CONTROLLED RELEASE SOCIETY

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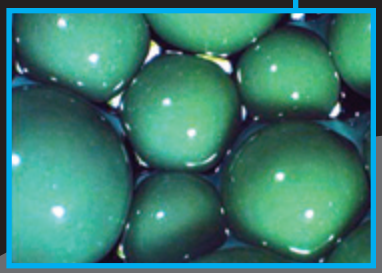
NEWSLETTER



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CONTROLLED RELEASE SOCIETY
NEWSLETTER

Volume 23 • Number 2 • 2006

inthisissue

On the cover –

Novel delivery systems designed by Lipo Chemicals Inc. These delivery systems provide opportunities to combine incompatible compounds into a single formulated product, convert liquids into solids, and control the release of components. Lipo Chemicals Inc. will be featured in detail in our next newsletter.

Steven Giannos
Industrial Editor

Cathy Ludwig
Editor

Bozena Michniak
Editor

Yvonne Perrie
Editor

Vladimir Torchilin
President

Editors
Bozena Michniak & Yvonne Perrie

Consumer & Diversified Products Special Feature Editor
Cathy Ludwig

Industrial Editor
Steven Giannos

Thanks to members of the Publications Newsletter Subcommittee for helping with this issue: Martyn Davies, Agis Kydonieus, Harlan Hall, and Mike Rathbone.

The Controlled Release Society Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published four times annually providing scientific and technical information pertinent to the controlled release community and news about society and chapter activities. Members receive the newsletter via mail. The newsletter may also be viewed online at www.controlledreleasesociety.org.

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FROM THE *Editors*

By Steven A. Giannos
Chrono Therapeutics, Inc., U.S.A.

Steven A. Giannos

It's time to make travel plans for the 33rd Annual Meeting and Exposition of the Controlled Release Society and to meet old friends, make new connections, share scientific discoveries, and learn about recent updates in the various aspects of controlled drug delivery! This year, the annual meeting destination is Vienna, Austria, and I hear that Vienna has been all astir celebrating Mozart's 250th birthday.

The CRS 2006 Program Committee has secured top-quality international scientists and industrial experts for cutting-edge Plenary and Invited Speaker sessions, as well as Industrial sessions.

Plenary sessions include Nanosystems Biology: Study of Cellular Processes in Live Single Cells (James Heath, California Institute of Technology, USA); Signal Transduction (Alexander Levitzki, Hebrew University of Jerusalem, Israel); Drug Transporters in the New Drug Discovery and Development (Yuichi Sugiyama, University of Tokyo, Japan); European Science: Forward Look on Nanomedicine (Ruth Duncan, Cardiff University, UK); and From Supramolecular Chemistry to Constitutional Dynamic Chemistry (Jean-Marie Lehn, ISIS – Université Louis Pasteur, France).

Educational Workshops on Saturday, July 22, include CMC Regulatory Issues for Controlled Release Parenterals; Drug-Device Combination Products: Novel Technologies and Regulatory Challenges; and Role of Intestinal and Hepatic Transporters on Oral Bioavailabilities of Drugs.

Sunday, July 23, is a busy day, with the Releasing Technology Workshops, the ever popular Soapbox Sessions, and Pearls of Wisdom. I challenge you to keep up with the rapid pace of the Soapbox Sessions or join in the discussion in one of the Pearls of Wisdom debates.

Mini-Symposia include Genomics—Drug Delivery; Innovations in Veterinary Drug Delivery; Nanomedicines and Cancer; Novel Vaccination Approaches; and Oral Delivery Macromolecular Drugs.

And don't forget the Educational Program for Young Scientists, planned by Drs. Mike Rathbone and Farid Dorkoosh of the Education Committee. Topics this year include "Colloidal Drug Delivery and Nanotechnology," "Nanogel Networks and Their Application in Drug Delivery," and "The Role of Nanotechnology in Targeted Drug Delivery and Imaging."

On another front, the only thing in life that's constant is change, and CRS has been growing and changing this past year. Most notably, our officers decided to move the CRS headquarters to Scientific Societies group. This move will facilitate our further

From the Editors continued on page 4

Vladimir Torchilin

From the President

By Vladimir Torchilin
Northeastern University

Dear Current and Future Members of the Controlled Release Society,

In less than a month we all will meet in Vienna for the 33rd CRS Annual Meeting and Exposition. I have good reason to believe that this will be one of our most successful meetings, with more than 1,100 abstracts submitted by those working in the field of controlled release.

I am pleased to inform you that our society remains the most important and influential society in the areas of experimental pharmaceutical sciences, drug delivery, and consumer products based on the phenomenon of controlled release. With members in more than 30 countries, powerful local chapters all over the world, our annual meetings, and our outstanding *Journal of Controlled Release*, we are looking into the future with deserved optimism.

Our growth and strengthening over the last few years, as well as our increasingly international character, have required the management of the society to be raised to the next level. From now on, the CRS will be managed by Scientific Societies group, which will provide us with outstanding experience, reputation, and offices both in the United States and Europe. Our new, updated website, with which you should be becoming familiar, will provide you with information on these changes.

The issue of the CRS Newsletter you are holding in your hands or opening on the screen of your computer will inform you about the recent developments in our common areas and show you how dynamic and challenging our science is and how the CRS is trying to coordinate and promote joint efforts.

In the near future, we are considering many new initiatives that will bring more influence and visibility to the CRS, enhance its reputation, and provide substantial financial revenues. These initiatives include new benefits for members, new educational resources, special arrangements for members from countries with developing economies, and new important publication activities under the logo of the CRS.

With all these activities on the horizon, I encourage you to maintain your membership in the Controlled Release Society if you already are a member, to become a CRS member if you have not done it before, and to attend the 33rd CRS Annual Meeting and Exposition in Vienna, July 22–26, 2006. This meeting will give us not only an outstanding scientific program, but also a unique opportunity to meet our peers face-to-face and discuss what we have to do in years to come to maintain and enhance the significance of our society.

Joining our efforts, we can raise the Controlled Release Society and the exciting science and technology we are involved in to new heights.

Sincerely,

Vladimir Torchilin
President

From the Editors continued from page 2

growth and provide us with outstanding experience and reputation, as well as offices both in the United States and Europe.

We also have a new website: http://www.controlledreleasesociety.org/. I hope you agree it is an improvement and please feel free to comment or send suggestions.

For the time being, Scientific Societies has named a specific representative to manage the CRS Newsletter, and her name is Amy Hope, Vice President of Operations at Scientific Societies (Phone: 651/994-3827, E-mail: ahope@scisoc.org).

In addition, we would like all our members to continue to give thought to submitting articles to the Newsletter. We would all like to see the Newsletter issues grow and include interesting articles on new controlled release platforms, strategies, and science, both academic and industrial. Small companies and start-ups, as well as academia, are encouraged to contact the editors and submit material that describes their novel and significant technologies. We also appreciate hearing about "hot topics" in science, faculty and student awards, and other noteworthy pieces of news. For larger companies and corporations, news on important appointments, drug approvals, and new products is always welcome.

On behalf of the CRS Newsletter editorial team, we hope to see you all in Vienna this summer!!! ■

Scientifically Speaking

Drug Release from Stimuli-Sensitive Polymers

By Majella E. Lane and Jonathan Hadgraft
School of Pharmacy, University of London, U.K.

Polymers underpin the chemistry of life. The three main classes of biopolymers (proteins, carbohydrates, and nucleic acids) provide the catalysis, genetics, and molecular machinery necessary for cellular function. One of the most important functional aspects of biopolymers is their dramatic property changes in response to small changes in their external environment. Efforts by researchers to replicate this response in synthetic systems have led to the development of functional polymers that respond in some way to, for example, pH, temperature, or electric or magnetic fields (Figure 1). Although originally called "stimuli-sensitive" polymers these molecules are also termed "smart" polymers because of their similarity to biopolymers. There are clear applications for such smart systems in drug delivery because of their potential for on-off or modulated drug release in response to an external stimulus. In this article we focus on two smart polymers, pluronic block co-polymers and poly(*N*-isopropylacrylamide) (PNIPAAm), and specifically the importance of drug properties when attempting to control the release rate from these systems.

Figure 1. Stimuli for responsive hydrogels. (Adapted from Gupta 2002)

Pluronic Polyols and Their Derivatives

The family of tri-block copolymers containing poly(propylene oxide) (PPO) and poly(ethylene oxide) (PEO) in the sequence PEO–PPO–PEO have the trade name of pluronic polyols. The hydrophobic PPO segments of pluronic aggregates can be designed to exhibit distinct phase transition at body temperature. Aqueous solutions of between 20 and 30%, w/w, Pluronic F-127 (PF-127) are liquid at refrigerated temperatures (4–5°C) but gel upon warming to ambient temperatures. The gelation is reversible upon cooling. The release properties of drugs from PF-127 have been studied previously using a series of *p*-hydroxybenzoate esters at three different temperatures (1). As lipophilicity of the solute is increased from the methyl *p*-hydroxybenzoate ester through to the butyl ester the apparent diffusion coefficient and release rate decreased. PF-127 gels have been thought to consist of micelles and aqueous channels, the latter being the region from which the incorporated solute is directly available for release. The more lipophilic the drug the more it will partition into micelles and the less will exist in aqueous channels. The effect of temperature decreases as the solutes become more lipophilic, and the more lipophilic the ester the more its diffusion is hindered. PF-127 has been studied for possible use as a vehicle for injectables by both intramuscular and subcutaneous routes. Emerging applications for this system include localised release, particularly in areas of brain or spinal cord injury, veterinary drug delivery, ocular drug delivery, and rectal drug delivery (2).

PNIPAAm

Thermoresponsive PNIPAAm hydrogels, have been the focus of much research in this area because they can exhibit a sharp phase transition near body temperature. The phase-transition temperature, referred to as lower critical solution temperature (LCST), is around 34°C. PNIPAAm-based hydrogels swell below the LCST and shrink or deswell above this temperature. Below the LCST, favourable interactions via hydrogen bonding between amide groups in polymer and water molecules lead to dissolution of polymer chains. Above the LCST, the hydrogen bonds are broken, and water molecules are expelled from the polymer, resulting in precipitation of the polymer. Thus, the phase transition may be used to achieve pulsatile on-off drug release in response to a stepwise temperature change either side of this critical temperature. By controlling the polymer composition and topology, the phase transition may be kinetically and thermodynamically controlled. Copolymerization of PNIPAAm with hydrophobic butylmethacrylate decreases the LCST of aqueous copolymer solution, and copolymerization with hydrophilic co-monomers, such as acrylic acid or hydroxy ethyl methacrylate, results in an increase in LCST.

In order to gain a mechanistic understanding of the importance of drug properties when attempting to control the release rate from these systems, drug-loaded PNIPAAm macrospheres (Figure 2) were prepared and evaluated for their swelling characteristics (3). The influence of the incorporated drugs, benzoic acid, sodium benzoate, and diltiazem hydrochloride, on swelling and release were also studied (Figure 3). Physicochemical properties of the drug, such as drug size and solubility, were of major importance in the ability to turn on and off drug release by modulating external temperature.

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Scientifically Speaking – Drug Release continued from page 5

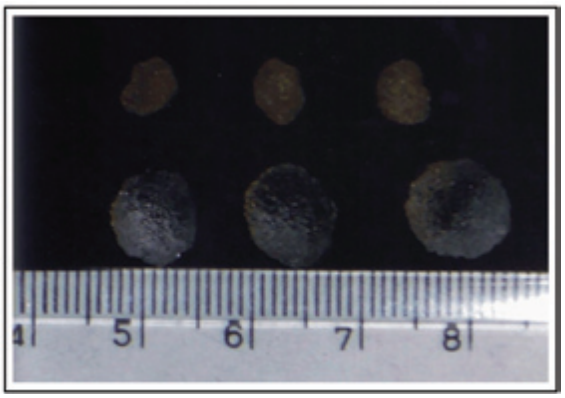

Figure 2. Macrospheres before and after swelling.

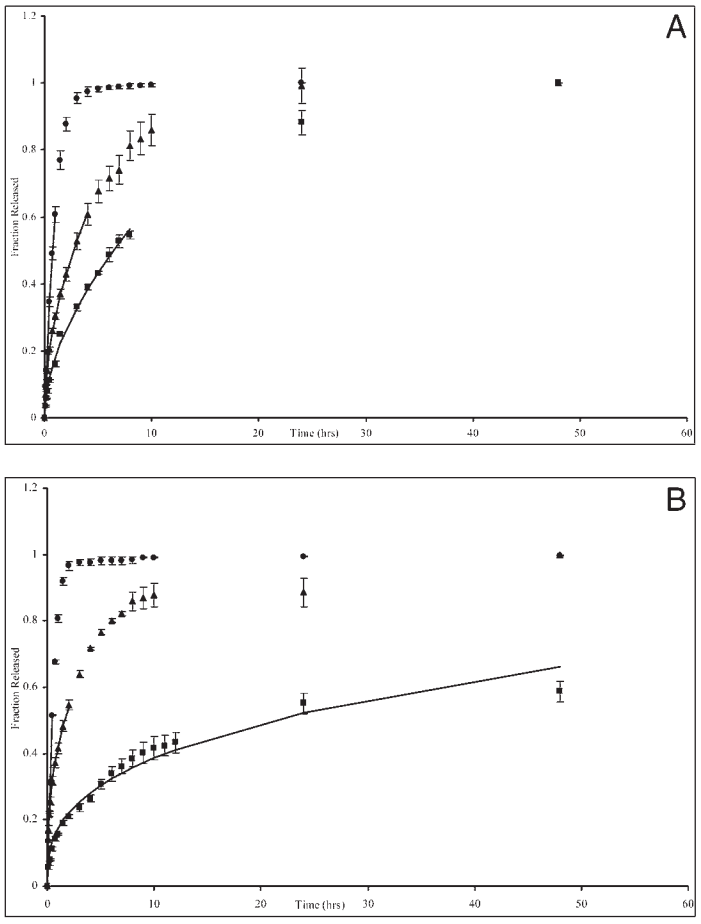

Figure 3. Fraction of drug release for benzoic acid (■), sodium benzoate (●), and diltiazem HCl (▲) loaded spheres at 25°C (A) and 37°C (B)

PNIPAAm Co-polymer Microgels

Incorporation of co-monomers containing acidic or basic functionalities into PNIPAAm microgels yields particles with pH-driven swelling. A co-polymer microgel of PNIPAAm, co-butyl acrylate, and co-methacrylic acid was synthesised and evaluated as a potential pH- and temperature-sensitive delivery device (3). Three compounds having different octanol/water partition coefficients and solubilities were incorporated into the microgel, namely salicylamide, methyl paraben, and propyl paraben. Physicochemical characterization showed that microgels incorporating methyl paraben and salicylamide have smaller volumes after changing environmental pH from 3 to 7 or with increasing temperature when compared with the unloaded microgel. The more hydrophilic the drug the more will be incorporated into the aqueous region of the microgel. Salicylamide and methyl paraben are quite soluble in water, with a log K_{oct} of 1.28 and 1.89, respectively. Large amounts of these drugs could be incorporated into the microgel, which has a shielding effect on the charged groups within the gel network. It is proposed that this shielding results in a reduction of the internal charge repulsion between the ionized methacrylic acid groups, together with a concomitant decrease in polymer–solvent interactions. As a result, these microgels will adopt a more compact conformation. Conversely, for the microgel-incorporating propyl paraben, the absolute volume remains constant compared with unloaded microgel with increasing pH or temperature. The log K_{oct} of propyl paraben is 2.83, and it is not very water soluble. Therefore, not as much of the drug is incorporated into the microgel particles, and as a consequence, it does not have a significant shielding effect between the charged groups.

