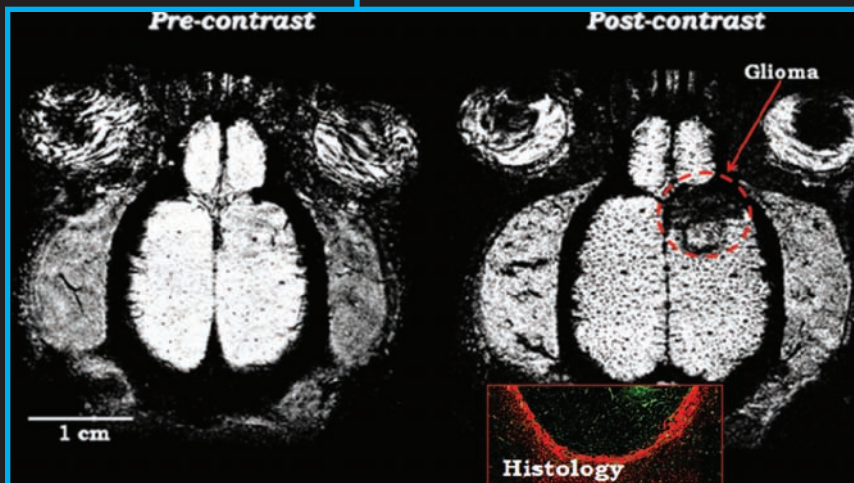
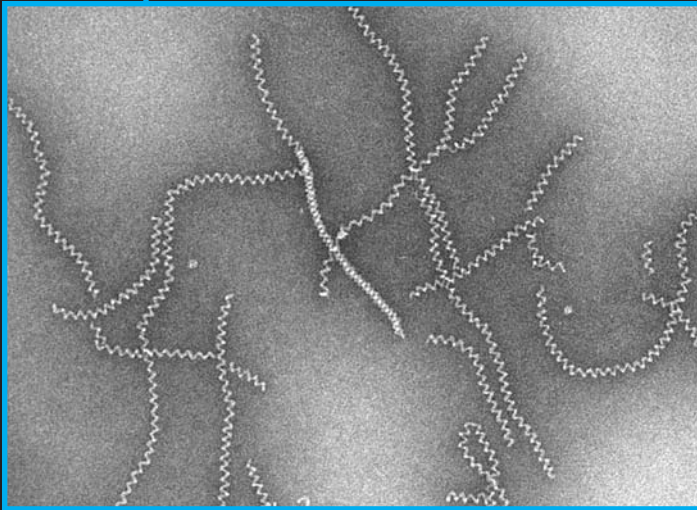


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NEWSLETTER



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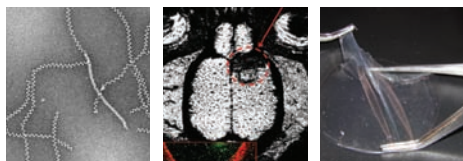
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FROM THE *Editors*

*By Bozena B. Michniak-Kohn, Ph.D.
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*Bozena B.
Michniak-Kohn*

Happy New Year to all our readers!! It seems as though it was just a couple of weeks ago that we were planning all our New Year's resolutions, and yet, Spring is around the corner (even if we still see some snow outside...I am in New Jersey) and soon we will be making plans for our 35th Annual Meeting & Exposition in New York.

In this issue you will read about PEGylated liposomes that encapsulate gadolinium-DTPA (magnetic resonance agent), with and without doxorubicin (chemotherapeutic), which were non-invasively tracked to brain tumors in a glioma rat model. A group from Brazil reports on the success of using papain incorporated in polymer membranes that were tested *in vitro* for their ability to release papain over a 12-hour period. The work has been performed *in vitro*, but potential applications for such devices would include wound treatments.

The first of three articles from the Vet Group discusses veterinary product development and the use of data generated on product performance. There is also a discussion of the risks and benefits of nanotechnology in drug delivery and medicine from speakers at the BPC 2007 conference, while Patent Watch and In the News round off your reading for this first issue of 2008.

I am sure you will be excited to know that we are redesigning the *CRS Newsletter* this year to enhance your enjoyment of the issues, so please be on the lookout for the new look of the *CRS Newsletter*!!!

We would also like to encourage more participation by our CRS members in submission of articles, reports, and news for publication. We would like to target in particular our younger scientists, students, post-docs and junior scientists in industry and academia to let us know about themselves. If you are part of an active CRS student chapter—let us all know what wonderful things you are doing and who may have spoken at your meetings! If you have received a major honor, such as an outstanding publications award—let us know and perhaps we can also get an article from you about the science you spent so many years on in the laboratory.

May we all have a wonderful 2008 and see each other in the Big Apple in July! ■



Susan Cady
CRS President

From the President

By Susan Cady
*Intervet Inc., a Part of Schering-Plough Corp.,
Yardley, PA, U.S.A.*

Happy New Year to all of you from the CRS Board of Directors! May we have a prosperous, successful, and enjoyable CRS year together. Our member volunteers are off to a great start in the new year, and I'd like to take a moment to highlight some of their activities and the value they are bringing to our Society.

Each year CRS provides a forum for our members to report on and share the latest advances in controlled release through the CRS Annual Meeting & Exhibition. This is a very busy time of year for many of our committee volunteers as they work through the process of finalizing the annual meeting program. More than 950 abstracts were submitted for the upcoming CRS Annual Meeting & Exhibition in New York City and are going through the review process. The Program Committee, under the capable leadership of CRS Scientific Secretary Ijeoma Uchegbu, is putting together an outstanding program. We can look forward to a scientifically stimulating program July 12–16 in NYC. Reduced meeting registration fees is one of your membership benefits. To take full advantage of this benefit, register for the meeting before May 1 to receive the lowest registration rate.

CRS also recognizes the significant achievements of our members through the CRS awards program. The CRS Award Committees, with the guidance of Vice President Diane Burgess, are currently reviewing the nominations for various CRS Awards. A few years ago, the CRS Board made a commitment to streamline the awards program, recognizing that these awards are important to our membership. The Board wanted it understood that each year these awards would be given to recognize our scientists and their achievements, whether there was a sponsor or not. We are very grateful to our present and past award sponsors and hope that we continue to enjoy fruitful collaborations with them long into the future. If you take a look at the Awards page on the CRS website, you will see that the Board has refocused the program to its original intent, which is to maintain an annual awards program that highlights the achievements of our members with prestigious awards. While it is too late to nominate a colleague for a 2008 award, you may know of someone who should be nominated for an award. If so, please consider getting the nomination documentation together and submitting it for a 2009 award.

I look forward to meeting the next Founder's, Industrial, and Young Investigator Awardees at the NYC meeting. These distinguished CRS members will be introduced and receive their recognition during the closing banquet, which will be held at the NYC Hilton. Watch the website for further details.

CRS is also exploring ways to support its members through the newly created CRS Foundation. Past President Randy Mrsny is working diligently on the new CRS Foundation, the mission of which is to provide a durable source of financial support for the advancement of educational and organizational activities that enrich and extend the research and development of CRS-associated technologies. Examples of such activities include set up and support of fellowships, lectures, and awards honoring individuals who have made notable advances in the areas of CRS related to bioactive delivery technologies.

As a tribute to Joe Robinson, the CRS Foundation has targeted the Joseph R. Robinson Postdoctoral Fellowship as the first prestigious scholarship offering of the coming year. Past President Kinam Park is heading the selection committee. The intent is to raise \$60,000 by June 2008 for this fellowship. Thank you to those of you who have already contributed! If you haven't, please consider making a donation to support this special educational platform. For more details, please contact CRS headquarters and our staff will be happy to assist you.

In closing, the future of CRS depends on its members. Please vote in the upcoming election and play a part in the future of the Society. As a CRS member, each year your vote for vice president supports a person who will serve the Society for the next four years. You will also be voting for members of the Board of Scientific Advisors, who will serve for a three-year term. Every member vote really does count. These people will be leading your Society into the future, so make sure your voice is heard!

Susan M Cady
Susan Cady ■

Scientifically Speaking

Novel Nanocarriers for Patient-Specific Brain Tumor Therapy

By Efstathios Karathanasis, Agarwal Agarwal, Kathleen McNeeley, Fuqiang Zhao, Vijal Patel, and Xiaoping Hu
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Introduction

Currently, intracranial tumors, especially gliomas of the brain, are extremely invasive and have very poor outcomes. The mean survival time after diagnosis of glioblastoma multiforme is approximately 9 months. Due to its invasive nature, complete surgical resection of gliomas is a rarity, and systemic chemotherapy is a necessary therapeutic option. The success of chemotherapeutic agent therapy for intracranial tumors is critically dependent on the access that these agents have to tumors via the so-called “leaky vasculature” across the blood brain barrier. However, no tools currently exist to rationally determine whether tumor blood vessels are amenable to nanocarrier-mediated therapy in an individualized, patient-specific manner. Such a determination would no doubt be of great benefit for the planning and assessment of multiple chemotherapeutic strategies, including one proposed in this study. For instance, non-invasive tumor vessel angiography and tumor vessel leakiness would enable the assessment of the probability of success of chemotherapeutic agents and would also enable determination of the optimal times for chemotherapy administration.

To address the need to “interrogate” tumor status and non-invasively track chemotherapy, we have developed a novel nanoscale, long-circulating carrier capable of carrying contrast agents for contrast enhanced MR angiography (CE-MRA), as well as chemotherapeutics. Conventional MR contrast agents, such as gadolinium (Gd) chelates, restrict the time window for image acquisition due to their rapid elimination from blood and their rapid diffusion into the extravascular space, which results in a low signal to noise ratio and prevents their use in CE-MRA. Our nanoscale particle consists of a PEGylated liposome, encapsulating Gd-DTPA (MR agent), and/or doxorubicin (chemotherapeutic). The long circulation this allows enhances the signal for long scanning times, resulting in high-resolution MR images of rat vasculature (1,2). Besides the longer scanning times, a major advantage of using long-circulating liposomes for tumor imaging results from the observation that carriers of relatively small size (≈ 100 nm) can preferentially accumulate in solid tumors by passive convective transport through leaky endothelium, because the abnormal tumor vascular is discontinuous with pores varying from 100 to 780 nm in size (3,4). Due to longer blood residence time, repeated passage

through the microvascular bed results in a much higher concentration of nanocarriers within the tumor compared with the parent small contrast agent. In addition to this passive accumulation, liposomes can be tagged with targeting molecules to induce targeting specificity to receptors overexpressed by brain cancer cells (5). In this work, we have validated the utility of our nanoscale contrast agent for non-invasive determination of tumor vessel characteristics in 9L glioma model rats by comparing immunohistochemical analysis to the imaging data using a 9.4-T Bruker Biospin MR system.

Results and Discussion

Gd chelates, paramagnetic agents, are the most frequently used T1 contrast agents. However, liposomal Gd exhibits a strong T2 effect under high magnetic fields such as the one used in this study (9.4 T). The *in vitro* T2 relaxivity of the nanoparticle carrying ≈ 80 mM Gd (all encapsulated) as determined on a 9.4-T Bruker Biospin MRI was $23.6 \text{ mM}^{-1} \text{ s}^{-1}$. Dynamic light scattering measurements showed that the mean diameter was 95 nm for the liposomes extruded through 100-nm membranes. The osmolality of the nanoscale contrast agent suspension was determined to be 280–305 mOsm/kg of water, indicating that the particle should be stable in blood circulation.

Upon intravenous injection of gadodiamide (Omniscan®) or liposomal gadodiamide to Fisher rats at a dose of 0.25 mmol Gd/kg of body weight, plasma samples were collected and measured *ex vivo* using the 9.4-T MR system. The changes in blood T2 relaxation time following administration of nanoparticles and gadodiamide are shown in Figure 1. A sharp decrease in the blood T2 from the pre-injection value of 120 ms to the post-injection value of 18 ms after 5 min was observed for the nanoparticle. The blood T2 remained stable and low for at least 3 hr after injection. In animals injected with gadodiamide, the T2 was 60 ms at 5 min after injection and then began to increase rapidly, reaching pre-contrast blood T2 relaxation by the end of 1 hr.

A rat glioma model was established by surgically implanting 5×10^5 9L glioma cells into the frontal lobe of male Fisher rats. MR angiograms were obtained using a 3D FLASH sequence with the following parameters: TR/TE = 50/15 ms; flip angle = 15° ; 78- μm in-plane resolution; 156- μm slice thickness; 8 averages;

scan time = 1 hr, 21 min. Figure 2 shows the high-resolution MR angiography images before and after the administration of the nanoscale agent at a dose of 0.25 mmol Gd/kg of body weight. The nanoscale contrast agent allowed clear visualization of the healthy brain blood vessels (appearing as black dots), as well as the details of the cancerous lesion. Histological analysis (Figure 2) verified the MR findings. The liposome distribution within the tumor lesion was obtained by scanning over a period of 4 days after injection, allowing enough time for extravasation to occur, as well as clearance of the particles from the blood pool. Indeed, the signal from the blood pool was eliminated at $t > 72$ hr. This was verified by measuring the T2 value of a blood sample that coincided with the blood pre-contrast T2 value. However, there was significant enhancement of the lesion, indicating nanoparticle accumulation in the tumor. The regional distribution of the liposomes (tagged with rhodamine) observed in the MR images was verified by fluorescence microscopy of histological sections.

