CONTROLLED RELEASE SOCIETY

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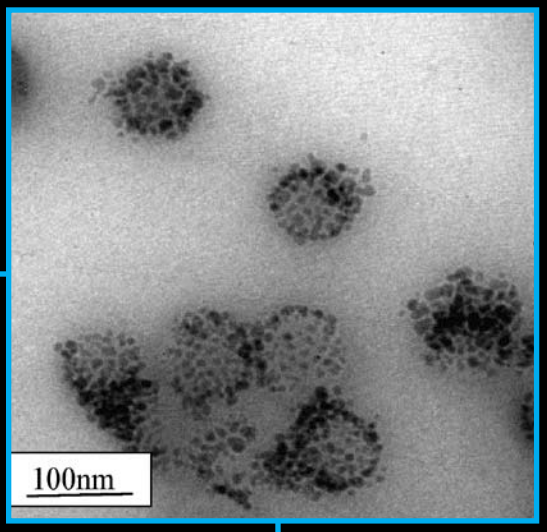
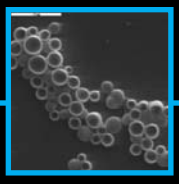
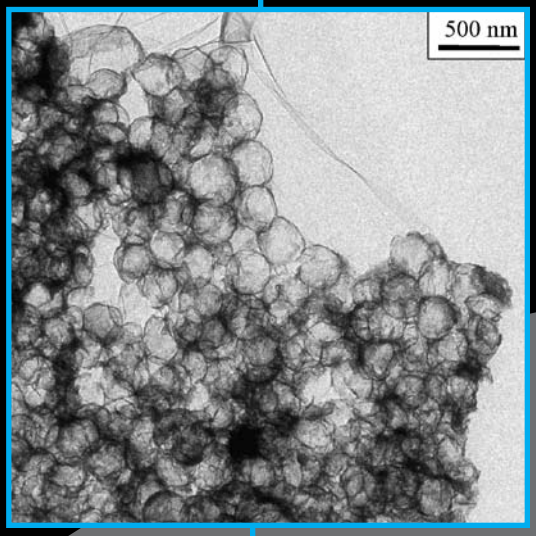
NEWSLETTER







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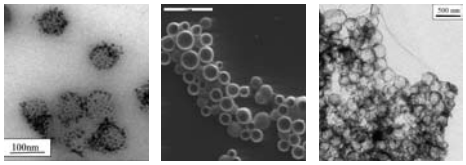
NEWSLETTER

Volume 23 • Number 1 • 2006

inthisissue

On the cover –



Cover picture shows various forms of nanocapsules prepared by the miniemulsion process. Full details can be found in Katharina Landfester's C&DP Article on Page 12.

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FROM THE Editors

By Bozena B. Michniak
IMDJN-NJMS, USA

Bozena Michniak

Greetings in the New Year!! I hope all your holiday activities were enjoyable, and like all breaks, the vacations went too fast. This is our first year with four (not three) issues of the Newsletter, and as the cover suggests, we are in the age of nanotechnology. It is the time for MEMS, nanoscale materials, quantum computing, nanomedicine, nanoelectronics, nanotubules, self assembly, and nanospheres and nanoparticles. Michael Dell [answered] "nanotechnology," when asked by an MIT student which areas he would focus on if he had to start his career all over again today (Nanotech Insider, May 14, 2004). In line with the trend, we have an article on "Generation of Nanocapsules by Miniemulsion Processes" (also featured on our cover this month) from Germany, and in the C&DP Patent Watch, we find out (not surprisingly) that in the first half of 2005, nanoencapsulation was scoring high in the number of patents in non-pharmaceutical areas. For injectables, nanotechnology is already generating new dosage forms that are easier to administer. For example, Johnson and Johnson revealed that Elan's new NanoCrystal™ technology would be used in a Phase III clinical trial for an injectable formulation of paliperidone palmitate, a drug for schizophrenia, whose insolubility problem has been overcome by reducing particle size to under 200nm.

It is also the year that our Annual Meeting takes place in Vienna Austria, and hopefully, we are all planning to submit papers and attend this meeting.

The Newsletter editorial team wishes you a very peaceful, healthy, and professionally successful New Year! ■

Vladimir Torchilin

From the President

By Vladimir Torchilin
Northeastern University

On behalf of the Board of Directors, I would like to extend our very best wishes for the New Year to all CRS current and future members! In this new millennium, pharmaceutical biotechnology will become increasingly important in all areas that improve the quality of living. Within this context, the role of the Controlled Release Society, which is the only international society unifying scientists from all over the world working in all areas of new formulations and new delivery systems of biologically active compounds, is significant like never before.

This year promises to be very important for the CRS. Currently, the Society enjoys a well-deserved international reputation. Annual meetings of the Society are among the most significant in biomedical sciences, and the *Journal of Controlled Release* is among the highest rated journals in the field of experimental pharmacology. However, we must be prepared to meet the challenges of the future and continue to work hard to maintain our current level of performance. The field is ever-growing. Thus, there is always room for improvement in all aspects of the Society. Although the CRS with its almost 2,000 members in more than 50 countries and 18 strong and active local Chapters is in good shape, the Board has recently taken additional measures that we believe should further strengthen the CRS and improve its international visibility and financial position.

Beginning in February 2006 the CRS is being managed by Scientific Societies, which will bring us its broad experience, international networking, and strong publication capabilities. I sincerely thank our immediate Past-President Jenny Dressman and our Treasurer Art Tipton for their outstanding efforts as members of the Transition Committee. Keeping our future developments in mind, we have also created a new Publishing Committee led by James Anderson within the Society to start producing our own books on controlled release. The new website of the Society at www.controlledreleasesociety.org will provide you with all the updated information.

With the help of Scientific Societies we will continue strengthening our educational initiatives, including building our virtual library and special programming for the Annual Meeting. Exciting events have been planned for Young Scientists at the upcoming Annual Meeting of the Controlled Release Society in beautiful Vienna, Austria, July 22–26, 2006, by Mike Rathbone and Farid Dorkoosh of the Education Committee. In addition to the Young Scientist Sessions, the main program offers a multitude of opportunities for all attendees to find exactly what they are looking for and more—6 Plenary Speakers and more than 30 Invited Speakers, Dedicated Industrial Track Sessions, lively and provocative debates in the Pearls of Wisdom Sessions, and Technology Transfer Sessions such as Soapbox and Releasing Technology Workshops. We have to send our special thanks to Mike and Farid for their devotion to the CRS and its educational activities.

We are trying to keep the Society in good financial status, and Art Tipton together with the Finance Committee is doing a great job to optimize our cost/benefit ratio to allow for the further investment in our infrastructure and programs to assist the Society and its members in reaching their strategic goals.

We have a great program in place for our Annual Meeting (please visit our new website for the details), and we are looking for outstanding attendance in Vienna. As usual, outstanding work by our Scientific Secretary, Martyn Davies, together with program chairs made it possible. Please submit your abstracts and register soon.

The site of the venue and the scientific program promise us a lot of good science and a lot of fun and enjoyment. We also expect to have a great Exhibition, which will represent all significant players in drug delivery and controlled release technologies from around the world.

We look forward to seeing many of you and to greeting you personally at the Annual Meeting in Vienna. We wish all of you the most happy and successful New Year.

Vladimir Torchilin ■

Scientifically Speaking

Transcriptomics of Delivery Systems for Gene-based Therapies

By Saghir Akhtar
Centre for Genome-based Therapeutics,
The Welsh School of Pharmacy, Cardiff University, United Kingdom

The effective intracellular delivery of nucleic acids remains one of the most important pharmaceutical challenges to the widespread clinical application of gene-based therapies, including classical gene therapy and gene-silencing technologies such as antisense oligonucleotides, ribozymes, DNAzymes, and RNA-interference (Akhtar, 2005; Gilmore et al., 2004). The use of viral vectors as delivery systems for gene therapy typically results in high transfection efficiencies, but this advantage is often offset by their ability to induce adverse immunological and toxicological responses in vitro and in vivo. Thus, non-viral vectors, like cationic lipids and cationic polymers, have increasingly been employed as potentially safer alternatives for nucleic acid delivery (Akhtar et al., 2000; Gilmore et al., 2004; Niidome and Huang, 2002).

At the Centre for Genome-based Therapeutics (CGT) in Cardiff, we have been addressing the pharmaceutical challenges to the delivery of gene-silencing nucleic acids, such as antisense oligonucleotides, ribozymes, DNA enzymes, and more recently, small interfering RNA (siRNA). These challenges include an understanding of the mechanisms of cellular uptake and trafficking of gene-silencing oligonucleotides alone and when complexed with a variety of delivery systems, including cationic lipids and dendrimers (reviewed in Akhtar et al., 2000; Gilmore et al., 2004). In addition to improving delivery, an ideal gene-delivery vector should be biocompatible, and furthermore, it should be "genocompatible," i.e., not elicit adverse gene expression or biological effects that may compromise gene therapy (Akhtar, 2005; Hollins et al., *submitted*; Kabanov et al., 2005). Thus, our group has also been studying the impact of delivery systems on gene expression (toxicogenomics) in cells using microarray-based gene expression profiling (transcriptomics).

Two recent reports from our group have highlighted that both cationic lipids (Omidi et al., 2003) and cationic polymer delivery systems (Omidi et al., 2005) not only can deliver their cargo (in this case nucleic acids) into cells but can also elicit changes in the cellular genomics that may have profound effects on the effectiveness of gene-based therapies. Using microarray-based gene expression profiling technology (transcriptomics), we showed that cationic lipids such as Lipofectin™ (Petch et al., 2003) and in particular Oligofectamine™ (Omidi et al., 2003) even at routinely used concentrations induced inadvertent gene expression changes that led to enhanced apoptosis in human epidermoid carcinoma cells (Omidi et al., 2003).

More recently, we reported on the toxicogenomics of generation 2 (DAB-8) and generation 3 (DAB-16) polypropylenimine (PPI) dendrimers in two human cell lines. Cationic PPI dendrimers have emerged as attractive non-viral vectors for the delivery of genes, antisense oligonucleotides, and siRNA (Hollins et al., 2004; Zinselmeyer et al., 2002). At concentrations and treatment protocols routinely used for gene and oligonucleotide transfection, PPI dendrimers alone elicited marked changes in endogenous gene expression in A431 epithelial cells (Figure 1). The extent of PPI-induced gene changes appeared to depend on the dendrimer generation, as the number of genes affected was greater with G3 compared with G2 PPI dendrimers in A431 cells. The signature of DAB-16–induced gene changes in A549 cells was different than those elicited in A431 cells, implying a strong dependence on cell type (Omidi et al., 2005). The DAB-16 polymer complexed with DNA (dendriplexes) also elicited marked gene expression changes in A549 cells but with a signature that was different than the polymer alone, implying that dendriplexes are "recognised" by cells as chemical entities that are distinct from the polymer alone.

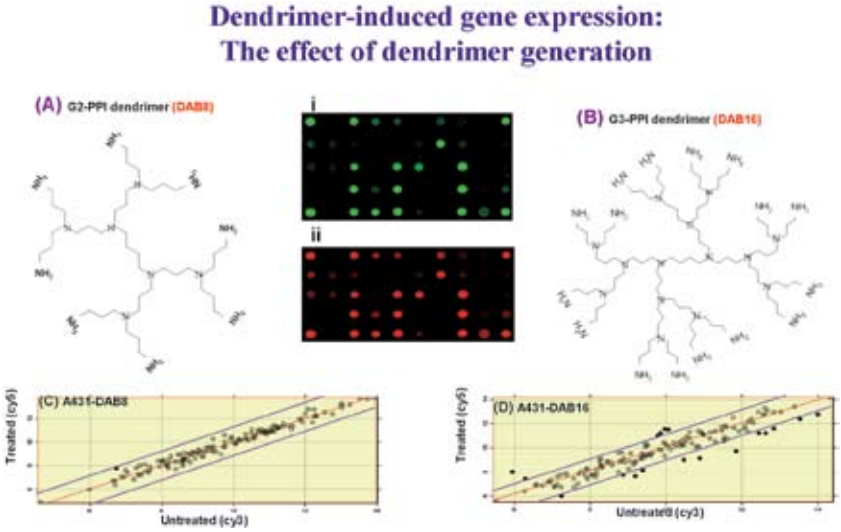

Figure 1. Transcriptome analyses showing the differential gene expression changes induced by DAB-8 and DAB-16 polypropylenimine dendrimers in A431 cells. The chemical structure (A and B) of the two polymer generations, along with panels showing the expression arrays (i for DAB-8 and ii for DAB-16) and the scatter plots of relative gene expression intensities of 200 genes in cells treated with either dendrimer compared with untreated cells. Each circle represents a gene, and those given in bold represent genes whose expression was altered by more than twofold by the polymer. The blue lines represent the limits of twofold change either up- (above) or down-regulated (below the red line, the line of no change) compared with untreated control cells. (Data redrawn from Omidi et al., 1995, with permission).

For both cationic lipids and cationic polymers, alterations in expression of a variety of gene ontologies were observed, including those involved in inflammation and defence responses, cell proliferation, and apoptosis. We have now extended these findings to several other delivery systems (Hollins et al., *submitted*). These data show for the first time that delivery systems, separate from their capability as transfection reagents, can intrinsically alter the expression of many endogenous genes, which could potentially lead to them exerting multiple phenotypic effects in cells. In some cases, these alterations in gene expression can lead to downstream functional consequences such as increased apoptosis. Also, such gene changes may impact the specific gene effects sought in gene-based therapies such as gene-silencing technology (Hollins et al., *submitted*). Thus, the global genomic impact of delivery vectors needs to be assessed, as the precise impact and consequences of polymer-induced gene changes should guide their rational use as delivery systems in the post-genomic era.

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Scientifically Speaking

Determination of the Mechanical Properties of Microcapsules by Micromanipulation

By Professor Zhibing Zhang
Department of Chemical Engineering,
University of Birmingham, Edgbaston, Birmingham, United Kingdom

Encapsulation has a wide range of applications in science, technology, and medicine, such as making pressure-sensitive materials, control of the release rate of active ingredients, and masking undesired properties of the active component. Information about the mechanical strength of microcapsules is critical for optimisation of their functions and minimisation of their production costs. A typical example is the manufacture of microcapsules for making carbonless paper, where their strength dominates the quality of the product. However, the mechanical strength of microcapsules remains largely uncharacterised.

There have been indirect methods for characterising the mechanical strength of microcapsules, such as measurement of breakage of microcapsules in a stirred tank or in a bubble column. The results from these indirect methods are difficult to use because the mechanical damage to the microcapsules depends not only on their mechanical strength, but also on the hydrodynamics of the process equipment. Direct methods include use of a micropipette aspiration technique or an atomic-force microscope probe to measure the elastic properties of single microcapsules. Unfortunately, the former technique cannot be used to determine the force required to burst the microcapsules, while the latter relies on compression of single capsules between a rigid spherical bead and a flat surface, which is difficult to implement. The mean strength of microcapsules in a sample may be quantified by compressing a layer of microcapsules between two plates and measuring the force required to rupture a given percentage of the microcapsules. Although this method is practically useful, it conceals any difference in strength between microcapsules within a sample.

Our work has demonstrated that a novel micromanipulation technique can be used to directly measure the mechanical strength of single microcapsules. The principle of the technique is to compress single microcapsules between two parallel surfaces and measure the force being imposed on the microcapsules using a sensitive force transducer simultaneously (Figure 1). The microcapsules measured can be as small as 1μm in diameter. This opens up a new avenue, enabling proper characterisation of the mechanical strength of microcapsules, with the possibility of modelling microcapsule structures by incorporating information on microcapsule size and wall thickness.

We have used the micromanipulation technique and measured the mechanical strength of microcapsules with different sizes, wall thicknesses, and wall compositions (types of wall materials)[1,2]. For example, the mechanical properties of single melamine formaldehyde (MF) microcapsules with diameters of 1–12μm were determined, including their viscoelastic and elastic-plastic properties. The microcapsules were mainly elastic up to a deformation of 19 ± 1%. Beyond this point, the microcapsules underwent plastic deformation and were ruptured at a deformation of 70 ± 1%. However, the corresponding deformations at the yield point and the rupture of urea-formaldehyde microcapsules were 17 ± 1% and 35 ± 1%, respectively, which implies that urea-formaldehyde microcapsules were more brittle than MF microcapsules. Besides wall composition, the rupture strength of these microcapsules depended on their size and wall thickness. The relationship between the force being imposed on single microcapsules and their deformation has been modelled to determine their intrinsic material parameters, such as Young's modulus, Poisson's ratio, and other parameters[3]. Such information is essential for quantifying the mechanical strength of microcapsules for a given sample and comparing the strength between different formulations.