Summary

For successful development of stimuli-sensitive drug delivery systems, the ability to understand, quantify, and predict the observed swelling effects and concomitant effects on release kinetics caused by the loaded drug is desirable. Drug–polymer interactions have implications for the rate of drug release before the phase transition occurs, the magnitude of drug pulse once a phase transition is achieved, and, therefore, the ability to control successfully drug release characteristics.

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Scientifically Speaking

Terahertz Pulsed Imaging—A Novel Tool for the Characterisation of Controlled Release Dosage Forms

By J. Axel Zeitler, School of Pharmacy, University of Otago, NZ; Cavendish Laboratory, University of Cambridge, UK; and TeraView Ltd., Cambridge, UK; Phillip F. Taday, TeraView Ltd., Cambridge, UK; and Thomas Rades, School of Pharmacy, University of Otago, NZ

Recent advances in the area of ultrafast optics and semiconductor technology have led to the development of a completely new approach to generate and detect radiation in the far-infrared part of the electromagnetic spectrum. Now it is possible to generate pulses of coherent radiation between 2 cm^{-1} and 130 cm^{-1} (0.06–4 THz), the so-called terahertz radiation, by exciting a special semiconductor device with ultrashort pulses of laser light.[1] This technology has the advantage that both generation and detection of the radiation can be performed at room temperature with no need for cryogens, as is the case in conventional far-infrared spectroscopy.

Technical Background

Far-infrared light has very interesting properties compared with light in the visible region of the spectrum. Even though most of the materials used for the formulation of pharmaceutical dosage forms are opaque to visible light, far-infrared radiation can penetrate through, or at least to a certain extent into, these materials. This allows, for example, nondestructive examination of structures below the surface of a tablet, such as the interface between a coating layer and the core of the tablet.[2] On a molecular level, the energy of terahertz radiation excites the vibration of the whole lattice within a crystalline material rather than single bonds within a molecule. Compared with the mid-IR (600–4,000 cm^{-1}), where intramolecular information (e.g., certain functional groups) can be extracted from the spectra, terahertz spectra contain intermolecular information about the interaction between molecules in their solid state environment. It has been demonstrated that using this information it is possible to clearly distinguish and quantify different polymorphic forms of pharmaceutical drugs by terahertz spectroscopy.[3,4] A recent review covers the current applications of terahertz technology in the pharmaceutical sciences.[5]

In terahertz pulsed imaging (TPI) coherent broadband terahertz radiation is pulsed at normal incidence onto the surface of a solid dosage form. While some of the light is reflected back at the outer surface, the remaining light penetrates into the sample. Whenever this radiation approaches an interface with a different refractive index, a fraction of the light is reflected back to the detector. The intensity of the back-reflected light is detected over time for the pulse of terahertz radiation (Figure 1). Using a time-of-flight analysis, the intensity maxima and minima of this time-domain waveform can then be used to calculate the depth of the buried interface that caused the reflection. To acquire a 3D image, a scan over the full surface of the dosage form is performed with the sample attached to a robot arm by a vacuum suction cap (Figure 2). The TPI imaga2000 (TeraView Ltd., Cambridge), the first fully automated instrument, can acquire a full scan of a single tablet within 20 to 40 minutes, depending on the size and shape of the sample.

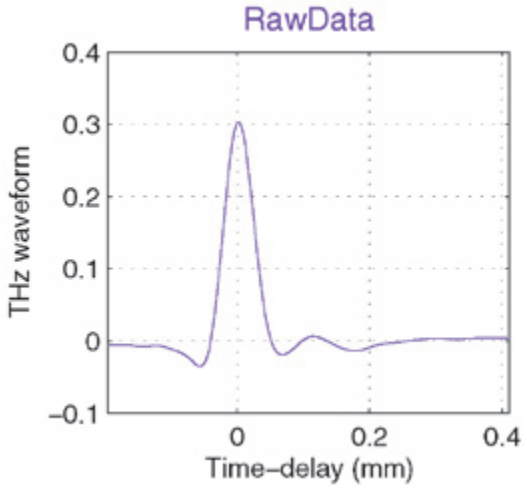

Figure 1. Terahertz time-domain waveform of a film-coated tablet. The initial strong peak at 0 mm corresponds to the reflection of the terahertz radiation from the surface. The first minimum at around 0.07 mm corresponds to the outer coating layer, and the subsequent minimum at around 0.18 mm is from the interface between the inner coating layer and the tablet core.

Applications for Controlled Release Dosage Forms

By analysing all pixels in the terahertz image, a statistical distribution of the coating layer thickness over the whole surface of the tablet can be generated (Figure 3). This information greatly improves quality control in production and speeds up the development of new coating formulations and processes. Because the tablets are not destroyed during analysis, further tests can be carried out after TPI using the same samples. This approach provides a tool for the detection of problems with coating processes in a very early stage of formulation development.

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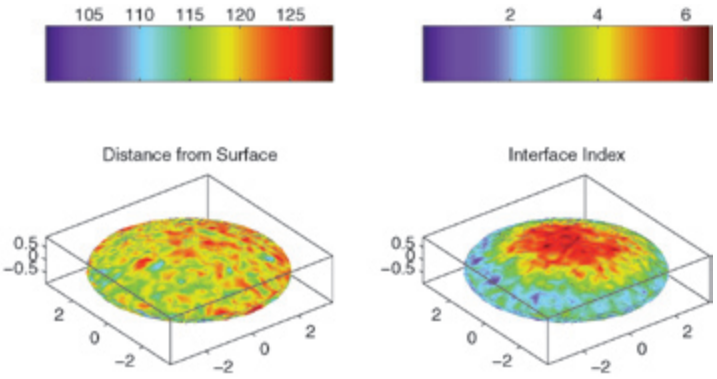

Figure 2. 3D map of the interface between the inner coating and the tablet core (colour bar on the left in micrometers). The image on the left illustrates the spatial distribution of the distance between the tablet surface and the interface. The image on the right represents the ratio between the peak intensity of the surface reflection and the reflection at the interface between the inner coating layer and the tablet core. This interface index reveals information on the quality of the interface.

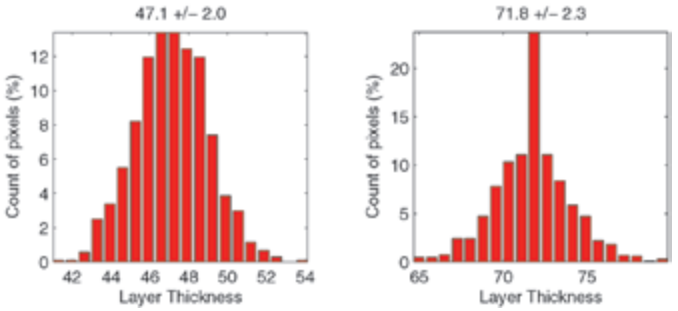

Figure 3. Histograms of the thickness distribution for the two coating layers of the film-coated tablet. The image on the left represents the thickness of the outer coating layer, and the image on the right the inner coating layer.

Furthermore, terahertz imaging technology allows the characterisation of coating performance in an objective way, e.g., during scale-up operations. Using the information provided by TPI, critical quality attributes for coating processes can be defined according to the PAT framework and controlled in-line throughout the production process.

In a 3D image the spatial distribution of the layer thickness can be visualised to facilitate the detection of local defects in the coating structure (Figure 2). It is possible to spot coating defects independent of whether the defect is located in the top layer or in any subsequent layer below the surface of multiple-coated tablets. The terahertz images make the information about the homogeneity of a coating accessible at a glance.

Non-destructive cross-sections through the tablet allow the analysis of buried structures or cracks in both tablet coatings and tablet body (Figure 4). Dislocations of the tablet core in embedded structures also can be detected. The spatial resolution for typical pharmaceutical coating materials in TPI is around 40 µm at present.

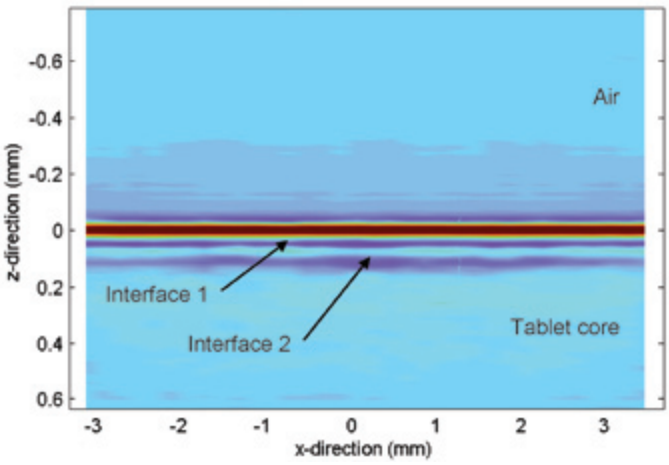

Figure 4. Cross-section through the film-coated tablet along the x-axis in z-direction. The red line at z = 0 mm represents the high intensity of the terahertz signal at the outer surface of the tablet. The dark blue lines represent the minima in the terahertz waveform at the two interfaces (interface 1 between outer coating and inner coating and interface 2 between inner coating and tablet core).

For tablets with a layered structure TPI can be used to examine properties of the interface between different layers. Delamination problems, as well as other potential challenges in the development and production of a layered dosage form, can be identified. Based on this information process parameters can be changed to optimise the production of the dosage form.

Work is currently in progress to combine structural imaging based on the differences in refractive index, as described above, with the spectral information contained in the terahertz signal. So far, 3D spectral imaging has already been demonstrated in a number of proof-of-principle studies, and this will add further exciting applications to this novel imaging technique.

Conclusions

With TPI, a novel technology has emerged that provides a unique tool for the development of solid dosage forms. Target applications in controlled release include the control of coating quality, correlation of coating properties with dissolution behaviour, and the study of disintegration processes based on the matrix characteristics provided by the terahertz structural information. A major advantage of TPI in the analysis of coatings is the ability to easily identify cracks and point defects at susceptible areas of the product. These are often difficult to analyse with other techniques such as the edges and sides of tablets.

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SPOTLIGHT:

Lipoxen plc
The Drug and Vaccine Delivery Company

By Professor Gregory Gregoriadis, Ph.D., D.Sc.
Founder and Chief Scientific Officer

Lipoxen plc is a biopharmaceutical company focused on product development through improving drugs and vaccines by the use of its proprietary patented technologies PolyXen®, ImuXen®, and VesicALL®. Our technologies allow us to pursue development of high-value and differentiated pharmaceutical products. Lipoxen's internal development is complemented by strategic partnerships with the world's largest biotech and pharmaceutical companies, which provide access to additional new products.

The company was founded in 1997 by Gregory Gregoriadis as a spin out of the School of Pharmacy, London University, where he was the head of the Centre for Drug Delivery Research, to exploit his inventions. These focused on the use of polysialic acids for the delivery of peptide and protein therapeutics (1,2) and liposomes for the delivery of DNA and protein vaccines (3,4). Over years of successful research and inventorships in the company's laboratories, Lipoxen's portfolio of intellectual property has mushroomed to include a wide range of granted and pending patents that cover key aspects of the company's core technologies. These developments together with worldwide strategic partnerships enabled Lipoxen to list early this year on the AIM market of the London Stock Exchange.

PolyXen® is a multifaceted enabling technology that uses the natural human polymer polysialic acid (Figure 1) to prolong the active life and improve the pharmacokinetics of therapeutic proteins, peptides, and other therapeutic entities to which the

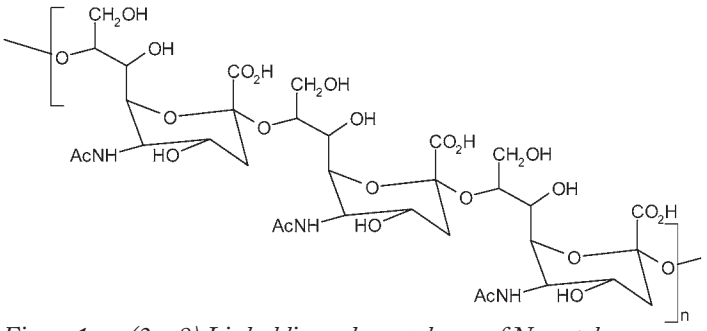

Figure 1. α-(2→8) Linked linear homopolymer of N-acetyl neuraminic acid (polysialic acid).

Spotlight continued on page 10

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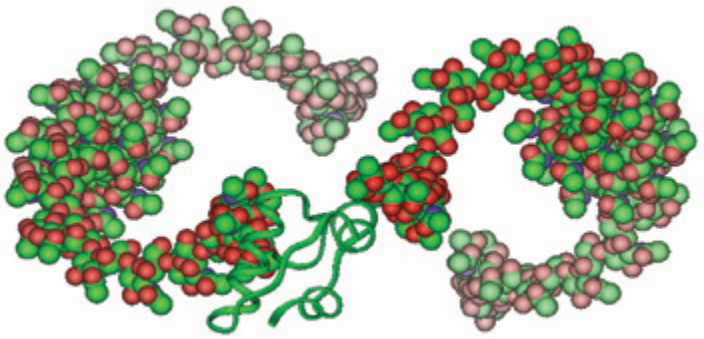

Figure 2. Molecular illustration of polysialylated-interferon α-2b (interferon in the centre).

polymer is conjugated by a wide range of proprietary techniques to satisfy particular needs (Figure 2). Because of the advantages of polysialic acid in terms of biodegradability, prolongation of the circulatory half-lives of protein and peptide drugs, and its stealth properties, which enable it to reduce or abolish the immunogenicity and antigenicity of actives (indeed, certain bacteria have high-jacked the polymer through millions of years of evolution to evade the immune system), PolyXen® is considered a next generation to PEGylation (5). The second major enabling technology of Lipoxen, ImuXen®, uses novel liposome-based constructs to boost the effectiveness of DNA, protein, and polysaccharide vaccines, as well as combination vaccines in which both the DNA and its encoded antigen are entrapped in the same liposome. ImuXen® can, through this co-delivery approach, achieve in a single dose with conventional vaccine antigens protective immunity (4) that otherwise requires multiple doses (Figure 3). Lipoxen's expertise in liposome technology has been extended to VesicALL®, a versatile and highly efficient method for the formulation of an extended

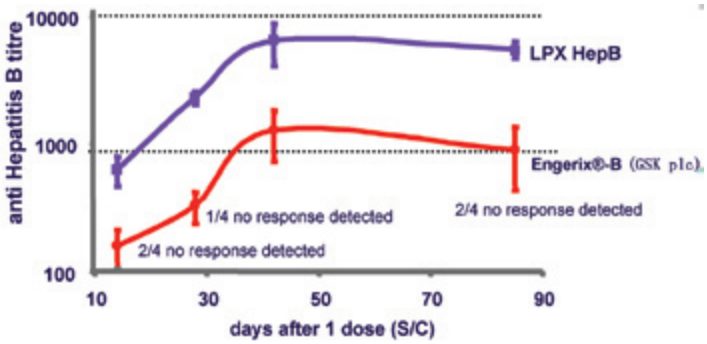

Figure 3. Improved performance of ImuXen® hepatitis B co-delivery vaccine.

repertoire of drug substances in liposomes. Lipoxen's technologies have been validated in numerous proof of principle preclinical studies, which have included recombinant human insulin, erythropoietin, granulocyte colony stimulatory factor, hepatitis B vaccine, and influenza vaccine.