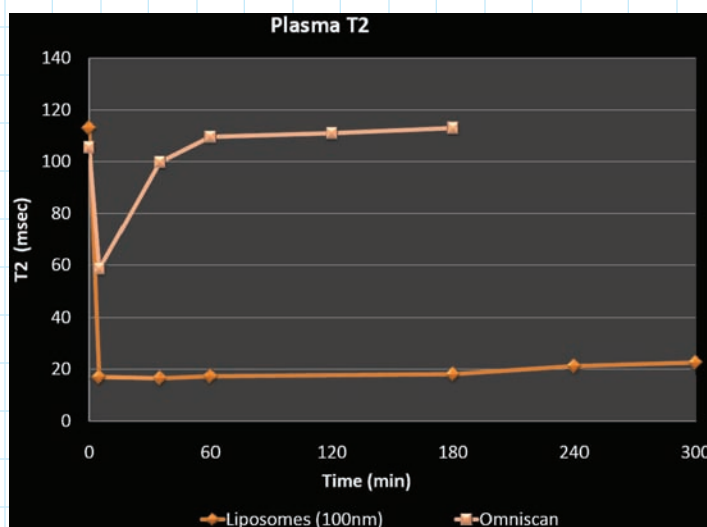


Figure 1. Plasma T2 relaxation values upon IV injection of liposomal gadodiamide or gadodiamide.

Conclusions

We have demonstrated the ability to track non-invasively the fate of a systemically administered nanoparticle. This allowed the evaluation of the nanoscale contrast agent uptake by a brain tumor. Future studies will be performed with the nanoparticle co-encapsulating a cytotoxic agent along with the MR contrast agent and determine that indeed a rationally determined treatment regime would significantly enhance therapeutic efficacy of chemotherapeutic nanocarriers.

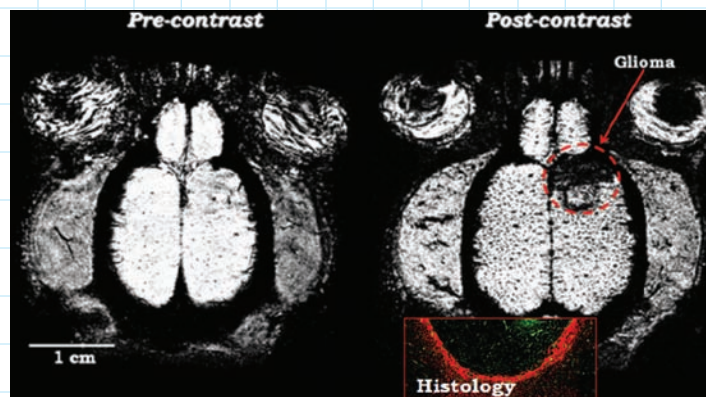


Figure 2. High-resolution axial images of rat brain before and after administration of 0.25 mmol Gd/kg of nanoscale agent. Inset: microscopical view (20 \times) of a frozen section of the bottom part of the tumor lesion. Astrocytes and blood vessels are seen in red and green, respectively.

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Scientifically Speaking

Polymeric Matrix Development for Incorporation and Controlled Release of Papain

By Gislaine Zulli, Nuclear and Energetic Research Institute, São Paulo, SP, Brazil; Patrícia Santos Lopes, University of Sorocaba, Sorocaba, SP, Brazil; Ademair Benévolo Lugão and Sizue Ota Rogero, Nuclear and Energetic Research Institute, São Paulo, SP, Brazil; Elissa Arantes Ostrosky and Maria Valéria Robles Velasco, Department of Pharmaceutics, University of São Paulo, São Paulo, SP, Brazil; Lígia Luriko Miyamaru and Maria Cristina Santa Bárbara, Adolfo Lutz Institute, São Paulo, SP, Brazil; and Monica Beatriz Mathor, Nuclear and Energetic Research Institute, São Paulo, SP, Brazil
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Introduction

Papain is a thiol protease extracted from latex obtained from the leaves and green fruit of papaya (2). African and American (Caribbean islands) tribes have been using latex from the green fruit of papaya to heal wounds for a long time (3). The enzyme is applied in difficult-to-treat wounds because it enhances the cleanliness of the wound, removing necrotic tissue and secretions. However, in spite of its wide use as a debriding and healing agent, papain has low hydrolytic stability, which makes its commercialization in a defined pharmaceutical form difficult. In Brazil, many hospitals use papain in solution, gel, or emulsion forms. Due to its instability, the enzyme in solution is prepared at the moment of use (5). The gel form does not offer protection against external agents and, in addition, enzyme stability remains low in this form.

The development of a topical drug delivery system would be one of the best options for using papain as a healing agent in an established dosage form. Furthermore, the permeation rate of the drug must be determined by its release rate to the skin surface so the release is not affected by individual variability in permeation (1). This profile is achieved when the drug is incorporated in a drug delivery system (DDS). Therefore, it would be interesting to develop a DDS containing papain with improved stability. Such a system would improve patient compliance with the healing procedure. The development of a system with a stable dosage is mandatory to take full advantage of papain's healing efficacy according to the pharmaceutical standards. However, due to papain's low stability it was necessary to incorporate the enzyme in a polymeric matrix. This work studied the release profile, surface morphology and biocompatibility of four selected medical-grade polymers for the matrix preparation.

Material and Methods

Four polymers usually applied as biomaterials were selected: natural rubber latex bi-centrifuged (NRLB), acrylic adhesive (AA), monocomponent silicone dispersion (MSD), and bicomponent silicone dispersion (BSD). The polymers were first assessed for cytotoxicity by the neutral red incorporation method using NCTC clone 929, (4). Non-cytotoxic and non-irritant polymers were used for the preparation of papain-containing membranes. Franz diffusion cells of static and vertical flux were

used in the release test, using a cysteine-EDTA phosphate buffer as fluid receptor and maintained at 37°C in a water bath. MSD membranes containing 2% (w/w) papain were evaluated in the release test using Franz diffusion cells. Some of these membranes were irradiated by γ rays with a 25 kGy dose for material sterilization. The effects of sterilization by γ irradiation on the drug release profile were simultaneously assessed on irradiated and non-irradiated MSD membranes.

Results and Discussion

As was expected, MSD and BSD polymers were shown to be non-cytotoxic polymers regarding the cell culture used (Figure 1). The cell viability for NRBL and AA polymers was lower than the index of cytotoxicity 50 (IC₅₀) for direct contact with dermal fibroblasts and so were not used (data not shown). MSD membrane was used as a control in the Franz diffusion cell experiments (Figure 2).

Results obtained from the release test showed a burst effect on papain release of approximately 11 USP/mL or 0.36 mg from irradiated and non-irradiated MSD membranes after 2 hr

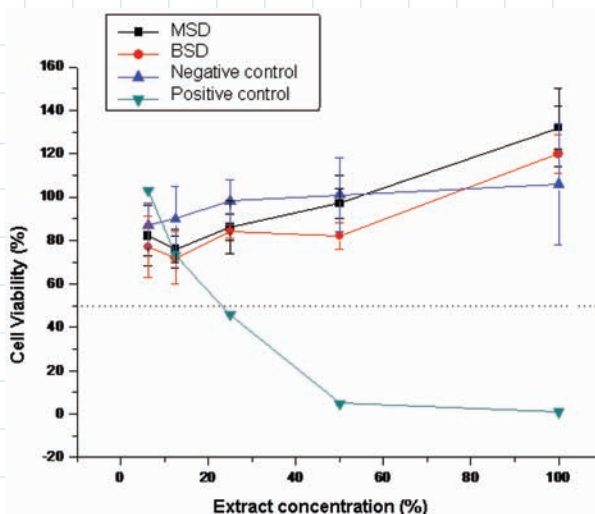


Figure 1. Cell viability for MSD and BSD polymers. Both of the polymers are non-cytotoxic, PVC pellets were used as a negative control, and a 0.02% phenol solution was the positive control.

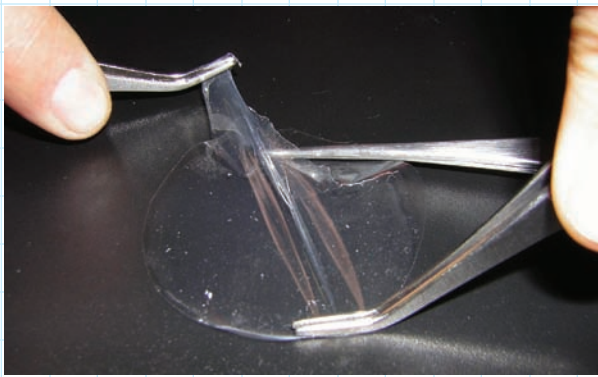


Figure 2. MSD membrane used as a control in the Franz diffusion cell experiments.

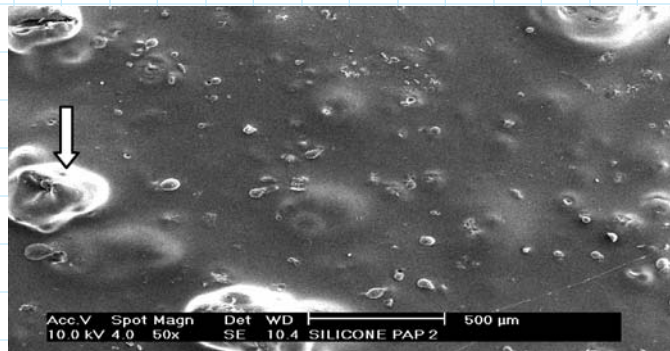


Figure 5. Irradiated MSD membrane not used in any test. The arrow shows a papain agglomerate.

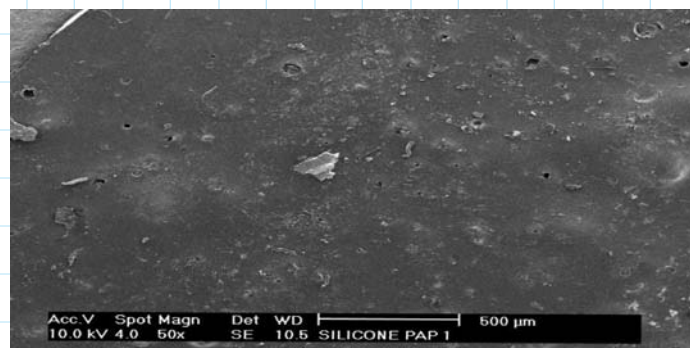


Figure 6. Irradiated MSD membrane submitted to releasing test in Franz diffusion cells.

(Figure 3). The accumulated amount of papain released from both membranes was very similar, around 24 USP/mL or 0.8 mg, indicating that the irradiation process did not modify significantly the release process (Figure 4), and also showed a controlled release of the enzyme over 12 hr.

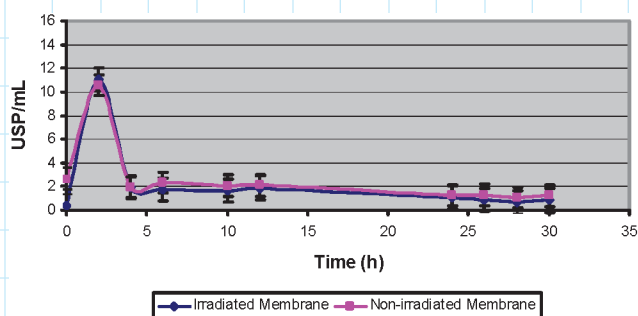


Figure 3. Flux of papain from irradiated and non-irradiated MSD membranes.

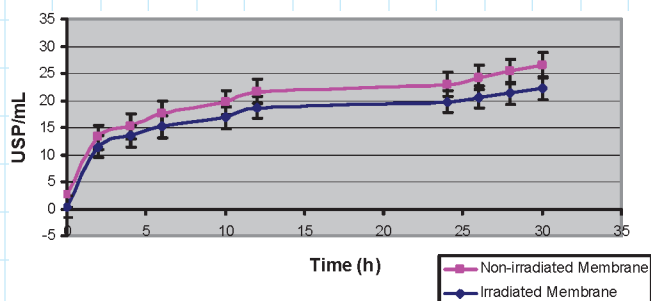


Figure 4. Accumulated amount of papain released from irradiated and non-irradiated MSD membranes.

An irradiated MSD membrane containing papain (Figure 5) and another submitted to the release test (Figure 6) were analyzed by scanning electron microscopy to visualize their relief and structure. Note, papain agglomerates (indicated by arrows in Figure 4) are not visualized in Figure 5, showing their release from the surface of the polymeric matrix and the pore formation that probably allowed papain release from the interior matrix.

Conclusions

MSD membrane was selected to incorporate papain because it was not cytotoxic or an irritant and was able to release papain in a controlled manner over a 12-hr period. However, *in vivo* tests must be performed to verify whether the amount of papain released is enough to enhance the wound healing process.

