cell therapies that do not have these constraints. One such company is Athersys, Inc., a biopharmaceutical company that is developing a novel stem cell product called MultiStem that contains multipotent adult progenitor cells (MAPC). MultiStem does not have product limitations seen in other adult stem cell products. This product has benefits, such as the ability to be made from stem cells obtained from a single donor and may be produced on a large scale, allowing the development of a standardized pre-made product. Additionally, most adult stem cells have the ability to develop into a limited number of cell types and tissues. MultiStem, however, has been found to exhibit a broad plasticity and is able to form a large number of different cell and tissue types, giving this product a promising therapeutic potential.

On the Road to Clinical Trials

In January 2009, Geron announced that the FDA had approved its investigational new drug application (IND) for GRNOPC1, making this the first human embryonic stem cell therapy to begin human clinical trials. Additionally, it signifies the start of a potential new class of therapies and paves the way for more of these therapies to start clinical trials. GRNOPC1, made from oligondendrocyte progenitor cells derived from human embryonic stem cells, is being developed to restore spinal cord function. For Geron, this announcement represents over a decade of research. Moreover, it represents the clearance of many significant challenges, including an earlier hold on the start of clinical trials by the FDA.

Geron plans to start human clinical trials for GRNOPC1 later this year using patients who have documented evidence of complete spinal cord injury. This therapy will be injected into the injury site within 7 to 14 days after the injury occurs. Results from animal studies indicate that GRNOPC1 is safe and does not exhibit evidence of teratoma formation. In addition, these studies show that this product could improve locomotor activity in a variety of different animals.

Advanced Cell Technology, a biotechnology company focused on developing stem cell therapies for regenerative medicine, hopes to follow Geron in forming human clinical trials for its embryonic stem cell product. The company is expected to file an IND for its product, retinal pigmented epithelial (RPE) cell therapy, later this year. RPE is being developed as a treatment of retinal degenerative diseases like age-related macular degeneration. To help initialize the process, Advanced Cell Technology has already completed a pre-investigational New Drug meeting regarding the requirements.

Removal of Federal Funding Ban

In March 2009, President Barack Obama signed an executive order lifting the 8-year ban on federal funding for embryonic stem cell research. This decision is expected to increase the amount of funds available for research and allow the study of hundreds of additional cell lines. Until now, these additional cell lines have been off limits for federal funding. There is hope in the scientific community that the pace and quality of embryonic stem cell research in the US will greatly improve.

Since the ban was imposed by President George W. Bush in 2001, embryonic stem cell research has received very little federal money, all of which was relegated to cell lines established prior to August 2001. As a result, embryonic stem cell research has had to rely on alternative means of funding, including private sources and monies from individual states. Despite this, there is a large discrepancy between the funding provided for adult and embryonic stem cell research. The main reason for this is that the federal government, in the form of the National Institutes of Health (NIH), is the largest contributor of funding for most types of US research.

One of the major implications of reduced federal funding has been that few investigators have researched embryonic stem cells. Embryonic stem cell labs have either focused on the federal approved cell lines, or set up completely separate labs. The result has been that the US is considered by many in this field to be behind other countries like China and India.

Going Toward the Future

Considering the many diseases that are either incurable or difficult to treat, the allure of embryonic stem cells offers great hope. Despite their potential, stem cells are surrounded by controversy, which has resulted in major roadblocks. Even with these setbacks, stem cell research is progressing, thanks to both private and state funding. Embryonic stem cell research is, however, still advancing slower than adult stem cells. With the ban on federal funding overturned and the clearance to start human clinical trials, the outlook for embryonic stem cell research is looking more positive.

Although adult stem cells show great therapeutic promise, most researchers agree that they cannot replace the capabilities available from embryonic stem cells. This point is highlighted in a letter written to President Bush in 2001 and signed by 80 Nobel Laureates, "Some have suggested that adult stem cells may be sufficient to pursue all treatments for human disease. It is premature to conclude that adult stem cells have the same potential as embryonic stem cells, and that potential will almost vary from disease to disease." Therefore, the best course of action is to continue researching both types of cells to maximize the potential returns from all stem cell research. ◆

Kathryn Symank

Research Analyst, Frost & Sullivan North America

Kathryn Symank 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 February 2007, Mrs. Symank has completed several research studies and consulting projects with recent works focused on monoclonal antibodies, stem cells, osteoporosis, lifestyle disorders, and respiratory diseases. Prior to joining Frost & Sullivan, Mrs. Symank worked for 7 years in pulmonary pathology at the University of Texas Health Science Center in San Antonio, where she studied bronchopulmonary dysplasia. She earned her BS from Texas A&M University in Molecular and Cell Biology and her MS from the University of Texas at San Antonio in Biotechnology.

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EXTERNAL DELIVERY

Don't Be The Bad News Bears

By: John A. Bermingham

I learned the hard way that there are two ways to say everything. About 6 weeks after I joined Rolodex Corporation to turn it around, I was invited by the Chairman of the holding company that owned Rolodex to make a presentation to its Board of Directors on my assessment of the company. As an early stage CEO, I made the decision to do a "Howard Cosell" and tell-it-like-it-is presentation.

I developed a laundry list of all the things wrong with Rolodex, with my strategy being to show the Board how I had quickly identified the problems and then the solutions I was putting into place to deal with the problems.

What the Board heard was the laundry list of problems I had identified. What they did not hear were the solutions going into place because when I got to those solutions, they were still back on the problems and heard nothing beyond that. The Board put Rolodex up for sale a few months after that meeting.

What I should have said was something like "there a solvable issues that are all being addressed, and we expect a viable company going forward." And then give a few examples rather than giving the Board a litany of problems.

Not only did I learn from this negative presentation that I put on for that Board, I have taught the "two ways to say everything" philosophy to every management team I have led since Rolodex. My belief is that you have to determine who your audience is and what information they are seeking from you. It is like a resume - you never have one, you have several. Why?

Because while always staying within the boundaries of total honesty, you should always tailor your resume to fit the position for which you are interviewing. In my case, if the interview is for a company in need of a CEO who can solve a sales and marketing problem, then my resume and cover letter will emphasize my sales and marketing background and qualifications. If the interview is for a company that has operations problems, then my resume and cover letter will emphasize my operations experience.

When I joined my new company this past January, our bankers asked me to meet with them to discuss the situation at our company. Had I presented a Rolodex scenario, I believe the bank might have pulled the plug on us.

What I did was present a general overview of the company's situation without drilling down into the minutia. I then presented my plan for the company going forward to include a very detailed *100-Day Recovery Plan* that showed the positive effects that plan would have on the company. I concluded my presentation with the naming of the turnaround project *Project Orange Grove*. Why?

Because there is so much low-hanging fruit in the company that we can quickly address that which will show immediate positive results. Our bank is now giving us very strong support going forward to include temporary relief on our covenants, additional liquidity, and plenty of time to turn the company around.

It's not just what you say…..it's how you say it! ◆

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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2009 CRS Young Investigator Award

Justin Hanes
Professor, Chemical and Biomolecular Engineering
Johns Hopkins University

Eurand congratulates **Professor Justin Hanes,** winner of the 2009 CRS Young Investigator Award.

- Attend Professor Hanes' presentation: *Nanomedicines That Overcome Biological Barriers,* at the Award Showcase session on Tuesday, July 21, 15:30–17:30
- Eurand will present Professor Hanes with his award at the Closing Banquet on Tuesday evening, July 21

Eurand is the proud sponsor of the CRS Young Investigator Award.

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