Lipoxen's supergenerics product pipeline under development with partners or in-house, based on its drug and vaccine delivery proprietary technologies, have the capacity to create new high-value, differentiated proprietary products from off-patent actives. Lipoxen also is collaborating with U.S., European and Asian biotech and pharmaceutical companies to develop new protein therapeutics and vaccines, with improved performance built-in from the outset via improved delivery. For instance, Lipoxen has major research and collaboration agreements with Baxter HealthCare Corp. to investigate the effectiveness of polysialylation on Baxter's Factor VIII; the Serum Institute of India (the world's largest manufacturer of vaccines) to develop a liposomal pneumococcal vaccine, a liposomal hepatitis B DNA vaccine, and a liposomal formulation of Paclitaxel; and with National Biotechnologies OAO to develop polysialylated insulin and interferon α-2b. Other collaborations in progress, involving products that cannot be disclosed, include three of the largest biotech companies in the world and one of the largest pharmaceutical companies. Collectively, our pipeline products, have market potential in the multibillion dollar range. Preparations are in progress for the initiation of clinical studies.

For further information on Lipoxen's product pipeline and contact details, visit www.lipoxen.com.

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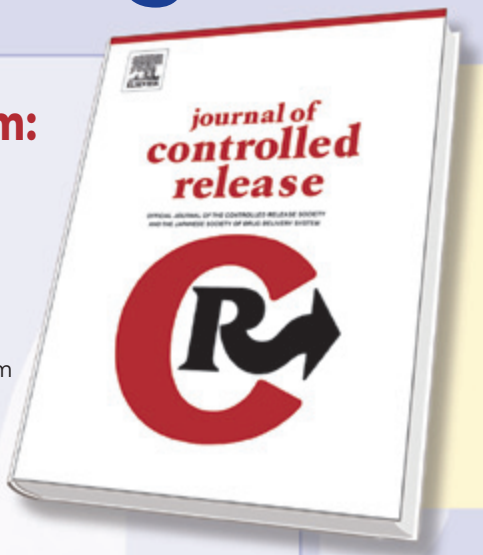

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Journal of Controlled Release

Highlights

By Morgan Leaming and Kinam Park

With grant proposals, research, and that much deserved vacation, the *Journal of Controlled Release* (JCR) realizes your time is limited. But, because of the give-and-take nature of article publishing, the members of the Controlled Release Society are consistently asked to serve as referees. JCR asks reviewers to evaluate each manuscript in terms of its originality, scientific quality, and significance of findings. These three criteria determine whether a manuscript deserves publication. In short, the reviewer can ask whether anybody would want to spend time reading the manuscript. To answer this, a useful review does not have to be a time-consuming task. The following are the main points to focus on when completing a critique.

1. **Originality: Anything new?**
   The observations a reviewer makes regarding the content of the manuscript can make or break the submission. The initial effort of the evaluation can be focused on finding the new information described in the manuscript. Without any new information, it is difficult to justify publication. As an expert, the reviewer should be able to identify the presence of new information upon first glance.

2. **Scientific quality: Clear and reproducible experiments?**
   The observation of scientific quality is based on experiments, and thus, it is critical to make sure that the experimental approaches described in the manuscript have no major flaws. Experiments should be described in detail for others to reproduce. Scientific quality also depends on the collection and interpretation of the experimental data.

3. **Significance of findings: Useful information?**
   The significance of the findings is related to the practicality of the information. A reviewer for JCR once pointed out that one could formulate cornflakes in a metered dose inhaler, but that does not mean it is a sensible thing to do. In the drug delivery area, we should consider whether the information described in the manuscript could advance the drug delivery technologies in a clinically useful way.

4. **References and grammar**
   In addition to the above key criteria, reviewers can compare the manuscript to previous literature that has been published. Reviewers know from the list of references whether the authors have shown a complete understanding of the previous research. In addition, it is generally not the job of a reviewer to critique every grammar problem within the manuscript. If, however, the whole idea behind the study is lost in the poor grammar, then it should be commented upon in the review. Otherwise, the reviewer can simply suggest that the authors have someone copy edit their paper.

Reviewers are unsung heroes in the peer-review process. Without them, peer review would not be possible, and yet we cannot recognize their efforts publicly. JCR has been fortunate to have so many great reviewers who spend their time going through submitted manuscripts carefully. The only comforting thing to reviewers is that they have a chance to see the brand new data before anybody else, and so we always cross our fingers to receive data that can wow the readers. JCR offers free drinks to all reviewers! ■

Marketing Trends in Delivery Systems for Cosmetic Preparations

By Nava Dayan, Ph.D.
Lipo Chemicals, Inc., U.S.A.

The skin is a barrier for a reason: to protect the body. Therefore, we should be careful when modifying the normal skin barrier and try to create reversible and rapid barrier changes. The cosmetic industry is currently facing the challenge of meeting growing consumer demands for safe and efficacious cosmetic products that will erase wrinkles in a short period of time, permanently and without surgical involvement. The ancient Greek philosopher Plato said, "Necessity is the mother of invention." The need for products to deliver perceivable qualities, be long lasting, and safer encourages cosmetic companies such as Estée Lauder and L'Oreal to seek ideas from other fields, such as pharmaceutics, food, and paint. Cosmetics is now not only about unique active compounds to benefit skin appearance, but also ways to deliver them to the skin. Innovation, however, is not the only driving force in the growth of delivery systems in the marketplace. Since research and development costs are on the rise, efficacy and safety are essential in order to assure a product's sustainability in the market and repetitive purchases. This has created increased interest in delivery systems, which has been growing at a double-digit rate since 2002. In fact, the U.S. market for delivery systems has increased from $19 billion in 2000 to more then $41 billion projected for 2007 (1).

The extensive competition is also fueled by the combination of different market trends, such as anti-aging, and the use of plant-derived products. In addition, although the cosmetic industry is self-regulated, the same need to elevate the therapeutic window that exists in pharmaceutics is desired in cosmetics. Moreover, the use of delivery systems addresses many practical problems, and these systems are being used to improve the stability of compounds, prevent incompatibilities by creating a physical barrier between components, change the form of a compound (e.g., from liquid to powder), and improve skin tolerance, as well as for consumer appeal (2).

The cosmetic industry appears to go through a change in perception with regard to what is considered a "delivery system." While a few years ago delivery systems were perceived mainly as particles that can be observed visually, today additional concepts are included under this category, such as sophisticated emulsions, creams with skin permeation enhancers, etc. When developing a formulation for treating cellulite, for example, one should design it to reach the fat tissue in the skin. A product designed by a large European company, for example, includes an active ingredient, which claims to block fat cell multiplication. It contains a plant extract to combat fat cell hypertrophy, one of the causes for "orange peel" looking skin (3).

There are many other examples of compounds included in cosmetic formulations that are known to affect biochemistry and, therefore, need to interact with viable sub-tissues in the epidermis. These include topical retinoids and anti-oxidants to slow skin aging and plant extracts that are rich in phytoestrogens to help reactivate the production of collagen and restore the skin's capacity to retain moisture. One can even find claims that some preparations affect skin cells on their DNA level. Another European company developed a formulation to support skin's natural DNA repair process. It contains a unique combination of vitamins and enzymes designed to imitate the skin's immune system.

The twentieth-century consumer is looking for more than elegance in the product; sensory attributes such as feel and odor are not enough any more. Consumers desire a broader variety of products, but also look for single products with multiple benefits. A cosmetic product is expected to deliver true noticeable benefits in order to drive consumers to repetitive purchases.

In order to find solutions and build strong market strategies, companies are looking for teamwork. One recent example is the collaboration established between Dow Corning and Lipo Technologies, Inc. Lipo Technologies has developed a variety of eight different encapsulation technologies to allow controlled release of compounds by friction, formulations with incompatible materials, and conversion of liquids into solids (4). These are being used in treatment products, cleansers, fragrances, and color cosmetics.

As for future developments, it conceals complicated challenges. The development of delivery systems can assist in extending anti-aging trends into the mass market, where there is a need for effective yet affordable noninvasive alternatives to cosmetic surgery. The diversity in applications creates a requirement to target actives to the skin sub-tissues. A unique patented delivery technology developed by Lipo Chemicals, Inc. is based on a lamellar delivery system. This system can be tailored to create a reservoir of the active compound either in the stratum corneum, as needed for moisturizers, or in the live epidermis and dermis, as required for anti-aging or skin brightening compounds (5).

Consumer and Diversified Products continued on page 14

Consumer and Diversified Products continued from page 13

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CRS Updates

The 2006–2007 CRS election results are in!

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We had an excellent response to this election, and CRS would like to thank everyone who participated. Be sure to renew your 2007 CRS membership by February 28, 2007, to be eligible to vote in next year's election.

Patent Watch

Transdermal Update

P. Batheja and B. Michniak
Ernest Mario School of Pharmacy, Rutgers, U.S.A.
A. Kydonieus
Samos Therapeutics, Inc., U.S.A.

Our patent search for the 2005 calendar year revealed 465 patents and patent applications. Of these, 221 were U.S. patents and patent applications, with 48 being U.S.-issued patents. There were also 111 EP patents and patent applications, 104 WO patents and patent applications, and for the first time, we captured 18 German and 11 Japanese patents. It should be noted that many of these patents are counted more than once, since a patent application can be filed in the U.S., WO, and EP patent systems at the same time. From the patents and patent applications mentioned above, 34 were iontophoretic or electroporation patents, 8 were based on sonophoresis, and 5 were based on microprotrusion/microneedle technologies.

In this Update, we have reviewed only the U.S. patents. Of those, 14 were based on iontophoresis, 2 were based on sonophoresis, 4 were based on microprotrusions, and 28 were based on methods and enhancers, which we have combined under the title "Passive Diffusion." Some of the most pertinent patents are summarized below.

Several activities of commercial interest were also announced during the year. In the area of treatment of pain, in July 2005 the FDA announced a health advisory to alert professionals and patients that deaths and other serious side effects took place with both brand name and generic fentanyl patches. In September 2005, Noven announced that the FDA did not expect to approve its generic fentanyl patch due to potential safety issues. None of the several generic fentanyl patches awaiting approval by the FDA got the green light in 2005. On a more positive note, Durect announced preliminary positive results from its Phase II trial with sufentanil, and Alza resubmitted to the FDA its iontophoretic fentanyl patch for acute post-operative pain. Alza in 2004 had received an approval letter from the FDA for this product.

In the treatment of depression, a selegiline (monoamine oxidase inhibitor) patch from Somerset Pharmaceutical got the good news from the advisory FDA panel that its low-dose patch (20 mg) does not need to have a black-box warning for its interactions with some foods, especially cheeses. The FDA granted conditional approval for the patch in 2004 but requested more data.

In October 2005, Noven and its marketing partner Shire Pharmaceutical announced that the Phase III clinical trial with their methylphenidine transdermal patch demonstrated statistically significant improvements in the symptoms of attention deficit/hyperactivity disorder, and it was generally well

tolerated in patients aged 6–12 years. In December 2005, the FDA issued an approval letter for the product.

In the hormone area, the Evra patch changed its label to indicate that women using the patch were exposed to about 60% more estrogen than women taking most pills for birth control. Some advocacy groups claimed that the level was high enough to increase some women's risk of blood clots. Over 4 million women have used the patch since it went on sale in 2002, but recently several law suits have been filed on behalf of women who suffered cardiovascular events.

Other announcements of interest include the following: NexMed announced statistically significant results from a 400-patient study using its alprostadil cream for female sexual arousal disorder; Zars obtained FDA approval for a lidocaine patch for use as a local anesthetic; a Sontra and EpiVax research collaboration is investigating the topical delivery of EpiVax's HIV vaccine and other DNA vaccines using Sontra's sonophoresis technologies; Transport Pharmaceuticals and Mack Molding are cooperating in a Phase III clinical trial with a device/drug combination system that uses iontophoresis to treat *Herpes labialis*.

PASSIVE DIFFUSION

Transdermal Delivery of Drugs (Acrux) US 6964777, US 6929801, US 6923983, US 6916487, US 6916486

A composition is described containing up to 10% of a dermal penetration enhancer, which is a safe, skin-tolerant ester of sunscreen of a specific formula, which includes the compound octyl salicylate. The composition also comprises more than 80% of a volatile liquid selected from a group consisting of ethanol and isopropanol and mixtures thereof. The patents use the above mentioned composition to deliver anti-anxiety, anti-Parkinson, hormone, analgesic, and anti-emetic drugs.

Dual Enhancer Composition (Dermatrends) US 6835392

A dual permeation enhancer composition is disclosed, comprising a hydroxide-releasing agent and a lipophilic co-enhancer. Hydroxide releasing-agents are selected from inorganic hydroxides, inorganic oxides, and metal salts of weak acids, such as sodium hydroxide, calcium hydroxide, and ammonium hydroxide. Lipophilic co-enhancers disclosed include fatty alcohols, fatty ethers, and fatty acid esters. The amount of the inorganic hydroxide is between approximately 0.5 and 4.0 wt % of the composition.

Transdermal Administration of Fenoldopam (Alza) US 6960353

A fenoldopam transdermal composition is claimed comprising fenoldopam with an enhancer or an enhancer mixture for the treatment of hypertension, congestive heart failure, and chronic and acute renal failure. Enhancers described include myristyl sarcosine and monoglycerides such as glycerol monolaurate. Co-enhancers to glycerol monolaurate include dodecyl acetate, lauryl lactate, isopropyl myristate, and ethyl palmitate. The pH of the composition is maintained below 5.5 and preferably between 2 and 4.5.

Patch for Delivery of Volatile Liquid Drugs (Elan) US 6974588

A patch is described comprising two layers containing nicotine and mecamylamine. The layer further from the skin is a pressure-sensitive silicone adhesive, and the one close to the skin is a pressure-sensitive acrylic layer. The relative thickness of the layers and the concentration of drug initially in the layers is selected to provide a drug flux profile that is characterized by an initial period during which the drug flux rises to levels adequate to provide therapeutic effect and a second period lasting for at least twice as long during which the flux is higher than that of the initial period. The patch is capable of delivering 0.2–1.5 mg of nicotine per hour and 0.02–1 mg of mecamylamine per hour.

Topical Spray Compositions (U&I Pharma) US 6962691

Specific sprayable compositions are described comprising polyvinyl pyrrolidone (PVP) or PVP-vinyl acetate copolymer as the film former and trichloromonofluoromethane or dichlorodifluoromethane as the propellant. Dimethyl isosorbide, ethanol, and acetone are disclosed as solvents or solubilizers. The two drugs claimed to be useful with the invention are estradiol and alendronate sodium.

Using Controlled Heat for Controlled Release Delivery of Medical Substances (Zars) US 6955819

A device for the rapid delivery of a drug from an implant or transdermal patch is described. The device comprises a heating component to generate heat and a control component capable of controlling the magnitude and duration of the generated heat. Fentanyl, sufentanil, and nicotine are disclosed as drugs useful with the invention.

Composition for the Treatment and Prevention of Cancer (Schrauzer) US 6867238

Compositions for topical drug delivery of cutaneous and subcutaneous cancerous or precancerous conditions are described. The compositions comprise lipid-soluble skin-penetrating organic selenium compounds that are medium linear chain, six to eight carbon atoms, dialkyl diselenides. A composition claimed comprises 6–12% by weight *n*-hexyl selenol in *n*-decane.