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From the Vet Group

Interspecies Differences Influencing Interspecies Extrapolations

Part I of III: General Considerations Influencing Veterinary Product Development

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Data generated on product performance in veterinary species may be used to support veterinary product development, or it may be used to screen potential products intended for human use. Regardless of its ultimate goal, it is important to consider the factors influencing the applicability of animal-derived data to support drug product development in the target species.

Recognizing the importance of understanding the impact of interspecies differences in product development, the Controlled Release Society (CRS) Veterinary Committee is providing a series of three articles to be published in three sequential issues of the *CRS Newsletter*. The articles will cover

- I. General Considerations Influencing Veterinary Product Development
- II. Interspecies Differences Influencing the Absorption of Oral and Parenteral Formulations
- III. Interspecies Differences in Metabolism and Toxicology

The development of veterinary pharmaceuticals is associated with numerous complexities not encountered by our human health counterparts. In addition to the challenges associated with between-individual variability (which is seen both in human and veterinary medicine), the development of new animal drugs also contends with such issues as

- Enormous diversity in size, behavior, metabolic needs, and lifespan between animal species
- Species and breed differences in both pharmacokinetic and toxicity profiles
- A wide spectrum of disease agents that produce different disease manifestations under different conditions
- A range of husbandry practices, which includes an array of settings in which animals are kept, ranging from animal companions in the home to large livestock operations
- Inability to communicate directly with the animal patient
- Public health concerns, including environmental safety, human food safety, and the potential influence of veterinary antimicrobial use on development of resistance in bacteria of concern to both veterinary and human medicine

There are even interspecies differences in responses to bacterial pathogens. For example, the pulmonary damage caused by *Mannheimia haemolytica* is due to the impact of this bacterial infection on the release of leukotoxins from the neutrophils of

ruminants. It is this leukotoxin that is the mediator of damage to the pulmonary parenchyma. Similar neutrophil leukotoxin release is not observed in response to *M. haemolytica* in other animal species (1).

Differences in product use characteristics and therapeutic goals also influence the nature of drug products developed for use in food-producing versus companion animal species. In the case of companion animals (e.g., dogs and cats), the patient is the focus of diagnostics and drug therapy. The goals of therapies are to prevent, treat, or manage a disease or to improve the quality of life for the individual animal, with some therapies continuing throughout the life of the companion animal. In contrast, the therapeutic focus for food-producing animals is generally the health of an entire group (herd or flock) rather than the individual. Although food-producing animals may be individually dosed using injectable or topical formulations, group dosing via medicated drinking water or feed is often used to minimize handling, thereby reducing animal stress and farmer costs and providing an efficient means of dosing a large number of animals during a disease outbreak.

Many drug products are developed for use in multiple species. In these cases, comparative physiology, animal behavior, and husbandry practices dictate which species are appropriately linked to a specific dosage form. For example, when we consider the various kinds of formulations approved for use in veterinary species, the following species tend to be linked to the use of the following kinds of formulations:

- **Oral suspensions, pastes, syrups:** All species
- **Pellets and granules:** Horses and cattle; occasionally swine, dogs, and cats
- **Tablet, suspension, capsules:** Dogs and cats
- **Medicated water:** Swine, poultry, and fish
- **Medicated feed:** Cattle, swine, horses, poultry, and fish
- **Oral bolus, drenches:** Horses and cattle

For solid oral dosage forms, about 65% of all tablet formulations are approved for use in dogs and that about 27% are approved for use in cats. About 22% of all approved tablets are indicated for use in both dogs and cats. Only about 8% of the oral tablets are approved for use in horses (based on information in the U.S. Code of Federal Regulations No. XXI, Section 520).

When considering the impact of physiological differences on product development, we need to consider interspecies differences in injection site physiology for parenteral formulations and interspecies differences in gastrointestinal (GI) physiology for oral dosage forms. A classic example of the impact of interspecies differences on drug absorption was observed in a study by Davis et al. (2), in which chloramphenicol was administered by intravenous (IV), oral, and intramuscular (IM) injection to dogs, cats, swine, ponies, and goats. Following IM injection, extremes of absolute bioavailability ranged from about 50% in swine to nearly 100% in ponies. In contrast, of all the species tested, the cats exhibited the highest chloramphenicol blood levels following oral administration, even though its bioavailability was similar to that of dogs following IM injection. The blood levels observed in dogs and ponies were essentially the same, even though ponies had markedly higher concentrations after IM injection. However, because of rumenal degradation, chloramphenicol oral bioavailability was effectively zero in goats.

In another example, the pharmacokinetics of selamectin was evaluated in cats and dogs following IV, topical, and oral administration. Plasma concentrations after IV injection declined polyexponentially in cats and biphasically in dogs, with mean terminal phase half-lives of approximately 69 hr in cats and 14 hr in dogs. After topical administration, bioavailability was 74% in cats and 4.4% in dogs. Following oral administration, bioavailability was estimated as 109% in cats and 62% in dogs (3).

These examples of interspecies differences segue to our next topic—the impact of animal physiology on oral and parenteral drug absorption. Comments on these articles are welcomed and encouraged. Please contact Marilyn Martinez at Marilyn.Martinez@fda.hhs.gov.

Additional information on factors influencing the development and use of veterinary pharmaceuticals, including information on U.S. Food and Drug Administration considerations associated with veterinary products have been published elsewhere (4).

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News

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From the Education Committee

Development and Regulatory Challenges for Controlled Release Formulations—CRS-AAPS Satellite Workshop a Resounding Success

By Ron Ortiz
3M Drug Delivery Systems
St. Paul, MN, USA

After much planning, 2007 marked the first Satellite Workshop held under the joint auspices of two organizations—the Controlled Release Society (CRS) and the American Association of Pharmaceutical Scientists (AAPS). The workshop, generously sponsored by Northern Lipids, Inc. and Pfizer, Inc., was held November 9–10, 2007, in San Diego, California, in conjunction with the AAPS Annual Meeting. The workshop featured 11 presenters, all experts in their fields, from industry, academia and regulatory agencies. Based on the stimulating discussions, audience participation, and positive feedback from many attendees, the organizers are pleased to announce that the workshop was a huge success, drawing in excess of 120 participants, including a few late registrants.

The event was an initiative organized by the Industrial Subcommittee of the CRS Education Committee, and the organizers were Avinash Thombre (Pfizer), Dody Reimer (Northern Lipids), Mike Rathbone (InterAg), Ron Ortiz (3M Drug Delivery Systems), and Ronda Thompson (CRS). The goals of the workshop were to

1. Provide an understanding of the challenges faced in the development of controlled release formulations, using examples of mature and evolving technologies.
2. Discuss and share the regulatory challenges encountered (and overcome) in the development of a controlled released drug formulation.
3. Provide a venue to meet other scientists and those from regulatory authorities.
4. Discuss the fundamentals of science and share personal and professional experiences that may be valuable to others facing challenges in the development of CR technologies.

The workshop was organized into three sessions and held over 2 days; 1) Mature CR Technologies—Non-oral Route, 2) Mature CR Technologies—Oral Route, and 3) Emerging CR Technologies—Biologicals and Nanotechnology.

1) Mature CR Technologies—Non-oral Route

The workshop was kicked off by Rick Norton (QLT) on the first

day with a presentation titled “The Road to the Six Month Eligard® Product.” Rick reviewed the development process and challenges that QLT faced in bringing Eligard® to market. He shared his insights on preparing IND and NDA sections and the process that was followed with Eligard® on its path toward successful market approval. This mature technology of a sterile polymeric formulation of leuprolide acetate delivered subcutaneously for the treatment of prostate cancer has proven to be a robust commercial product with approval in five countries around the world.

Rick’s success story was followed by two speakers from Noven Pharmaceuticals, Juan Mantelle and David Kanios, who delivered their presentation, “Development Considerations for Innovative Passive Transdermal Delivery Systems.” A particularly interesting concept highlighted by these two speakers was to anticipate IP-related challenges, in addition to regulatory and traditional development challenges, when dealing with mature technologies. Mature technologies are usually represented in a heavily crowded IP landscape that brings forth its own set of challenges when attempting to develop innovative products. The Noven team presented the background on the current-state-of-the-art on passive transdermals. Additionally, they reviewed their transdermal technology and the development considerations that must be addressed when developing successful transdermal delivery systems.

The morning session finished on a high note, with Andy Clark (Nektar Therapeutics) delivering a presentation titled “Development and Regulatory Challenges in Pulmonary Delivery.” Andy provided a comprehensive overview of the technologies and important technical considerations in delivering APIs systemically via the lung. He highlighted and reviewed the different classes of devices used today and the specific delivery and regulatory challenges associated with each of them.

The presentations were followed by a very lively panel discussion with plenty of thought-provoking questions and comments from the attendees whose attention was undivided. These presentations

undoubtedly provided an opportunity for the audience to ponder the challenges that they may face when developing their own controlled release formulations.

2) Mature CR Technologies—Oral Route

The first of two presentations on mature technologies via the oral route was delivered by Suneel Gupta (Alza Corporation). His talk was titled “Development and Regulatory Challenges in Osmotic Technology.” Suneel reviewed the commercial products that were marketed using OROS® technology and the creative approaches that have resulted in new products that meet current market needs. He emphasized that the goal of CR formulations should be controlling the release and not merely providing sustained release to achieve more efficacious products. Suneel concluded his talk by presenting the idea that the ultimate pharmaceutical goal is to help patients reach their full potential, while the ultimate drug delivery goal is to help molecules reach their full potential.

The second presentation was delivered by Scott Herbig (Pfizer Inc.). His talk, “Microparticulate-Based Drug Products: Process Understanding and Control,” focused largely on the technology used to manufacture microparticulates. He identified some manufacturing problems that were encountered, and solutions to those challenges were presented, not the least of which was the need for a better understanding of the process. Scott pointed out the need to identify and understand all steps and critical variables in the manufacturing process. Knowledge of these key criteria would maximize manufacturing robustness while meeting the technical requirements of the product with minimized regulatory risk.

The presentations and discussions around mature CR technologies, including non-oral and oral routes of delivery, were brought together in a concluding presentation delivered by Krishnan Tirunellai (Health Canada). Krishnan tied together the presentations with a regulatory perspective on the scientific and regulatory challenges facing CR formulations. Krishnan shared existing and emerging trends in the industry regarding life-cycle management, including quality by design (QbD). He also discussed regulatory challenges, including those due to API properties, type of dosage form, developmental issues, and manufacturing issues, as well as providing examples of market recalls.

3) Emerging CR Technologies—Biologicals and Nanotechnology

The second day, dedicated to emerging technologies in the areas of biologicals and nanotechnology, was launched by Manmohan Singh (Novartis). Manmohan's talk, “MF59 Is a Safe and Potent Vaccine Adjuvant for Human Use,” shared the Novartis experience with the development of a submicron suspension vaccine adjuvant product. He covered the early technical challenges associated with its development and provided a comprehensive overview of the manufacturing strategy that led naturally into the extensive amount of work associated with identifying the adjuvant's mechanism of action. Much of what was learned on the road to success contributed to the continuous optimization and understanding of new-generation vaccines.

The first of two presentations in the field of nanotechnology was delivered by Mark Saltzman (Yale University). During his presentation, “Nanotechnology Opportunities in Drug Delivery,” Mark reviewed recent applications of CR implants for the treatment of cancer and discussed how local delivery effectiveness may be enhanced through advances in nanotechnology.

The second presentation in nanotechnology was delivered by Barrett Rabinow (Baxter Healthcare), who addressed the topic of drug nanosuspensions. In his lecture, titled “Drug Nanosuspension: From PK Modification to Disease Targeting,” Barrett used NanoEdge as a model of CR formulation to share how the role of nanosuspensions has evolved from their use in formulations as PK modifiers to a means of disease targeting.

No session on emerging technologies of CR formulations would be complete without a discussion on DNA vaccines. Sean Sullivan (Vical Inc.) delivered a comprehensive presentation titled “Clinical Development of DNA Vaccines for Treatment of Cancer and Infectious Diseases.” He presented an overview on the historical perspective of the development of DNA delivery systems that have led to more recent technological considerations in the development of CR formulations that form part of the Vical technology portfolio. Despite the fact that the field of gene delivery and DNA vaccine development has experienced numerous road blocks in past years, it continues to show great promise as a treatment strategy for a number of diseases, as was pointed out by Sean.

Just as on the first day, the afternoon session concluded with a regulatory perspective, and the final presentation of this 2-day venture was delivered by Mansoor Khan (U.S. FDA), who provided examples of regulatory challenges and past learning about CR products with emerging technologies. In a talk titled “The Science and Regulatory Perspectives of Controlled Release Products with Emerging Technologies: Examples and Regulatory Challenges” that was well received by the attendees, Mansoor provided an excellent conclusion to the workshop. Following the presentation, the organizers opened the session to questions from the floor, resulting in a stimulating discussion with plenty of questions, contributions, and opinions from attendees who represented a variety of backgrounds.