Some microcapsules, e.g., calcium alginate beads coated with chitosan, have a certain permeability. When they are compressed, there can be a loss of liquid from the capsules, and consequently, their rupture force depends on compression speed. To minimise speed-dependent behaviour, such microcapsules can be compressed at a high speed, e.g., 1,000μm s^{-1}, which can be achieved using a newly developed micromanipulation rig[3]. This new high-speed micro-compression tester, with two complementary high-speed videos, is a powerful tool for investigating the mechanical properties of hydrated materials at the microscale.

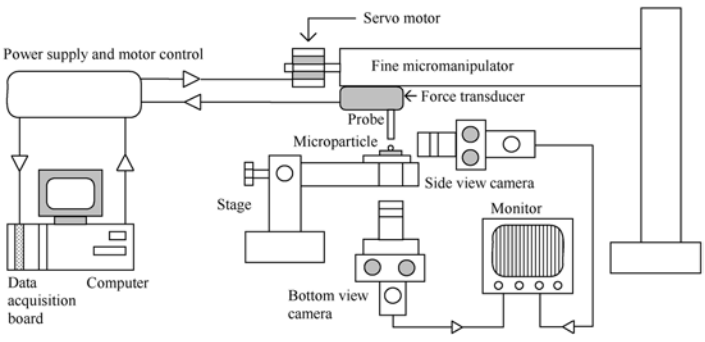

Figure 1. Schematic diagram of the micromanipulation rig.

The mechanical properties of single hydrated dextran microspheres (<10μm in diameter) with a model protein drug embedded were also measured by the micromanipulation technique, and the information obtained was used to derive the average pore size of the microspheres and further the protein release rate[4]. This study showed that micromanipulation provides insight into the average pore sizes of dextran microspheres, which is an important characteristic that can be used to modulate the release of encapsulated proteins.

Recently, a novel nanomanipulation technique has been developed[5]. For sub-microparticles, we have to rely on scanning electron microscopy (SEM) or environmental scanning electron microscopy (ESEM). ESEM is primarily used to visualise materials on micro- or nanoscales under wet mode. To enable the mechanical properties of materials on such small scales to be measured, we have built a nanomanipulation device with a force transducer, placed it in the chamber of an environmental scanning electron microscope, used it to deform the materials, and measured the force imposed on the materials simultaneously. The nanomanipulation technique has been applied to the characterisation of the mechanical properties of sub-micro poly(methyl methacrylate) particles as small as 400nm. ESEM with the nanomanipulation device is being used to investigate the fracture mode of micro- and nanoparticles (Figure 2).

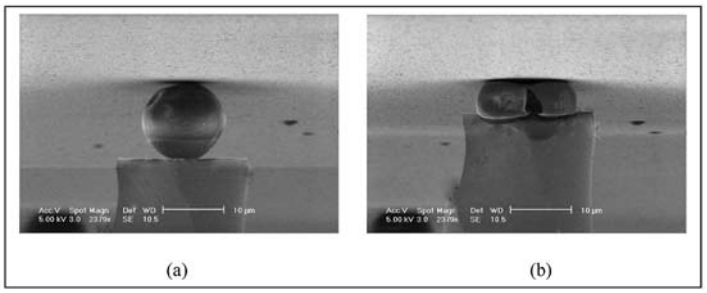

Figure 2. A single MF microcapsule held between a force probe and a slide in the chamber of an environmental scanning electron microscope: (a) before compression; (b) after rupture.

In summary, understanding the mechanical strength of microcapsules is essential to a wide range of applications in controlled release of active ingredients. The micromanipulation technique developed at Birmingham, UK, is a very powerful and unique tool for determining the mechanical properties of capsules made from different materials and structures.

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Attend a Workshop to Make the Most of your Meeting Experience!

The following workshops will be offered at the 33rd Annual Meeting & Exposition of the Controlled Release Society in Vienna. These three educational workshops are scheduled for Saturday, July 22.

Workshop 1: Regulatory Issues for Controlled Release Parenterals

Co-chairs: *Diane J. Burgess, University of Connecticut, and Kinam Park, Purdue University*

This workshop will focus on CMC and regulatory issues with respect to controlled release parenteral dosage forms. In particular, *in vitro* and *in vivo* testing methods and specifications for controlled release parenteral products including microspheres, liposomes, emulsions, stents and other implantable devices will be reviewed and discussed. An overview of the different dosage forms, their manufacturing and performance testing will be presented. *In vitro* release testing will be discussed with a view to *in vivo* relevance. *In vitro-in vivo* relationships will be addressed and a regulatory perspective on these products will be provided. Industrial case studies will be presented.

Workshop 2: Drug-Device Combination Products: Novel Technologies and Regulatory Challenges

Co-chairs: *Tejal Desai, University of California, San Francisco, and John Santini, MicroCHIPS, Inc.*

This workshop will provide attendees with a solid understanding of the concepts involved in and the challenges of developing drug-device combination products. The workshop is divided into three sessions. The first session focuses on novel technologies, primarily passive versus active drug-device combinations. The second session covers the regulatory approval processes in the United States and Europe. The third session is a case study in combination product development.

Workshop 3: Role of Intestinal and Hepatic Transporters on Oral Bioavailabilities of Drugs

Co-chairs: *Yuichi Sugiyama, The University of Tokyo, and Per Artursson, Uppsala University*

Work is in progress to examine the major factors that govern drug disposition in the body and to clarify the mechanisms involved in membrane transport in the liver, brain, kidney, and intestine. The prediction and control of drug effects and safety will never be fully achieved unless we develop methodology to reconstruct quantitatively *in vivo* phenomena from *in vitro* data. Before drugs can exert their ultimate effects, they have to undergo a variety of processes. Among them, absorption from the gastrointestine and first–pass hepatic removal are the most important processes for predicting drug effects. Workshop attendees will learn the frontier, cutting-edge approach for predicting oral bioavailability of drugs and learn how the transporters will play roles in the extent of bioavailability.

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Visit www.controlledreleasesociety.org for registration information and more details on both the workshops and the Annual Meeting & Exposition.

Abstracts

Investigation of *in vitro* transdermal absorption of fentanyl from patches placed on skin samples obtained from various anatomic regions of dogs. *Paul C. Mills, BVSc, PhD; Beatrice M. Magnusson, PhD; Sheree E. Cross, PhD.* Am. J. Vet. Res. 65:1697-1700 (2004).

Objective—To investigate in vitro transdermal absorption of fentanyl from patches through skin samples obtained from various anatomic regions of dogs.

Sample Population—Skin samples from 5 Greyhounds.

Procedure—Skin samples from the dogs' thoracic, neck, and groin regions were collected postmortem and frozen. After samples were thawed, circular sections were cut and placed in Franz-type diffusion cells in a water bath (32°C). A commercial fentanyl patch, attached to an acetate strip with a circular hole, was applied to each skin sample. Cellulose strips were used as control membranes. Samples of receptor fluid in the diffusion cells were collected at intervals for 48 hours, and fentanyl concentrations were analyzed by use of high-performance liquid chromatography.

Results—Mean ± SD release rate of fentanyl from the patch, defined by its absorption rate through the non–rate-limiting cellulose membrane, was linear during the first 8 hours (2.01 ± 0.05µg/cm^2 of cellulose membrane/h) and then decreased. Fentanyl passed through skin from the groin region at a faster rate and with a significantly shorter lag time, compared with findings in neck or thoracic skin samples.

Conclusions and Clinical Relevance—*In vitro*, fentanyl from a patch was absorbed more quickly and to a greater extent through skin collected from the groin region of dogs, compared with skin samples from the thoracic and neck regions. Placement of fentanyl patches in the groin region of dogs may decrease the lag time to achieve analgesia perioperatively; however, *in vivo* studies are necessary to confirm these findings.

Prevention of naturally occurring infectious bovine keratoconjunctivitis with a recombinant Moraxella bovis cytotoxin-ISCOM matrix adjuvanted vaccine. Vaccine 23(4):537-545 (2004).

The efficacy of a recombinant Moraxella bovis cytotoxin subunit vaccine to prevent naturally corneal ulcers and conjunctivitis (IBK) was evaluated in cattle in a field trial. Ninety-three calves were vaccinated with either saline, ISCOM matrix (adjuvant control), or a recombinant M. bovis cytotoxin carboxy terminus peptide plus ISCOM matrix and boostered 21 days later. Ocular examinations were performed once weekly for 20 weeks. At week 12, the proportion of calves with ulcerated eyes in the recombinant vaccine group was statistically significantly lower than in the saline control group. Throughout the trial, the proportion of ulcerated eyes in calves remained lowest in the recombinant vaccine group. By week 7, calves with non-ulcerated eyes in the recombinant vaccine group had significant increases in neutralizing and cytotoxin specific antibody titers in serum and tears as compared to control calves. These results in vaccinated calves during the trial suggests that a recombinant M. bovis cytotoxin vaccine may be beneficial in helping to prevent conjunctivitis and corneal infections in calves.

An assessment of different DNA delivery systems for protection against respiratory syncytial virus infection in the murine model: Gene-gun delivery induces IgG in the lung. Vaccine 22(19):2438-2443 (2004).

Immunization with plasmid DNA (pDNA) has the potential to overcome the difficulties of neonatal vaccination that may be required for protection against infection with respiratory syncytial virus (RSV). But little is known about delivery modalities. This study compared mucosal delivery of pDNA encoding RSV F protein encapsulated in poly(DL-lactide-co-glycolide) microparticles with delivery of pDNA by gene-gun for the induction of immunity in mice. Oral or intra-nasal immunization with various doses of microparticles induced low levels of RSV-specific serum antibodies in mice. However, gene-gun vaccination led to protective immunity associated with a humoral response with RSV-specific antibody detected in lung following intradermal vaccination with the gene-gun.

Controlled release of avermectin from porous hollow silica nanoparticles. *L. X. Wen, Z. Z. Li, H. K. Zou, A. Q. Liu, and J. F. Chen.* Pest Manage. Sci. 61(6):583-590 (2005).

Porous hollow silica nanoparticles 100 nm in diameter and possessing a pore size of 4.5 nm were synthesized via a sol-gel route using inorganic calcium carbonate nanoparticles. The synthesized nanoparticless were subsequently employed as pesticide carriers to evaluate the controlled release of avermectin. The avermectin-nanoparticles were characterized by BET, thermogravimetric analysis, and IR. These analyses showed that the amount of avermectin encapsulated in the nanoparticles could reach 58.3% w/w by a simple immersion loading method, and that most of the adsorption of avermectin on nanoparticles was probably physical. Avermectin may be loaded on the external

surface, the pore channels in the wall and the inner core of the nanoparticles. This results in a multi-stage sustained-release pattern from the nanoparticles. Increasing pH or temperature intensified the avermectin release.

Mucosal adjuvants and delivery systems for protein-, DNA- and RNA-based vaccines. *M. Vajdy, I. Srivastava, J. Polo, J. Donnelly, D. O'Hagan, and M. Singh.* Immunol. Cell Biol. 82(6):617-627 (2004).

Mucosal vaccination offers several benefits over parenteral routes of vaccination. However, mucosal vaccines have to overcome several formidable barriers including food particles, enzymatic degradation, and low pH before reaching the target immune cells. Vaccination through mucosal membranes requires potent adjuvants to enhance immunogenicity, as well as a delivery system to protect and target the vaccine to the site of immune stimulation. This review is a summary of current approaches to mucosal vaccination. It focuses on adjuvants as immunopotentiators and vaccine delivery systems for mucosal vaccines based on protein, DNA or RNA. In this paper, adjuvants are defined as protein or oligonucleotides with immunopotentiating properties co-administered with pathogen antigens. Vaccine delivery systems are defined as chemical formulations that protect and deliver the vaccine to the site of administration. Although vaccines can be quite diverse in their composition, this review focuses on recombinant protein antigens, plasmid DNA, and alphavirus-based replicon RNA vaccines and delivery systems.

Selamectin is a potent substrate and inhibitor of human and canine P-glycoprotein. *J. Griffin, N. Fletcher, R. Clemence, S. Blanchflower, and D. J. Brayden.* J. Vet. Pharmacol. Ther. 28(3):257-265 (2005).

The transport of the antiparasitic agents ivermectin, selamectin and moxidectin was studied in human intestinal epithelial cell monolayers (Caco-2) and canine peripheral blood lymphocytes (PBL). Both models expressed the mdr1-coded 170 kDa ATP-binding cassette (ABC) transporter P-glycoprotein (P-gp). Fluxes of the P-gp substrate rhodamine-123 (Rh-123) across Caco-2 monolayers showed that ivermectin and selamectin acted as potent P-gp inhibitors with IC50 values of 0.1 micron. In contrast, moxidectin was a weaker P-gp inhibitor with an IC50 of 10 micron. The transport of radiolabelled ivermectin, selamectin and moxidectin through Caco-2 monolayers showed that ivermectin, selamectin and moxidectin were P-gp substrates with secretory/absorptive ratios of 7.5, 4.7 and 2.6, respectively. Secretory transport of [3H]-ivermectin and [3H]-selamectin was blocked by the P-gp inhibitor, verapamil. Ivermectin and selamectin inhibited the efflux of Rh-123 from PBL and the concentration of inhibition was similar to that of verapamil. In contrast, moxidectin did not have a significant effect on Rh-123 efflux from PBL. The data suggest that ivermectin and selamectin are potent P-gp substrates, while moxidectin is a weak one.

Mycobacterium avium subsp. paratuberculosis enters the small intestinal mucosa of goat kids in areas with and without Peyer's patches as demonstrated with the everted sleeve method. *O. G. Sigurdardottir, A. M. Bakke-McKellep, B. Djonne, and O. Evensen.* Comp. Immunol. Microbiol. Infect. Dis. 28(3):223-230 (2005).

The main lesions of paratuberculosis in ruminants are in the small intestine. Previous studies have shown that the bacterium enters the small intestine through M cells found in the follicle-associated epithelium lining the domes of the Peyer's patches. The everted sleeve method, devised for the in vitro study of intestinal absorption, was used in this study to investigate the uptake of Mycobacterium avium subsp. paratuberculosis in goat intestine. Everted small intestinal sleeves of goat kids, prepared from areas with and without Peyer's patches, were incubated for 60 min in 3H-labeled bacterial solution. The results of this study imply that the bacteria can enter the intestinal mucosa of the jejunum, both in areas with and without Peyer's patches. These findings indicate, therefore, that M. avium subsp. paratuberculosis bacteria not only enter through M cells but also through enterocytes. ■

Generation of Nanocapsules by Miniemulsion Processes

By Katharina Landfester
Department of Organic Chemistry III –
Macromolecular Chemistry and Organic Materials,
University of Ulm, Ulm, Germany

Nanocapsules are submicroscopic colloidal drug carrier systems composed of an oily or an aqueous core surrounded by a thin polymer membrane. The formulation and application of nanocapsules composed of a polymeric or an inorganic shell material and a solid or liquid, inorganic or organic core is of high interest for many release systems. Many different approaches are used to generate nanocapsules with the required properties, e.g., the interfacial polymerization of a monomer or the interfacial nanodeposition of a preformed polymer.[1] Also, liposomes and block copolymers[2] can be used for encapsulation, or layer-by-layer deposition of polyelectrolytes[3] can be applied.

With lipophilic and copolymer approaches, the units are not tightly bonded, which leads to unwanted leakage of the encapsulated material. For the other approaches, adsorption on the surface is required, and the formation is kinetically driven.

It is an old "dream" to take advantage of a potential thermodynamic control for the design of nanoparticles and the concept of "nanoreactors," where the essential ingredients for the formation of the nanoparticles are already in the beginning. For this purpose, the process of miniemulsion is well suited. For a typical oil-in-water miniemulsion, an oil, a hydrophobic agent (or several), an emulsifier, and water are homogenized by high shear (Figure 1) to obtain homogeneous and monodisperse droplets in the size range of 30 to 500nm. One of the tricks to obtain droplet stability is the suppression of the Ostwald ripening, which can be achieved by the addition of a hydrophobic agent that dissolves in the dispersed phase, but is insoluble in the continuous phase. This agent cannot diffuse from one droplet to the other and provides osmotic pressure inside the droplets that counteracts the Laplace pressure.

Because of the high stability of the droplets, each miniemulsion droplet can be treated as a small nanoreactor. This enables a whole set of new reactions that lead to nanoparticles or nanocapsules that were not accessible before. Some examples will be given in the following to show the wide applicability of this technology, e.g., in biomedicine, pharmaceutics, and cosmetics.