Topical Eutectic Compositions (Galen) US 6841161

A composition is claimed for the mutual enhancement of a first and second drug, comprising an emulsion of a discontinuous phase that is a eutectic mixture of the first and second drugs having a melting point below 40°C and a continuous phase of an acceptable carrier. First drugs claimed include chlorocresol, triprolidine, oxybutinin, testosterone, and methyl nicotinate, among others. Second drugs claimed include ketoprofen, ibuprofen, fentanyl, clindamycin, methyl nicotinate, oxybutinin, and iodine, among others.

Topical Delivery of Oligonucleotides (ISIS Pharma) US 6841539

The invention pertains to compositions for enhancing the permeation of oligonucleotides via topical administration.

Patent Watch continued on page 16

Patent Watch continued from page 15

Liposomes containing the enhancer isopropyl myristate, which give enhanced permeation of the oligonucleotide Isis 2302, are described. There is only one claim, for a composition to enhance the permeation of an oligonucleotide that is complementary to a portion of a mRNA sequence coding for tumor necrosis factor and inhibiting the expression of the tumor necrosis factor.

SKIN PERFORATORS

Solid Solution Perforator (TheraJect) US 6945952

A solid drug solution perforator (SSP) containing a selected drug is disclosed. The compound is made to penetrate into the epidermis by an activatable pressure mechanism, and the drug is promptly released from the dissolving SSP. Additional drug can be delivered from a patch reservoir through the pores created by the SSP. Matrix perforator materials claimed include carbohydrates, water-soluble glass, water-soluble halide, and a non-ionic hydrophilic surfactant. Drugs claimed include peptides, proteins, DNA components, genes, and synthetic organic and inorganic compounds.

Microprotrusion Member Retainer for Impact Applicator (Alza) US 6855131

A microprotrusion member having a plurality of microprotrusions and a retainer that is releasably attached to the microprotrusion member is claimed. The retainer is releasably attached to an impacting device that allows the microprotrusion member to perforate the stratum corneum and, thus, increase transdermal drug flux.

Transdermal Administration of a Substance (Becton Dickinson) US 6960193

A reservoir containing a drug substance to be delivered under pressure is described as having a top wall that is connected to a coupling member for supplying the drug to the reservoir. The reservoir has a bottom wall with a plurality of individual microneedles with a length of about 50–250 µm for directing a drug substance under pressure from the reservoir into and below the stratum corneum of the patient. The reservoir can be divided into a plurality of chambers by internal walls for supplying different drugs simultaneously or sequentially.

Microneedles for Minimally Invasive Drug Delivery (Hospira) US 6980855

A minimally invasive drug delivery system is claimed comprising a disposable cartridge with a housing and an array of microneedles through which the drug is infused, under pressure, to the patient. Each microneedle comprises a conical-shaped body that has a beveled non-coring tip, with a fluid channel extending through the conical-shaped body providing fluid communication between the tip and the housing. The microneedle size is between 50 and 100 µm. Methods for fabricating microneedle arrays are disclosed utilizing conventional semiconductor derived micro-scale techniques.

IONTOPHORESIS/ELECTROPORATION

Method and Apparatus for Skin Absorption Enhancement and Transdermal Drug Delivery of Lidocaine and/or Other Drugs (Mattioli Engineering Ltd.) US 6980854

Transdermal delivery of a skin treatment drug to a patient's skin is carried out with electrodes provided on the head of a probe that is placed against the patient's skin. The system applies electrical bursts of pulses onto the patient's skin, and the drug substance disposed within the trough surrounding the central electrode is absorbed within the skin due to opening up of the skin pores. The system also includes a vibrating plate placed adjacent to the head of the probe, which applies mechanical vibrations, preferably of the same frequency and phase as the electrical pulses applied to the skin. The drug is placed in one of two solution-absorbing pads between the electrodes and the patient's skin.

Method for *In Vivo* Delivery of Therapeutic Agents (Hisamitsu) US 6978172

Controlled delivery of a therapeutic agent through the skin or mucosa can be achieved by this device, which consists of an agent permeable membrane to which electroporation electrodes are laminated to form an electrode membrane. The device can incorporate an iontophoretic electrode that can be jointly utilized for electroporation and iontophoresis and can be used for multiple applications over extended periods of time.

Quantitative Titration of the Autonomic Nervous System (George Dechev) US 6961609

The device consists of a fastening belt attached to the surface of the human body that is composed of electrodes covered with filter paper circles soaked with predetermined concentrations of the natural mediators noradrenaline and acetylcholine. The method is based on the iontophoretic application of these natural mediators and the subsequent assessment of the concentrations causing vasoconstriction and vasodilatation of the cutaneous vessels. The assessment helps in objective measurement of the functional state of the autonomic nervous system, including the balance between its two divisions, sympathetic and parasympathetic.

Methods and Apparatus for Using Controlled Heat To Regulate Transdermal and Controlled Release Delivery of Fentanyl, Other Analgesics, and Other Medical Substances (Zars) US 6955819

The invention comprises a drug depot site beneath the skin, a heating component to generate heat for heating the drug depot site, and a control component that controls the heating temperature on the depot site. The heating component is preferably an electric heating component. Applying controlled heat to the depot site releases a portion of the drug from the depot site to the systemic circulation, wherein the magnitude and duration of heat generated by the heating component can be controlled. The device can be used to rapidly deliver extra drug to the patient to accommodate his/her changing needs.

Method and Apparatus for Electrically Assisted Topical Delivery of Agents for Cosmetic Applications (Genetronics) US 6947791

The invention uses an electric pulse of a sufficient strength and duration for cosmetic delivery of L-ascorbic acid-containing compositions to the layer of the skin, where it enhances the production of collagen, thereby combating some of the effects of aging and oxy-radical damage on skin. The electric pulses temporarily create new pathways through the lipid skin barrier, to deliver L-ascorbic acid through the stratum corneum, improving the condition of the region of skin without substantial pain or skin irritation.

Methods and Compositions for the Treatment of Cerebral Palsy (Allergan) US 6939852

A method of treating juvenile cerebral palsy is described, which includes pre-treatment of a skin surface with a skin permeation enhancer, followed by transdermal administration of a therapeutically effective amount of a botulinum toxin type A, present as a depot with a polymeric carrier in an adhesive patch, and iontophoresis of the skin to further enhance transdermal delivery of the botulinum toxin. The juvenile patients are preferably up to 6 years in age.

Iontophoretic Drug Delivery Electrodes and Method (Biophoretic Therapeutic Systems) US 6895271

The invention describes a unit dosage medicament applicator electrode adapted for use with a portable iontophoretic transdermal or transmucoscal medicament delivery apparatus to be used for the self-administration of a unit dose of a medicament into the skin. The device is particularly suited for the localized treatment of herpes infections and can also be used for acne. The medicament delivery electrode is attached to a user-wearable glove, enabling the user to tactly position the medicament delivery electrode to make contact with the area to be treated. The delivery electrode, when used in accordance with the medicated electrode and method described herein, has demonstrated >90% treatment efficacy in clinical trials for the treatment of genital herpes.

Method and Device for Transdermal Electrotransport Delivery of Fentanyl and Sufentanil (Joseph B. Phipps, Mary Southam, Keith J. Bernstein, Henk Noorduin) US 6881208

An electrotransport delivery device having a silver anodic donor electrode, a cathodic counter electrode, and a donor reservoir containing a loading amount of a drug is described. The device is described for the delivery of analgesic drugs, namely fentanyl and sufentanil, which is provided as a water-soluble salt dispersed in a hydrogel formulation. The concentration of fentanyl or sufentanil salt in the donor reservoir solution is maintained at or above a pre-determined level, such that the transdermal flux remains substantially independent of the drug concentration in the donor reservoir solution and substantially proportional to the level of electrotransport current applied by the delivery device.

Iontophoretic Drug Delivery Device and Reservoir and Method of Making Same (Vyteris) US 6862473

A reservoir electrode assembly is described for an iontophoretic drug delivery device that includes an electrode and a hydrophilic reservoir situated in electrically conductive relation to the electrode. The reservoir contains a hydrophilic cross-linked polymeric material that has a first surface and a second surface that is adhesively adherent to the electrode. The first surface of the polymeric material is releasably adherent when applied to an area of a patient's skin, such that upon removal of the reservoir assembly from the applied area of the patient substantially no polymeric material remains on the applied area.

Methods of Monitoring Glucose Levels in a Subject and Uses Thereof (Cygnus) US 6862466

The invention describes methods of monitoring glucose levels and/or concentration in a subject having a disease state or a condition brought about by fluctuating glucose levels. The glucose extraction is carried out using an iontophoresis system comprising first and second iontophoretic electrodes. The extracted glucose reacts with glucose oxidase to produce hydrogen peroxide, which is detected with a sensor element. The invention also comprises a method for monitoring an effect of at least one non-insulin–containing pharmaceutical composition on glucose levels in a subject receiving the pharmaceutical composition. The system can also be used for evaluating compliance with a weight-management program in a subject, where a reference range of glucose amounts or concentrations is determined that correspond to achieving a weight management goal in the subject.

PHONOPHORESIS

Device for a Transdermal and Phonophoretic Combination Therapy and the Use Thereof in a Method for Medical Application (Lohmann Therapie-System) US 6868286

The device achieves combination treatment by means of a transdermal therapeutic system (TTS) and simultaneous initial treatment by means of ultrasound in the initial phase and the subsequent application of the TTS without additional ultrasonic treatment for a subsequent long-term treatment phase. The action of the TTS commences without or only with a slight time delay, and the therapy form is particularly advantageous for the treatment of severe or chronic pain. An aqueous contact gel is used for improving ultrasound transmission, while the TTS contains a layer of a pressure-sensitive adhesive, a porous layer, or a layer of a hydrogel.

Method and Apparatus for *In-Vivo* Transdermal and/or Intradermal Delivery of Drugs by Sonoporation (Ultra-Sonic Technologies) US 6842641

An apparatus for performing *in-vivo* sonoporation of a skin area for transdermal/intradermal delivery is described. The drug solution is placed in a container with one end covered with a porous membrane and the tip of an ultrasound horn submerged in the drug solution. Ultrasound applied at a frequency in the range of 15 kHz and 1 MHz, at a certain intensity for a period of time and at a distance from the skin area, creates cavitation bubbles that collapse on the skin surface, thus transferring their energy into the skin area and causing the formation of pores in the skin. The apparatus can also be used to generate ultrasonic jets that drive the drug solution through the formed pores into the skin. The invention allows painless and rapid delivery of drugs through the skin for either topical or systemic therapy. ■

Chapter News

CRS Research in Indian Pharmaceutical Industry

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C.U. Shah College of Pharmacy, Mumbai, India

General Overview of Indian Pharmaceutical Industry
The Indian pharmaceutical industry today is in the front rank of India's science-based industries, with wide-ranging capabilities in the complex field of drug manufacture and technology. A highly organized sector, the Indian pharmaceutical industry is estimated to be worth $4.5 billion, growing at about 8–9% annually. It ranks very high among countries with developing economies in terms of technology and quality and range of medicines manufactured. The Indian pharmaceutical sector is highly fragmented, with more than 20,000 registered units. The leading 250 pharmaceutical companies control 70.0% of the market. International companies associated with this sector have stimulated this dynamic development and helped to put India on the pharmaceutical world map.

Rapid advances in controlled release (CR) drug delivery systems the world over have caused an amazing 56% surge in the R&D expenses of pharmaceutical companies. As a percentage of sales turnover, this amounts to 4.4%. Entering highly regulated markets is possible for Indian pharmaceutical companies only if they have intensive research and production capabilities along with strong R&D skills in the field of novel drug delivery systems (NDDS) that meet international standards.

Considering the cost and uncertainty of new drug discovery in the post-GATT era, one alternative strategy is to produce and competitively exploit technologically advanced products in new areas with demonstrable benefits. This strategy includes the development of CR and NDDS.

Summary of CR Companies in India
In recent years, in tune with the global scenario, the Indian pharmaceutical industry has been witnessing a transition marked by mergers, acquisitions, consolidations, and strategic tie-ups with multinational companies for domestic and overseas markets. Many Indian companies have become multinationals themselves, e.g. Ranbaxy's international operations have marketing and sales organizations in 26 countries and manufacturing facilities in 7 countries. Besides developing exports and setting up production bases overseas, Indian companies are entering into strategic alliances with multinationals to get global reach.

Larger Indian companies are pumping in additional funds in search of new chemical entities (NCEs) and for NDDS. Companies like Sun Pharma, Dr. Reddy's Laboratories Ltd., Ranbaxy Ltd., Cipla Ltd., Lupin Ltd., Wockhardt Ltd., and many others have made enviable progress in a short time both in NCEs and NDDS.

CR Research Activities in Indian CR Companies
The most successful drug delivery formulations have been oral CR formulations. Currently, Bayer AG's Adalat CC for hypertension leads the oral sustained-release market. Reformulated in 1993 from a 3–4/day to a 1/day formula, Adalat CC has climbed to sales of $1.1 billion worldwide.

Ranbaxy's first NDDS innovation, the once-a-day Ciprofloxacin, has been licensed to Bayer AG for a fee of $65 million. It has also successfully developed four products in the area of oral CR systems for the Indian market, using its patented "platform technologies":

1. Clarithromycin (Crixan OD) once-a-day tablet (500 mg)
2. Didanosin (Virosine DR) once-a-day capsule (250 mg/400 mg)
3. Tamsuloin (Contiflo OD) once-a-day capsule (0.4 mg)
4. Pioglitazone + metformine (Pioglar M) once-a-day tablet (15 mg + 500 mg)

The four platform technologies are
1. Aerogel
2. Gastric Retention
3. pH Independent Matrix
4. Microencapsulation and Particle Coating

Research continues on time-delayed formulations, with the objective of developing chronopharmaceutical delivery of drugs in accord with circadian rhythms of disease states. Press-coated tablet formulations are being developed with erodible coatings providing controlled time delays. Hydrophobic and hydrophilic pellet matrices of drugs like ciprofloxacin and NSAIDs to provide controlled drug release are also currently under development.

In the field of CR, Wockhardt Ltd. has introduced venlafaxine capsules, using NDDS technology, under the brand name FLAVIX-XR. This once-a-day formulation is used in the treatment of depression and accompanying anxiety. It has also developed a NDDS for diltiazem (Cardizem CD), used in the treatment of angina and hypertension.

Another company, Cipla, has focused its research on NDDS and has filed patents for NDDS of cyclosporin and omeprazole.

Sun Pharma has developed six new products using non-conventional delivery platforms such as controlled/extended release, biodegradable membrane, and formulation complexity. Their portfolio includes

1. The antipsychotics Zypsidon and Qutipin.
2. The once-a-day antidepressant formulation Prodep LA.
3. The once-a-month anticancer/endometriosis product Lupride Depot.
4. Surfact for neonatal respiratory distress.
5. Rilutor for the neurological disorder ALS.

Indian University CR Activities
There are several examples of university-based researchers developing NDDS. For example, the Department of Pharmaceutics at Hamdard University has successfully developed a colon-specific oral microsphere delivery system for the treatment of familial adenomatus polyposis. The study was undertaken with an objective to develop a delivery system for celecoxib, a COX–2–specific NSAID that could prevent the release of the drug at gastric and small intestinal pH but release most of the drug load at colonic pH. Microspheres of celecoxib have been formulated using a combination of Eudragit L 100 and Eudragit S 100 and a spray-drying method.