In summary, the first ever CRS Satellite Workshop was an outstanding success. The impressive attendance is a testament to the immense interest in workshops that combine the developmental challenges of technology with input on meeting regulatory requirements. Follow-up workshops to address regulatory needs from an international perspective may be considered. The planning committee is now seeking input for topics and themes for future Satellite Workshops. Let us know what topics are of most interest to you; if you have an idea for a future Satellite Workshop, contact Dody Reimer, Education Committee Industrial Sub-committee Chair, at dodyreimer@northernlipids.com. ■

35th CRS Annual Meeting & Exposition

By Ijeoma Uchegbu
University of London, London, U.K.



Ijeoma Uchegbu

Dear Members,

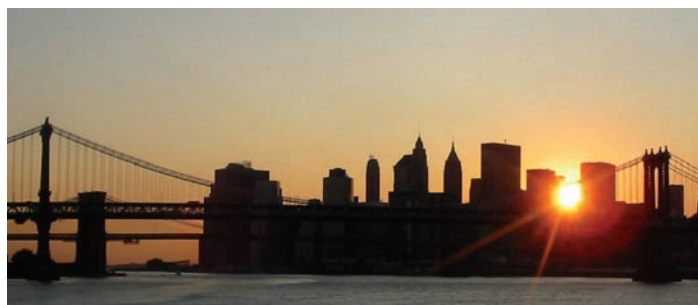
Summer is almost upon us, which can mean only one thing—time to plan your conference programme. So, pause for a minute as you manage your projects, plan the decisive experiment, pen your reports, and complete your registration for the world's premier event dedicated solely to bioactive processing and delivery. Of course, I refer to none other than your very

own Controlled Release Society Annual Meeting & Exposition, which this year makes its presence felt in the wonderful and vibrant city of New York; a city that never sleeps and so offers excellent opportunities for day and night networking! Make sure that your calendars, diaries, and wall charts are marked with the dates of your meeting: July 12–16, 2008. I shall be there, and I hope that you will too.

I cannot promise you excellent weather outside the conference venue (I shall pray for sunshine and very little rain though), but within the conference venue, none other than the New York Hilton on the Avenue of the Americas in mid-town Manhattan, the atmosphere will be stimulating, warm, friendly, and altogether affirming of our scientific endeavours. As you might have guessed, I am really excited about this year's conference, not least because it is my first as the CRS Scientific Secretary, but mainly because we have some top-notch speakers signed up. Mark Tracy, Kam Leong, Martyn Davies, Nava Dayan, Teresa Virgallito, Raid Alany, Terry Bowersock, Sevda Senel, and I have raided our contact books and scoured the literature to bring you the very best science available today. Speakers include Rakesh Jain, who for decades has studied the tumour vasculature; Jackie Ying, an effervescent scientist who is building organs in her laboratory; Mark Davis, whose work on cancer therapies is revolutionary; Thomas Tuschl, who will talk about his very interesting gene regulation studies;



*Statue of Liberty at Night,
© Jeff Greenberg*



*Downtown Skyline through Brooklyn Bridge,
© Jordan Gary/NYC & Company*

Raymond Bartus, who is working on groundbreaking new therapies for neurodegenerative disorders; and Dora Akinluyi, who has made safe medication a reality for Nigerians and is regularly targeted with death threats as a result! Quite a line up, no doubt you will agree. You simply cannot afford not to be part of this science extravaganza, especially as this is the 35th Annual Meeting & Exposition of the Controlled Release Society, and what a long way we have come. As it is a special anniversary, there will be some treats in store for you. I shall let you discover these once you hit the Hilton's front steps.

Well, I shall round up by saying simply that your presence at the meeting is absolutely vital as there can be no networking without a network! And, what a high-quality network CRS members make, too. I am sure that you want to find out what your competitors are up to in the field. Also, would you not like to know which companies are near to market with their brand new products? A conference such as the Controlled Release Society Annual Meeting & Exposition is a great place to catch up with cutting-edge science, share a drink with old friends, and definitely make some new friends.

Talking about making new friends, if you see me wandering around the conference hall, just stop me and say hi!

See you soon,

A handwritten signature in black ink, appearing to read 'Ijeoma'.

Ijeoma Uchegbu
Scientific Secretary ■

See These Exhibitors at the 35th CRS Annual Meeting & Exposition

July 12–16, 2008 • New York, New York

Exhibiting companies that have reserved space at the 35th Annual Meeting and Exhibition of the Controlled Release Society, as of press time, are listed below. For ongoing updates, visit www.controlledreleasesociety.org/meeting/exhibitors/currentExhibitors.cfm.

3M Drug Delivery Systems	DSM Biomedical	OctoPlus NV
Adhesives Research	Duoject Medical Systems	O'Hara Technologies
Aicello Chemical Co Ltd	DURECT Corporation	Oxford Instruments
Alkermes	Elan Corporation	Patheon Inc
Almac Group	Elsevier	Pharmaceutical Profiles Group
Aptuit Limited	Erweka America Corp	Pharmatek Laboratories Inc
Aqualon	Evonik Industries AG	Philips Research
Asahi Kasei Chemicals Corporation	Fuji Health Science	PII
Avanti Polar Lipids Inc	Gattefosse	PolyMicrospheres-Advanced
Avantium Technologies	Gaylord Chemical Corp	Nanotechnologies
Aveva Drug Delivery Systems	Genzyme Pharmaceuticals	Polymun Scientific GmbH
Azopharma	Glatt Pharmaceutical Services	PURAC America
Banner	Halozyme Therapeutics	Rohm & Haas Company
BASF Corp	Hanson Research Corp	RTS Life Science
Bilcare Inc	Hisamitsu Pharmaceutical Co Inc	Scintipharma Inc
Bio-Images Research Ltd	ICON Development Solutions	Shin-Etsu Chemical Co Ltd
Biovail Contract Research	Informa Healthcare	Simulations Plus Inc
Boehringer Ingelheim Chemicals Inc	Intertek MSG	Skin Scientifica Inc
Brookwood Pharmaceuticals	Irvine Pharmaceutical Services	Soliqs
Buchi	LCI Corporation	SOTAX AG
Catalent Pharma Solutions	Lipoid LLC	Southwest Research Inst
ChemAgis USA Inc	LTS Lohmann Therapy Systems	Surface Measurement Systems NA
ChemImage Corp	Lubrizol	SurModics Inc
CMA/Microdialysis Inc	Molecular Profiles Ltd	Sympatec Inc
Coating Place Inc	Mylan Technologies Inc	Technology Catalysts Intl
Colorcon	National Starch & Chemical Co	Texture Technologies
Croda Inc	Nisco Engineering AG	Thermo Scientific
Depomed Inc	Nisso America Inc	Travanti Pharma Inc
Dermatrends Inc	NOF Corporation	Varian Inc
DPT Laboratories Ltd	Northern Lipids	Vector Corp
Drug Delivery Technology	NovaMatrix/FMC BioPolymer	XSpray Microparticles
	Noven Pharmaceuticals	

Questions?

Contact Debby Woodard, CRS Business Development
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Chapter News

Australian Chapter of the Controlled Release Society Holds 1st Annual Meeting

*By Dr. Pavla Simerska, Scientific Secretary
On behalf of the AUS-CRS Committee*

The 1st Annual Meeting of the Australian Chapter of the Controlled Release Society (AUS-CRS), held in conjunction with the Australasian Pharmaceutical Science Association (APSA) conference on December 9, 2007, in Manly, Sydney, was a very successful and interesting event.

Over 100 participants with an interest in controlled release science attended the symposium, indicating the high level of support for the formation of the AUS-CRS Chapter and the need for a forum for controlled release science in Australia. It was a great pleasure and honour to have Prof. Ijeoma Uchegbu (CRS Scientific Secretary) as a plenary speaker. Ijeoma's introduction to her very interesting research and prolific scientific contributions was followed by 12 national speakers: Dr. Chris Barbe, Dr. Adam Watkinson, Dr. Patrick Hartley, Prof. Clive Prestidge, Dr. Paul Young, Assoc. Prof. Lee-Yong Lim, Dr. Heather Benson, Prof. Mark Kendall, Assoc. Prof. Michael Monteiro, Dr. Pavla Simerska, Dr. Ross Kennedy, and Dr. Ben Boyd. The high quality of presentations was reflected by

the large attendance, as the conference room was completely full from the beginning of the morning and afternoon sessions.

An important task during the symposium was the election of the first AUS-CRS Committee. An election was held, and the committee officially was formed, comprising the following officers and members-at-large: Prof. Istvan Toth (President); Dr. Ben Boyd (Vice President); Dr. Pavla Simerska (Scientific Secretary); Prof. Clive Prestidge (Treasurer); Assoc. Prof. Allan Coombes (Secretary); and Dr. Daniela Traini, Dr. Ross Kennedy, and Dr. Heather Benson (Members-at-Large).

The success of the first AUS-CRS meeting was in large part due to the generous support of our sponsors. Major sponsors of the symposium were the Faculty of Biological & Chemical Sciences, The University of Queensland; Victorian College of Pharmacy, Monash University; Phosphagenics Ltd.; Implicit; TetraQ; and UniQuest. We appreciate their support and thank them for helping to establish the newly formed Australian Chapter of the CRS. We also acknowledge ATA Scientific and VCP for providing poster prizes (1st prize: iPod; and 2nd prize: \$100 cheque) for the best controlled release-related posters, which were won by Abu-Baker Abdel-Aal (University of Queensland) and Shalini W. S. Yapa (Victorian College of Pharmacy), respectively. The AUS-CRS Committee is also very thankful to the organizers of the APSA meeting, in particular Dr. Daniela Traini and Dr. Jane Hanrahan, for giving us the opportunity to hold our first AUS-CRS meeting in conjunction with APSA.

Planned activities for 2008 include a joint workshop with the New Zealand Chapter of CRS, and the second annual AUS-CRS symposium (planning to be held in conjunction/parallel with APSA). For those who attended this AUS-CRS meeting, thank you very much for your support, and for those who are now interested, we look forward to seeing you next time! ■



From left: Allan Coombes, Istvan Toth, Pavla Simerska, Ijeoma Uchegbu, Ben Boyd, and Clive Prestidge.



Ross Kennedy prepares for his presentation (background, list of sponsors).



Clive Prestidge give AUS-CRS 1st poster prize to Abu-Baker Abdel-Aal.

UKICRS Hosts “Nanotechnology in Drug Delivery and Medicine” at BPC 2007: The Medicines Maze—Balancing Risks and Benefits

Introduction

The use of nanotechnology, in its various guises, has long played a role in the formulation of medicines. However, continued advances in ways to characterise and test such systems have fuelled new developments and investigations. The UK and Ireland Chapter of the CRS organised a 1-day meeting focusing on recent advances and applications of nanoformulations, as well as the possible concerns raised by delivering drugs in such formats.

Nanoparticulate Systems for the Delivery of Sub-unit Vaccines

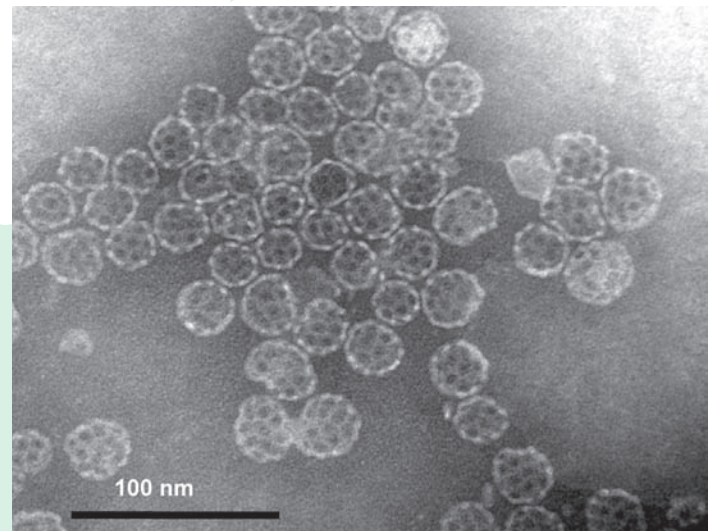
Prof. Thomas Rades (Otago University, New Zealand) opened the session by highlighting the successes vaccines have already had in improving global health, emphasising that some diseases are now effectively eradicated. Yet, it is clear that there is still a need to develop new vaccines, since there remain old (e.g., TB, pandemic flu vaccines) and new (e.g., cancers) diseases from which we need protection. In the development of new vaccines, we face several restrictions: it is no longer possible to introduce “live” vaccines such as oral polio vaccines or, most probably, killed vaccines due to regulatory concerns about these systems, with the risk of adverse events outweighing their perceived benefits. This is particularly evident in environments where the risk from disease is now low. Therefore, it is clear that in terms of safety profiles, sub-unit vaccines are the way forward. However, these vaccines themselves have a range of problems, including their low immunogenicity and their need for multiple dosing and booster injections. To address these problems, the group from Otago is looking at an array of nanoparticulate systems, including liposomes, ISCOMs, Pluscoms, and nanoparticles to deliver these sub-unit vaccines.