Different Kinds of Polymer Shell Materials

Miniemulsification can be performed to obtain different polymers for use as shell materials. In principle, hydrophilic monomers can be miniemulsified and polymerized in an organic phase and hydrophobic ones in water. The formation of the polymer can then be achieved by a subsequent polymerization process in each droplet. The type of polymerization is not limited to radical reactions; polyaddition, polycondensation, or enzymatic polymerization reactions also can be carried out in such miniemulsion droplets (Figure 2). Therefore, the miniemulsion process allows one to obtain polymer shell materials like biocompatible polyacrylates (also poly(butyl cyano-acrylate)), polystyrene, epoxies, polyurethanes, and polyesters.[4]

Generation of Encapsulated Inorganics

It is of course of high interest to combine inorganic material and polymeric particles to obtain nanocapsules. If the inorganic particles are dispersed in a monomer and if this dispersion undergoes a miniemulsification process, polymeric particles with

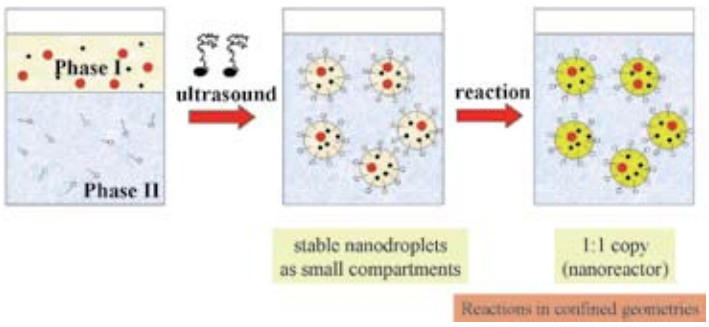

Figure 1. Principle of the miniemulsion process.

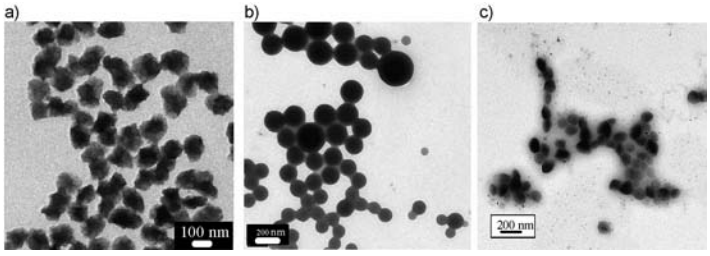

Figure 2. Different polymer nanoparticles obtained in the miniemulsion polymerization process: a) polyacrylonitrile nanoparticles obtained by radical polymerization; b) polyurethane nanoparticles obtained by polyaddition; c) polyester nanoparticles obtained by enzymatic polymerization.

fully encapsulated inorganic material are obtained. The polymeric shell protects the inorganic particle efficiently. It is possible to incorporate just one (large) inorganic particle per polymer particle, or one can incorporate many small particles, e. g., magnetite particles or gadolinium complexes, in each polymer particle (Figure 3).[5] The magnetic or gadolinium particles can be used for medical applications, e.g., for the detection of cells via magnetic resonance imaging (MRI) and the destruction of cells via magnetic fields.

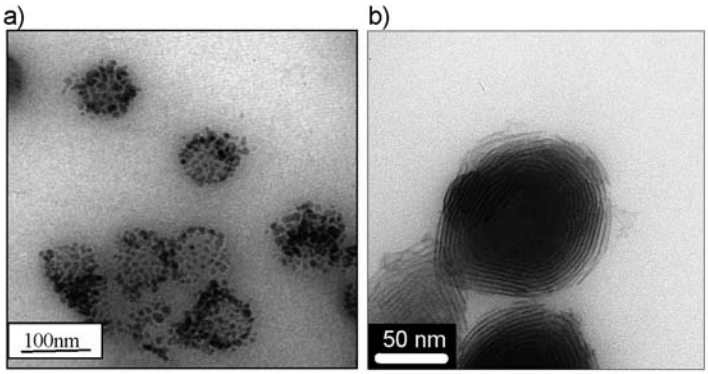

Figure 3. Incorporation of inorganic materials: a) magnetite particles; b) gadolinium complexes.

Direct Generation of Polymer Nanocapsules and Hollow Particles

It was also shown that the encapsulation process is not limited to solid materials; liquids that are insoluble in the polymeric shell material can be encapsulated to obtain nanocapsules. For the synthesis, a monomer and an oil are chosen that both are mixable in the monomeric state. But, as soon as polymerization occurs, a phase separation takes place. The differences in the hydrophilicities of the oil/polymer and polymer/water interfaces have to be designed so the formation of nanocapsules is favored (Figure 4a).[6] Encapsulation can also be achieved using the stabilizer chitosan, which can be transformed to a stable shell by a polyaddition reaction with diepoxides (Figure 4b).[7] An inorganic shell can be formed by adsorbing small silica plates on the surface that are linked by a condensation process (Figure 4c).[8] The wall either can be formed so no leakage occurs or it can be formed as a permeable shell that allows a controlled release, e.g. perfumes, medicines, etc.

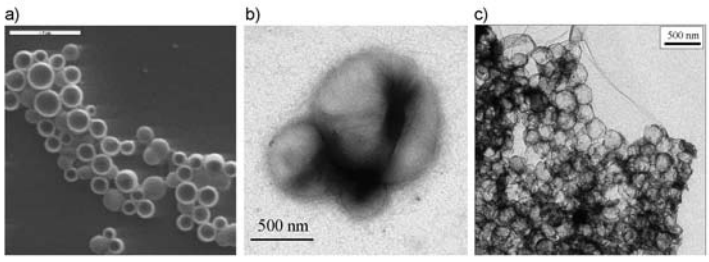

Figure 4. Formation of nanocapsules with a) polymer shells; b) biodegradable chitosan shells; and c) inorganic SiO_2 shells.

Functionalization of the Surfaces and Uptake in Cells

The pre-functionalization of the nanocapsules can be achieved easily by copolymerization with a functionalized monomer. Here, for example, carboxylic or amino containing surfaces with well-defined surface charges can be created. A final functionalization can be obtained by binding amino acids, peptides, or antibodies onto the pre-functionalized nanocapsules to achieve high selectivity for certain cells.

Conclusions

Dispersion of liquid matter in stable nanodroplets into a "miniemulsion" opens new possibilities for the synthesis of nanocapsules. Inorganic particles and liquids can be encapsulated by a subsequent second miniemulsion process into a polymer shell to avoid leakage. This protects the interior against external influences, but it may also protect the environment, e.g., the human body, against toxic materials. A permeable shell allows the controlled slow release of substances into the environment. The type of polymer can be changed in a wide range. The strength of miniemulsion is that polymeric nanocapsules can be produced that consist of polymers or polymer structures, including a functional surfaces that are not accessible by other types of heterophase polymerization.

In my opinion, the field of miniemulsion is still on the rise since there are many possibilities for the design of new nanocapsules for controlled release.

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SPOTLIGHT:

Controlled Therapeutics
Two Decades of Success

By Janet Halliday BSc, MRPharmS, PhD
Director of Research and Development

Controlled Therapeutics is an established drug delivery company that specialises in vaginal and buccal delivery using its proprietary hydrogel technology[1–3]. As a wholly owned subsidiary of parent company Cytokine PharmaSciences Inc. based in King of Prussia, Pennsylvania, the company has commercialised its polymer drug delivery technology over a period of 20 years. The delivery system is capable of providing controlled release of a range of drug molecules over periods up to 24 hr. The company already has one successful product on the market for labour induction, marketed around the world as Cervidil®/Propess®. A follow-up product for a similar indication is about to enter Phase 3 trials, and further products, including a treatment for xerostomia (dry mouth) and another for bacterial vaginosis, are in early clinical trials.

This is the story of a company with two decades of commercial success in drug delivery. The company was established in 1985 to exploit the hydrogel technology invented by Prof. Neil Graham of The University of Strathclyde in Glasgow, Scotland. Although now retired from academia Prof. Graham maintains his interest in nonpharmaceutical applications of hydrogel technology and continues his links with Controlled Therapeutics. In 1986 the company moved to its current location (See photograph 1). This 9,000-m^2 FDA- and MHRA-approved facility contains the development, manufacturing, clinical trial, regulatory, and distribution functions required of a globally operating organisation.

Cervidil®/Propess® is approved in over 40 countries, and the number of partners and distributors totals 25. The most significant of these is Forest Laboratories, who markets Cervidil® in the US, and Ferring, who markets Propess® in Europe. The hydrogel technology is based on a polyurethane polymer composed of polyethylene glycol, chain-extended with an isocyanate and cross-linked with a triol described in various patents and standard texts (Figure 1). By adjusting crystallinity and solvent uptake properties, the polymer controls the release of the drug over a period of many hours. In the case of dinoprostone, the drug used in the marketed product, this release extends to 12 hr[4] (Figure 2). and beyond[5] *in vivo*.

With a successful product on the market, the company has worked on extending its product portfolio. Phase 3 clinical trials are about to start on an improved product containing misoprostol with a similar indication to Cervidil®[6] (See photograph 2) The product is already partnered with

Photograph 1. CT facility in East Kilbride, Scotland.

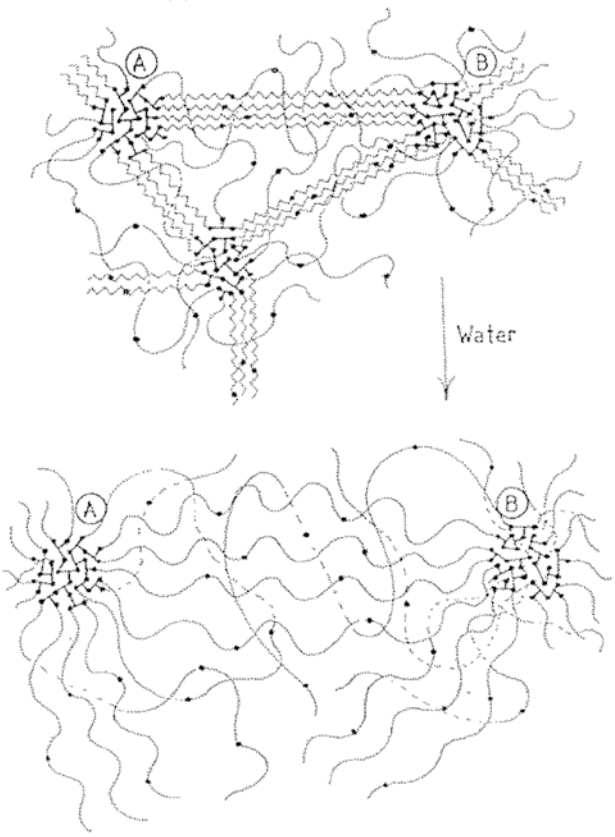


Figure 1. Structure of cross-linked hydrogel from Peppas[1].

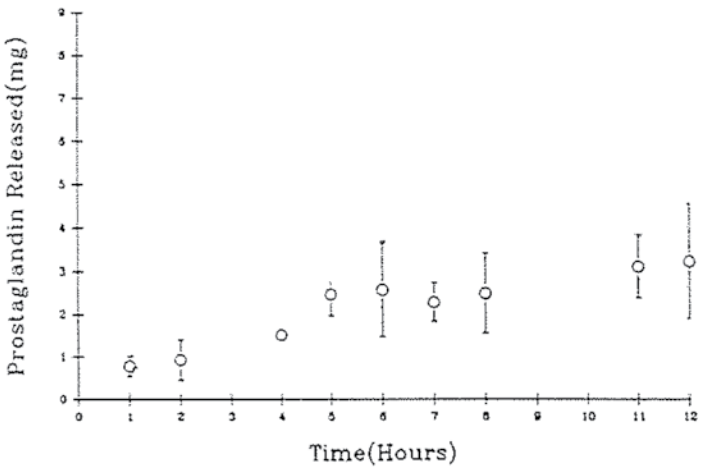
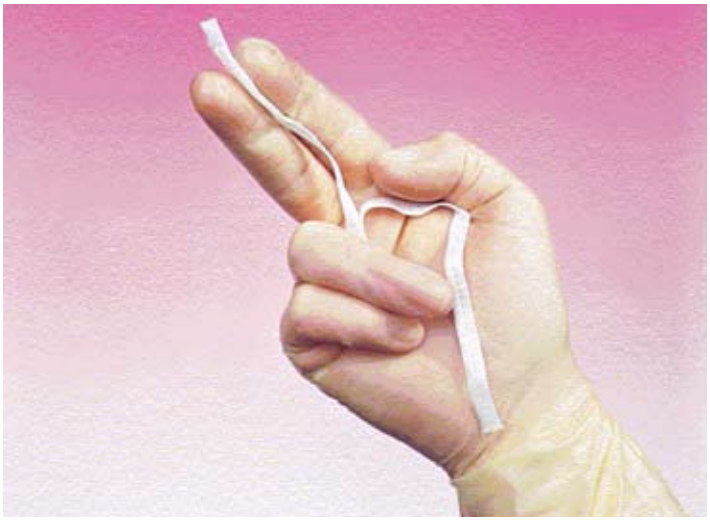


Figure 2. In vivo 12-hour release graph.



Photograph 2. Vaginal insert in its patented retrieval system.

Xanodyne™ in the US and Controlled Therapeutics is in discussions with potential European partner organisations. Another vaginal application being examined is the administration of clindamycin over an extended period of time. Early results show release of the drug for 18 hr. This gives longer exposure time to the active drug than is achieved by creams and pessaries, which melt and leak into the underwear.

The properties pf the hydrogel also make it suitable for use in buccal delivery. As with the vaginal formulations, the polymer is removed at the end of the dosage period, and drug delivery can be easily interrupted in the case of unwanted effect simply by removing the insert from the site of application. Phase 2 trials with Pilobuc™, a buccal insert containing pilocarpine, show a reduction in side effects compared with Salagen® oral tablets and an improvement in both oral and eye comfort accompanied by increased saliva flow.

With so many organisations involved in drug delivery suffering setbacks and failure to bring products to market, it is pleasing to know that this drug delivery technology applied in niche market areas has provided commercial success for the research and manufacturing personnel involved over the 20 years of the company's existence.

Controlled Therapeutics is seeking trading partners to market products from its development pipeline. The company is also interested in co-development projects to deliver drug molecules using its hydrogel system.

For further information contact janet.halliday@ctscotland.com. or vdelacruz@cytokinepharmasciences.com.

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Patent Watch

Consumer & Diversified Products

Jack Burger
Quest International

In the first half of 2005, 262 patents were found via the Derwent World Patent Index on encapsulation technologies for flavours and food additives and their applications in food products. As in previous years, the technologies ranged from simple spray-drying to convert liquids into easy-to-handle powders to the manufacturing of sophisticated multi-component delivery systems consisting of solid nanoparticles within a microparticle (US 2005/0112235 from Shefer and Shefer) for the delivery of active materials to biological surfaces.

Health Claims

Patents with health claims is a growing area. Cognis filed a patent on microcapsules made via coacervation containing an active agent (a "functional food") that strengthens the immune system by stimulation of the metabolism (EP 1,481,596). A food product comprising an encapsulated satiety agent for controlling body weight has been patented by Unilever (WO 2004/105520). Upon consumption of the food product, the satiety agent is predominantly released from the encapsulation material in the intestine. Weight loss is also claimed by Indfrag Ltd. (WO 2004/100682). National Starch filed a patent on the encapsulation of vitamins in liposomes, which are further encapsulated in a matrix comprising a starch derivative containing a hydrophobic group that has been degraded by at least one enzyme, cleaving the 1,4-linkages of the starch molecule to produce short chain saccharides (EP 1,484,055). The dry powder can be used as a dietary supplement. An ubiquinone-containing matrix composition, obtained by coating a carrier agent containing ubiquinone on the surface, with emulsifier containing at least alginic acid is claimed by Eisai Co Ltd. for preventing reduction in cardiac function (JP 2004/331597). All these patents show that industrial companies are increasingly focusing on health issues.