Current Indian Initiatives and Needs
Various organizations like the Controlled Release Society Indian Chapter, B.V. Patel PERD Centre, Ahmedabad, and AAPS discussion groups have been active in the promotion and development of NDDS. They work with the objective to bring internationally reputed scientists on to the common platform to provide an update on the progress in the science and technology of NDDS. These organizations regularly conduct symposia and workshops to promote effective technology transfer from basic scientific discovery to industrial development.

The research in new drug delivery systems is now being liberally supported by the Indian government as well as the pharmaceutical industry. To achieve great progress in this field, the Indian pharmaceutical industry is also taking advantage of recent advances in biotechnology and information technology by developing its bioinfo-genomics resources. A nationally coordinated project on Novel and Targeted Drug Delivery Systems is being executed by four universities throughout India: Manipal Academy of Higher Education, Annamalai University, Hamdard University, and Bharthi Vidyapeeth. This academia–industry interaction will result in the development of techniques for the delivery of new molecules in the form of targeted CR systems, with the aim of reducing the side effects of toxic drugs. Thus, pharma industries in India are stimulated to face the challenges of the post-GATT era by developing innovative, novel, patent non-infringing technologies for new drug delivery technologies. ■

InTheNews

Drug Nanoshuttles Target 'Zip Codes' in Human Body

Scott Fields, LiveScience.com: Mar. 26, 2006 – Scientists have developed a way to build self-piloted "nanoshuttles." These tiny structures, just a few billionths of a meter long, could someday attack troublesome tissue, carry drugs, or reflect signals back to imaging systems.

The nanoshuttles' guidance system depends on two parts. Onboard the nanoshuttle itself is a special type of virus called a bacteriophage, or phage for short, that infects only bacteria. The scientists engineer these phages to include peptides—molecules that include at least two but no more than 50 amino acids each—that exactly match certain proteins in the body. The other part of the guidance system is a kind of phage library that scientists have spent years building. The work is led by the University of Texas husband-and-wife team of Wadih Arap and Renata Pasqualini.

"We do molecular mapping of zip codes in the body," Pasqualini, a professor of medicine and cancer biology, told LiveScience. "We now have a large collection of phage particles that display peptides that can be directed at nearly any organ or disease."

Each phage in the library corresponds to a protein located somewhere in the body's vascular highway of veins and arteries. When injected into a vein, for example, a phage could find its way through the body until it reached a protein counterpart on the vessels of a kidney tumor. When the phage reached its tumor, however, there would not be much it could do. This is where the cargo section of the nanoshuttle comes in. Researchers are constructing shuttle bodies of gold, a material often seen in "nano-bio" applications because the body does not reject it or react strongly to it.

The group had assumed that finding a way to connect the homing-device phage to a golden structure, sometimes referred to as a "scaffold," would be a formidable task. However, when Glauco Souza, a post-doctoral fellow in the team, mixed phage and gold flecks, he found that they assembled spontaneously. Gold, although it is friendly to most biological material, can bond with some chemically compatible materials, including, as it turns out, phages.

Pasqualini says these self-assembling structures, which have not yet been tested in animals, could be customized to ferry drugs to the places they are most needed in the body, to attack tumors, to carry stain to highlight certain cells, and to enhance other imaging technologies as well. Scientists at other laboratories, for example, have designed gold nanostructures for such applications as laser-activated, fluorescing imaging systems, but those structures must be injected near the area to be imaged. "Now you have a way to target gold particles to where you want them to be," Pasqualini said. "You integrate this nanoshuttle with the vascular map and all of a sudden you can form the shuttle and then direct it to whatever address in the body you want to find."

9-Aminocamptothecin-HPMA Copolymer Conjugates Developed for Colon Cancer Drug Delivery

NewsRx.com: Mar. 26, 2006 – *N*-(2-Hydroxypropyl)methacrylamide (HPMA) copolymer-9-aminocamptothecin (9-AC) conjugates were developed for colon cancer drug delivery. "The drug, 9-AC, was attached to the polymer carrier via a spacer containing a combination of an aromatic azo bond and a 4-aminobenzylcarbamate group," scientists in the United States reported.

"The design of the spacer ensured a fast and highly efficient release of unmodified 9-AC from the polymer in the colon by azo bond cleavage followed by a 1,6-elimination mechanism. An *in vitro* degradation study indicated that this conjugate was stable in simulated upper GI tract conditions, including small intestine (ST) contents, SI mucosa suspension, and PBS (pH 1.5 and 7.4). A fast release of the unmodified drug (85 ± 10% of 9-AC in 12 hr) was detected in rat cecal contents," explained S. Q. Gao and colleagues, University of Utah. The researchers concluded, "This drug delivery system has potential in the treatment of colon cancer."

Gao and colleagues published their study in the *Journal of Controlled Release* (Colon-specific 9-aminocamptothecin-HPMA copolymer conjugates containing a 1,6-elimination spacer. J Control Release, 2006;110(2):323-331).

A Biodegradable Polymer Functions as a Carrier Material

Gene Therapy Weekly via NewsEdge Corporation (NewsRx.com): Mar. 23, 2006 – Researchers in Japan conducted a study that reported a biodegradable polymer functions as a carrier material for the delivery of recombinant human bone morphogenetic protein-2 (RhBMP-2). "To improve the efficacy of a block copolymer of poly-D, L-lactic acid with randomly inserted p-dioxanone and polyethylene glycol (PLA-DX-PEG) as a drug delivery system for recombinant human bone [morphogeneic] proteins (rhBMPs), we examined the relationship between the volume of PLA-DX-PEG, the dose of rhBMP-2, and osteoinduction in a mouse model of ectopic bone formation."

"In a series of studies," wrote M. Kato and colleagues, Osaka City University, "we compared the size and bone mineral content (BMC) of ectopically induced bone by PLA-DX-PEG and collagen sponges carrying different quantities of rhBMP (0, 1, 2, 5, 10, 20 mcg)." The authors wrote, "An additional experiment was designed to investigate how range of PLA-DX-PEG polymer volumes (15, 30, 60 90 mg) with a fixed rhBMP concentration (0.01 wt%), altered the size and BMC of the induced ossicle. The influence of polymer volume was also examined in a further experiment wherein a fixed amount of rhBMP was placed in a range of PLA-DX-PEG copolymer volumes to give different concentrations of the protein per implant (0.02–0.0017 wt%).

"The results indicate that the bone yields were linearly dependent on the dose of rhBMP and also were proportional to the polymer volume above the minimal concentration of rhBMP-2 (0.0017 wt% in this series). The optimal concentration of rhBMP-2 in PLA-DX-PEG was 0.003 wt% in mice."

"The data provide important insights into the fabrication of implants that provide efficacious delivery of rhBMP-2 using the lowest possible dose of this expensive osteoinductive protein. This information will be of value for the clinical use of BMPs," Kato and coinvestigators concluded. Kato and colleagues published the results of their research in *Biomaterials* (Optimized use of a biodegradable polymer as a carrier material for the local delivery of recombinant human bone morphogenetic protein-2 (RhBMP-2). Biomaterials, 2006;27(9):2035-2041). For additional information, contact M. Kato, Osaka City University, Graduate School of Medicine, Department of Orthopedic Surgery, Abeno Ku, 1-4-3 Asahi Machi, Osaka 5588585, Japan.

Neuro-Hitech Pharmaceuticals, Inc. Signs Alzheimer's Transdermal Development Agreement with Xel; Transdermal Patch To Deliver Huperzine A in up to Weekly Doses

NEW YORK (Business Wire): Mar. 21, 2006 – Neuro-Hitech Pharmaceuticals, Inc. (OTC BB: NHPI), a drug development company engaged in the development and commercialization of Huperzine A (HupA) and its analogues for Alzheimer's and other degenerative neurological disorders, today announced that it has signed a development agreement with Xel Herbaceuticals, Inc., a privately held company based in Salt Lake City, Utah, to develop a transdermal patch to treat Alzheimer's disease. The therapeutic agent is Huperzine A, a molecule currently undergoing U.S. Phase II clinical testing as an orally administered treatment for mild to moderate Alzheimer's disease.

Reuben Seltzer, president and CEO of Neuro-Hitech, said, "We are very excited by this agreement, especially so because Xel has two world renowned scientist[s] Dr. Dinesh Patel and Dr. Danyi Quan both pioneers in transdermal patch technology, both founders and driving forces behind Xel's transdermal drug delivery program." He added, "A transdermal patch is the ideal way to deliver any Alzheimer's treatment for several reasons. First, because of the nature of the disease, patients often forget to take their medication; a transdermal patch may provide the drug for up to a week meaning greater compliance. Second, because transdermal delivery is a more efficient way to deliver the drug, avoiding the gastrointestinal tract, more drug gets into the bloodstream meaning a smaller dose size is needed to treat the condition. Third, the patch approach enjoys the support of a large majority of health care professionals meaning there is no need to educate them on its benefits; they already know."

Dinesh Patel, chair of the board and founder of Xel and past founder of transdermal patch pioneer TheraTech, currently a unit of Watson Pharmaceuticals ("WPI"), said, "Delivery of any Alzheimer's treatment by way of a transdermal patch is clearly preferable to other methods of drug delivery. What makes Huperzine A especially promising is its low therapeutic dose and low molecular weight, which make it ideal for transdermal delivery. Some other agents require higher dosages and are large molecules making them inappropriate for transdermal delivery."

Biodegradable Nerve Guidance Channels with Protein-Eluting Microspheres Developed

Pain & Central Nervous System Week via NewsEdge Corporation (NewsRx.com): Mar. 20, 2006 – "Nerve guidance channels (NGCs) promote axonal regeneration after transection injury of the peripheral nerve or spinal cord, yet this regeneration is limited," according to scientists in Canada.

"To enhance regeneration further, we hypothesize that localized delivery of therapeutic molecules combined with the NGC is required," noted A. Goraltchouk and colleagues at the University of Toronto. "In an attempt to achieve such an NGC," they "designed and synthesized a novel NGC in which protein-encapsulated microspheres were stably incorporated into the tube wall." "Specifically, poly(lactide-co-glycolide) (PLGA 50/50) microspheres were physically entrapped in the annulus between two concentric tubes, consisting of a chitosan inner tube and a chitin outer tube," the collaborators explained.

"Released EGF was found to be bioactive for at least 14 days as assessed by a neurosphere forming bioassay," the researchers concluded.

Goraltchouk and coauthors published their study in the *Journal of Controlled Release* (Incorporation of protein-eluting microspheres into biodegradable nerve guidance channels for controlled release. J Control Release, 2006;110(2):400-407).

Liposome-Entrapped DNA Oral Vaccines

U.S. Patents via NewsEdge Corporation: Mar. 15, 2006 – Pub. Number US7008791; Appl. Data 10 20001002 (PCT filed); Applicant Lipoxen Technologies Limited; Inventor(s) Gregoriadis, Gregory, and Perrie, Yvonne; Title Liposome-Entrapped DNA Oral Vaccines; Abstract An oral vaccine contains liposomes and complexed or, preferably entrapped, DNA operatively encoding an antigen in which the liposomes are formed from components, including cationic compounds and zwitterionic phospholipids. The hydrophobic groups within the liposome-forming components must include at least one group which is saturated. This is believed to raise the transition temperature, rendering the liposomes more stable when delivered orally. The compositions have been found to give detectable increased IgA levels, secreted immunoglobulins of importance in efficacious oral vaccine delivery.

Schweizerhall Moves Further into Generics with Novosis Acquisition

Gregory Roumeliotis Pharma Technologist: Mar. 15, 2006 – Looking for an advantage in the high-value generics market and a boost to its contract development services for research-driven pharmaceutical companies, Swiss chemicals and pharmaceuticals group Schweizerhall has bought German drug delivery firm Novosis in a deal worth up to €82.6m.

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A particular attraction of Novosis is a full pipeline of new products scheduled to reach the market over the next few years, as well as drugs already in the market performing strongly, such as transdermally delivered fentanyl patches for the treatment of chronic pain.

Among the most advanced projects in the R&D pipeline of Novosis are transdermal systems for contraception, the treatment of central nervous system diseases, novel patches to relieve pain, as well as biodegradable implants for the treatment of prostate cancer. The company also boasts developing and manufacturing contracts with pharmaceuticals and generics companies such as Schering, Sandoz/Novartis, and Ratio-pharm.

The generic industry is expected to grow by roughly 13% in 2006, with drug patents expiring this year valued at €18bn. Combining the technological know-how in both the development and manufacturing of oral formulations at Schweizerhall with the expertise of Novosis in transdermal and implantable drug delivery systems will better position the two companies to cash in on the opportunities available in Europe.

New Nanotech Drug Delivery Systems Under Study for Cancer Therapy

Cancer Weekly via NewsEdge Corporation (NewsRx.com): Mar. 14, 2006 – To help get the most potent anticancer drugs off the shelf and into the clinic, University of Michigan (U-M) researchers are looking at two nanotechnology approaches to deliver drugs precisely and visualize individual cells. One system is a star-shaped synthetic molecule called a dendrimer, and the other is a tiny plastic bead called a PEBBLE.

A dendrimer is a star-shaped synthetic molecule that can be as small as 3 or 4 nm in diameter, about the size of a single molecule of hemoglobin in a red blood cell. That means it is also fine enough to slip through the walls of blood vessels and get inside cells. James R. Baker, Jr. is leading the dendrimer projects as director of the Michigan Nanotechnology Institute for Medicine and Biological Sciences, with support from the U.S. National Cancer Institute, NASA, and the Bill and Melinda Gates Foundation.

A group led by toxicologist Martin Philbert and biophysicist Raoul Kopelman is working with tiny plastic beads called PEBBLES—probes encapsulated by biologically localized embedding. Sized at 20–600 nm, PEBBLES can be coated with targeting molecules and used as a very precise contrast agent for imaging and drug delivery. Once they reach their goal, sound or light can trigger them to carry out their mission. In some cases, the killer agent can be something as simple as reactive oxygen, says Philbert, a professor of toxicology and senior associate dean for research in U-M's School of Public Health.

Though the PEBBLEs group has done work to get the tiny balls inside cells, including using a gene gun that blasts them like little bullets and attaching them to liposomes and letting the body's own fats provide the transportation, Philbert notes that penetration is not always necessary to get the medical benefits. He says the tiny balls latched on to the outside of selected cells can deliver "killer oxygen" on cue to kill off the cell without penetrating it.

The researchers discussed their work on February 17, 2006, as part of a special panel at the Association for the Advancement of Science Annual Meeting in St. Louis, Missouri.

Scientists Use Wireless MicroCHIPS To Control Drug Release *In Vivo*

BEDFORD, Mass. (Business Wire): Mar. 13, 2006 – Researchers at MicroCHIPS, Inc., have demonstrated for the first time that it is possible using an implanted microchip device and wireless technology to actively control the release of drugs in the body over a prolonged period of time.

"This research is an important step toward development of novel drug delivery systems in which small devices filled with potent, therapeutic drugs are used to release medicines into the body as needed," said John Santini, Ph.D., president of MicroCHIPS. The technology, described in the March 12 online edition of *Nature Biotechnology*, is unique in its use of wireless signaling, its system of reservoirs allowing precise, efficient delivery of solids, liquids, or gels, and its small size. It is not expected to replace all pills or other forms of drug delivery. Rather, it will deliver proteins, small molecules and other drugs that are highly potent, have limited stability, and must be delivered in precise doses at specific times.