Liposomes, which are well reported for their efficacy as delivery systems, offer a range of advantages as possible vaccine adjuvants, including their strong biocompatibility profile and ability to entrap a variety of proteins and peptides. However, these systems are inherently non-immunogenic; therefore, for application as a vaccine delivery system, they require further formulation. One approach is to supplement the bilayer with mannosylated phosphatidyl ethanolamine. This approach is based on the fact that many pathogens express glycoproteins on their surface and to facilitate their recognition and clearance macrophages and dendritic cells carry cell-surface mannose receptors. To investigate mannosylated liposomes, the group formulated three liposomal systems (neutral, anionic, and mannosylated systems), and their physico-chemical properties and immunological activity were tested.

In terms of their physical attributes, the size of the liposomes was shown to be influenced by the charge of the liposomal bilayer, with mannosylated liposomes being smaller than their anionic and neutral counterparts. Looking at how these attributes influenced blood monocyte-derived dendritic cell uptake, it was found that the presence of mannose on the surface

of liposomes improved antigen uptake compared to non-mannosylated liposomes; however, the authors noted that actual antigen uptake from solution, rather than from particulates, was the highest for those tested. Despite this, when the authors then looked at the maturation of the dendritic cells it was significantly higher for the particulate systems compared with antigen in solution. This was further validated using microscopic examination, which revealed morphological changes in the dendritic cells from antigen-capturing to antigen-presenting cells. Mannosylated liposomes also gave significantly higher T cell proliferation, and in a tumour challenge model, these liposomes significantly enhanced the time mice remained tumour free. The efficacy of these liposomes was further enhanced by supplementing the bilayer with Quil A, a potent adjuvant, derived from the bark of *Quillaja saponaria*, a South American tree. The authors summarised that an effective sub-unit delivery system required not only a particulate nature but also a danger signal.

By varying the ratio of phospholipid, cholesterol, and Quil A in aqueous dispersion, the authors formulated a range of nanoparticle systems, including ring-like micelles (approximately 10 nm in diameter), helical micelles, lipidic particles, and, most importantly, cage-like spherical particles, termed immune-stimulating complexes (ISCOMs), with characteristic soccer ball-like morphology and a very narrow size distribution around 40 nm. As these systems are “open,” the antigen has to be inserted into the colloidal structure, in contrast to liposomes where the antigen can be encapsulated into the core of the liposome. Whilst these systems are highly immunogenic, loading of hydrophilic antigens is difficult, and the sub-unit antigen had to be chemically modified, e.g., by adding a fatty acid or phospholipid moiety, to achieve incorporation of the antigen in



Electron micrograph of ISCOM particles containing phospholipid/cholesterol/Quil A.

the adjuvant-containing nanoparticle. The group has also developed a cationic alternative to the anionic ISCOMs (termed Pluscoms) by replacing cholesterol with the cationic cholesterol derivative DC-cholesterol, thereby greatly enhancing uptake of the mostly anionic sub-unit proteins through electrostatic interactions.

Fabrication of Nano-sized Self-Assemblies Composed of Novel Amphiphilic Graft Polymers for Protein and Drug Delivery

Dr. Woei Ping Cheng (Robert Gordon University, Aberdeen) reported on her work looking at the use of novel polymers for the delivery of proteins and poorly soluble drugs. Low solubility in drugs is a major problem for delivery and bioavailability, with 40% of new drugs failing in the development stage due to undesirable physical properties, including low aqueous solubility. One of the most commonly used technologies to circumvent this problem is to formulate micelles from low molecular weight surfactants. However, a major problem with micellar systems is their breakdown *in vivo* as a result of dilution within the plasma, resulting in their concentration dropping below their critical micelle concentration (CMC). As an alternative to surfactants, amphiphilic polymers, which are polymers containing both hydrophilic and hydrophobic fragments within the same macromolecule, can be used. When these polymers are brought into solution, their hydrophobic regions associate to form a hydrophobic core that is surrounded by a highly hydrated coat. Unlike low molecular weight surfactants, these polymers can be formed with diverse architectures, including graft and block copolymers. Work from Dr. Cheng's group is looking at the development of novel graft polymers based on water-soluble polymers such as polyallylamine (PAA). These novel PAA polymers form nano-sized self-assemblies in an aqueous environment, in the size range of 100 to 400 nm. Manipulation of the polymeric structure allows the properties of these systems to be controlled, including their CMC, drug solubilisation properties, and protein complexation efficacy. For example, grafting of cholesteryl groups to the PAA was shown to reduce

the critical aggregation concentration, and addition of quaternary ammonium groups increased the overall solubility and stability of these complexes in an aqueous solution. Using two model hydrophobic drugs, griseofulvin and propofol, the authors were able to show a linear relationship between polymer concentration and drug loading, and using these systems, they were able to improve solubility by 17- and 25-fold for griseofulvin and propofol, respectively, when PAA was grafted with 5% of cholesteryl groups and 45% of quaternary ammonium groups.

Dr. Cheng also looked at the application of these polymers to improve the delivery of proteins. Unlike conventional small drug molecules, proteins have poor penetration of the intestinal membrane and easily undergo enzymatic degradation in the gastro-intestinal fluid. Using their PAA systems, polymer-insulin nanocomplexes were formed that were shown by negative-staining scanning electron microscopy to be dense spherical particles with the insulin incorporated within the structure. It was proposed that this insulin complexation by their quaternised polymers is through electrostatic as well as hydrophobic interactions, since most proteins are negatively charged in nature at neutral pH. These nanocomplexes were able to protect the insulin for up to 4 hr in a trypsin-degradation study, with only 5–7% degradation occurring compared with complete degradation of insulin from solution over the same time.

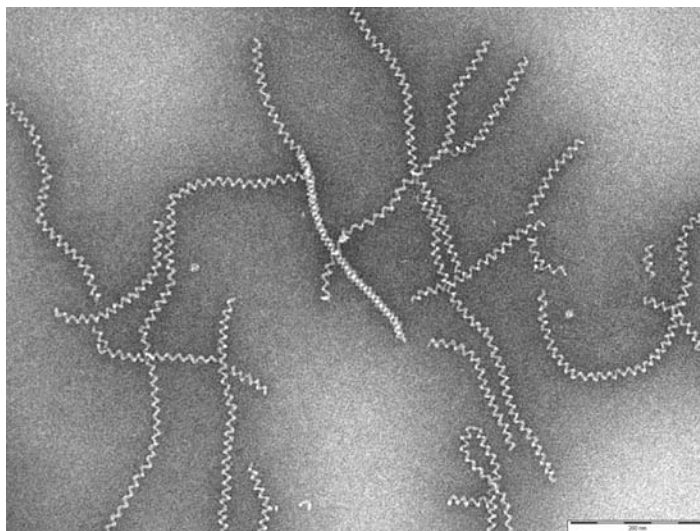
Dr. Cheng concluded that these novel PAA-based polymers offer considerable potential for the future development of nano-sized delivery systems applicable to hydrophobic drugs, proteins, and peptides.

Inhalation of Nanotoxicology and How It May Impact Drug Delivery to the Lung

Dr. Lea Ann Dailey (King's College, London) first emphasised how nanomaterials are all around us, in our food, our clothes, and most everyday items—but, she raised the question, should we be looking at how these nanomaterials are affecting us and our environment? Dr. Dailey highlighted that our definition of nanotechnology actually varies from particles 1–100 nm in size to the broader definition used in the pharmaceutical sciences, which regards nanosystems as anything below 1,000 nm in size. The Environmental Protection Agency uses a 4-class system for nanoparticulates:

- Carbon-based nanoparticles, e.g., fullerenes, nanotubules
- Metal-based nanoparticles, e.g., ZnO nanostructures and quantum dots
- Dendrimers
- Composite nanoparticles, e.g., the polymeric nanoparticles developed by Dr. Cheng's research or the lipid nanoparticles of Prof. Rades' group.

Dr. Dailey's research focused on what happens when we inhale materials less than 100 nm in diameter. These types of particulates can stimulate inflammation, long-term lung damage, fibrosis, and lung cancer. The key issue was to investigate the causes of these inflammatory responses—oxidative stress caused by the material, shape, size, and/or surface area of the particles? It was noted that few studies had been done to see if what we considered to be inert indeed had a toxicity profile when delivered in the nanoscale. The research from Dr. Dailey's group



Electron micrograph of helical micelles formed from phospholipid/cholesterol/Quil A mixtures developed by Rades et al.

is aimed at systematically investigating the safety of inhaled nanomedicines in terms of their physico-chemical characteristics, *in vitro* toxicity, and *in vivo* safety. This is being disseminated to the public through a website portal and to the scientific community through a series of monographs for each system. Physico-chemical characteristics studied are size/polydispersity, surface charge, surface area, hydrophobicity, density, water content, swelling, biodegradation, and stability of the nanosystems in various media. *In vitro* studies focus on particulate deposition and dosimetry, protein adsorption, surface interactions, reactive oxygen species generation, and cytokine release. Finally, *in vivo* studies consider protein content, cytokine release/expression, macrophage recruitment, and tissue morphology. Dr. Dailey envisions the ability to evaluate toxicology profiles of new nanomedicines will be a very powerful tool to support their development and application.

Screening of Pharmaceutical Materials Through Nanoscale Measurements

Prof. Clive Roberts (Nottingham University, UK) reported on the use of nanoscale analysis of materials through the application of probe microscopy, confocal microscopy, Raman microscopy, time of flight secondary ion mass spectrometry, and micro-CT systems. There is an increasing demand for nanoscale control and characterisation of pharmaceuticals due to the challenges of low-solubility drugs and new-generation biopharmaceuticals already alluded to by Dr. Cheng. To study these systems, Prof. Roberts noted we should take a multi-factorial approach to the analysis of formulations. Of these techniques, Prof. Roberts has been looking in detail at using atomic force microscopy (AFM). AFM is a high-resolution scanning probe microscopical technique that can resolve images down to the nanometer range. It is based on the principle of a microscale cantilever fitted with a probe. When the probe is brought into contact with a sample surface, the forces between the probe and the sample lead to a deflection of the cantilever. This deflection can be interpreted to give an image of surfaces. Work at Nottingham is particularly focussed on intra-particulate forces that can be measured by attaching moieties to the surface of the probe, which will subsequently interact with a surface or particle. This can be used to compare interactions between two surfaces, frictional forces, electrostatic interaction, or even biological interactions. For example, the adhesive forces between metered dose inhaler components, e.g., the active pharmaceutical ingredient and excipients can be measured to see if there are any adhesive problems. Similarly, such probe systems can be used to determine localised dissolution rates and to identify polymorphic and amorphous forms, spatially resolved in the nanometer range. He commented that the level of sophistication, robustness, and increased speed of analysis of the above mentioned techniques offer the opportunity to provide a “smart” screen for materials and formulations much earlier than was previously possible.

EPR-Effect, Its Mechanism, and Further Extension Towards More Tumour Selective Cancer Therapy

Prof. Hiroshi Maeda (Sojo University, Japan) received the *Journal of Drug Targeting* Lifetime Achievement Award in recognition of his distinguished work in the field of inflammation, cancer treatment, and recognition of the enhanced permeability and retention (EPR) effect. In his presentation, Prof. Maeda outlined

how the EPR-effect was first observed and how it has now been observed with many polymeric and lipidic nanomedicines, improving their pharmacokinetic profile by improving tumour targeting, reducing toxicity, and providing more patient-friendly and cost-effective medicines. The EPR-effect is a result of the leaky vasculature at sites of inflammation, which allows the escape of macromolecules and nanoparticles from the circulation into the tumour site. Factors that controlled this effect include molecular size (40- to 800-kDa molecules accumulate in tumours, with progressive increase in levels as a function of molecular size). Prof. Maeda concluded that the EPR-effect is the first step to the “magic bullet” concept in drug delivery. A special issue of the *Journal of Drug Targeting* has been published and edited by Prof. Ruth Duncan and Prof. Len Seymour in honour of Prof. Maeda defining the pathway to targeted cancer therapy.

Endocytic Pathways: Gateways for Intracellular Drug Delivery

Dr. Arwyn Jones (Welsh School of Pharmacy, University of Cardiff) opened his presentation by noting that many drug targets are located intracellularly and drug delivery systems need to be formulated to overcome the plasma membrane of the cell and intracellular compartments, including those of the early and late endosomes and the lysosomes that can destroy fragile molecules such as proteins and genes. Therefore, Dr. Jones explained that for effective formulation of nanomedicines, an understanding of the specific endocytic pathways that are inherent in the target cell, the trafficking and fate of the nanomedicine within the cells and through the various compartments, is required. To provide insight into these pathways Dr. Jones focused on the techniques he has used to better understand these routes and the molecules that can be used to enhance intracellular delivery. Using various fluorescent markers Dr. Jones and his co-workers were able to demonstrate that the translocation of L- and D-octa-arginine across the plasma and nuclear membrane of cells was dependent on temperature, concentration, and plasma membrane cholesterol content.



The UKICRS organising committee, with some of the speakers from the day.