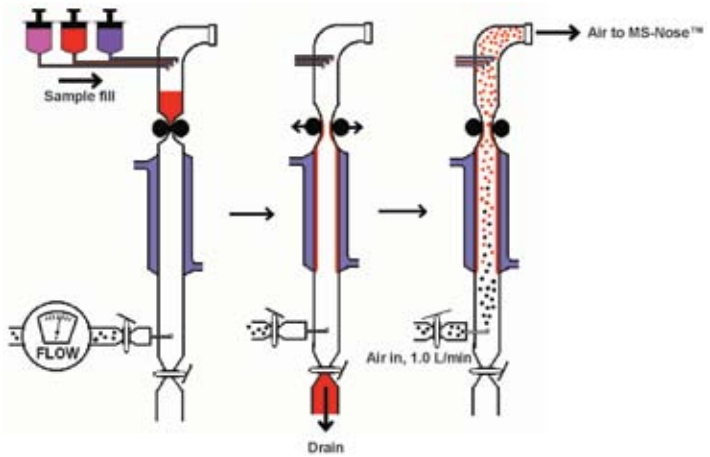
Nanoencapsulation

Nanoencapsulation scored high in the first half of 2005. Next to the patent described above, Shefer and Shefer filed another patent on nanoparticles. This second patent (US 2005/0065047) describes a controlled delivery system comprising solid positively charged nanospheres, each comprising a first active agent and formed of hydrophobic material consisting of wax and another material like PVP. The nanospheres are encapsulated in a moisture-sensitive microsphere formed of a moisture-sensitive matrix material that releases the nanospheres upon contact with moisture. In WO 2004/98555 (IFAC GmbH), a solid lipid nanoparticle dispersion is claimed for the targeted release of perfumes and/or flavours. The dispersion contains lipid-based nanoparticles that are stabilized by an emulsifier monolayer, one or more membrane layers, or other auxiliaries in which the perfume or flavour is incorporated into the nanoparticle and/or into the monolayer or the membrane layer. According to the patent, the claimed compositions require less flavour and provide targeted (e.g., delayed or "cascade-like") flavour release and protect the flavour against oxidation. The nature or duration of the release of the flavour depends on its distribution between the solid lipid and the membrane layers and on the melting point of the lipid phase.

In the area of materials for nanoencapsulation, the manufacturing of calcium phosphate nanoplatelets with a length of 250–800nm, useful as encapsulating agent for foods, is claimed by CNRS (FR 2,856,672). According to CNRS, the platelets have desirable gas diffusion barrier properties.

Encapsulation

Encapsulation goes hand-in-hand with research on release properties. In this area, ICI filed a patent on an artificial throat for



simulating and analyzing aroma release (EP 1,494,027). The instrument comprises a tube with an inlet and an outlet, a sample supply system at the upper portion of the tube, an inlet and an outlet closure, and a gas ventilation system for providing air flow through the tube (see figure). After pouring a liquid food product through the tube in one direction, air is passed through the tube in the opposite direction of the flow of the sample. The air leaving the tube is directly analyzed. The invention provides for fast and reliable testing for the aroma release properties of flavours. The details of the individual component release can be studied more exactly, making the design of more balanced, more palatable flavours much easier. ■

Journal of Controlled Release Highlights

By Morgan Leaming and Kinam Park

"Sticks and stones may break my bones, but words will never hurt me." This children's adage may ring true on the playground, but in the world of article publishing, it is an entirely different story. The words one chooses to classify a manuscript determine how easily a paper can be located. This in turn, plays a role in how many scientists read the article. By choosing the most specific words to define the work, the chance of a manuscript being located by a quick keyword search is increased. To prove how important five little words can be, the keywords from ten manuscripts published in 2005 were evaluated.

Everyone knows that keywords allow the topic of the work to be identified. But, did you know that the order of the words might affect the outcome of a search? To find one manuscript, it took eleven different sequences of a set of three keywords to produce the desired result in the PubMed database. With each triad, alternate articles were identified.

To allow scientists access to your article, it is best to select specific keywords to represent the work. More often than not, authors use generic keywords to fulfill this role. Inserting these types of words into a search engine oftentimes proves to be a futile attempt to locate the paper. In only 40% of the searches, the article was found by inputting all keywords into the database. In three of the manuscripts, however, the article could only be found with the omission of a keyword: protein stability, modified release, or energetics of phase transitions. With these simple keywords included, each entry returned no result. Keywords can also fail if they do not provide access to the desired manuscript. This problem was encountered when one of the selections could not be identified through its representative words. When different variations of the keywords were tried, other articles were displayed.

While there are other ways to search for an article, such as by title or author, it is rare that one searches for the document with this information. The complete title of a new paper is not often remembered. In one case, however, the article could only be found by using the title.

Because of the important role keywords play in the accessibility of an article, it is recommended that they be picked with care. Hopefully, through the use of specific words more scientists will be led to the published article. ■

Chapter News

Controlled Release Society Filial Argentina

The following short article was prepared by CRS FILIAL ARGENTINA (November 2005).

CRS Filial Argentina was founded almost 10 years ago, one of the pioneer local chapters, and since then it has been dedicated to promoting controlled release knowledge by organizing scientific meetings and inviting recognized professors and researchers. The aim of our Local Chapter consists is to encourage people from our country and other countries of South America to learn, teach, and perform research in the field of controlled release.

The last meeting, which was organized in 2004, was very successful. We had 89 attendants: 48 of them from the academia (33 undergraduate and graduate students), 36 from industry, and 5 from Argentine regulatory agency. We also had attendees from other South American countries, including 5 from Chile, 2 from Uruguay, and 1 from Paraguay.

Another successful activity was the organization of the II Technological Forum on Controlled Release Systems. The forum took place simultaneously with the symposium. This meeting was organized to encourage researchers from our country and other countries of South America to share their experiences in this area. We received abstracts from different faculties and universities in Argentina and Chile, such as engineering, chemical sciences, pharmaceutical, and biotechnological schools from Buenos Aires University, La Plata University, Córdoba University, Quilmes University, and the University of Chile. Twenty groups participated, discussing topics that varied from microencapsulation to vaccines, bioadhesive systems, liposomes, nanotechnology, ISCOMS, food additives encapsulation, etc.

In 2004 our Chapter also cooperated with the Pharmacy and Biochemistry National Academy in the organization of a roundtable discussion on Pharmaceutical Education with Prof. Dr. Alexander Florence, Prof. Dr. Paolo Colombo, and Prof. Dr. Regina Wikinski (Dean of the School of Pharmacy and Biochemistry, Buenos Aires University).

We are currently organizing our VIII International Symposium and III Technological Forum on Controlled Release Systems for October 2006 in collaboration with the Pharmaceutical Technology Department of the University of Córdoba. Prof. Dr. Ruggero Bettini, Associate Professor, School of Pharmacy, University of Parma, and Prof. Patrizia Chetoni, Department o f Pharmaceutical Sciences, University of Pisa, are the invited speakers. The main topics will be micro- and nanoparticles for drug delivery employing supercritical fluids and their application in pulmonary delivery and cell cultures and animal models to evaluate controlled release systems. To encourage people from different places in our country to work in the controlled release area, the meeting will take place in Córdoba (in the center of our country), where one of our most important and oldest universities is located: Universidad Nacional de Córdoba, which is part of an active research group in the pharmaceutical technology area.

Executive Committee of the CRS Filial Argentina
The current members of the Executive Committee of the CRS Filial Argentina are:

President: Dr. Silvia Giarcovich
Vice-President: Dr. Joaquina Faour
Scientific Secretary: Prof. Dr. Marcelo Nacucchio
Secretary: Dr. María Luz Cassará
Treasurer: Dr. Rodolfo Rubio García
Board of Advisors: Dr. Darío Carrara
Dr. Francisco Goyogana
Prof. Dr. Cosme de los Santos Carballido
Prof. Dr. Rubén Manzo
Dr. Eder Romero
Dr. Gabriel Porto
Dr. Betina Martínez ■

InTheNews

Targeted Drug Delivery

PRNewswire: ST. PAUL, Minn. – Nov. 30, 2005 – V-Kardia Incorporated announced that academic investigator, David Kaye, MD, PhD, of the Baker Heart Research Institute presented preclinical results on the successful use of the Company's new targeted delivery system (V-Focus™) for administering therapeutic genes directly to the heart. The results demonstrated the ability of the system to selectively deliver therapeutic levels of a gene to the heart, with minimal leakage into the systemic circulation, significantly restoring heart function in a large animal model of heart failure. These data were presented at the recent American Heart Association Scientific Sessions in Dallas, Texas.

Prof. Kaye, working with colleagues from Massachusetts General Hospital and Harvard University, presented data, which described the ability of the V-Focus™ System to allow targeted delivery of genes, molecules, and cells to the heart and potentially other organs and tissues. In the cardiac application, Prof. Kaye described how the V-Focus™ system was used to isolate the coronary circulation from the general circulation and effectively deliver gene therapy to a large animal model of heart failure. The system was introduced percutaneously and delivered the agent safely and efficiently. High, uniform levels of the test agent were found within the heart tissue, while little to no agent was found in the lungs, liver, or kidneys. The results confirmed that this delivery system can be used for the delivery of gene therapy to the severely failing heart, significantly restoring heart function.

Local Delivery of IL-2 and Adriamycin Has Synergistic Effects

NewsRx.com: Nov. 30, 2005 – Local delivery of ADR "via biodegradable polymers has been shown to improve survival in rats challenged intracranially with 9L gliosarcoma," oncologists in the United States explained. "Likewise, local delivery of interleukin-2 (IL-2) has been shown to extend survival in experimental brain tumor models," noted W. Hsu and colleagues at the University of Chicago, who "hypothesized that local delivery of ADR and IL-2 might act synergistically against experimental intracranial glioma."

In their study, "polyanhydride polymers (PCPP-SA) containing 5% ADR by weight were prepared using the mix-melt method," and "IL-2 polymer microspheres (IL-2 MS) were produced via the complex coacervation of gelatin and chondroitin sulfate in the presence of IL-2." "Both ADR and IL-2, when delivered locally, are effective monotherapeutic agents against experimental intracranial gliosarcoma," and the "combination ADR and IL-2 therapy is more effective than either agent alone," the researchers concluded.

Hsu and coauthors published their study in the *Journal of Neuro-Oncology* (Local delivery of interleukin-2 and adriamycin is synergistic in the treatment of experimental malignant glioma. J Neurooncol, 2005;74(2):135-140).

Capsulution Nanoscience AG—Further Fundamental Patent Grant Is Imminent

BERLIN, Germany – Nov. 28, 2005 – Following a recent notice from the European Patent Office, Berlin-based Capsulution Nanoscience AG can announce that a further fundamental patent grant for its innovative nano- and microencapsulation technology—known as the LBL-Technology®—is imminent. The patent, number EP 1064087, covers the manufacture of multifunctional nano- and micron-sized capsules. The tiny capsules can be filled with pharmaceutical drug compounds as well as with other active substances. On the basis of the LBL-Technology®, Capsulution develops advanced drug delivery systems, which bring drugs more safely and effectively to the right site of the body.

The LBL-Technology® represents a versatile encapsulation system. For the actual encapsulation, a wide range of FDA-approved polymers can be used. In addition, the capsules' surface can be functionalized to suit a targeted release in the human body. Broad field of applications: Capsulution's LBL-Technology® platform will soon be used for a wide range of applications. LBL-Solv® is a means of drug reformulation, where water insoluble active compounds are nanoencapsulated to increase their bioavailability. In addition, LBL-Intra® is an application specific to intracellular drug delivery. The capsules may also be applied to improve the function of drug-releasing implants, as well as to aid the development of nanodiagnostics.

Multivesicular Liposomes Are Useful for the Sustained Delivery of Breviscapine

NewsRx.com: Nov. 25, 2005 – According to recent research from the People's Republic of China published in the *International Journal of Pharmaceutics*, multivesicular liposomes (MVLs) are useful for the sustained delivery of breviscapine.

"Breviscapine, a well-known bioactive flavonoid ingredient extracted from the traditional Chinese medicine, has been extensively used in clinic to treat ischemic cerebrovascular and cardiovascular diseases in China. "In order to prolong the duration of the drug in the circulation, reduce the frequency of injection administration and subsequently afford patient compliance, MVL (namely DepoFoam) was utilized as a sustained-delivery system for breviscapine," wrote H. J. Zhong and colleagues of Shenyang Pharmaceutical University.

Zhong and colleagues published their study in the *International Journal of Pharmaceutics* (Multivesicular liposome formulation for the sustained delivery of breviscapine. Int J Pharm, 2005;301(1-2):15-24).

In the News continued on page 18

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Shin Nippon Biomedical Laboratories Subsidiaries, Tokai Pharmaceuticals To Collaborate in Nasal Drug Delivery Technology

JCN Newswire via COMTEX: TOKYO, Japan – Nov. 25, 2005 –Shin Nippon Biomedical Laboratories (SNBL) announced on November 24 that its two subsidiaries, Translational Research (TRL) and Bioactis (BA), have agreed with Tokai Pharmaceuticals (TP) to collaborate in the field of nasal drug delivery technology. The SNBL subsidiaries specialize in nasal drug delivery: Translational Research has expertise in drug delivery technologies designed for insulin, morphine, and antiemetics, while Bioactis has developed Fit-lizer, a proprietary medical device for delivering agents to the nose. Tokai Pharmaceuticals is a Massachusetts bioventure company that specializes in endocrine treatment and has Apple Tree Partners as a majority shareholder. Under this partnership, TRL and BA will license their technologies and device to TP. Consequently, TP will strive to develop a nasal drug for endocrine and metabolic diseases.

New Device Launched To Help Combat Bioterrorism

NewsRx.com: Nov. 21, 2005 – Antares Pharma, Inc. (AIS) unveiled its novel device platform for delivering antidotes to various biological threats and said that talks with military and other government officials to assess the use of its patented pre-packed mini-needle injectors were progressing as planned.

Peter Sadowski, director of the device group operations for Antares, said that military officials had approached Antares, and found its platforms "appear suitable for the delivery of many known antidotes to nerve gas and other biological threats, including atropine, pralidoxime chloride, morphine, and diazepam." Additionally, Sadowski said that preliminary tests had established the products as "durable and reliable enough to withstand the rigors required of a critical delivery system that needs to be highly dependable even in severely adverse conditions." He said that the officials were particularly impressed with the portability of the company's mini-needle devices, and with the low cost to manufacture.

According to Jack Stover, Antares' president and CEO, "To meet the challenge of bioterrorism, private industry is going to have to develop antidotes that can be manufactured in large quantities at a low cost, stored at room temperature for extended periods of time, and delivered, if necessary, by civilians who may lack formal medical training. As a world leader in drug delivery technology, Antares has responded to that challenge with a platform, and a series of potential products that we think address this very large and rapidly expanding market in a uniquely effective way."

Novel Microemulsion System Shows Promise for Transdermal Aceclofenac Delivery

NewsRx.com: Nov. 21, 2005 – A novel microemulsion system shows promise for transdermal delivery of the nonsteroidal anti-inflammatory drug aceclofenac. In a recent study from South Korea, an "ONW microemulsion system was developed to enhance the skin permeability of aceclofenac."

"Of the oils studied, Labrafil M 1944 CS was chosen as the oil phase of the microemulsion, as it showed a good solubilizing capacity," explained J. Lee and coauthors at Chung Ang University. "Pseudo-ternary phase diagrams were constructed to obtain the concentration range of oil, surfactant, Cremophor ELP, and co-surfactant, ethanol, for microemulsion formation." "Eight different formulations with various values of oil of 6–30%, water of 0–80%, and the mixture of surfactant and cosurfactant (at the ratio of 2) of 14–70%," the researchers noted. "The in vitro transdermal permeability of aceclofenac from the microemulsions was evaluated using Franz diffusion cells mounted with rat skin."

"The level of aceclofenac permeated was analyzed by HPLC and the droplet size of the microemulsions was characterized using a Zetasizer Nano-ZS," according to the study report. "Terpenes were added to the microemulsions at a level of 5%, and their effects on the skin permeation of aceclofenac were investigated." "The mean diameters of the microemulsions ranged between approximately 10–100 nm, and the skin permeability of the aceclofenac incorporated into the microemulsion systems was 5-fold higher than that of the ethanol vehicle," test results revealed. "Of the various terpenes added, limonene had the best enhancing ability."

These findings "indicate that the microemulsion system studied is a promising tool for the percutaneous delivery of aceclofenac," the investigators concluded.

Lee and colleagues published their study in the *Archives of Pharmacal Research* (Formulation of microemulsion systems for transdermal delivery of aceclofenac. Arch Pharm Res, 2005;28(9):1097-1102).

Dermisonics: Proprietary Ultrasonic Patch Uses Painless, Needle-Free Transdermal Drug Delivery Technology

Business Wire: WEST CONSHOHOCKEN, Pa. – Nov. 21, 2005 – Dermisonics, Inc. (OTCBB: DMSI)(FWB:FQC), a developer of painless, injection-free, ultrasonic transdermal drug-delivery patches and technologies with broad pharmaceutical and consumer applications announces its pain-free, needle-free transdermal drug delivery technologies; the key advantages of Dermisonics' proprietary delivery technology in development, called the U-Strip™. In particular, it may be applied to improved insulin delivery to benefit diabetics; the milestone clinical pilot trials on Dermisonics' insulin delivery system will occur in early 2006.