Santini, along with Massachusetts Institute of Technology Professors Robert Langer, Sc.D., and Michael J. Cima, Ph. D., began work on the concept of so-called "intelligent drug delivery devices" more than a decade ago. Langer called the current publication a "landmark" study. "One could envision that, some day, many of a patient's drugs could be placed on a chip programmed to release needed doses at precisely the right times," he said.

The current study, which used a microprocessor and a power source, demonstrates the feasibility of what Santini calls "active" reservoir control. According to Santini, while one important use of reservoirs is to contain drugs for release, reservoirs can also be used to selectively expose biosensors in order to monitor and provide feedback on conditions in a patient's body. Biosensors may one day be interactively paired with drug delivery. MicroCHIPS is also working on another type of reservoir technology, which Santini terms "passive." Passive reservoir systems use specially designed, layered polymers which when implanted regulate drug release over time without microprocessors or power sources.

NSAID Microencapsulation Via Extrusion-Spheronization May Allow Site-Specific Delivery

NewsRx.com: Mar. 13, 2006 – Microencapsulation of ibuprofen and other drugs in extrusion-spheronization pellets may improve site-specific delivery. According to a recent report published in the *Journal of Microencapsulation*, researchers in South Africa conducted a study "to develop a stable and reproducible modified release pellet formulation containing ibuprofen" using "extrusion-spheronization technology to produce pellets."

"The percentage yield, size distribution and overall pellet shape within the desired size range of 1000–1400 microm was

found to be dependent on various process variables," D. Lutchman and coauthors at the University of KwaZulu-Natal found. "These include extrusion and spheronization speed, spheronization time and composition of the granulation fluid."

"Formulation factors such as viscosity grade of hydroxypropylmethylcellulose and concentration of microcrystalline cellulose were shown to influence the drug release rate of the pellets," the scientists added. "In vitro dissolution studies revealed that the pellets behaved in a pH-dependent manner."

"Pellets exposed to different drying techniques exhibited an increase in drug release rate in the order corresponding to oven-dried, vacuum-dried, fluid bed-dried and freeze-dried pellets," test results revealed. "In conjunction with scanning electron microscopy, kinetic modeling and statistical treatment of dissolution data, it was confirmed that the predominant release rate-controlling mechanism was diffusion, as evidenced from the power law expressions incorporating Fickian and relaxational parameters. "Matrix swelling and erosion were not significant factors in modulating the drug release rate," according to the study report.

"The pH-dependent property of the pellets may be strategically employed towards development of a site-specific drug delivery system for non-steroidal anti-inflammatory agents," the investigators concluded. "In general, targeting the delivery of an agent with potential for gastric irritation to the proximal intestine/colon may effectively reduce its ulcerogenic effect and ultimately contribute towards improved patient compliance."

Lutchman and colleagues published their study in the *Journal of Microencapsulation* (Formulation of rate-modulating pellets for the release of ibuprofen: An extrusion-spheronization process. J Microencapsul, 2005;22(6):643-659).

Nasal Carbamazepine Delivery Improved by Loading in Chitosan Glutamate Microspheres

NewsRx.com: Mar. 10, 2006 – Chitosan glutamate microspheres can be used to improve nasal delivery of the anticonvulsant drug carbamazepine (CBZ). "The nasal route is used both for local therapies and, more recently, for the systemic administration of drugs, as well as for the delivery of peptides and vaccines," pharmaceutical researchers in Italy explained.

In a recent study, E. Gavini and coauthors at the University of Sassari evaluated nasal CBZ administration "using microspheres constituted by chitosan hydrochloride (CH) or chitosan glutamate (CG)." "The microspheres were produced using a spray-drying technique and characterized in terms of morphology (scanning electron microscopy [SEM]), drug content, particle size (laser diffraction method) and thermal behavior (differential scanning calorimetry, DSC)."

"In vitro drug release studies were performed in phosphate buffer (pH 7.0). In vivo tests were carried out in sheep using the microparticles containing chitosan glutamate, chosen on the basis of the results of in vitro studies," according to the report. "The results were compared to those obtained after the nasal administration of CBZ (raw material) alone."

They found that "spray-drying was a good technique of preparation of CBZ-loaded microspheres. "The loading of the drug into the polymeric network always led to an increase in the dissolution rate compared to CBZ raw material," test results indicated. "The microspheres obtained using chitosan glutamate had the best behavior both in vitro and in vivo." Chitosan glutamate-based microspheres "increased the drug concentration in the serum when compared to the nasal administration of the pure drug (Cmax 800 and 25 ng/mL for microspheres and pure drug, respectively)," published data showed. "The results obtained indicate that the loading of CBZ in chitosan glutamate microspheres increases the amount of the drug absorbed through the nose," the investigators concluded.

Gavini and colleagues published their study in the *International Journal of Pharmaceutics* (Nasal administration of carbamazepine using chitosan microspheres: In vitro/in vivo studies. Int J Pharm, 2006;307(1):9-15).

Connetics Licenses Technology for the Treatment of Hyperhidrosis

Business Wire via NewsEdge Corporation, PALO ALTO, Calif.: Mar. 7, 2006 – Connetics Corporation (Nasdaq: CNCT), a specialty pharmaceutical company that develops and commercializes dermatology products, today announced it has obtained an exclusive, worldwide license to certain patented technology that has potential utility in the treatment of hyperhidrosis. Connetics has initiated a formulation development program utilizing this technology with the goal of developing a safe, effective, well-tolerated, and cosmetically elegant topical formulation. The company intends to begin clinical development immediately after completion of the formulation development activities. Financial terms include upfront, milestone, and royalty payments.

"For patients with hyperhidrosis, excessive sweating often results in daily embarrassments in professional, academic and social life. Patients often suffer both physically and psychologically," said Lincoln Krochmal, M.D., executive vice president of research and development for Connetics. "Treatment options range from topical therapy, local injections, or surgery. The currently available topical therapy options tend to irritate the skin, while the injections need to be repeated and are frequently painful. We have an exciting opportunity to develop a novel treatment for this disorder by incorporating this licensed technology into one of Connetics' innovative topical delivery vehicles."

Biophan Files Broad Patent on Use of Halloysite Nanotubes for New Drug Delivery Applications

Business Wire via NewsEdge Corporation, BIOWIRE2K ROCHESTER, N.Y.: Mar. 3, 2006 – Biophan Technologies, Inc. (OTCBB: BIPH) (FWB: BTN), a developer of next-generation medical technology, announced today that it has filed a broad patent as part of its collaboration with strategic partner NaturalNano (OTCBB: NNAN) on novel drug delivery technologies involving applications of naturally

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occurring nanotubes found in halloysite clay.

Biophan and NaturalNano are collaborating to develop products using the nanotubes as advanced drug delivery systems in a number of proprietary biomedical applications. Biophan's newly filed patent application covers biomedical uses of the nanotubes for a range of products, including bandages, wound healing applications, and other uses. Other advanced drug delivery technologies that Biophan will focus on involve using electromagnetic fields for active elution. Under a previously reached agreement between the companies, Biophan holds the worldwide exclusive rights to NaturalNano's nanotube technologies for the medical and pharmaceutical markets.

Chrono Therapeutics Makes Drug Delivery Tick

In Pharma Technologist, TRENTON, NJ: Feb. 27, 2006 – Drug delivery company Chrono Therapeutics has unveiled a wristwatch-like device for the non-invasive automatic administration of drugs based on the amount and time instructed, thus improving patience compliance.

ChronoDose is programmed like an alarm clock and worn like a watch to accurately deliver predefined-sized doses to coincide with peak disease symptoms. This is important because hormones, neurotransmitters, and other intra-body compounds are released in different amounts at different times of the day pursuant to daily patterns. Because certain disease symptoms follow a daily pattern, with peak symptoms at certain times of the day, drug effects can be optimized when administered in a defined, usually varying dosage at predefined times. Therefore, by precisely timing the administration of drugs so they reach peak levels when symptoms are likely to be at their worst, drug administration efficacy is greatly improved.
Crucially, apart from allowing administration during sleep hours, it greatly increases the chances of patients taking their drugs when and at the level they are supposed to. According to the company, over 20% of hospital admissions annually result from patient non-compliance, costing the healthcare industry over $100bn (€84.3bn) per year. The "smart" transdermal drug delivery device may be worn for 7 days without recharging power or replacing active. It administers higher doses automatically when disease symptoms statistically peak and less when symptoms are lighter. Initial applications target conditions as diverse as depression, urinary incontinence, and migraines.

Guy DiPierro, president of Chrono Therapeutics, states that initial difficulties with turning off the miniaturized pump which releases the drug have been overcome in the latest prototype. "We plan to use the device ourselves for two over-the-counter generic drugs, clinical trials on humans are beginning in May and we estimate we are 12 to 18 months away from commercialization," he said, without revealing the indications of the drugs. "Two big pharma companies have approached us with their drugs for depression and cardiovascular disease and they will be licensing them with ChronoDose." The unit costs Chrono Therapeutics $20 to make, though DiPierro stressed this number will go down when production is expanded.

ChronoDose is composed of the company's patent pending micro-modulated dispensing device, microprocessor, drug reservoir, power source, LCD, and programming buttons, using its patent-pending AccuFuse technology. The device has great potential for patient groups where compliance is an issue, such as the elderly, hospitalized, mentally ill, inmates, military, or anyone with chronic diseases.

Q Chip Customises Drug Delivery

In Pharma Technologist: Feb. 24, 2006 – British company Q Chip has upped the stakes in the drug delivery market with its new tailor-made bioencapsulation technology, claiming to improve drug effectiveness, reduce side effects, and increase patient acceptance.
Using polymers as drug delivery vehicles has proven to be very demanding because of the difficulties in developing capsules with the desired release rates, achieving product uniformity and quality, maintaining drug stability, and scaling-up lab-based production technologies. Q Chip has responded to these challenges with a proprietary microfluidic technology that is modified based on the requirements of an individual therapy or administration route. The result is a stabilised and immuno-isolated drug demonstrating reliable controlled release and localisation of action at the disease site.

Jo Daniels, Q Chip's chief scientific officer, states that their technique is less wasteful and far more efficient than other traditional polymer approaches and that the cost of the kit is minimal. The microfluidic platform, called Microplant, employs assisted droplet break-up to microspheres from a continuous stream of polymer. The systems are flexible, allowing the encapsulated drug to be added as part of the polymer stream or separately, enabling controlled dosing of each microsphere. The technology has been developed on several platforms, using an in-house circuit manufacturing capability to allow the production of spherical polymer capsules.

Therefore, by selecting a desired particle size from sub 100 to 2,000 µm, many microfluidic circuits work in parallel to produce monodisperse polymer microcapsules with less than 2% variation in size. This efficient process eliminates the waste associated with much wider size distributions from other manufacturing methods. Because of the repeatable nature of the system, the capsule size distribution is very tight, and each production platform allows a different method of capsule production.

These capsules can then be loaded with precise amounts of biological agents, active pharmaceutical compounds, and cells for cellular therapies. They are produced under GMP-regulated conditions and can be used for the controlled release of biopharmaceuticals and small molecules, combination products, cell or adjunct therapies, and vaccines. The Cardiff-based company is now focusing its marketing strategy on co-developments with partners who require delivery strategies for product life-cycle extension or new product development. They are already working on programmes involving type I diabetes and cancer and are looking for collaborations in areas such as chronic life-threatening conditions, combination products, and cell therapies.

VaxGen and BD to Jointly Evaluate Novel Dermal Injection Technology for Delivery of VaxGen's Anthrax Vaccine

PRNewswire-FirstCall, BRISBANE, Calif.: Feb. 21, 2006 – VaxGen, Inc. (Pink Sheets: VXGN.PK) announced today that they have entered into an agreement with BD (Becton, Dickinson and Company) (NYSE: BDX) on a program to evaluate the potential advantages of using BD's Micro Injection technology to deliver VaxGen's recombinant anthrax vaccine candidate. Funding will be provided through BD's research contract with the Department of Defense (Award No. DAMD 17-03-2-0037).

The joint program is designed to determine if dermal administration (injection into the skin) of VaxGen's anthrax vaccine with the patented BD Micro Injection technology can enhance the immune response generated by the vaccine, versus standard intra-muscular injection, and/or reduce the required amount of vaccine to produce immunity. If the use of BD's technology in combination with VaxGen's anthrax vaccine proves safe and effective, and is approved by the U.S. Food and Drug Administration (FDA), it may be considered for use in future generations of VaxGen's recombinant anthrax vaccine as well as other vaccines. The evaluation being performed with BD will have no effect on VaxGen's existing contract to deliver 75 million doses of its anthrax vaccine to the U.S. government for civilian biodefense.

The collaboration will include a Phase I clinical trial to evaluate the use of BD's Micro Injection technology, featuring a microneedle technology, for vaccination with VaxGen's anthrax vaccine. The objectives of the study are to compare the safety and effectiveness of dermal injection versus traditional intramuscular administration of VaxGen's anthrax vaccine.

Dermal delivery has been studied in combination with a variety of vaccines. BD's Micro Injection technology is designed to easily and reliably deliver vaccine into the dermal layer of the skin with the potential to make dermal vaccination a practical alternative to intramuscular inoculation. There is evidence that delivery of vaccines specifically and accurately to the dermal tissue can produce an immune response that is more robust and/or requires less antigen or adjuvant than required with intramuscular inoculation.

Battery Powered Device, "MD Turbo™" May Provide Burst of Good News for Asthma Sufferers

PR Newswire via NewsEdge Corporation, TAMPA, Fla.: Feb. 21, 2006 – Worldwide some 300 million people suffer from asthma or other pulmonary diseases. In order to deliver medicine to their lungs, most of these sufferers rely on inhalers that dispense the drug in metered doses. Hence their name: metered dose inhalers (MDIs). MDIs offer an advantage over oral medications since they deliver the drug to the patient's lungs directly with onset of action within 15 minutes, compared to the 2–3 hr it can take for oral medications to take effect. However, an estimated 70% of these inhaler users are not able to get the relief they need because they are not using their inhalers properly. Published studies have shown that when the inhaler is not used correctly much of the intended drug dose is deposited in the back of the throat instead of being properly delivered to the lungs.

The good news is that last summer the FDA approved a breath-activated device specifically for use with metered dose inhalers. This device, the MD Turbo™ is designed to more reliably deliver a specific amount of medication to the user's lungs. In fact, MD Turbo™ successfully addresses the two biggest problems associated with MDIs: 1) it coordinates the activation of the canister with the user's breathing in, and 2) it includes an electronic dose counter that shows how much medication is left in the canister. Through this electronic dose counter the MD Turbo™ helps parents, the elderly, and caregivers monitor how many doses have been delivered of a particular drug.

Dr. Frank O'Donnell, CEO of Accentia Biopharmaceuticals, Inc., a public biopharmaceutical company (Nasdaq: APBI), said: "We are launching MD Turbo to help as many as possible of the 35 million patients in the U.S. with respiratory conditions who depend on drugs delivered into the lungs by metered dose inhalers. The MD Turbo was specifically designed to remedy the two major shortcomings of these metered dose inhaler devices."

The launch will take place in the second quarter of 2006, at which time TEAMM Pharmaceuticals, the specialty pharmaceutical division of Accentia, will market the device, which was developed by Respirics, Inc. MD Turbo™ will require a doctor's prescription. Handheld and battery-powered, it can be used with most inhalers and has an expected lifetime of one year. For more information, please visit: http://www.accentia.net.