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Oral Multi-Particulate Drug Delivery Systems: Challenges and Scope
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**Strategies to Advance the
Bioavailability of Low Solubility Drugs**
*Chairs: Yvonne Perrie, Aston University, U.K.
Thomas Rades, University of Otago, New Zealand*



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UKICRS Hosts continued from page 17

Design, Synthesis, and Characterisation of Biorecognizable Polymers for Drug Delivery

Prof. Henry Kopecek (University of Utah, USA) looked at the concept of targeted polymer-drug conjugates to deliver low molecular weight drugs to malignant cells. He outlined the key features needed to design an effective conjugate, including a polymer-drug linker that is stable during transport and can release the drug at the target site be it a diseased cell or tissue. A water-soluble polymeric drug carrier that Prof. Kopecek discussed was *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymer, which he noted has been shown to be effective for chemotherapy, photodynamic therapy, combination therapy, and imaging targeting. However, acknowledging what Dr. Jones had outlined, targeting of such macromolecules to cell surface receptors was well established, the manipulation of their intracellular delivery required further investigation, and future conjugates would require a double targeting strategy. This would allow them to recognise the diseased cells and be internalised by exploiting endocytic or other pathways.

Delivery of Poorly Water-Soluble Drug Using NanoCrystal Technology—Clinical Challenges, Commercial Opportunities

Presenting technology developed by Elan Pharmaceuticals, Ireland, Dr. Leonard O'Mahony outlined the use of their NanoCrystal technology to improve the profile of megestrol acetate. Using a NanoCrystal form of the drug, they were able to improve the bioavailability of the drug compared to its micronised form. The NanoCrystal formulation dramatically minimised fed/fasted variability (food effects): both the $C_{max}(fed)/(fasted)$ and the $AUC(fed)/fasted$ ratios for the NanoCrystal formulation were close to 1 (an approximate sevenfold reduction in the C_{max} ratio and a twofold reduction in the AUC ratio) when the NanoCrystal form was used compared to the micronized form. This was due to the nanocrystal particles being 50 times smaller and more homogeneous in size compared with those prepared using conventional micronisation. Dr. O'Mahony outlined how the NanoCrystal technology is produced by proprietary high-energy wet milling of the drug and stabilised against agglomeration. The particles are approximately 80–400 nm in diameter, and the specific stabilisers used to provide both steric and/or electrostatic stabilisation are generally regarded as safe.

Overall, this was a highly interesting and stimulating day, which clearly demonstrated there is much we know but even more we still need to look at. ■

What's on Board?

CRS Moves Forward with Satellite Meeting Plans

In 2006, the CRS Board continued their ongoing discussion about member value. The highlights from the serious and productive dialogue were the defining of member value, member value perception, and offering new CRS products for members. One of the outcomes was the plan to hold satellite meetings with more focused topics that would not conflict with the CRS Annual Meeting & Exposition.

Criteria were agreed on, a Satellite Meeting Review Committee was established, a call for satellite meeting applications was sent to members, and the rest, as they say, is history. The Education Committee Industrial Section's application was approved and led to a successful joint workshop with the AAPS at their annual meeting in San Diego, California, in November 2007.

The success of this first satellite meeting led the Board to vote unanimously to continue with the satellite meeting plan established in 2006. In fact, the goal is to host two satellite meetings in 2008.

The first offering out of the gate for 2008 is the Oral Multi-particulate Drug Delivery Systems: Challenges and Scope Satellite Meeting chaired by Ali Rajabi-Siahboomi and Gurminder Singh Rekhi. This event, to be held April 3–4, 2008, will cover what you want to hear and be delivered by the people you want to hear from, all in the warmth and sunshine of Orlando, Florida. Register with CRS by March 1, 2008, for the best rates.

Oral Multi-particulate DDS will be an excellent opportunity for those new to the use of multi-particulates, as well as those who are familiar with and experienced in the area. Attendees will be able to apply what they learn from the meeting to their daily work in API selection and a suitable technology to achieve desired release profiles.



Courtesy of the Embassy Suites Orlando Lake Buena Vista Resort.

The meeting will take place at the Embassy Suites Lake Buena Vista Resort, Orlando, Florida. The \$175 a night (plus tax) suite rate is for single or double occupancy and includes a cooked-to-order breakfast each morning, as well as the manager's reception each evening. The hotel also provides complimentary, scheduled shuttle service to the Walt Disney World® theme parks.

Make your hotel reservations early, as it is spring break time (high season) in Florida. **The deadline for making hotel reservations is March 11, 2008.** After March 11, hotel rooms may not be available at the CRS rate. The discounted CRS rate is offered three days pre- and post-meeting dates, based on availability.

Reservations at the Embassy Suites can be made via telephone or online. By telephone, call Embassy Suites at 1.800.Embassy (1.800.362.2779). Inform the reservationist that you are attending the CRS satellite meeting at the Embassy Suites Lake Buena Vista Resort, in Orlando, Florida, and provide your



Courtesy of the Embassy Suites Orlando Lake Buena Vista Resort.

arrival and departure dates. To reserve online, go to www.embassysuiteslbv.com and enter the Group Code CON. You must enter the group code to receive the discounted CRS rate. ■

Patent Watch



By Jamileh Lakkis, Ph.D.

The following review highlights notable patents (US and international) pertaining to controlled release and delivery systems in foods, flavors, and other consumer products that were filed or granted during the last six months of 2007.

US 7,312,252 B2 to Eastman Kodak, Co. (U.S.A.) – Nanoparticulate Anionic Clays

This patent describes a process for preparing stable layered anionic clay nanoparticles for industrial, medical, and consumer goods applications. The preparation comprises mixing salts of divalent or trivalent metals and an alkali in a high-shear mixing zone and precipitating the clay particles to form interlayer anions contained within layered double hydroxides, chlorides, nitrates, or other functional moieties that possess good leaving properties. Such an assembly is claimed to be beneficial for enhancing intercalation of anionic clay by organic anionic actives in cosmetics and drug formulations. The uniqueness of the layered compounds lies in their strong chemical bonding in two-dimensions but only weak interactions in the third dimension and their ability to adsorb or intercalate ions and compounds.

US 2007/0258879 A1 to Philip Morris (U.S.A.) – Carbon Beads with Multimodal Pore Size Distribution

Methods for preparing activated carbon with multimodal pore distribution and its use for enhancing delivery of actives in cigarette formulations are claimed. The novel material can be prepared by mixing a solution of a polymer precursor, such as pectin or alginates, with a cross-linking polymer precursor followed by carbonization of the mixture and activation of it to form a functional carbon material with a multimodal pore size distribution. The larger pores in the multimodal carbon are claimed to be advantageous for enhancing the adsorption and transportation (i.e., kinetics and diffusion) of the actives, while the smaller pores can entrap those actives in the body of the adsorbing carbon matrix, thus providing a long-lasting effect.

US 7,247,377 B2 – Absorbent Composition of Matter for Controlled Release of Essential Oils

A natural delivery system for entrapping and delivering insecticides is disclosed. The hydrophobic active (insecticide) can be an essential oil such as allyl iso-thiocyanate (a garlic extract) that is entrapped in a natural carrier material. The latter is composed of microparticles that can be generated from milling and classification of corn cobs and that possess a woody ring appearance (viewed via electron microscope) and an internal sponge-like structure that enables them to absorb 1.5–3 times their own weight of the active (oil). This novel material is claimed to be an effective alternative to cyclodextrins for entrapping oils and other hydrophobic substances.

US 7,262,157 B2 to Lubizol Advanced Materials, Inc. (U.S.A.) – Cationic Cassia Derivatives and Applications Thereof

This patent discloses cationically derivatized polygalactomanans (CDPG) from *Cassia tora* and *C. obtusifolia* and their use in personal care, household, and other consumer product applications. CDPGs have been used in a variety of controlled release and delivery systems as stabilizers and carriers. Using the novel CDPGs from *Cassia* is claimed to be effective in overcoming the challenges encountered when using those derived from guar gum, where the high ratio of galactose side units on the polymannose backbone and their role in shielding the –OH groups on the C₆ atom of mannose leads to a low degree of substitution and lower functionality upon delivery of actives and their controlled release.

US 2007/0259097 A1 – Method and Apparatus for the Preparation of Capsules

An apparatus and method for the continuous generation of industrial-scale polysaccharide-based seamless capsules are disclosed. The capsules are claimed to possess a high oil payload that can replace gelatin capsules in the delivery of nutraceuticals such as fish oils. The apparatus is essentially a vibrating tube made up of flat coils and a winding with coils deposited in an aqueous gelling solution. The emulsion-containing oil (active), water, and a gelling agent (e.g., alginates) is introduced into the apparatus and subsequently into the gelling bath (calcium solution). Encapsulation takes place via rotation of the winding, which transports the mixture through the length of the winding and into the aqueous gelling solution. A seamless capsule can be made in a variety of shapes. The latter can be determined by adding the emulsion/dispersion to the gelling solution and by the specific composition of the emulsion/dispersion.

US 7,238,655 B2 to Quest (now Givaudan, Switzerland) – Perfume Encapsulates

Perfume-containing capsules that are stable in the presence of surfactants and aqueous media are claimed. The system comprises aminoplast capsules, a shell consisting of urea-formaldehyde or melamine-formaldehyde polymer, and an anhydride such as ethylene/maleic anhydride copolymer. The latter is incorporated to increase shell resistance to surfactants, thus improving perfume retention properties and enabling use of the capsules in aqueous surfactant-containing products.

US 7,309,685 B2 to Cognis IP Management (Germany) – Textile Finishing Agents for Imparting a Sensory Effect During Use

New textile water-based finishing preparations containing active components with sensory effects are disclosed. The patented preparations comprise a mixture of waxes (melting point just above body temperature), emulsifiers, and crystallization regulator so a small crystal size is maintained ($\approx 6 \mu\text{m}$). Release of the sensory component (active) from the textile material or yarn is triggered by skin temperature or heat generated by ironing or drying.

WO 2007/136263 A1 to Nizo Food Research (The Netherlands) – Protein Encapsulated Particles

A process for modifying the functionality of food proteins, in particular their encapsulation and release properties, is disclosed. The process is, in essence, a physical treatment (heat or high pressure) that can activate the protein rather than denaturing it, so protein aggregates containing a critical number of free sulfhydryl groups can be formed. The protein solution is further mixed with the active substance and is subjected to spray-drying to form a resistant shell material that degrades in the gut to release the entrapped active. The process is described as an effective approach for entrapping air and fat droplets as well as other core actives.

US 2007/122613 A1 to Technion University (Israel) – Casein Micells for Nanoencapsulation of Hydrophobic Compounds

Reassembled casein micelles (rCM) for delivering hydrophobic biologically active compounds such as ω -3 fatty acids are disclosed. Traditional applications of caseins and caseinates, as wall materials, in microencapsulation applications has often resulted in destruction of the original micellar structure, thus changing their natural functional behavior and forming large microcapsules. The latter are likely to impair product smoothness. This patent claims that non-covalent binding of the active to the caseinates results in a delivery system where the casein micelle appears to be undisturbed (micellar size $\approx 150 \text{ nm}$). Incorporating vitamin D into such structures showed minimal effects on the micelle morphology, as observed via transmission electron microscopy.

US 2007/0292508 A1 to Balchem (U.S.A.) – Orally Disintegrating Dosage Forms

This patent discloses a composition containing lipid-coated particulates and their use in various dosage forms. The uniqueness of the composition lies in the incorporation of silica (Prosolv SMCC90), which is claimed to significantly reduce the agglomeration of dry premixes prior to compression for tablet making, thus reducing sieve clogging and providing enhanced chemical and mechanical stability of the dosage.

US 2007/0274930 A1 to Quest (now Givaudan, Switzerland) – Particulates Flavor Composition

This patent describes an approach for forming particulates in which discrete elements of flavor-containing fats are dispersed in a gelatin matrix and for predicting their release behavior. The process consists of pre-dissolving the flavor in oil, emulsifying with an aqueous solution of gelatin, xylitol, and gum arabic, followed by homogenizing and freezing in a cryogenic pelletizer to form small particles. The latter are further ground to a small

particle size ($50\text{--}1,500 \mu\text{m}$) for chewing gum applications. Relative flavor release (X) is claimed to be highly dependent on the type of gelatin and fat concentration, and can be predicted from the following correlation:

$$X = [(\text{bloom number})/150] + [(\% \text{ w/w gelatin})/30] \times [(\% \text{ fat})/10].$$

US 7,288,318 B2 to Nanohybrid Co. Ltd. (Korea) – Cosmetic Raw Materials Having Improved Properties and Process for Preparing the Same

A method and composition for preparing hybrid hydroxyl double salts (HDS) and layered double hydroxides (LDH) containing active cosmetic agents are disclosed. Layered metal hydroxides are weak basic or neutral inorganic materials that possess good skin affinity. Their layered crystal structure shows peculiar reactivity between the layers due to their anion exchange capacity for some components of cosmetic preparations. The hybrid materials can be formed via co-precipitation, ion-exchange, or adsorption methods followed by surface coating. The metal hydroxide salts are dispersed in an alkali medium to form layered metal hydroxides. The latter is further dispersed in an aqueous solvent to which the active can be added to cause an ion-exchange reaction. The resulting HDS materials were claimed to be excellent carriers and stabilizers of vitamins, alpha-hydroxy acids, konjac acid, and other cosmetic actives.