As part of its strategic business plan, Dermisonics is focused initially on commercializing the insulin delivery system, which potentially could benefit millions of diabetics worldwide. The Company believes it can further develop delivery capabilities for up to 175 other "large molecule" drugs based on its core technology and underlying licensing revenue model.

"Dermisonics' patented U-Strip™ system employs proprietary microelectronics and ultrasonic technologies with a drug-carrying patch to enable the painless

delivery of drugs through the skin's natural pores and hair follicles," Mr. Bruce K. Redding, Jr., VP of Licensing and VP of Corp. Strategy, said. "The U-Strip™ Insulin Patch alone could improve the lives of insulin-dependent diabetics, reaching 55 million diabetics, or nearly 30% of the total 185 million diabetic population worldwide, who endure painful needle injections to survive this disease."

Positive Preliminary Results Reported from Trial of inhaled Narcotic Analgesics

NewsRx.com: Nov. 21, 2005 – LAB International Inc. (LAB), a drug development company with subsidiaries developing therapies for the inhalation market and providing contract research services, announced positive preliminary results from an additional comparative phase I trial for Fentanyl Taifun. Taifun is the company's dry powder inhaler platform. Fentanyl belongs to the group of medicines called narcotic analgesics, which act in the central nervous system to relieve pain.

The study was conducted in 32 healthy volunteers to obtain additional pharmacokinetic data and examine dose proportionality using single doses of 100–800 µg of Fentanyl Taifun. The study also compared the pharmacokinetics of Fentanyl Taifun with Actiq 200 µg, the commercially available Fentanyl lozenge.

The study results indicate that the absorption of fentanyl after a single inhalation of 200 µg Fentanyl Taifun was very rapid with an average peak concentration of 935 pg/ml (geometric mean Cmax) reached in one minute (median Tmax). Comparatively for the 200 µg Actiq lozenge, the average peak concentration of 371 pg/ml (geometric mean Cmax) was reached one hour (median Tmax) after the start of administration of the lozenge. Subsequent to the rapid peak with the Fentanyl Taifun, the concentration dropped within the first 15 minutes to a plateau at the same level compared with the peak obtained with Actiq, the plateau lasted at least one hour after the administration. The profile observed indicates instantaneous alveolar (deep lung) absorption, followed by absorption from other parts of the airways, the throat, and to some extent the GI-tract.

Drug Delivery Developer Secures New Investors

NewsRx.com: Nov. 18, 2005 – MicroChips announced that Boston Scientific Corporation and Medtronic, Inc. have joined the company as strategic investors. Both of the companies have made equity investments in MicroChips. In addition, Medtronic is working with MicroChips on a joint product development program.

Boston Scientific and Medtronic join existing investors in the company, including Polaris Venture Partners, IDG Ventures, Care Capital, Intersouth Partners, and Boston University. In addition to the investment, Dr. James Barry, vice president, corporate research and development at Boston Scientific, and Dr. Stephen Oesterle, senior vice president, medicine and technology at Medtronic, have joined the company's board of directors. MicroChips is a developer of drug delivery and biosensing technologies.

Development Program Initiated for Intranasal Formulation of Rapid-Acting Insulin

NewsRx.com: Nov. 14, 2005 – Nastech Pharmaceutical Company Inc. (NSTK) announces the initiation of a development program for a proprietary intranasal formulation of rapid-acting insulin.

The formulation is being developed using Nastech's formulation science expertise and high-throughput human tissue culture screening process, a proprietary system for developing large molecule therapeutics that are delivered across the nasal mucosa. Nastech's human tissue culture studies have been demonstrated to have a high correlation with *in vivo* clinical drug bioavailability.

Proteins and peptides such as insulin are typically delivered by injection because they cannot be delivered orally without being degraded in the stomach. Nasal administration of insulin would represent a patient friendly alternative to the multiple daily injections required to control diabetes. A rapid-acting insulin delivered via the nasal route could offer diabetics the ability to adjust their insulin dose "on the fly" during a given meal.

Small-Volume Ultrasonic Nebulizer Shows Promise for Ophthalmic Drug Delivery

NewsRx.com: Nov. 11, 2005 – Ophthalmologists in Taiwan conducted a study "to determine the intraocular bioavailability of a novel embodiment for vitamin B12 delivered to the ocular surface by a piezo-electric ultrasonic nebulizer."

"The semisolid embodiment contained 0.02% (w/w) vitamin B12 in 1 g of ointment, which was immiscible and insoluble in 5 mL sterilized warm water," explained M. Kahn and coauthors at Taipei Medical University. "To confirm *in vitro* functionality, nebulized mist particles of the embodiment were collected and analyzed for vitamin B12 content." "The *in vivo* arm of the study was designed as randomization of 23 patients who were scheduled to undergo cataract surgery in hospital," the investigators added. "Fourteen patients were treated with nebulized vitamin B12, five patients had one drop of 0.02% vitamin B12 instilled in the conjunctival cul de sac, and four control patients had no medication."

"Twelve hours after the vitamin was delivered, the patients underwent the cataract procedure and a sample of aqueous humour was collected from each," according to the report. "High performance liquid chromatography was used for detection of vitamin B12 in all samples." "The *in vitro* analysis of mist particles showed increasing concentrations of vitamin B12," published data indicated. "In the patient tests, analysis of the aqueous humour samples showed that none of the controls or those receiving eye drops had detectable vitamin B12 in the aqueous humor." "However, 4 of 14 in the nebulizer group had vitamin B12 detected in the aqueous humor in the amount of 10-7 mol," test results revealed.

"The small-volume nebulizer system might provide another method of ophthalmic drug delivery," the researchers concluded.

Kahn and colleagues published their study in *Clinical and Experimental Ophthalmology* (Bioavailability of vitamin B-12 using a

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small-volume nebulizer ophthalmic drug delivery system. Clin Exp Ophthalmol, 2005;33(4):402-407).

Bacterial Substrate Coating Improves Colonic Targeting of Single-Unit Tablets

NewsRx.com: Nov. 11, 2005 – "The bacterial substrate amorphous amylose, in the form of a film coating, provides a means of delivering drugs to the colon," pharmacologists in England explained. "This coating has traditionally been applied to multi-unit systems, in part because of the small size and divided nature of this type of dosage form, which provides a large surface area for enzymatic attack and drug release," noted P. J. Wilson and colleagues at the University of London. They conducted a study "to explore the utility of the coating for colonic targeting of single unit tablet systems."

"Amylose was combined with the water-insoluble polymer ethylcellulose, which acts as a structuring agent, in different proportions to produce film coatings of various thicknesses for application to mesalazine (mesalamine or 5-aminosalicylic acid)-containing tablets," the scientists said. "Drug release from the coated products was assessed under pH dissolution conditions resembling the stomach and small intestine, and also in conditions simulating the colon using a batch culture fermenter inoculated with human fecal bacteria."

"The rate and extent of drug release was related to the ratio of amylose to ethylcellulose in the film and the thickness of the coating," test results showed. "Increasing the proportion of ethylcellulose in the film and/or the thickness of the coating depressed the rate of drug release in the conditions of the upper gastrointestinal tract." "Drug release from the coated products was accelerated in the fermentation environment of the colon," according to the study report. "This is attributed to bacterial digestion of the amylose component of the film coat producing pores for drug diffusion."

"This work indicates that amylose coated tablet formulations are promising vehicles for drug delivery to the colon," the researchers concluded.

Wilson and coauthors published their study in the *International Journal of Pharmaceutics* (Exploiting gastrointestinal bacteria to target drugs to the colon: An *in vitro* study using amylose coated tablets. Int J Pharm, 2005;300(1-2):89-94).

Polynitrosated Polyesters Show Potential For Topical Delivery of Nitric Oxide

NewsRx.com: Nov. 11, 2005 – According to recent research published in the journal *Biomacromolecules*, "New nitric oxide (NO) donor macromolecules, containing multiple S-nitrosothiol (S-NO) groups covalently attached to the polymer backbone, were prepared through the polycondensation reaction of diols (ethylene glycol and poly(ethylene glycol)) with mercaptosuccinic acid, followed by the S-nitrosation of the SH groups by a gaseous NO/O-2 mixture."

"The polynitrosated polyesters (PNPEs) obtained were characterized by IR spectroscopy and gel permeation chromatography and displayed biological activity as vasodilators, leading to local hyperaemia when applied topically on healthy skin," wrote A. B. Seabra and colleagues, University Estadual Campinas.

Seabra and colleagues published their study in *Biomacromolecules* (Polynitrosated polyesters: Preparation, characterization, and potential use for topical nitric oxide release. Biomacromolecules, 2005;6(5):2512-2520).

PAA and PTMC Blends Offer Controlled Clomipramine HCl and Buprenorphine HCl Release

NewsRx.com: Nov. 11, 2005 – Poly adipic anhydride and poly trimethylene carbonate blends offer controlled clomipramine HCL and buprenorphine HCL release. "Controlled drug-delivery technology is concerned with the systematic release of a pharmaceutical agent to maintain a therapeutic level of the drug in the body for modulated and/or prolonged periods of time. This may be achieved by incorporating the therapeutic agent into a degradable polymer vehicle, which releases the agent continuously as the matrix erodes," researchers in Iran report.

"In this study," wrote R. Dinarvand and colleagues, University of Teheran. "poly trimethylene carbonate (PTMC), an aliphatic polycarbonate, and poly adipic anhydride (PAA), an aliphatic polyanhydride, were synthesized via melt condensation and ring-opening polymerization of trimethylene carbonate and adipic acid, respectively. "The release of clomipramine HCl and buprenorphine HCl from discs prepared with the use of PTMC-PAA blends in phosphate buffer (pH 7.4) are also described. Clomipramine HCl and buprenorphine HCl were both used as hydrophilic drug models. Theoretical treatment of the data with the Peppas model revealed that release of clomipramine HCl (5%) in devices containing 70% PTMC or more followed a Fickian diffusion model. However, the releases of buprenorphine HCl (5%) in the same devices were anomalous."

"For devices containing 50% and more PAA, surface erosion may play a significant role in the release of both molecules," proposed the authors.

Dinarvand and colleagues published their study in the *Journal of Biomedical Materials Research Part a* (*In vitro* release of clomipramine HCL and buprenorphine HCL from poly adipic anhydride (PAA) and poly trimethylene carbonate (PTMC) blends. J Biomed Mater Res A, 2005;75A(1):185-191).

Company Picked To Develop Electrotechnology for Intelligent Drug Delivery Device

NewsRx.com: Nov. 10, 2005 – Micromuscle has been selected as an official provider of materials and technology for the E.U. financed IntelliDrug project. The aim of the project is to develop an intelligent drug delivery device based on microsystem technology. Micromuscle's part in the project will be to develop and supply electro-active polymer components that control the release of liquid medications.

The IntelliDrug project is developing an intra-oral device for controlled drug delivery. The device will provide new therapeutic opportunities for people suffering from chronic diseases and drug addiction. The IntelliDrug device is based on microsystem technology and will

incorporate functions enabling intelligent drug delivery, such as microsensors, microactuators, and control units. The approach is to place the device in the mouth inside a dental appliance resembling a natural tooth. The device will then make sure that the drug is correctly delivered according to the patient's needs.

Micromuscle's part in the project will be to develop and manufacture microactuators that control the release of liquid medications. While the overall IntelliDrug project coordination is in the hands of Assuta Medical Centers Ltd., Israel, this part of the project is led by the German research institute HSG-IMIT. Micromuscle's electro-active polymer (EAP) technology was selected for the project after an evaluation of several different technologies.

Lipophilic Counter-Ions Improve Benzydamine Membrane Diffusion

NewsRx.com: Nov. 7, 2005 – Lipophilic counter-ions improve benzydamine membrane diffusion and thus may improve transdermal drug delivery.

"Many topically applied drugs are ionized molecules that exhibit poor penetration across the lipid domains of the stratum corneum," pharmacologists in Australia explained. "Reduction of the charge on the molecule would be expected to enhance skin penetration." With this in mind, V. Sarveiya and colleagues at Curtin University of Technology conducted a study to characterize "the interaction of the non-steroidal anti-inflammatory drug benzydamine hydrochloride with suitable counter-ions including ibuprofen sodium."

"The influence of pH of the donor solution and hence degree of ionization on partitioning between n-octanol: buffer and the flux of benzydamine hydrochloride across polydimethyl siloxane (PDMS) membrane and human epidermis was determined," the scientists said. "The maximum flux was determined at pH 7.6 when the fraction unionized was 2.51%, rather than at pH 9 when the fraction unionized was 38.7%." "This suggests that at higher pH, although the permeability coefficient is increased, the decrease in solubility and therefore concentration of dissolved benzydamine in the medium results in a decrease in flux across the PDMS membrane," according to the report. "Ion-pair formation or interaction with each of the counter-ions was confirmed by NMR spectroscopy."

"Significant increases in log P and flux across PDMS membrane were determined for the ion-pairs (0.087, 12.54, 11.31, 0.121 microg/cm-2/h for benzydamine hydrochloride and ion-pairs with ibuprofen sodium, sodium benzoate and sodium octane sulfonate respectively)," published data indicated. "This study shows that it is possible to significantly enhance the flux of salts across a lipophilic membrane in the presence of counter-ions, resulting from intermolecular interaction and/or ion-pair formation," the researchers concluded.

Sarveiya and coauthors published their study in the *European Journal of Pharmaceutical Sciences* (Effect of lipophilic counter-ions on membrane diffusion of benzydamine. Eur J Pharm Sci, 2005;26(1):39-46).

Drug-Delivery Company Reports on Its Capability To Deliver Proton-Pump Inhibitors Transdermally

NewsRx.com: Nov. 4, 2005 – Dermatrends, Inc. announced that it has developed the capability to deliver proton-pump inhibitors (PPIs) transdermally via a patch and has demonstrated it can deliver these drugs with potentially increased effectiveness compared with oral dosage delivery of PPIs. PPIs are the most prevalent treatment method to treat gastroesophageal reflux disease (GERD), and they are available in oral form in both prescription and over-the-counter formats.

Gastric acid-pump inhibitor therapies constitute an estimated $12.8 billion global market. The PPI class represents the most prevalent treatment for GERD, a common problem that, if untreated, can cause severe damage to the esophagus. Dermatrends has completed extensive in vitro tests with multiple formulations using omeprazole, a common PPI, and has demonstrated effective permeation at therapeutic levels with many formulations. The tests included formulations that are equivalent to oral dosages with a patch size between 9–24 square cm. Dermatrends' proprietary hydroxide-releasing-agent enhancer system is combined with omeprazole to deliver the drug via a matrix patch, an ideal combination as the hydroxide provides the environment required for effective delivery, according to the company.

Novel Silica Gel-based Controlled Release Systems Designed

NewsRx.com: Nov. 4, 2005 – In a recent study from Japan, "silica gel was used as core particles to design a simple preparation for controlled delivery system with a high drug content."

"Drug loading was carried out by immersing the silica gel in a pre-heated drug solution or suspension," explained K. M. Ohta and coauthors working at Toray Industries Ltd. in Kanagawa. "HPLC, SEM, DSC, PXRD analysis and N2 adsorption studies evaluated the drug-loading process."

Silica gel "could adsorb great quantities of the drug, up to about 450 mg/g, by repetition of the loading process," test results revealed. "Evaluation of the drug-loading process indicates that drug deposition in the pores occurs during the loading process," and that "the drug-loading efficacy is strongly related to the drug solubility." "On the other hand, the dissolution test showed that the drug release could be controlled by polymer coating the drug-loaded silica gel," according to the report. "An HPMC undercoating effectively suppresses the drug release, as it smoothes the drug-loaded core surface and aids in the formation of a continuous Aquacoat coating film."

Ohta and colleagues published their study in the *European Journal of Pharmaceutical Sciences* (Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content. Eur J Pharm Sci, 2005;26(1):87-96).

U.S. Patent Approval Granted for Multiple Drug Dose Delivery Device

NewsRx.com: Nov. 4, 2005 – Intranasal Therapeutics, Inc. (ITI) announced that the U.S. Patent Office has approved a

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patent for a multiple unit dose delivery device to which ITI holds exclusive worldwide licensing rights.
The programmable delivery system, the product of a research relationship between ITI and the University of Kentucky, is suited for the nasal delivery of narcotics and controlled substances and for ensuring patient compliance. The device can deliver up to 12 individually packaged doses of medication, and it features an electronic lockout system to ensure that a drug is administered no more frequently than the prescription permits. In addition, since doses are packaged individually, dosing accuracy and precision is higher compared with multi-dose pumps.