Procter To Develop Nastech Osteoporosis Drug

In Pharma Technologist: Feb. 15, 2006 – Biotechnology firm Nastech has chosen Procter & Gamble to develop and commercialize its osteoporosis nasal spray worldwide, in a lucrative deal that could reach $577m (€480m) over the life of the project and give both companies the upper hand over injectable alternatives in the $6.2billion osteoporosis drug market.

Currently in Phase II, Nastech's PTH(1-34) contains a naturally occurring human parathyroid hormone (PTH), an important regulator of calcium and phosphorus metabolism, and promises easy and convenient delivery in the form of a nasal spray. Its competitor would be Eli Lilly's Forteo, a similar parathyroid hormone drug already in the market but administered by injection, making it less appealing to patients. Nastech hopes to submit an FDA application for its spray in 2007 and receive approval in 2008, around the same time Forteo is expected to lose patent protection.

Alkermes Announces New Drug Application

Business Wire via NewsEdge Corporation, CAMBRIDGE, Mass.: Feb. 17, 2006 – Alkermes, Inc. (Nasdaq: ALKS) today announced the submission of a complete response to the approvable letter issued in December 2005 by the U.S. Food and Drug Administration (FDA) regarding the new drug application (NDA) for VIVITROL™ (naltrexone for

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extended-release injectable suspension). Alkermes expects the FDA to classify the complete response as a Class 1 resubmission, under which the FDA will seek to complete its review of the resubmission within 60 days from the time of resubmission.

VIVITROL™ is under review for the treatment of alcohol dependence in combination with a treatment program that includes psychosocial support. In March 2005, Alkermes submitted an NDA for VIVITROL™. In June 2005, Alkermes and Cephalon, Inc. (Nasdaq: CEPH) entered into a collaboration agreement to develop and commercialize VIVITROL™ in the United States for the treatment of alcohol dependence.

Emisphere Achieves Second Milestone in Roche Collaboration

PR Newswire via NewsEdge Corporation, TARRYTOWN, N.Y.: Feb. 15, 2006 – Emisphere Technologies, Inc. (Nasdaq: EMIS) announced today that it has achieved a second milestone under its November 2004 agreement with Roche to develop new oral formulations of a Roche small-molecule compound for the treatment of bone-related diseases. The achievement of this milestone, resulting in an undisclosed payment from Roche, arises from Roche's initiation of a clinical study utilizing Emisphere's eligen® delivery technology in a formulation for a second product. Emisphere previously received a milestone payment for developments relating to a different product and indication announced in July 2005. With two products now being developed by Roche using the eligen® technology, milestone payments could total $37 million.
Emisphere's broad-based oral drug delivery technology platform, known as eligen® technology, is based on the use of proprietary, synthetic chemical compounds, known as EMISPHERE® delivery agents, or "carriers." These molecules facilitate or enable the transport of the therapeutic macromolecules across biological membranes, such as those of the gastrointestinal tract, to exert their desired pharmacological effect. The delivery agents have no known pharmacological activity themselves. Emisphere's eligen® technology makes it possible to orally deliver a therapeutic molecule without altering its chemical form or biological integrity. Emisphere is pursuing shortened registration timelines for currently marketed drug products whose performance is improved using the eligen® technology through supplemental new drug applications or 505(b)(2) filings with the U.S. FDA. Successful achievement of these regulatory strategies may not require large-scale studies to support product registration.

Transdermal Drug Delivery Formulations with Optimal Amounts of Vasodilators Therein

European Patents via NewsEdge Corporation: Pub. Number EP1621192; Appl. Data EP05015469 20050715; Applicant BioChemics, Inc.; Inventor(s) Carter, Stephen G., Zhu, Zhen, and Patel, Kanu; Title: Transdermal Drug Delivery Formulations with Optimal Amounts of Vasodilators Therein; Abstract: Topical drug delivery formulations with optical amounts of vasodilator therein. Vasodilator chemicals applied topically dilate the blood vessels in the skin tissue, which have been shown to facilitate or inhibit systemic or skin tissue deposition of drug substances. The level of stimulation and/or inhibition has been found to be dependent on the concentration and the identity of the specific vasodilator chemical(s) used as well as the drug molecule(s) to be delivered. This work teaches the need to consider specific formulation requirements when dealing with vasodilator chemicals for the creation of successful delivery vehicles in the transdermal drug delivery system. These requirements for very low concentrations of vasodilators were an unexpected and a surprise finding, in contrast to the concentrations of the vasodilators typically used to elicit an increase in skin blood flow.

SkinMedica Targets Acne with Timed Release Approach

In Pharma Technologist: Feb. 15, 2006 – U.S. pharmaceuticals and skincare specialist SkinMedica has developed a timed-release delivery system for the active ingredients of an acne treatment that is said to up efficacy and lower the chances of skin irritation.

NeoBenz Micro is described as the first benzoyl peroxide (BPO) prescription product formulated with MICROSPONGE DELIVERY TECHNOLOGY for the treatment of mild to moderate *Acne vulgaris*.

Because of the delivery system, the formula allows the gradual release of the BPO over time. Although the ingredient has proven efficacy in the treatment of acne, it can also have a harsh effect on the skin, leading to soreness, irritation, and rashes that can reduce efficacy. The formula has been developed containing three different strengths of BPO—3.5, 5.5, and 8.5%—each of which is delivered gradually to remain effective over a longer period of time, as well as having a less harsh action on the skin.

"In previous studies, novel BPO formulations with this delivery system have been shown to be less irritating than conventional formulations with comparable BPO drug concentrations," states Aaron Levine, product manager for Neobenz Micro. Although the delivery system had been used in a number of other pharmaceutical and cosmetic products, this is the first time it has been used in a prescription-based treatment. The system works by entrapping the active ingredient, in this case the BPO, in microsponges, that are then gradually released throughout the course of the day following the initial topical application.

Enhanced delivery systems have in recent years made a huge difference to the efficacy of a range of cosmetic treatments and products. Particularly in the skincare arena, such systems have helped to enhance a range of products, from anti-aging treatments to skin toners and sunscreens.

SkinMedica says that the effectiveness of NeoBenz Micro has been backed up clinical studies showing that inflammatory and non-inflammatory lesions were reduced from 22 to 40% during a 4-week treatment course, that continued with use up to 12 weeks. According to Dr. Stacy Smith, lead investigator in the company's clinical study, NeoBenz Micro can also be used in combination therapies that include antibiotics or retinoid treatments. The company says some 5.7 million people in

the United States are affected by *Acne vulgaris*, of which approximately half consulted a dermatologist, making it the most frequently diagnosed disease within the profession.

Wound Care Market Benefits from Antiseptic Wand

In Pharma Technologist: Feb. 13, 2006 – Dermisonics has come up with the first working model of an antiseptic delivery system, which the company hopes to provide the U.S. army with a battlefield version, reducing the severity of infection and providing a much needed tool for medics in the field.

News of this latest delivery system brings a much-needed solution to the problem soldiers face on the battlefield. Infection is a potentially lethal hazard for wounded soldiers before they can receive full medical treatment in a hospital. Current methods of treatment use antiseptic and bandages, but the antiseptic only affects the outermost layers of the damaged tissue. Infection frequently results and is a major cause of amputations.

Dermisonics' A-Wand is a handheld, portable, ultrasonic wand device for applying antiseptic solutions to cuts, abrasions, and wounds with a replaceable Patch-Cap, which holds up to 40 mL of antiseptic solution. It uses alternating ultrasonic waveforms to enlarge the diameter of the skin pores, enabling antiseptics to permeate through the skin. "The A-Wand represents a huge opportunity for Dermisonics and the various patients who could benefit from increased infection-resistant technologies," said Bruce Redding, technology inventor and Dermisonics executive vice president.

"Dermisonics especially is pleased by the response from the US Army and we hope this technology finds acceptance in the field as soon as possible." The A-Wand is designed primarily for use by medics in the field, by Mash units, and for follow-up wound care to significantly reduce this hazard. Through the use of the A-Wand's ultrasound system, the antiseptic solution is "pushed" to the deeper tissue where it can more effectively fight infection by surrounding and encapsulating the wounded area with antiseptic. It also has the added advantage of being able to penetrate scarred tissue without damaging this basic body defense system.

Medpharm Announces Evaluation Agreement for Medspray

Phoenix, AZ: Jan. 25, 2006 – U.K. pharmaceutical development expert predicts stream of licensing enquiries for its innovative Patch in a Can™ delivery technology. U.K. pharmaceutical development specialist MedPharm Ltd. today announced at the 10th Annual Drug Delivery Partnerships meeting in Phoenix, Arizona, that it has signed the first in a predicted series of licensing evaluation agreements for its new MedSpray™ technology. The name of the partner, a leading international pharmaceutical company, was not disclosed, although it was confirmed that Medpharm will receive an undisclosed fee for the evaluation. Spray technology is rapidly becoming the delivery method of choice in the dermatology market due to its increased patient acceptance and consumer appeal, particularly among the young, and ability to deliver increased efficacy with lower dosage rates. MedSpray also shows considerable promise for transdermal delivery.

Announcing the agreement, MedPharm CSO and co-inventor of the technology Dr. Marc Brown commented, "MedSpray has a wide range of applications for both dermal and transdermal delivery. Our initial target for MedSpray is the dermatology market, which continues to grow at record rates. We've chosen dermatology because patients expect not only increased efficacy from a product or brand, but also greater ease and convenience of use." MedPharm's CEO, Dr. Andrew Muddle, added, "We are convinced our technology offers a significant competitive advantage over creams, ointments and gels that together are losing favour amongst young adults in particular. By addressing these challenges MedSpray will be attractive to all companies active in the sector. Firstly we can reformulate existing drugs and thus extend patent life, and secondly we can offer more competitive products. We have already initiated a number of clinical development projects ourselves and are now looking to license MedSpray on an indication by indication basis to interested parties. We expect the Evaluation Agreement we have signed today to lead to the first of many licensing relationships for the technology. Already the interest levels have been very high."

Generex Developing New Chewing Gum for Diabetes

In Pharma Technologist: Jan. 09, 2006 – Buccal drug delivery pioneer, Generex, is expanding its diabetes treatment pipeline to include a new metformin chewing gum that aims to avoid the significant adverse gastrointestinal side-effects that often accompany the use of metformin tablets.

Generex, which recently launched the world's first non-injectable insulin in the form of an oral insulin spray, is now developing a form of metformin that can be chewed, thereby delivering metformin into the human body by way of the buccal cavity (the mouth). This new method of drug delivery may provide relief for the approximately 30% of metformin users who develop significant adverse gastrointestinal effects from taking metformin tablets, including diarrhea and nausea/vomiting.

Metformin is used with or without insulin for the treatment of type 2 diabetes and is also used to prevent the development of diabetes in people at risk, as well as treating polycystic ovary syndrome (PCOS), and non-alcoholic steatohepatitis (liver disease). Diabetes results when there is a reduced production of insulin or when there is state of resistance to its action. Metformin increases the sensitivity of liver, muscle, fat, and other tissues to the uptake and effects of insulin, and lowers blood glucose levels.

A recent small clinical trial with Generex's metformin gum showed that it displayed a pharmacokinetic profile similar to that of the currently available metformin tablets and, therefore, shows promise as an alternative method of delivering metformin. However, this study only involved 10 people, and much larger and more structured clinical trials will need to be conducted before there is any conclusive evidence of its effectiveness and benefits. ■

Forthcoming Conferences

33rd CRS Annual Meeting and Exposition

The Art of Science, Technology, and Living

Resources. Tools. Regardless of what you call them, we use them every day to meet the day-to-day challenges of the fast-paced, complex industry in which we work. Books and websites provide data and case studies to guide our decisions. Coworkers support and challenge us with an internal frame of reference. Industry meetings provide us with different viewpoints within the industry and new perspectives on how to approach our work.

This year's best source for new tools will be the 33rd Annual Meeting and Exposition of the Controlled Release Society, July 22–26, 2006, in Vienna, Austria. The program chairs have planned an outstanding technical program with a wide variety of networking events that will provide you with the necessary tools to expand your portfolio of resources.

Because this year's meeting received a record-breaking 1,115 abstracts submitted from industry, academia, and government, you are guaranteed to find new solutions, data, and processes. With all of the information made available in these abstracts, the Program Committee is crafting a program that will provide attendees with a cumulative, global look at the latest industry research. Plenary presentations from renowned experts, mini-symposia, and scientific sessions all will address topics pertinent to controlled release and delivery. In addition, all of this is complemented by three Educational Workshops, a Young Scientists Program, a two-day Industrial Session, Releasing Technology Workshops, Soapbox Sessions, and Pearls of Wisdom. Here's a glimpse of some of the topics you will hear discussed at this year's meeting:

Plenary Sessions
- Nanosystems Biology: Study of Cellular Processes in Live Single Cells
- Signal Transduction
- Drug Transporters in the New Drug Discovery and Development
- European Science: Forward Look on Nanomedicine
- From Supramolecular Chemistry to Constitutional Dynamic Chemistry

Mini-Symposia
- Genomics—Drug Delivery
- Innovations in Veterinary Drug Delivery
- Nanomedicines and Cancer
- Novel Vaccination Approaches
- Oral Delivery Macromolecular Drugs

Educational Workshops
- CMC Regulatory Issues for Controlled Release Parenterals
- Drug-Device Combination Products: Novel Technologies and Regulatory Challenges
- Role of Intestinal and Hepatic Transporters on Oral Bioavailabilities of Drugs

Young Scientists Program
- Young Scientists Workshop
- Get Up! Get Educated!
- Nanogel Networks and Their Application in Drug Delivery
- Role of Nanotechnology in Targeted Drug Delivery and Imaging
- Fork in the Road
- Highlights of Student Posters

The 2006 CRS Annual Meeting and Exposition will also be filled with opportunities to network, collaborate, and explore ideas with a global community of your colleagues focused on controlled release and delivery. You can walk through the Exhibit Hall and discover the latest information on equipment, technical developments, publications, and other services provided by the more than 100 exhibitors. In addition, you can discuss cutting-edge research with the more than 800 poster presentation authors. From the Opening Reception at the Vienna Town Hall to the Closing Party at the Palais Pallavicini, and everything in between, the CRS Annual Meeting and Exposition will be your connection to friends, peers, and colleagues from around the world.

Although the world-class networking, learning, and relationship building are reason enough to attend, don't forget to factor in the hospitality and beauty of Vienna. Before, during, and after the meeting you can take in the rich history of the city. Celebrate Vienna's lively music scene, and Mozart's 250th birthday, by taking in a concert in the park or attending the opera. Stroll through the streets and enjoy the captivating architecture and beautiful gardens that dot the Vienna landscape. If you need a break, there are plenty of quaint coffee shops and cafés along the way.

The goal of the 33rd Annual Meeting and Exposition of the Controlled Release Society is to deliver knowledge and service by advancing science, technology, and education in the field of controlled delivery of bioactive substances. In essence, we will provide you with the tools necessary to be successful. Mark your calendars and make plans to join your colleagues in Vienna July 22–26, 2006.

Fourth International Nanomedicine and Drug Delivery Symposium

By Alexander V. Kabanov, Ph.D.
Center for Drug Delivery and Nanomedicine and
Department of Pharmaceutical Sciences, College of Pharmacy,
University of Nebraska Medical Center, U.S.A.