US 2007/0104866 A1 to University of Massachusetts at Amherst (U.S.A.) – Encapsulated Emulsions and Methods of Preparation

This patent describes a controlled release system composed of two or more emulsions in the form of a stable, dry reconstitutable delivery system. One of the emulsions can be made up of the active oil, such as ω -3 fatty acids, and an emulsifier component, such as monoglyceride esters, carrying a positive charge. The second emulsion is composed of a food-grade polymer, such as gums, polysaccharides, or chitosan (pK_a of $6.3\text{--}7.0$), carrying an opposite charge to that of the first emulsion. Emulsion properties and the active's release pattern are claimed to be altered by varying the pH of the medium, thus promoting or reducing electrostatic interactions. The reconstituted emulsion is claimed to be stable at $\text{pH} < 5.0$ but not at higher pH's, presumably due to lowered zeta-potential and subsequent promotion of electrostatic repulsion between the droplets, leading to droplet flocculation.

US 7,229,818 B2 – Formulations to Increase In Vivo Survival of Probiotic Bacteria and Extend Their Shelf Life

A probiotic composition stabilized by the addition of dried monovalent alginates to the bacteria in the dry state and filling the mixture into gelatin or cellulose capsules is disclosed. The protective effect of monovalent alginates is claimed to be due to their ability to convert to insoluble alginic acid. The latter forms a gel-like shell that encases the majority of the mixture, holding it in a semi-dry condition at a pH substantially higher than that of the external environment. At higher pH's, i.e., in the intestinal section of the GIT, the gel structure dissolves and releases viable probiotic bacteria, and the insoluble alginic acid converts back to a soluble alginate salt.

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IONSYS™, a Needle-free System for Management of Acute Post-operative Pain, Available in Germany, the UK, and Ireland

Pain & Central Nervous System Week via NewsEdge Corporation: January 24, 2008 – Janssen-Cilag International NV has announced that IONSYS™ (fentanyl iontophoretic transdermal system), a new innovative, needle-free system indicated for the management of acute post-operative pain in a hospital setting, is now available in Germany, the UK, and Ireland. These countries represent the first markets to launch this novel product, and additional launches in other European countries are planned for the coming months.

As a patient-activated system, the fentanyl iontophoretic transdermal system does not require needles, pumps, catheters, or intravenous (IV) pump stands for the management of post-operative pain. Being needle-free, this treatment eliminates the risk of needle-stick injuries and infection due to analgesic administration with intravenous patient controlled analgesia (IV PCA). This system has the potential to make the administration of post-operative pain management a less time-consuming task for healthcare professionals and less intrusive for patients.

The fentanyl iontophoretic transdermal system is a compact, self-contained, preprogrammed system designed to simplify the delivery of post-operative pain relief for hospitalized patients and their healthcare professionals. It is small and lightweight and has an adhesive backing that securely adheres to the patient's upper outer arm or chest. After the patient presses a button on the system, IONSYS uses a virtually imperceptible low-intensity electrical field to rapidly transport fentanyl through the skin and into the bloodstream in a technologically advanced process called iontophoresis.

The European Commission granted marketing authorization for IONSYS™ throughout the EU based on the findings

of a comprehensive clinical trial program. In November 2007, a Type II variation was approved by the commission, in reference to a change in product packaging and a change in the package leaflet. The fentanyl iontophoretic transdermal system has been demonstrated to be as effective as IV PCA morphine for the management of acute post-operative pain.

Research from Johns Hopkins University, Department of Biomedical Engineering, Yields New Data on Drug Delivery

Blood Weekly via NewsEdge Corporation: January 24, 2008 – A report, "3D Lithographically Fabricated Nanoliter Containers for Drug Delivery," recently published in *Advanced Drug Delivery Reviews* contains new data. According to recent research published in the journal, "Lithographic patterning offers the possibility for precise structuring of drug delivery devices. The fabrication process can also facilitate the incorporation of advanced functionality for imaging, sensing, telemetry and actuation."

"However, a major limitation of present day lithographic fabrication is the inherent two-dimensionality of the patterning process. We review a new approach to construct three dimensional (3D) patterned containers by lithographically patterning two dimensional (2D) templates with liquefiable hinges that spontaneously fold upon heating into hollow polyhedral containers. The containers have finite encapsulation volumes, can be made small enough to pass through a hypodermic needle, and the 3D profile of the containers facilitates enhanced diffusion with the surrounding medium as compared to reservoir systems fabricated in planar substrates. We compare the features of the containers to those of present day drug delivery systems.... We also review possible applications in drug delivery and cell encapsulation therapy (CET)," writes C. L. Randall and colleagues, Johns Hopkins University, Department of Biomedical Engineering. The researchers conclude,

"The results summarized in this review suggest a new strategy to enable construction of 'smart', three dimensional drug delivery systems using lithography."

Randall and colleagues published their study in *Advanced Drug Delivery Reviews* (3D lithographically fabricated nanoliter containers for drug delivery. *Advanced Drug Delivery Reviews*, 2007;59(15):1547-1561). For additional information, contact C. L. Randall, Johns Hopkins University, Department of Biomedical Engineering, 720 Rutland Ave., Baltimore, MD 21205, USA.

Vyteris Announces First Successful Non-invasive Delivery of Peptide Using Smart Patch Technology

Business Wire via NewsEdge Corporation (Business Wire): January 22, 2008 – FAIR LAWN, N.J. – Citing a significant advance in drug delivery, Vyteris, Inc. (OTC BB: VYHN) and Ferring Pharmaceuticals have announced their results from a completed Phase I clinical trial demonstrating that Vyteris' patented Smart Patch transdermal technology successfully delivered a peptide molecule in humans (multiple pulse) without the use of needles (non-invasively) in therapeutic levels aimed at the treatment of female infertility.

"These trial results represent a significant accomplishment for Vyteris in demonstrating that our delivery system [is] capable of achieving therapeutic levels of a peptide without using any needles," said Timothy J. McIntyre, chief executive officer of Vyteris. "This is the initial step in potentially clearing the pathway to pursue eventual commercialization of this technology and its broader applications to other peptides, which as a class of biotechnology drugs, are severely limited to delivery by subcutaneous (subQ)/intramuscular (IM) injections or intravenous (IV) infusions."

As part of the trial agreement between Vyteris and Ferring Pharmaceuticals, the study results showed that therapeutic levels of the peptide in humans are achievable without the use of injections or infusion pumps. The clinical trial was conducted in the U.S. with 30 healthy volunteers under an investigational new drug (IND) application. Specific technical data will undergo peer review for future disclosure.

Kenneth Kashkin, chief medical officer and senior vice president global clinical research and development of Ferring Pharmaceuticals, provides an assessment on the importance of this clinical advance, "Significant technological advances, not previously achieved in peptide delivery, have been accomplished by the Ferring/Vyteris team, and we look forward to successfully completing Phase I."

In the Phase I clinical trial, a pulse profile controlled the transdermal delivery of the peptide from patches loaded with different concentrations of the peptide. The amounts of peptide delivered using the patch were comparable or higher than with subcutaneous (subQ) injection. The study used different formulations within the Vyteris patch that were compared with subQ delivery of the peptide. No unexpected adverse side effects were observed in any of the trial participants.

The product under development by Vyteris and Ferring would employ Vyteris' patented Smart Patch drug delivery technology, which is positioned to provide a safe and effective method of delivering drugs via a pre-programmed regulating system, a characteristic important in the delivery of therapeutics for the treatment of female infertility, while offering the possibility of administering the peptide without needles, and is being designed to deliver multiple transdermal pulses automatically, around the clock, in a painless, convenient and cost-effective manner.

Novo Nordisk Halts Work on AERx Inhaled Insulin

Reuters: January 14, 2008 – NEW YORK, N.Y. – Danish drugmaker Novo Nordisk (NOVOB.CO: Quote, Profile, Research)

(NVO.N: Quote, Profile, Research) has announced that it is halting development of its AERx inhaled insulin product and will lay off most of the approximately 300 company employees working on the product. The company said it decided the product, meant to deliver inhaled droplets of liquid insulin, did not have adequate commercial potential given the recent failure to attract patients of Pfizer Inc.'s (PFE.N: Quote, Profile, Research) own inhaled insulin drug, called Exubera.

Pfizer in October abandoned its involvement with Exubera, which delivered inhaled insulin powder through a bulky device, because of dismal sales. "In simply looking at the market and the convenience of our device, we decided it is not really there," Novo Nordisk spokesperson Christian Qvist Frandsen states. Frandsen says Novo Nordisk plans to lay off the majority of its 300-person team developing the product, based primarily in Hayward, California. "We will continue to research inhaled insulin powder and inhaled liquid insulin, but starting from scratch," Frandsen says.

Novo Nordisk is one of the world's biggest sellers of insulin drugs, which are taken by injection several times a day to control excessive amounts of sugar in the bloodstream. Novo Nordisk had licensed rights to the AERx product from Aradigm Corp (ARDM.OB: Quote, Profile, Research), a tiny biotechnology company. "We will have to negotiate to give the rights back to Aradigm," says Frandsen. Frandsen says Aradigm would have received a "small single-digit royalty" on sales of AERx if Novo Nordisk had brought the product to market. Eli Lilly and Co. (LLY.N: Quote, Profile, Research) and its partner, Alkermes Inc. (ALKS.O: Quote, Profile, Research), are continuing to develop a powdered form of inhaled insulin called Air Insulin.

Noven Announces FDA Tentative Approval of Stavzor™ Valproic Acid Delayed-Release Capsules

Medical Letter on the CDC & FDA via NewsEdge Corporation: January 13, 2008 – Noven Pharmaceuticals, Inc. (NASDAQ: NOVN) has announced that the U.S. Food and Drug Administration (FDA) has issued a tentative approval letter related to the new drug application (NDA) for Stavzor™ (valproic acid

delayed-release capsules) in 125-mg, 250-mg, and 500-mg strengths. The tentative approval relates to the use of Stavzor™ in the treatment of manic episodes associated with bipolar disorder, monotherapy and adjunctive therapy in multiple seizure types (including epilepsy), and prophylaxis of migraine headaches.

The FDA states in the letter that it has completed its review of the amended Stavzor™ NDA and that it is tentatively approved. "Tentative approval" generally means that the FDA has concluded that a drug product has met all required quality, safety, and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States.

The NDA for Stavzor™, which was submitted by Banner Pharmacaps Inc. (the NDA holder and developer of the product) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, references Abbott Laboratories' Depakote® product. Based on receipt of the tentative approval letter and Noven's understanding of Depakote® exclusivity, Noven continues to expect FDA final approval of Stavzor™ by the end of July 2008.

Stavzor™ was developed using Banner's patent-pending EnteriCare™ enteric soft gelatin capsule delivery system. Noven acquired a license to market and sell Stavzor™ in the United States as part of Noven's acquisition of JDS Pharmaceuticals in August 2007. If approved for marketing, Stavzor™ will be a branded product; it will not be AB-rated to or generically substitutable for Depakote®, nor will Depakote® or any Depakote® generics be substitutable for Stavzor™. Promotion of the Stavzor™ brand will occur through the Noven/JDS sales force.

"We are very pleased that Banner's response to the FDA's October 2007 approvable letter for Stavzor™ was deemed a complete response by the FDA, and that the FDA has granted tentative approval of this important new product for the treatment of three indications," states Robert C. Strauss, Noven's president, CEO, and chair. "Stavzor™ launch and production planning is underway in support of an expected 2008 launch

through the Noven/JDS sales and marketing organization.”

NEOPHARM Files IND for Novel Liposomal Delivery System of Docetaxel

Medical Letter on the CDC & FDA via NewsEdge Corporation: January 10, 2008 – NEOPHARM, Inc. (NASDAQ: NEOL) has filed an investigational new drug (IND) application with the U.S. Food and Drug Administration (FDA) for a novel, proprietary liposomal delivery system of docetaxel, the active ingredient of Taxotere® (docetaxel), for the treatment of patients with locally advanced or metastatic solid tumors after failure of prior chemotherapy.

“This filing is a notable milestone in the advancement of our NeoLipid platform, which I believe reflects our commitment to progressing our portfolio, while concurrently optimizing the Company’s cost structure,” comments Laurence Birch, president and chief executive officer of NEOPHARM Inc. “In August 2007, we announced our drug development timeline, and the IND for LE-DT is the first step in achieving that plan. We are on track and are now in a position to further our portfolio in 2008 and are optimistic for what the coming year should bring.”

Assuming FDA acceptance of the IND application, NEOPHARM intends to enter a Phase I clinical study to assess the maximum tolerated (MTD) dose and dose limiting toxicity (DLT) of liposome entrapped docetaxel for injection (LE-DT) in approximately 30 patients. Additionally, NEOPHARM will use this Phase I study to evaluate the pharmacokinetics of LE-DT therapy and any anti-tumor effects of LE-DT.

Pre-clinical data suggest that LE-DT may improve the safety profile of docetaxel, eliminate the risk of hypersensitivity reactions, maximize the therapeutic benefit, minimize side effect, and, overall, exhibit a better efficacy profile.