Patent No. 6,948,492 for the programmable multi-dose intranasal drug delivery device was issued September 27, 2005, to the University of Kentucky Research Foundation in Lexington. The product's inventors are Daniel Wermeling, PharmD, a faculty member of the U.K. College of Pharmacy who also is ITI's chief scientific officer, as well as members of the U.K. College of Engineering. Under an agreement with U.K., ITI holds exclusive rights to market the multiple dose delivery device worldwide.

Liquid Filled Nanoparticles Proposed for Drug Delivery of Protein Therapeutics

NewsRx.com: Oct. 21, 2005 – Liquid filled nanoparticles proposed for drug delivery of protein therapeutics. "In the present study, an attempt was made to study the feasibility of nanoparticulate adsorbents in the presence of an absorption enhancer, as a drug delivery tool for the administration of erythropoietin (EPO) to the small intestine. Liquid filled nano-and micro-particles (LFNPS/LFMPS) were prepared using solid adsorbents such as porous silicon dioxide (Sylysia 550), carbon nanotubes (CNTs), carbon nanohorns, fullerene, charcoal and bamboo charcoal," scientists in Japan reported.

"Surfactants such as a saturated polyglycolysed C8-C18 glyceride (Gelucire 44/14), PEG-8 capryl/caprylic acid glycerides (Labrasol) and polyoxyethylene hydrogenated castor oil derivative (HCO-60) were used as an absorption enhancer at 50 mg/kg along with casein/lactoferrin as enzyme inhibitors," explained N. Venkatesan and colleagues at Kyoto Pharmaceutical University. "The absorption of EPO was studied by measuring serum EPO levels by an ELISA method after small intestinal administration of EPO-LFNPS preparation to rats at the EPO dose level of 100 IU/kg."

"Among the adsorbents studied, CNTs showed the highest serum EPO level of 62.7 ± 11.6 mIU/ml. In addition, with the use of casein, EPO absorption was improved, Cmax 143.1 ± 15.2 mIU/ml. Labrasol showed the highest absorption enhancing effect after intra-jejunum administration than Gelucire 44/14 and HCO-60, 25.6 ± 3.2 and 22.2 ± 3.6 mIU/ml, respectively. Jejunum was found to be the best absorption site for the absorption of EPO from LFNPS, discovered researchers."

"The use of CNTs as LFNPS," they concluded, "improved the bioavailability of EPO to 11.5% following intra-small intestinal administration."

Venkatesan and colleagues published their study in *Biomaterials* (Liquid filled nanoparticles as a drug delivery tool for protein therapeutics. Biomaterials, 2005;26(34):7154-7163).

European Authorities Recommend IONSYS Approval

NewsRx.com: Oct. 17, 2005 – European authorities recommended the first needle-free system for acute postoperative pain for approval this week, which allows patient-controlled delivery of fentanyl in post-operative pain control. Intravenous patient-controlled analgesia systems (IV PCA) are the current standard for post-operative pain management. They are used to administer medications for acute pain in the hospital environment. Normally, they consist of a programmable machine, a pole, and connective tubing, which are attached to the patient via an intravenous line into their arm.

The system is lightweight and approximately the size of a credit card that adheres to a patient's upper arm or chest. IONSYS, produced by the ALZA Corporation, a member of the Johnson & Johnson family of companies, aims to become a viable alternative to daily injections for patients. When applied to the skin on the upper arm or chest, the low-intensity electrical current delivers the medication directly through the skin and into the systemic circulation.
Patients control their analgesia by pushing a button, and the system immediately delivers a small dose of the short-acting analgesic fentanyl, a prescription pain medication.

Use of Cyclodextrins Improves Delivery of Hydrophobic Drugs from Hydrogels

NewsRx.com: Oct. 11, 2005 – "A simple and effective technique of improving delivery of hydrophobic drugs from swellable systems is presented," scientists in Ohio reported. "Conventional methods of drug loading in hydrogel systems are limited by the characteristics of the pharmacological agent."

"The approach we present uses complexants to modulate drug release. Crosslinked poly(ethylene glycol) (PEG) hydrogels were synthesized, characterized, and used for vascular applications," wrote D. Kanjickal and colleagues, University of Akron. "The release of cyclosporine (CyA) from PEG hydrogels is significantly altered by the sterilization techniques.

"It was hypothesized that the release of CyA from PEG hydrogels can be modulated by using complexants. A cyclodextrin-CyA complex solution was prepared and used for drug loading. The sterilized PEG hydrogels that were loaded using the cyclodextrin-CyA complex solution had favorable release characteristics compared with the release from PEG hydrogels that were loaded using the conventional technique." "Hence," the investigators concluded, "drug release from swellable systems can be tailored by the application of this strategy."

Kanjickal and colleagues published their study in the *Journal of Biomedical Materials Research Part a* (Improving delivery of hydrophobic drugs from hydrogels through cyclodextrins. J Biomed Mater Res A, 2005;74A(3):454-460).

Transdermal Iontophoretic Delivery of Vapreotide Characterized

NewsRx.com: Oct. 4, 2005 – The pharmacokinetics of vapreotide delivered through transdermal iontophoresis have been determined in a pig skin model. Pharmaceutical researchers in Switzerland conducted a study "to evaluate the feasibility of delivering vapreotide, a somatostatin analogue, by transdermal iontophoresis."

"In vitro experiments were conducted using dermatomed porcine ear skin and heat-separated epidermis," explained Y. B. Schuetz and coauthors at the University of Geneva. "In addition to quantifying vapreotide transport into and across the skin, the effect of peptide delivery on skin permselectivity was also measured." "The influence of (1) current density, (2) pre- and post-treatment of the skin, (3) competitive ions, and (4) inclusion of albumin in the receptor on vapreotide delivery was investigated," the scientists said. "Epidermis proved to be a better model than dermatomed skin for vapreotide transport studies."

"Despite the susceptibility of vapreotide to enzymatic degradation, a flux of 1.7 microg/cm_2 per hour was achieved after 7 h of constant current iontophoresis (0.15 mA/cm_2)," published data showed. "Post-iontophoretic extraction revealed that, depending on the experimental conditions, 80–300 microg of peptide were bound to the skin."

"Vapreotide was found to interact with the skin and displayed a current-dependent inhibition of electroosmosis. However, neither the pretreatment strategies to saturate the putative binding sites nor the post-treatment protocols to displace the bound peptide were effective," the investigators concluded. "Based on the observed transport rate of vapreotide across porcine epidermis and its clinical pharmacokinetics, therapeutic concentrations should be achievable using a 15-cm_2 patch."

Schuetz and colleagues published their study in *Pharmaceutical Research* (Transdermal iontophoretic delivery of vapreotide acetate across porcine skin in vitro. Pharm Res, 2005;22(8):1305-1312).

Team Develops Therapy with "Hitchhiking" Viruses as Cancer Drug Delivery System

NewsRx.com: Oct. 4, 2005 – A Mayo Clinic research team has devised a new virus-based gene therapy delivery system to help fight cancer. Researchers say their findings will help overcome hurdles that have hindered gene therapy cancer treatments. The Mayo research team, which includes a collaborator from the United Kingdom, describes its new approach in the September edition of *Nature Medicine*. The approach relies on "therapeutic hitchhikers"—particles derived from retroviruses (RNA-containing viruses that incorporate into the genomes of infected cells and then produce a therapeutic gene).

The viral particles attach to a specific kind of T cell in the immune system and "hitchhike" to the tumor because T cells home in on tumors naturally; T cells are the immune system's major line of defense against tumors. By hitching a ride on the T cells, the therapeutic particles can hit their tumor target while avoiding detection (and destruction) by the immune system. When the Mayo team experimented with the hitchhiking approach in mice using human and mouse cancer cells, they observed significant cure rates of metastatic—or spreading—tumors.

Dr. Vile emphasizes that the work is still experimental and not yet ready for use in human patients. But, if larger studies validate these findings, the therapeutic hitchhiker approach may be employed in clinical trials of new treatments.

The Mayo investigators have invented a simpler method for using modified viruses to transport therapeutic genes to tumors. They are the first to exploit traits of retroviruses during the infection process of a cell in which attachment to the cell can occur in a nonspecific way. This opens up new opportunities for using viruses therapeutically because this method of attachment allows researchers not only to target particular cells, but also to more easily gain entry into the cells—which they must do to deliver therapeutic genes to destroy tumors. The T cells also help kill tumors.

Using mice, the Mayo Clinic team showed that retrovirus particles could successfully attach to the surface of primary T cells and then safely hitchhike—be carried through the bodies of mice that had fully functioning immune systems and evade detection by the immune system—to reach tumors, the sites of T cell accumulation. They further showed that once it reached the tumor, the viral transporter successfully transferred a gene to both mouse and human tumor cells that then infected the cells. This proved that the concept works.

Microgel and Encapsulation Techniques for Proteins Developed

NewsRx.com: Oct. 3, 2005 – Researchers have developed new microgel and associated post-fabrication encapsulation techniques for proteins. According to recent research published in the *Journal of Controlled Release*, "A novel negatively thermo-sensitive and biodegradable microgel was prepared by combination of macromer synthesis and inverse suspension polymerization. A new post-fabrication encapsulation technique based upon this kind of intelligent microgel was developed. Model proteins (hemoglobin, bovine serum albumin and insulin) were encapsulated into the microgels at 4 degrees C and released *in vitro* at 37 degrees C."

"Relatively high loading levels and sustained release profiles demonstrate the feasibility of the encapsulation strategy," said Ying Zhang and colleagues at Fudan University. "Since the encapsulation of proteins was performed at low temperature and after the preparation of microgels, organic solvent and high temperature were completely avoided in drug encapsulation. FTIR, Raman, and circular dichroism measurements confirmed that the ordered structure of proteins was not destroyed during encapsulation and after release. Thus, the post-fabrication encapsulation technique in this paper is much unique and beneficial for controlled release of biomacromolecular drugs."

Zhang and associates published their study in the *Journal of Controlled Release* (A novel microgel and associated post-fabrication encapsulation technique of proteins. J Control Release, 2005;105(3):260-268).

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Clinical Study of Nasal Insulin Therapy in Alzheimer Disease Reported

NewsRx.com: Oct. 3, 2005 – Kurve Technology, Inc. a developer of nasal drug delivery devices and systems, will participate in a upcoming clinical study conducted by investigators at the Veterans Affairs Puget Sound Health Care System and the University of Washington.

As part of the study Kurve, will donate 10 ViaNase electronic atomizer devices customized to the study's requirements. The 21-day trial will study the effect of intranasal insulin delivery on the short-term memory of 30 patients with early stage Alzheimer disease. Previous studies conducted at the U.S. VA and the University of Washington have demonstrated that a single dose of intranasal insulin improved memory function for some patients with Alzheimer disease.

The blood-brain barrier that separates the brain interstitial fluid from the circulating blood provides an efficient barrier for the diffusion of most drugs from the blood to the brain and central nervous system (CNS). In recent years, interest has been expressed in the use of the nasal route to deliver drugs to the brain for treatment of common neurological diseases such as Alzheimer and Parkinson.

Effect of Electroporation on Iontophoresis-Induced Electroosmosis Clarified

NewsRx.com: Sep. 30, 2005 – In a recent study from Japan, the "effect of electroporation on the iontophoresis-produced electroosmosis across the skin was evaluated by measuring the permeability of hairless mouse skin to mannitol, a nonelectrolyte, in vitro."

"Immediately after electroporation by squared pulses (10 times/s) at 100, 150 or 200 V for 1 ms, anodal iontophoretic permeations were determined at 0.4 mA/cm2 for 4 h," explained S. Tokumoto and coauthors at Josai University. "The observed iontophoretic permeability of mannitol was higher with electroporation pretreatment than without pretreatment."

"The enhanced flux of mannitol induced by electroporation, however, was due to increased passive diffusion," the scientists wrote in the *Journal of Controlled Release*. "The contribution of convective or osmotic flow caused by anodal iontophoresis on skin permeation of mannitol was decreased by the pretreatment." "In addition, osmotic flow was decreased with an increase in the applied voltage for electroporation," test results revealed. "In contrast, mannitol flux during cathodal iontophoresis at 0.4 mA/cm2 after 150 or 200 V electroporation was higher than without electroporation as well as anodal iontophoresis, but cathodal iontophoretic flux after electroporation was lower than without iontophoresis."

"The neutral high-molecular compound dextran rhodamine B was also used as a second model," according to the report. "Anodal iontophoresis alone did not increase skin permeability of the compound. However, electroporation pretreatment before anodal iontophoresis enhanced the skin permeation of dextran rhodamine B, which was due to increased osmotic flow induced by this combination."

These findings "suggest that electroporation decreases the electroosmosis produced by iontophoresis, and that electroporation increases skin permeability to neutral low and high model compounds (mannitol and dextran rhodamine B) probably due to an enlarged permeation pathway. Thus, electroporation affects osmotic flow from the anode to cathode during iontophoresis," the researchers concluded. "Therefore, one has to pay attention to the change in electroosmosis produced by iontophoresis for the combined use of electroporation and iontophoresis to attain a high skin-penetration enhancing effect."

Tokumoto and colleagues published their study in the *Journal of Controlled Release* (Effect of electroporation on the electroosmosis across hairless mouse skin in vitro. J Control Release, 2005;105(3):296-304).

Low Drug Levels Found in Sailors Unresponsive to Scopolamine Patch

NewsRx.com: Sep. 30, 2005 – "Scopolamine is highly effective for the treatment of seasickness. Nevertheless, transdermal therapeutic system (TTS) scopolamine, despite high compliance on the part of persons treated by the drug, fails to provide protection against seasickness in 26–38% of patients," scientists in Israel explained.

"To the best of our knowledge, the correlation between scopolamine levels in plasma and its therapeutic effect under sailing conditions in the open sea is investigated for the first time in the present study," conducted by A. Gil and coauthors at the Israel Naval Medical Institute. "Subjects were 61 crewmembers of naval vessels treated by TTS scopolamine." "The therapeutic response at sea was documented by questionnaire. During a period ashore, a TTS scopolamine patch was applied in the same subjects," the collaborators noted. "Blood samples were taken and an adverse effects questionnaire completed 8 h after scopolamine patch application."

"Scopolamine levels were determined using an established radio-receptor assay procedure," according to the report. "To verify the reproducibility of these measurements, blood samples were taken twice from most subjects, on separate days after different patch applications." "Subjects were divided into 'responders,' who reported at least a moderate decrease in seasickness severity compared with their previous experience at sea without TTS scopolamine therapy, and 'non-responders,' who had only slight symptomatic relief or no relief at all," published data showed. "The mean scopolamine concentration in the plasma of the 37 responders (156.77 ± 77.03 pg/mL) was significantly higher than the mean level in the 24 nonresponders (97.03 ± 73.34 pg/mL; p = 0.005, simple t-test)."

"Attempts to increase scopolamine levels in plasma by increasing the drug dosage or improving transdermal absorption should be considered for the treatment of 'nonresponders,'" the researchers concluded.

Gil and colleagues published their study in *Aviation Space and Environmental Medicine* (Scopolamine patch to prevent seasickness: Clinical response vs. plasma concentration in sailors. Aviat Space Environ Med, 2005;76(8):766-770).

Australia's pSivida To Buy U.S. Drug Delivery Firm

Reuters: NEW YORK, N.Y. – Oct. 3, 2005 – Australian bio-nanotech company pSivida Ltd. (PSDV.O: Quote, Profile, Research) (PSD.AX: Quote, Profile, Research) said on Monday it had agreed to buy Control Delivery Systems Inc. (CDS), a privately owned U.S. drug delivery company, for about $104 million, as it expands into the U.S. market. pSivida said it would fund the deal, which is expected to close in the fourth quarter of 2005, by issuing about 16 million American Depositary Shares to CDS shareholders, representing about 40% of the combined company. pSivida said the transaction was part of its U.S. growth strategy, giving it an operating base in the Boston biotech hub and access to the U.S. scientific and investment communities.

Lollipop Painkiller Goes Sugar Free

NewsRx.com: Sep. 13, 2005 – Sugar is a useful excipient for use in medications because of its ability to mask bitter tastes, but its use in drugs intended for chronic use, or which reside in the mouth for an extended period, raises the risk of dental caries. One company seeking to circumnavigate this problem is Cephalon, which sells a lozenge-on-a-stick formulation of an opioid analgesic, called Actiq (fentanyl), intended for on-demand relief of breakthrough pain in patients suffering from cancer. Each lozenge of Actiq contains 2 grammes of sugar.