The Fourth International Nanomedicine and Drug Delivery Symposium will take place in Omaha, Nebraska, October 8–10, 2006. The objective of the symposium is to provide a comprehensive overview of the latest advances in all aspects of nanomedicine and drug delivery. By gathering basic and clinical scientists with the common interest of using nanotechnology in the delivery of therapeutic and diagnostic agents, this symposium series aims to narrow the gap between research communities in academia, government, and industry.

During two and a half days the symposium will feature the lectures of some of the world's leading scientists in the pharmaceutical and medical fields. The keynote speakers are Kazunori Kataoka (University of Tokyo), who will discuss novel polymeric complexes for drug and gene delivery, and Henry Friedman (Duke University), who will speak on new therapeutic strategies for malignant glioma. The program also includes 16 plenary lectures, 6 research reports, a poster session, and a panel discussion of the clinical prospects of nanomedicines.

The principal plenary sessions include Nanomaterial Chemistry and Engineering, Fate and Function of Nanoparticles in Cells, Nanomedicines for Cancer Therapy, Nanotechnology Approaches for Bioimaging, Pathology and Therapy of Neurodegenerative Disorders, and Nanotechnology Approaches for Pathogen Detection. The speakers from seven countries will represent leading research institutions in the United States, Europe, and Japan, as well as others, and are among the pioneers in their respective areas of research. Together with the members of the scientific advisory board and other distinguished scientists who will moderate the symposium's sessions, the speakers will provide a unique appraisal of the nanomedicine and drug delivery field and provoke discussions of its most important and challenging aspects.

The innovative Nanomedicine Research Reports session will provide an overview of some of the newest developments in design of intelligent drug delivery materials, characterization of intracellular traffic of therapeutic macromolecules, targeted drug delivery, therapy of cancer, noninvasive monitoring of cell movement, and modulation of immune response. The panel discussion will focus on the challenges that exist or are likely to emerge during the clinical development of novel nanomedicines.

The poster session will be the highlight of the symposium. During the symposium, time will be dedicated for poster viewing, with an opportunity to meet the authors and answer questions related to the abstracts. Additionally, a number of posters will be selected for short oral presentations. The call for posters, program description, registration, and abstract submission are available at www.nanodds.org. The symposium will be held at the Embassy Suites Hotel Downtown/Old Market, Omaha, Nebraska, which is a short 5-minute drive from Omaha's Eppley Airfield.

Overall, this symposium will emphasize the opportunities of the "next generation" of nanomaterials and nanodevices to diagnose, treat, and monitor diseases. The knowledge and experience in interactions of nanosized drug delivery systems is invaluable for researchers in nanomedicine. This research promises breakthrough advances and addresses clinical needs. Several nanosized drug delivery systems have already been approved for clinical use, and more nanomaterials are being evaluated in clinics. Nanomedicine is not only a "futuristic" but also a "realistic" field with a near-term prospective to improve human health.

CReators
Controlled Release Education Articles on Technology Original Research and Science

From the Education Committee

Controlled Release Education, Research, and Industry in Iran

By Farid Dorkoosh, Tehran University of Medical Sciences, Tehran, Iran, and Synthon BV, Nijmegen, The Netherlands
Rassoul Dinarvand, Tehran University of Medical Sciences and Ministry of Health and Medical Education, Tehran, Iran

This is the third in a series of short education articles that look at Controlled Release education, research, and industry initiatives in various parts of the world.

Introduction

Iran is one of the largest developing countries in the Middle East, with more than 68 million inhabitants. General health considerations and affording the highest standards of medical care have been the focus of the Ministry of Health (MOH) during the last 15 years. Although the annual per capita drug expenditure in the country is only 20 USD, many novel and controlled release (CR) pharmaceuticals are available. Strict regulation of drug pricing may be the main reason for keeping the total drug expenditure lower than the regional average. Local pharmaceutical manufacturers produce 95% of the market requirement. However, 45% of the market share can be attributed to imported products (5% of the market volume). Therefore, local products are mainly generic and are sold at low cost, whereas imported products are mainly expensive brand medicines, such as oncological agents, blood products, and biopharmaceuticals, amongst others, and many of the imported medicines are heavily subsidized by government agencies. The Food and Drug Department in the MOH is the national drug regulator and is responsible for making sure that safe, high-quality drug and biological products are available, accessible, and affordable in the country. The authorities are very keen to make sure that new life-saving technologies, in particular CR products, are available for use by those who need them. At present CR products are all imported and command only 5% of the market share. However, many researchers at pharmaceutical research and educational centers are currently involved in CR research endeavors, and it is conceivable that very soon national production sites will become active in the field of novel drug delivery system development and manufacture.

Education

There are 11 Schools of Pharmacy in Iran located in various parts of the country (Figure 1). Education in pharmacy in Iran is divided into an undergraduate program, following which one obtains a Pharm.D. (doctor of pharmacy) degree, and a post-graduate program, which culminates in the award of a Ph.D. degree. There are no classical bachelors and masters of pharmacy degrees in Iran, and all Faculties of Pharmacy offer Pharm.D. programmers, amongst these Tehran, Shahid Beheshti, Esfahan, Mashhad, Tabriz, and Shiraz also offer a Ph.D. degree.

The Pharm.D. degree is a 5.5-year undergraduate professional program covering various disciplines, including pharmaceutics,

Figure 1. A map of Iran indicating locations where pharmacy degrees are offered: 1–Tehran University, 2–Shahid Beheshti University, 3–Azad University, 4–Esfahan University, 5–Tabriz University, 6–Mashhad University, 7–Kerman University, 8–Shiraz University, 9–Ahvaz University, 10–Sari University, and 11–Kermanshah University.

pharmacology, biopharmaceutics, drug therapy, hospital pharmacy, medicinal chemistry and pharmacognosy, in which each discipline is a sum of multiple-unit courses and laboratory assignments. Students need to have 205 units in order to graduate. Annually, more than 500 students graduate as pharmacists. In addition, approximately 40 post-graduate students annually obtain their Ph.D. degrees in various fields of the pharmaceutical sciences. It is interesting to note that approximately 38% (15 candidates) are awarded a Ph.D. degree in pharmaceutics per year. There are currently approximately 12,000 registered pharmacists in Iran, of which more than 80% work in pharmacies. Of the remaining 20%, 6% are employed in industry, 10% in non-profit or governmental organizations, and only 4% in academia.

CR and drug delivery have been the focus of the Departments of Pharmaceutics at many universities. Conventional dosage forms are taught as a standard program of undergraduate studies, while novel drug delivery systems are mostly covered during Ph.D. programmers and are largely based on the interests of each member of the faculty.

Research Activities on CR in Iranian Education Centers
Research activities in the field of CR in Iranian pharmacy research and education centers are very diverse. Many researchers are involved in the field of development and assessment of polymeric drug delivery systems. However, in recent years, with increased financial support from the government, new initiatives have been introduced in the areas of biopharmaceutical research and development and nanotechnology applications in drug delivery. In general, research projects are primarily sponsored by university research grants, and to a lesser extent, local industry and national research bodies may sponsor projects.

One of the essential needs for research in the field of CR and drug delivery is the implementation of applied sciences and bringing new technologies to Iran. Mutual collaboration between universities and industries must be increased in order to be able to initiate more applied research in the area of CR technology development. One of the biggest challenges in Iran is the need to facilitate the possibility for collaboration between researchers in industry and academia. Education in CR for Ph.D. students should be changed from the classical model in which students follow course work prior to embarking on a research project, to a more research-oriented model where students have to focus on completing extensive research projects.

Pharmaceutical Industries Developing CR Dosage Forms
The pharmaceutical industry in Iran is mainly composed of generic companies in which most, if not all, manufacturing is undertaken. Brand or innovator companies tend to import their medicines via local agents who market and distribute the relevant products. There are, however, some changes within the pharmaceutical industrial policy to support the idea of capital investment by foreign companies. Most local pharmaceutical companies are looking for the possibility of licensing new technologies and are open for the production of such technologies under license from international companies.

Currently there are no drug delivery companies in Iran. However, there is the potential to start such CR or drug delivery companies as the country is progressing rapidly in the field of novel technology development.

Current Initiatives and Needs
CR and drug delivery in Iran is facing a new era, one in which scientists at universities and in industry are looking to focus on novel technologies and establishing collaborations with foreign universities and companies in order to promote CR research at a higher level. Recently a local Controlled Release Society Chapter has been formed, with the intention of seeking sanction by the broader CRS community, to support ongoing CR research activities at an international level. The Controlled Release Society of Iran plans to hold its first Iranian Conference on Controlled Drug Delivery Systems in May 2007 in Tehran. All local scientists have been invited to prepare their research results to be presented at this conference. Some Iranian scientists who are currently undertaking research projects at universities in the United States and Europe have also been invited to present papers at the conference. ■

Veterinary Group Activities

David Brayden, University College Dublin, Ireland

The Veterinary Committee has been busy organizing its unique brand of events for the CRS Annual Meeting in Vienna in July 2006. This year we have tried to increase the profile of this small but important component group of the Society. We have organized a Veterinary Mini-symposium for the first time in several years; a session that comprises four internationally recognized experts in veterinary therapeutics and controlled release:

- **Pierre-Louis Toutain** (National Veterinary School, Toulouse, France) "Pharmacokinetic and Pharmacodynamic Responses To Veterinary CR Formulations in Veterinary Species: Effects of Dosing Regimes"
- **Katrina Mealey** (College of Veterinary Medicine, Washington State University, U.S.A.) "Potential Drug Interactions at the level of P-Glycoprotein in Canine *mdr* Gene Knock Out Models"
- **Sevda Senel** (Faculty of Pharmacy, Hacettepe University, Ankara, Turkey) "Innovative Applications of Chitosan in Veterinary Medicine"
- **Scott Brown** (Pfizer Animal Health, Kalamazoo, U.S.A.) "Ceftiofur Crystalline Free Acid: A Novel Sustained Release Parenteral Suspension for Livestock"

The session should be of real interest to other groups in CRS. For example, Professor Toutain's pharmacokinetic work is well known to "human" pharmacologists. Dr. Mealey's work on P-glycoprotein (P-gp)-related drug toxicity in collies is a genuine knock-out model and will be of interest to all P-gp researchers, especially those whose world of animal models is no larger than mice! Dr. Senel's work on chitosan will interest those researching vaccine adjuvants, while Dr. Brown's case study on an injected controlled release antibiotics is of relevance to all interested in how a veterinary project goes through development stages to market and how this might compare to a development work in humans.

We will reprise our unique "Veterinary-Get-Together" session in Vienna. As ever, this social event it is open to all at the meeting, and this year are most grateful to Pfizer Animal Health for sponsorship. Our master of ceremonies will be Dr. Keith Ellis of CSIRO (Australia), who will address a topic of veterinary controlled release in his well-known entertaining way. Finally, our veterinary podium session was entirely selected from submitted abstracts, so the chances of getting a podium slot were quite high this year. Just to assure you that the system of selection is fair, all abstracts were graded individually by up to four experts, and the scores were totted up. Since we are in the business of making an attractive session, we obviously looked to spread around the slots between institutions and topics accordingly.

On other matters, CRS is co-sponsoring the 2nd Joint AAPS/AAVPT/CRS Workshop on "Collaboration in the Research and Development of Veterinary Pharmaceuticals" in San Antonio, TX, October 27–29. This is a satellite meeting of the AAPS Silver Anniversary Conference in San Antonio, so there is an opportunity to attend both. This meeting will bring together pharmaceutical scientists and veterinary pharmacologists to discuss areas of mutual interest and will provide a forum in which current issues and future objectives and directions in veterinary medicine can be presented and discussed. The focus of the meeting is on dosing issues for veterinary drugs, and a superb programme has almost been finalized. Those of you who attended the first meeting in Chicago in 2002 should not be disappointed! Confirmed speakers include Mike Rathbone (InterAg, New Zealand), Mark Papich and Jim Riviere (North Carolina State University, U.S.A.), Simon Blanchflower (Pfizer Animal Health, U.K.), Mike Apley, (University of Kansas, U.S.A.), Laura Hungerford, Raafat Fahmy, and Marilyn Martinez (FDA), Kishan Kumar (Merial, U.S.A.), David Brayden (University College Dublin, Ireland), and Jorge Heller (AP Pharma, U.S.A.).

Finally, the vet group in CRS is always on the look-out for new active members and for people who can serve on the committee. If interested in helping with our activities, please contact current co-chairs, David Brayden (david.brayden@ucd.ie) or Craig Bunt (c.bunt@auckland.ac.uk). It's a great way to network, and you will inevitably get more back than what you put in! ■

Welcome New Members

Ahmed M. Abdalla
Oliver W. Ackaert
Ulrike Adam
Ilbeyi Agabeyoglu
Buket N. Aksu
Ingo Alberti
Karin Albrecht
Ayman Allahham
Theresa M. Allen
Resu Alloza
Lori Alquier
Marco Anelli
Marion Anhorn
Dhawal D. Ankola
Nicolas Anton
Fatemeh Atyabi
Christian Augsten
Konstantinos Avgoustakis
Hirohito Ayame
Yun-Mi Bae
Alexandra Balkina
Stephen George Barnwell
Katharine M. Barrow
Thomas E. Beckert
Steven L. Bennett
Stephane Bernard
Damien Berthier
Ahmed I. Besheer
Sushila Bhattarai
Erem Bilensoy
Raj Birudaraj
Gabriele Blume
Katherine Bolton
Olga M. F. Borges
Ibticem Boughellam
Katherine W. Bowman
Richard Buchta
Paul Bulpitt
Michael Bur
Shenshen Cai
Monica Campisi
Fabiana Canal
Mirta Canevari
Adam S. Cantor
Maria Margarida Cardoso
Daniel A. Carr
Myrra Carstens
Jennyfer Cazares
Woei Ping Cheng
Patrizia Chetoni
Young Ho Cho
Hye Choi
Hyungsoo Choi
Joon Sig Choi
Kar Wai Chooi
Dafeng Chu
I-Ming Chu
Brian C. Clark
Richard Cohen
Kilian Conde-Frieboes
Daisy P. Cross
Noemi Csaba
Kunyuan Cui
Afendi Dahlan
Wenbin Dang
Nabil B. Darwazeh
Tina Dasbach
Clifford M. Davidson
Iain Davidson
James Rian Davis
Samuel Deacon
Maria De La Fuente
Stefano De Luigi Bruschi
Manaud De Raspide
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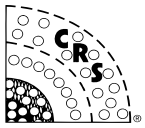

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calendar of events

who…what…where…when

Health Information Technology Symposium

July 17-20, 2006
MIT Stata Center for Computer Information and Intelligence Sciences
Cambridge, Massachusetts, USA

33rd Annual Meeting of the Controlled Release Society

July 22-26, 2006
Austria Center
Vienna, Austria
www.controlledrelease.org
ph: 651-454-7250

Advances in Tissue Engineering Short Course

August 16-19, 2006
Rice University
Houston, Texas, USA
http://tissue.rice.edu

Advances in Tissue Engineering Short Course

August 16-19, 2006
Rice University
Houston, Texas, USA
http://tissue.rice.edu

Pharmaceutical Sciences World Congress

April 22-25, 2007
Amsterdam, The Netherlands
www.fip.org/PSWC/index1.htm

34th Annual Meeting of the Controlled Release Society

July 7-12, 2007
Long Beach Convention Center
Long Beach, California, USA
www.controlledrelease.org
ph: 651-454-7250

35th Annual Meeting of the Controlled Release Society

July 12-16, 2008
Hilton New York
New York City, New York, USA
www.controlledrelease.org
ph: 763-512-0909