The risk of tooth decay with Actiq is a well recognised phenomenon which eventually required a change to the product's labelling to highlight the risks. Actiq is particularly prone to the problem because, like all opioids, it inhibits the production of saliva, causing dry mouth which exacerbates the risk of decay. Saliva inhibition is often encountered, particularly in elderly people with numerous drugs prescribed on a long-term continuous basis and in psychiatric patients. It remains a neglected clinical problem.

Cephalon has just received an approval letter from the US Food and Drug Administration (FDA) to market a new sugar-free formulation of Actiq which is bioequivalent to the currently available product, which will be marketed for the same indication as ACTIQ using the same name.

Cephalon recently merged with drug delivery specialist CIMA Laboratories, which has been developing a fast-melt formulation of fentanyl for controlling cancer pain.

Ultrasound-Assisted Atomizer Produces Drug-Loaded Microparticles

NewsRx.com: Sep. 9, 2005 – In the *Journal of Pharmaceutical Sciences*, scientists in Italy described "the application of a spray-congealing technique, using a new ultrasound-assisted atomizer, to prepare microparticles of diclofenac/Gelucire 50/13." In their study, C. Cavallari and coauthors at the University of Bologna sought to develop an enhanced-release formulation of diclofenac, "at 10% w/w drug-to-excipient ratio, without any employ of solvent."

"Scanning electron microscopy showed that it was possible to obtain almost spherically shaped and non-aggregated microparticles, with good encapsulation efficiency (90% in most size fraction) and with a prevalent particle size in the range 150–350 micron," according to the report. "Image analysis results by SEM and the high fractal dimension value suggested that most particles have actually an ellipsoidal shape and a rather rough contour."

"Hot stage microscopy, differential scanning calorimetry, and X-ray powder diffractometry analysis were carried out to evaluate the nature of the solid state and the thermal behavior of the microparticles thus prepared. The in vitro tests displayed a significant increase of the diclofenac dissolution rate from ultrasound microparticles, compared with pure drug and with drug/Gelucire 50/13 physical mixtures," the researchers concluded.

Cavallari and colleagues published their study in the *Journal of Pharmaceutical Sciences* (Thermal and fractal analysis of diclofenac/Gelucire 50/13 microparticles obtained by ultrasound-assisted atomization. J Pharm Sci, 2005;94(5):1124-34).

DelSite Seeks US OK for Nasal Delivery Polymer

NewsRx.com: Sep. 14, 2005 – DelSite Biotechnologies has filed a Drug Master File (DMF) with the US Food and Drug Administration for an excipient used for drug delivery, GelSite, used to formulate vaccines, proteins, and peptide drugs that are delivered across mucosal surfaces, such as the nasal cavity. Under US law a DMF, which can over an active pharmaceutical ingredient (API), inactive excipient, or even some elements of packaging, is filed with the FDA. Once reviewed and approved, the DMF can be cited by companies seeking to make use of the technology it describes. This does away with the need for each licensee of the technology to file a dossier covering its use in finished products. It can contain confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of a drug product.

DelSite's DMF is for the manufacturing of the GelSite polymer and its use in nasal and other mucosal applications. The company, a subsidiary of US firm Carrington Laboratories, is developing a nasal formulation for influenza vaccinations based on the delivery system, and is initially targeting the H5N1 bird flu strain that some fear could cause the next flu pandemic in humans.

The DMF will also cover use of the polymer in DelSite's GelVac delivery system for powdered drugs. Dry powder formulations delivered nasally provide several potential advantages, including better stability, room temperature storage, no need for preservatives, and no need for needles. Nasal immunization induces both systemic and mucosal immune responses. The GelSite polymer is manufactured by Sabila Industrial, a subsidiary of Carrington located in Costa Rica.

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In the News continued from page 25

Intrac Changes Name to Javelin Pharmaceuticals

Business Wire; NEW YORK, N.Y. – Sep. 7, 2005 – Today at its annual meeting of shareholders, Intrac, Inc. (OTC BB: ITRD) changed its name to Javelin Pharmaceuticals, Inc. as part of a reincorporation in the State of Delaware. Javelin common stock will trade under the symbol JVPH on the OTC Bulletin Board. The shareholders also elected the management slate of directors and ratified the Omnibus Stock Incentive Plan.

This renaming reflects the array of pain management opportunities that the Company plans to pursue as it expands beyond its present boundaries. The new name took effect after receiving shareholder approval and completing regulatory filings. Intrac's wholly owned subsidiary, Innovative Drug Delivery Systems, Inc., is now a wholly owned subsidiary of Javelin.

"This important strategic step reflects where we have come as a company since our inception in 1998 as well as our dedication to advancing targeted pain management," said Dr. Dan Carr, Chief Executive Officer of Javelin. "We have a very promising pipeline of pain relief products that rely upon well known compounds with proven safety and efficacy. By the close of 2005 we expect to file a marketing authorization application (MAA) for Dyloject™, an injectable form of diclofenac. Our Rylomine™ (intranasal morphine), and PMI-150 (intranasal ketamine) product candidates likewise target acute moderate-to-severe pain, including post-operative pain, orthopedic injury pain, trauma pain and burn pain."

Upon reincorporation, each outstanding share of Intrac common stock was automatically exchanged for one share of Javelin common stock. Javelin's stock transfer agent will be sending a Letter of Transmittal to all record holders to enable them to exchange their Intrac stock certificates for Javelin stock certificates.

In Vitro-in Vivo Correlation for Topical Preparations Evaluated

Medical Letter on the CDC & FDA via NewsEdge Corporation (NewsRx.com): Sep. 4, 2005 – According to a study from the United States, "In vitro-in vivo correlation (IV-IVC) is the relationship between an in vitro parameter (drug release or other rheological properties/measurement such as viscosity and spreadability) and an in vivo parameter (pharmacodynamic (PD) or dermato-pharmacokinetic (DPK) or other measurement). In a true sense of correlation, in vitro measurement should predict in vivo performance of the product."
"For topically applied preparations, one of the in vitro measurements is the drug release from the formulation and in vivo measurement is the drug concentration in the stratum corneum, DPK, or the PD measurements," said Vinod P. Shah at the U.S. Food and Drug Administration. "The in vitro release of the drug is the property of the dosage form and is a measure of product quality and 'sameness', especially after certain scale-up and post-approval changes after initial drug approval. To obtain an IV-IVC for a topically applied drug product is a difficult challenge."

"However, some success has been achieved in showing a relationship between the drug release and PD and/or DPK measurement," reported Shah. "Interestingly, one of the in vitro rheological properties was found to relate to the observed PD and DPK response for clobetasol dipropionate products. Different rheological properties of the two formulation products explained the difference in DPK results obtained by two laboratories for the same tretinoin gel products. In the scientific arena, it is difficult to obtain a classical IV-IVC even for orally administered products and is more so difficult for topically administered drug products."

Shah published the study in the *European Journal of Pharmaceutics and Biopharmaceutics* (IV-IVC for topically applied preparations—A critical evaluation. Eur J Pharm Biopharm, 2005;60(2):309-314).

MIV Therapeutics' Newest Technology Breakthrough Expands Family of Proprietary "Smart" Drug Delivery Systems; Advanced Coating Composite for Enhanced Medical Devices Complements Company's Proprietary HAp Technologies

Business Wire: VANCOUVER, British Columbia – Sep. 2, 2005 – MIV Therapeutics, Inc. (OTCBB:MIVT), a developer of next-generation biocompatible stent coatings and drug delivery technologies for the treatment of cardiovascular disease and therapeutic applications on implantable medical devices, announced today a milestone scientific achievement related to the development of a new drug delivery system with "smart" drug-eluting coating technologies.
This is the newest member of a family of "smart" and highly innovative proprietary coating technologies developed by MIVT, which could have important, innumerable therapeutic benefits for patients who require the controlled, gradual release of drugs from implanted medical devices.

MIVT's innovative technology of separating the drug molecules from the polymeric coating molecules in this coating is intended to eliminate the risk of undesired interactions between the two molecule types. In addition, this advanced technology is capable of controlling both the pace and amount of drugs delivered, further enhancing the device's potential therapeutic benefits and its potential for "multi-platform" applications.

Among the coating technology's most novel characteristics is its well-organized configuration of encapsulated nano-chambers that can provide more effective and gradual drug release. These chambers, each of which measures between a few nanometers and several micrometers in diameter, are contained in a multi-layered configuration in which the respective size and structure of the cells can be controlled to suit specific drug release requirements.

MIVT's proprietary coating technologies are increasingly being recognized for providing an exceptional degree of biocompatibility compared with traditional bare metal stents and less

advanced coating technologies on the market. The Company believes its arsenal of novel coating technologies also has the potential for medical applications, including dental, hip, and bone repair implants.

Researchers' Work Adds to Drug Delivery Body of Knowledge

NewsRx.com: Sep. 2, 2005 – Drug delivery data are the focus of recent research from Japan and Canada.

Study 1: Modified liposomes carry photosensitizer to tumor vessels. "For the improvement of therapeutic efficacy in photodynamic therapy (PDT) by using a photosensitizer, benzoporphyrin derivative monoacid ring A (BPD-MA), we previously prepared polyethylene glycol (PEG)-modified liposomes encapsulating BPD-MA (PEG-Lip BPD-MA)," according to scientists writing *in the Journal Biochimica Et Biophysica Acta – Biomembranes*. Ichikawa and colleagues published their study in *Biochimica Et Biophysica Acta – Biomembranes* (Antiangiogenic photodynamic therapy (PDT) by using long-circulating liposomes modified with peptide specific to angiogenic vessels. BBA-BIOMEMBRANES, 2005;1669(1):69-74).

Study 2: Polyethylene glycol shifts the dynamics of liposomal clearance. "Polyethylene glycol (PEG) is used widely in the pharmaceutical industry to improve the pharmacokinetics and reduce the immunogenicity of therapeutic and diagnostic agents. The incorporation of lipid-conjugated PEG into liposomal drug delivery systems greatly enhances the circulation times of liposomes by providing a protective, steric barrier against interactions with plasma proteins and cells," according to investigators in Canada. "Here we report that liposome compositions containing PEG-lipid derivatives and encapsulated antisense oligodeoxynucleotide (ODN) or plasmid DNA elicit a strong immune response that results in the rapid blood clearance of subsequent doses in mice," wrote S. C. Semple and colleagues, Inex Pharmaceuticals Corp. Semple and colleagues published their study in the *Journal of Pharmacology and Experimental Therapeutics* (Immunogenicity and rapid blood clearance of liposomes containing polyethylene glycol-lipid conjugates and nucleic acid. J Pharmacol Exp Ther, 2005;312(3):1020-1026).

Study 3: Liposomes targeting tumor vessel systems help eradicate cancerous cells. According to a study from Japan, "for the purpose of cancer anti-neovascular therapy (ANET), we previously isolated 5-mer peptide Ala-Pro-Arg-Pro-Gly (APRPG) that specifically bound to the tumor angiogenic site and observed that APRPG-modified liposomes encapsulating adriamycin were effective for the suppression of tumor in tumor-bearing mice." "Since polyethylene glycol (PEG) modification of liposomes endows them with a future of long circulation, we modified liposomes with PEG and APRPG-conjugated distearoylphosphatidylethanolamine (DSPE-PEG-APRPG) and examined the applicability of the liposomes on ANET," described N. Maeda and colleagues, University of Shizuoka, School of Pharmaceutical Sciences. Maeda and colleagues published their study in the *Journal of Controlled Release* (Anti-neovascular therapy by use of tumor neovasculature-targeted long-circulating liposome. J Control Release, 2004;100(1):41-52).

Aegis Therapeutics Licenses Drug Delivery Technology

NewsRx.com: Aug. 4, 2005 – Aegis Therapeutics announced it has entered into a licensing agreement for its patented Intravail drug delivery technology for applications in several pediatric therapeutics. Aegis' Intravail technology allows intranasal delivery of peptide and protein therapeutics that are otherwise deliverable only by injection and speeds the onset of action of small molecule drugs as well. Financial terms of the agreement were not disclosed.

Intravail has been developed to eliminate the need for injections for a number of key therapeutics important to pediatric medicine. Patient comfort, ease of use, and acceptance are key to long-term compliance and effective medical treatment in adults and children alike.

In June 2005, Aegis announced the expansion of its earlier licensing agreement with Intranasal Technologies to include beta-interferon and low molecular weight heparin and has since initiated feasibility studies on a number of additional peptide and protein therapeutics for several pharmaceutical clients.

Intravail advantages include the non-invasive delivery of protein and peptide drugs up to 30,000 Daltons with no alteration of chemical form or biological integrity. More importantly Aegis claims there is no irritation of sensitive nasal tissues, as well as the elimination of injections for greater patient convenience and compliance.

SurModics Collaborate To Develop Drug Delivery Stents

NewsRx.com: Aug. 2, 2005 – Surmodics has announced a collaborative partnership with CardioMind in which SurModics' Encore Drug Delivery Polymer Matrix will be used in conjunction with CardioMind's low-profile stent system for the treatment of coronary and peripheral artery disease. The partnership aims to develop drug-eluting stents, which overcome the problem where traditionally sized stent delivery technologies have difficulty reaching complex lesion applications.

Drug eluting stents have made it feasible for cardiologists to treat increasingly complex lesions in more difficult patient populations such as diabetics. As a result, there is a need for new technology that will allow the navigation and delivery of stents through patient vasculature. The partnership aims to bring a drug-eluting version of CardioMind's stent to market as quickly as possible, entering a market with close to 100% penetration in the US and 50–60% in the UK.

Surmodic's Encore Drug Delivery Polymer Matrix is a second-generation drug delivery alternative to the Bravo matrix that allows delivery of small hydrophobic drugs. The Encore coating shares the physical durability and the drug elution control available from the Bravo matrix, but allows use of a broader range of drugs. ■

Special Feature

Relative Values: Featuring Prof. Sandy Florence and Dr. Alastair Florence

By Yvonne Perrie

This is the first article in our new series where we interview family members who work within the general Pharmaceutics/ Controlled Release field. I would like to claim this idea as my own, but all credit goes to Dr. Hannah Batchelor (my colleague at Aston University) for spotting the potential of plagiarising a weekly article presented in the Sunday Times. Therefore, we should also at this stage acknowledge their indirect input.

For the first in this series we have managed to coerce two UK pharmacy academics, Prof. Alexander (Sandy) Florence and his son Dr. Alistair Florence—a fine combination indeed with many similarities, for instance both are sons of pharmacists, both are pharmacy graduates from the University of Strathclyde, Glasgow, and both are awardees of the British Pharmaceutical Conference Medal (admittedly 32 years apart).

Therefore, to see if we could perhaps get some secrets to their success they were both posed a series of questions. Their responses follow:

Q: ***What first got you interested in Pharmacy?***

Alastair: Having a grandfather and father who were pharmacists, I had a knowledge of both what the subject involved and the career possibilities. I always enjoyed chemistry and physics, and the multidisciplinary content of the pharmacy degree appealed to me more than a straight chemistry degree, for example.

Sandy: I was brought up in a pharmaceutical household, my father being a community pharmacist, so it was kind of natural that I became interested.

Q: ***Did your dad encourage you to go into Pharmacy?***

Alastair: Not directly. However, he has always been a staunch proponent of the profession, and looking back, it would have been nearly impossible not to have been influenced to some extent by his enthusiasm for the subject.

Sandy: I was interested also in architecture and in civil engineering, but not medicine as many of my contemporaries were, so I chose pharmacy with the encouragement of my dad, but not pressure.

Q: ***What was your PhD thesis about?***

Alastair: My PhD was in the area of single crystal neutron diffraction studies of organic molecular solids. This was something of a departure from traditional pharmaceutical subject areas; however, I was attracted by the power of crystallography as an analytical method. It is fascinating to actually "see" atoms in a crystal structure in three dimensions. I have been particularly fortunate that I have been able to continue to pursue these interests beyond my PhD.

Sandy: My PhD was on the synthesis and physicochemical properties of non-ionic surfactants. I worked with Peter Elworthy who had lectured to us as undergraduates on colloidal systems. I became interested in such systems and their possibilities, and when the time came to choose a PhD topic, it was non-ionic surfactants or neuromuscular blocking agents. Surfactants won.

Q: ***Have you looked at undertaking any collaborative projects together, or has your work been influenced by each others?***

Alastair: Simply put, no. Our research interests, whilst both founded in physical chemistry, are directed in quite distinct directions. I am concerned with periodic, crystalline structures, whereas my father has devoted his energy into studying largely soft matter and colloidal systems. There are common themes, such as molecular association; however, these systems are very different in terms of scale and the methods required to study them.

Sandy: We have not tried to work together. Alastair chose the solid state, and I have always worked with soft matter.

Q: ***Compared to your PhD studies, what one thing makes the biggest difference to studying for a PhD today?***

Alastair: A big improvement is the wide availability of electronic journals across all disciplines: getting access to information is a much more direct process than even 10 year ago.

Sandy: PhD students today can hardly believe that there were no word processors and electronic databases, and the one photo-copier we had printed onto photographic paper that soon faded. Much of the equipment was made in the workshops, even the light scatterer that we used. Today, the ability to sift the literature at your desk and to keep immaculate records of data is a help. But, perhaps there is just too much information around and that can be daunting. One might imagine that it has all been done already.

Q: ***What was your biggest experimental 'faux-pas' you made during your early research career?***

Alastair: This simply never happened…
[Editorial note: the CRS takes no responsibility for the accuracy of this statement!]

Sandy: Collectively, in the laboratory it was using a new instrument for several months which still had, unbeknown to us, some packaging material obscuring part of the optics.

Q: ***What is your biggest 'bug-bear' at the moment?***

Alastair: Academic administration: a common gripe amongst academics, but in recent years the volume of administration which accompanies teaching and research activities has ballooned. Email is also increasingly a cause of annoyance, with institutional, departmental, student, and group mailings come flooding in daily, making it increasingly difficult to discern the 'useful' from the 'useless.' There is nothing more demoralising than realising you have just spent a whole morning/afternoon dealing with nothing but email backlogs. Perhaps for my next PDP project I should focus on simply deleting everything that comes in (particularly those marked "high priority") and seeing if anything bad results.

Sandy: I hate the talk of people 'networking' at conferences, rather than enjoying listening to the science, and the fact that it seems essential now for every scientist to have his or her own company.

Q: ***Out of all the scientific discoveries/theories/advances made to date, which one (not of your own) would you have liked to have discovered/reported?***

Alastair: I greatly admire the early pioneers of crystallography from the early 20th century who made the key discoveries underpinning modern crystallography and, of course, did so without the aid of high-tech instrumentation, PCs, and sophisticated software. It is difficult to single out one discovery from the work of individuals, including Wilhelm Röntgen (discovery of X-rays), Max von Laue (discovery of diffraction of X-rays by crystals) and William and Laurence Bragg (pioneers of crystal structure analysis by X-ray diffraction), as they all made major contributions to our understanding of the world around us.

Sandy: That's difficult to answer. Every time there is an advance in the pharmaceutical sciences I wonder why I hadn't thought of it. But I know why!

Q: ***If you were to do it all again—would you?***

Alastair: Perhaps it is too early to say. Ask me again in 30 years, as by that time I'll be able to judge whether I got it right first time round.

Sandy: Would I do it again? The way my career developed almost accidentally and allowed me to be an administrator, research group leader, lecturer, and to be involved internationally, probably yes.

Q: ***If you were not to go into Pharmacy, what do you fancy doing instead?***

Alastair: Formula One drivers seem to have a pretty good lot: they get paid well, drive fast cars, and travel the world—though on second thought, perhaps they are not so different from your average school of pharmacy dean!

Sandy: It's maybe not too late to think of a new career. Now that I am about to retire I need to concentrate more on my oil painting, writing, and overcoming my limitations on the organ.

Q: ***Finally, if you were asked for one piece of advice for the future what would it be?***

Alastair: Never dissolve your crystals unless you know categorically what they are!

Sandy: My advice to younger scientists would be not to jump on research band wagons, because these soon get overpopulated, but to find an area which is poorly researched and to major on this. It is always useful to have a second line of research too as backup.

Sandy (left) and Alastair (right) dressed and ready for a usual day in the lab (actually at a recent celebration for Sandy's 65th birthday).

Dr. Alastair Florence is a senior lecturer in pharmaceutical sciences, at the University of Strathclyde. Alastair runs the Solid State Research Group (SSRG) in collaboration with Dr. Norman Shankland. The SSRG specialises in crystallographic investigations of pharmaceuticals, including all aspects of solid-state polymorphism, ranging from crystallisation, to phase transformations, through to crystal structure solution from single-crystal and powder X-ray diffraction data. The group works closely with the Data Analysis and Visualisation Group within the ISIS Facility at CLRC's Rutherford Appleton Laboratory. Alastair's recent funding sources include EPSRC funding for a low-T attachment for the Bruker D8 to develop advanced strategies for solving structures from XRPD data and UK Research Councils' Basic Technology project Control and Prediction of the Organic Solid-State. In 2004 Alastair was awarded the British Conference Science Medal Award in recognition of his outstanding independent research.

Prof. Sandy Florence is dean of The School of Pharmacy, University of London, a post held since 1989. Prior to this he was professor of pharmaceutics and head of the Department at the University of Strathclyde. His contribution to pharmacy is well recognised through numerous international pharmaceutical awards, including the Harrison Memorial Medal of the Royal Pharmaceutical Society of Great Britain (RPSGB; 1986), the Scheele Prize of the Swedish Academy of Sciences (1993), the Høst-Madsen Award from FIP (1997), the GlaxoSmithKline International Achievement Award (2001), and the Journal of Drug Targeting Life Time Research Award (2005). He is also a fellow of the RPSGB and was made a Commander of the British Empire by the Queen in 1994.

Acknowledgements
I would really like to extend my utmost thanks to both Sandy and Alistair for very kindly agreeing to participate in this article, and giving such good responses—obviously without them the article would have been somewhat short. I am also very grateful to Hannah for providing this idea and letting me use it in the CRS Newsletter. Finally, many thanks to the *Sunday Times* for their unwitting inspiration. ■

CReators
Controlled Release Education Articles on Technology Original Research and Science

From the Education Committee

Controlled Release Education, Research, and Industry in New Zealand

By Craig R. Bunt and Raid Alany
University of Auckland, New Zealand

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

Introduction
New Zealand is a relatively young country with a diverse population. Its relative isolation in the South Pacific has produced a quiet and independent people with a rich and fascinating history reflecting its Maori and European heritages. Both English and Maori are official languages and contribute to what is known as New Zealand English, which has its own sound but is often confused with Australian English.

Roughly the same size and shape as Great Britain, New Zealand is one of the world's least crowded countries, with a population of only 4 million. A temperate climate with relatively small seasonal variation has led to the popular myth that we spend Christmas at the seaside; however, this is a time of the year when the weather may disappoint. Sir Edmund Hillary conquering Mt. Everest, Sir Ernest Rutherford "splitting" the atom, frozen meat, the jet boat, and the bungee jump are probably our most famous achievements. New Zealanders are also responsible for the disposable syringe and tranquilizer gun (both by the same pharmacist), seismic "base" isolators, freezer vacuum pumps, stamp vending machines, and the electronic petrol pump—to name only a few!

New Zealand, in common with most countries, has its own specific unique health needs, particularly among the Maori and Pacific Island communities. Diet, cultural, and economic factors contribute to disproportionate incidences of obesity, mental illness, diabetes, asthma, infectious diseases, and some cancers compared with the greater population. The New Zealand government has encouraged an integrated approach to dealing with these health issues, with pharmacists contributing alongside doctors and nurses to provide target health services.

Education
There are eight universities in New Zealand; however, a bachelors degree in pharmacy is offered at only the Universities of Auckland and Otago located in Auckland and Dunedin, respectively (Figure 1). The BPharm degree consists of a four-

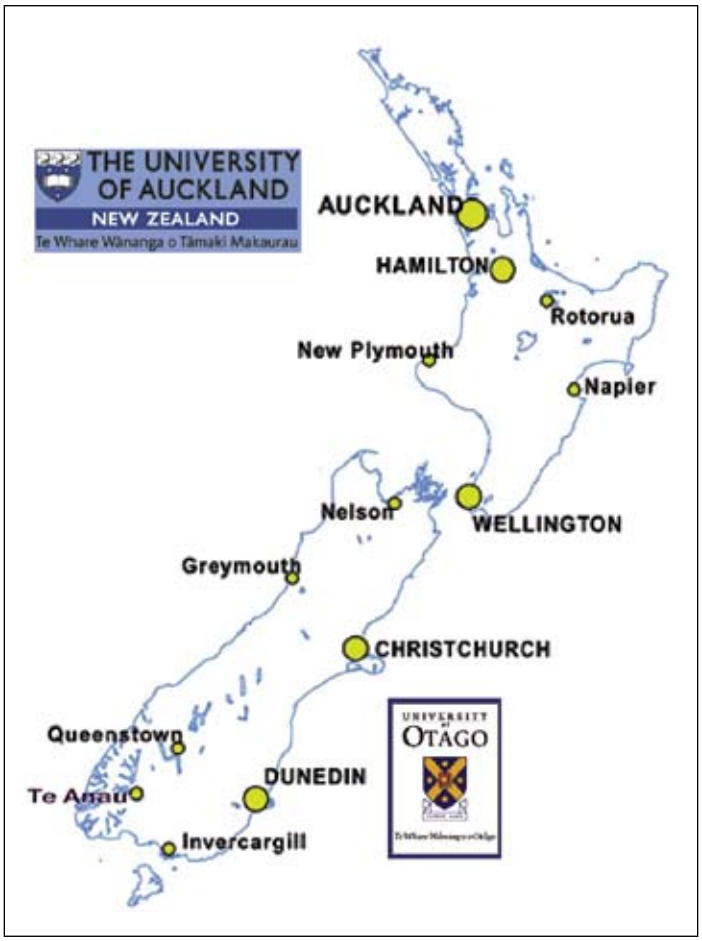

Figure 1. A map of the North and South Islands of New Zealand. The University of Auckland and University of Otago are located in the cities of Auckland and Dunedin, respectively.

year program for which there are approximately 800 students enrolled across all years, and approximately 200 students graduate in total on an annual basis. Both universities offer post-graduate masters of pharmacy and doctor of philosophy degrees, and The University of Auckland has recently introduced a DPharm (doctor of pharmacy) degree. There are approximately 30 fulltime PhD students at the Schools of Pharmacy in New Zealand.

Pharmaceutics is taught to the fourth year at both schools, with controlled release as part of broader pharmaceutics papers to the third year or selected as a research dissertation in the final year. The New Zealand Local Chapter of the CRS awards one student at each school a prize in pharmaceutics.

Table 1. *Summary of research in areas of controlled release at New Zealand universities*

Area of Interest	University Group
Targeted delivery Transdermal delivery Veterinary pharmaceuticals Delivery of oligonucleotides Ocular drug delivery Possum/marsupial pest control Conventional and novel drug delivery systems Nanotechnology	School of Pharmacy, The University of Auckland
Polymers and drug delivery	Polymers and Coating Science Sections, The University of Auckland
Post-ruminal drug delivery	Bioseparations and Biomolecular Engineering Research Group, The University of Waikato
Encapsulation and controlled release of bioactive and flavour ingredients	Riddet Centre, The University of Auckland and University of Massey and University of Otago
Polymer therapeutics	Department of Chemistry, University of Canterbury
Delivery of antibacterial agents to the oral cavity	Department of Microbiology and Immunology, University of Otago
Controlled release of food ingredients	Product Development Research Centre, Department of Food Science, University of Otago
Sustained release implants Topical delivery Colloidal drug delivery systems Lipid-based delivery systems Development of controlled release delivery systems for novel bioactives. Possum/marsupial pest control Transdermal delivery	School of Pharmacy, University of Otago

Following successful completion of the BPharm degree, registration as a pharmacist is with the Pharmacy Council, first as an intern pharmacist and then as a pharmacist after successful completion of the pre-registration training programme (40 weeks duration) administered by the Pharmaceutical Society of New Zealand Inc.

Employment rates for registered pharmacists are high (>90%), with demand expected to increase in coming years due to a likely increase in the number of pharmacists seeking registration in the United Kingdom.

University Controlled Release

Controlled release research activities at the post-graduate level at New Zealand universities are not restricted, of course, to the Schools of Pharmacy and reflect a broad range of interests (Table 1). These areas of research attract reasonable funding from both the government and private industry.

TABLE 1

New Zealand universities are quite well funded in terms of equipment compared with the private sector; however, as with tertiary institutes elsewhere in the world there continues to be a differential in terms of remuneration rates for staff between universities and the private sector. This, in part, has contributed to recruitment problems for New Zealand universities attempting to attract and retain appropriately qualified and experienced staff to teach programs in pharmaceutics.

There would appear to be little problem in identifying and attracting potential post-graduate students. However, foreign students, apart from Australian, German, and French students who pay domestic fees to study in New Zealand, must pay full fees or apply for a fee waiver. University graduates with pharmaceutical or analytical skills are in demand and easily recruited by the local pharmaceutical industry; however, many companies are experiencing recruitment problems as there is a shortage of skilled labour.

Industry Controlled Release

The pharmaceutical industry in New Zealand consists of large international innovator companies that maintain a distribution capacity and manufacture offshore and locally owned generic manufacturers. The veterinary pharmaceutical industry undertakes more local manufacturing compared with the human pharmaceutical industry. Eighty percent of government research funding goes directly to Crown Research Institutes, which have provided significant research inputs to the local pharmaceutical industry and, in some instances, have independently commercialized their intellectual property.

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From the Education Committee continued from page 31

There are a number of human and veterinary drug delivery pharmaceutical companies in New Zealand (Table 2), and the veterinary pharmaceutical industry has embraced controlled release technologies. New Zealand veterinary pharmaceutical companies have been quite successful at developing controlled release products, e.g., injectable microcapsules, gastro retentive boli, patch-less transdermals, and intravaginal inserts. Initially targeted at unique New Zealand needs, this research has since resulted in a number of world firsts and innovative products.

Current Initiatives and Needs

The Otago School of Pharmacy Formulation and Delivery of Bioactives Research Theme has been recognized by the University of Otago as a centre of research excellence. This theme brings together people with an interest in controlled release from across a variety of disciplines, including the University of Otago and other New Zealand universities, Crown Research Institutes, and industry. This theme has facilitated the annual Formulation and Delivery of Bioactives conference, which will hold its 8th meeting in February 2006, again in partnership with the New Zealand Local Chapter of the CRS. The success of this conference may be measured in many ways; for example, the regular attendance of 100 or more delegates and the establishment of the New Zealand Local Chapter of the CRS.

The New Zealand Local Chapter of the CRS has played a very active role in controlled release education in New Zealand (http://www.controlledrelease.org/chapters/newzealand/). In 2003 a two-day Controlled Release Products—Development and Regulatory Issues workshop was held. In 2004 two PhD students were awarded scholarships to attend the annual meeting of the CRS in Hawaii, and in 2005, two more PhD students were afforded the opportunity to attend the annual CRS meeting in Miami.

Table 2. *Summary of research in areas of controlled release at New Zealand pharmaceutical companies or Crown Research Institutes*

Area of Interest	Company or Crown Research Institute
Electronically controlled drug delivery inserts	Advanced Animal Technology
Ruminal boli Parenteral microparticles	AgResearch*
Pour-ons	Ancare
Delivery of natural pesticide compounds	BioDiscovery
Vitamin B12 implants	Bomac
Extended release	Douglas Pharmaceuticals
Biopolymer encapsulation of Bacteria-based products	EnCoate
Ruminal boli Delivery of natural pesticide compounds	HortResearch*
Ruminal boli Implants and inserts	InterAg
Encapsulation of viable mammalian cells for implantation	Living cell technologies
Microencapsulation of vitamin B12 Long active intramammary infusions	Stockguard

TABLE 2

Various formulation and drug delivery groups actively engaged in areas of controlled release research would benefit from increased contact and communication. The New Zealand Local Chapter of the CRS and Formulation and Delivery of Bioactives are pleased to help to facilitate this and intend to maintain and ideally increase such activities in the future.

Concluding Remarks

For a small country such as New Zealand, the attention directed toward controlled release interests may appear out of proportion. However, this situation is a reflection of New Zealand's emerging innovative technology industries and the strong research base supported by Crown Research Institutes, universities, and industry. Government targeted funding has encouraged growth of the research base at national and international levels, and many New Zealand scientists have ongoing collaborations with colleagues in the United States, Europe, Australia, and South Africa. ■

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who…what…where…when

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May 13-16, 2006
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33rd Annual Meeting of the Controlled Release Society

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http://tissue.rice.edu

4th International Nanomedicine and Drug Delivery Symposium

October 8-10, 2006
Embassy Suites, Old Market
Omaha, Nebraska, USA
http://cddn.unmc.edu; http://nanomedicine.unmc.edu

Pharmaceutical Sciences World Congress

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

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