Watson Announces Positive Results from Its Pivotal Study of Oxybutynin Topical Gel for Treatment of Overactive Bladder

PR Newswire-FirstCall: January 7, 2008 – CORONA, Calif. – Watson

Pharmaceuticals, Inc. (NYSE: WPI), a leading specialty pharmaceutical company, has announced positive results from its Phase III study of oxybutynin topical gel (OTG) in patients with overactive bladder (OAB). The study met its primary endpoint of a statistically significant reduction in incontinence episodes and secondary endpoints of reduction in frequency and increases in void volume compared with placebo, while demonstrating a low incidence of side effects.

“We are extremely encouraged with the results from this trial which will support our NDA submission, and we are on track to file with FDA in the second quarter of 2008,” states Paul Bisaro, Watson’s president and chief executive officer.

“Additionally, we have the potential to introduce the first gel formulation for the treatment of overactive bladder in 2009.” “Offering patients the ease and comfort of a daily gel for the treatment of OAB may provide greater patient acceptability and persistence on treatment,” says Peter K. Sand, M.D., director of the Evanston Continence Center, Evanston Northwestern Healthcare, Northwestern University, Feinberg School of Medicine, and professor of obstetrics and gynecology and director of the Division of Urogynecology, Evanston, IL.

It is well recognized that transdermal delivery of oxybutynin is a safe and effective treatment for OAB. By delivering oxybutynin transdermally, first-pass gastric and hepatic metabolism is bypassed, which is believed to result in lower anticholinergic side effects such as dry mouth and constipation. These side effects result in a significant level of patient non-compliance among existing oral OAB treatments, according to Dr. Sand.

“Watson’s oxybutynin gel is an elegant topical formulation that is clear, odorless and fast drying and will offer healthcare providers a unique treatment option for OAB patients,” states Dr. Sand.

The Phase III multi-center, double-blind, placebo-controlled study evaluated the efficacy and safety of OTG in 789 patients with overactive bladder. The primary objective of the study was to demonstrate that daily treatment of a 1-g dose (approximately 1 mL) of OTG for 12 weeks was superior to placebo for the relief

of OAB symptoms. Changes from baseline to endpoint were calculated from a 3-day patient urinary diary and included a reduction in incontinence episodes and urinary frequency and an increase in void volume. Additionally, 216 patients participated in a 14-week, open-label, safety-extension study for a total of 26 weeks. During the double-blind portion of the trial, highly statistically significant improvements relative to placebo were seen on all of these endpoints.

Phase I studies have demonstrated that the steady-state plasma levels of oxybutynin show little fluctuation during the 24-hr dosing interval, and absorption of oxybutynin is similar when applied to the abdomen, thigh, or upper arm/shoulder.

Alexza Partners with Endo for AZ-003 (Staccato® Fentanyl) in North America

PR Newswire-FirstCall: December 27, 2007 – PALO ALTO, Calif. – Alexza Pharmaceuticals, Inc. (Nasdaq: ALXA) has initiated a license and development partnership with Endo Pharmaceuticals Holdings Inc. (Nasdaq: ENDP) for AZ-003 (Staccato® fentanyl) and the fentanyl class of molecules for North America. Currently in Phase I clinical development, AZ-003 is a hand-held drug device that uses Alexza’s proprietary Staccato® system inhalation technology to deliver fentanyl for the treatment of breakthrough pain in cancer and non-cancer patients.

“We have consistently reiterated how important it is for Alexza to develop the possible tamper and diversion-resistant attributes of our AZ-003 product with an established market leader in pain management,” states Thomas B. King, president and CEO of Alexza. “We believe Endo is an ideal partner for AZ-003. We look forward to working together with them to develop this important new technology and product for the opioid markets.”

In the partnership, Alexza has primary responsibility for the development of the Staccato® electronic multiple dose device and the exclusive right to manufacture the product for clinical development and commercial supply. Endo has primary

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responsibility for pre-clinical, clinical and regulatory development, and, if AZ0003 is approved for marketing, for commercializing the product in North America.

New Company Formed for Drug Delivery Technology

In-PharmaTechnologist.com: December 21, 2007 – Jerusalem-based Yissum has formed a spin-off company, Nanolymf, that will be dedicated to advancing a nanotechnology controlled release drug delivery platform. The biotechnology start-up company was founded as a subsidiary of Israel-based Shizim and will advance the technology, which has been exclusively licensed from Yissum.

The platform increases the bioavailability of orally administered lipophilic drugs, which are poorly soluble in water, by bypassing the intestinal and liver metabolic filters. "The ability to deliver lipophilic drugs orally while bypassing specific potent barriers in the intestine and the liver carries tremendous potential," Yissum Chief Executive Nava Swersky says. "Professor [Simon] Benita has once again demonstrated his ingenuity in developing a novel mechanism addressing many unmet medical needs. Shizim is an excellent partner for launching this new company."

Lipophilic drugs are poorly water soluble and so have limited bioavailability. Only 25% of the drug is absorbed when administered orally because it activates an intestinal pump barrier and is metabolized in the intestines and liver. The oral route, therefore, is limited, and many of these types of drugs are injected instead.

The Nanolymf technology is able to bypass the intestine and liver filters without altering the drug molecules or affecting the normal physiological activity of the metabolic filters. The technology has been successfully tested on animals, resulting in 2.4 times higher bioavailability of the model drug Tacrolimus in large animals and is now ready for clinical trials on humans. "We are very excited with the potential of Nanolymf's technology to offer a significant breakthrough in the oral administration of many drugs and

encouraged by the extraordinary pre-clinical results," Nanolymf founder, Chief Executive and Chair Yossi Bornstein states.

Nanolymf has acquired exclusive rights, and Yissum will receive royalties, sublicense fees, and an equity stake in Nanolymf. The company has raised about \$500,000 from private investors and is seeking to raise an additional \$2 million to fund initial clinical studies.

Kalypsys Initiates Phase IIa Clinical Trial of Topical iNOS Inhibitor

December 18, 2007 – SAN DIEGO, Calif. – Kalypsys Inc. has initiated a Phase IIa clinical trial of KD7040, an inducible nitric oxide synthase (iNOS) inhibitor formulated as a topical gel, for the treatment of postherpetic neuralgia (PHN). Kalypsys will conduct a double-blind, placebo-controlled trial, which will enroll approximately 50 patients at 12–15 centers in the United States, to demonstrate proof-of-concept for KD7040 as a treatment for neuropathic pain. Trial participants, who have had PHN-related pain of moderate-to-severe intensity for at least 3 months, will receive KD7040 or placebo for a period of 14 days. The endpoints of the trial include assessment of changes in worst and average daily pain scores, as well as impact on sleep, mood, and function.

"KD7040 topical gel is our most advanced compound from a broad portfolio that we are building to create long-term value through the discovery and development of treatments for pain and inflammation," notes Paul Grint, M.D., chief medical officer for Kalypsys. "Over the course of 2007 this project has moved in rapid progression from first-in-human studies to the initiation of the Phase II study. This progress demonstrates the quality and speed with which Kalypsys is bringing novel therapeutic candidates forward for the treatment of chronic pain conditions." August Watanabe, M.D., vice chair of Kalypsys adds, "While our initial focus is on the investigation of the therapeutic effects of the topical gel on PHN, we believe that KD7040 has potential in other indications. Therefore, KD7040 has a profile that fits nicely into a franchise focused on underserved chronic pain markets."

DURECT Announces Positive ELADUR™ Phase IIa Study Results

PR Newswire-FirstCall: December 18, 2007 – CUPERTINO, Calif. – DURECT Corporation (Nasdaq: DRRX) has announced positive results from a Phase IIa clinical trial for ELADUR™, DURECT's proprietary investigational transdermal pain patch. In this study of patients suffering from post-herpetic neuralgia, ELADUR™ showed improved pain control versus placebo during the 3-day continuous treatment period. In addition, ELADUR™ appeared well-tolerated overall, and patients treated with ELADUR™ and placebo exhibited similar safety profiles.

"To our knowledge, this is the first topical local anesthetic formulation that supports a full 3 days of pain control from a single application," states James E. Brown, DVM, president and CEO of DURECT. "In this study, ELADUR™ showed comparable safety to placebo patches as well as good wearability characteristics as patients went about their normal daily activities such as exercising and showering while wearing the patches."

This Phase IIa study was a randomized, multi-center, double-blind, placebo-controlled, two-way cross-over study of 60 patients suffering from post-herpetic neuralgia (post-shingles pain or PHN). The objectives of the study were to assess the safety as well as the magnitude, duration, and characteristics of analgesic activity of ELADUR™. DURECT anticipates that detailed results will be submitted for presentation at the American Pain Society Annual Meeting in May 2008.

Phosphagenics Announces Successful Phase I Transdermal Oxycodone Clinical Trial Results

PR Newswire-FirstCall: December 17, 2007 – MELBOURNE, Australia – Phosphagenics Limited (ASX: POH, AIM: PSG, OTCQX: PPGNY) has announced positive results of its Phase I clinical trial that showed its delivery technology, TPM, delivered the leading pain-relief drug oxycodone through the skin without causing disruption or irritation of any kind. These results support Phosphagenics' aims to be the first

company to commercialize a sustained release oxycodone patch for the management of chronic pain. "Oxycodone, with worldwide annual sales of more than \$1 billion, is more potent than morphine with fewer adverse effects; however, oxycodone is not available transdermally due to serious issues relating to skin sensitization and irritation," states Dr. Esra Ogru, executive vice president of research and development at Phosphagenics. "Our trial results show that TPM can deliver oxycodone through the skin in a sustained release formulation without causing skin irritation."

This trial, which was conducted by CMAX (an independent clinical research organization located at the Royal Adelaide Hospital), was a single-centre, single-blinded, pharmacokinetic trial in 16 healthy subjects. The trial endpoints were to evaluate the safety and tolerability of the TPM/oxycodone formulation and the ability of the TPM technology to deliver oxycodone into the body. The oxycodone, administered as a single transdermal application, was safe with no adverse events reported. Oxycodone was detected in the subjects for at least 48 hr. The results demonstrate that the formulation is bioavailable and effective in delivering oxycodone into the body.

A collaborative program is now under way with a world-leading patch-development company to incorporate the current formulation into a patch system. Plans are also underway to undertake a pivotal clinical study in the first half of 2008. Harry Rosen, president and CEO of Phosphagenics, notes, "Completing this Phase 1 trial was an important milestone for our pain management program. We are delighted to have successfully completed this trial and look forward to progressing to the next phase."

Phosphagenics is a Melbourne-based, globally driven biotechnology company focused on the discovery of new and cost-effective ways to enhance the bioavailability, activity, safety, and delivery of proven pharmaceutical and nutraceutical products. Phosphagenics' core technology is built around the science and application of phosphorylation, a process where the addition of a phosphate group has been found to enhance the bioavailability, activity, and safety of

existing pharmaceuticals and nutraceuticals, as well as to assist in the production of drug delivery platforms.

Access Pharmaceuticals Demonstrates Ability to Significantly Reduce Glucose Levels in Pre-clinical Testing of Cobalamin™ Oral Insulin

December 7, 2007 – DALLAS, Tex. – Access Pharmaceuticals, Inc. (OTC BB: ACCP) has demonstrated the ability, using the company's proprietary Cobalamin™ technology, to significantly reduce glucose levels in an animal model of diabetes through its oral insulin product candidate. Several formulations using Cobalamin™, which is based on the body's natural absorption of vitamin B₁₂ in the gastrointestinal tract, were tested in an animal model of diabetes. Additional pre-clinical studies are planned.

Access has patents and formulations based on vitamin B₁₂ attachment to polymers and nanoparticles, which carry an attached or encapsulated drug. The vitamin B₁₂ absorption mechanism transfers the macrostructure from the gut to the blood, facilitating the absorption of drugs that otherwise could not be delivered orally. Access' Cobalamin™ technology has the potential to enable and improve the oral bioavailability of active drugs, which currently have to be administered by injection, including proteins, antibodies, and siRNA.

"While Access already has proof-of-principle data using this technology with a variety of proteins and peptides, we are delighted to have attained preclinical study results which indicate that a meaningful pharmacological effect can be achieved," states Dr. David P. Nowotnik, Access' senior vice president, research and development. "As a result of this very promising result, we plan to complete a short series of formulation optimization studies and then to select a clinical development candidate."

Access intends to develop the Cobalamin™ oral delivery technology in collaboration with other pharmaceutical and biotechnology companies. Access has in the past and continues to conduct sponsored research programs with leading pharmaceutical companies based on its Cobalamin™ technology. The company is

also actively seeking additional partners for both its oral insulin and other potential programs.

"While the primary focus of our company remains the development of products for the treatment and supportive care of cancer patients, we are excited by these promising results in an animal model," adds Stephen R. Seiler, Access' president and CEO. "In addition to providing a potential oral delivery option for insulin which would be attractive to a large number of pharmaceutical companies and which we would develop in partnership with a collaborator, we believe that our Access Pharmaceuticals, Inc. Cobalamin™ technology has applicability to a variety of cancer products, such as LHRH which are part of our developing cancer and supportive care franchise."

Transport Pharmaceuticals Receives Frost & Sullivan Technology Innovation Award

PR Newswire: December 6, 2007 – FRAMINGHAM, Mass. – Transport Pharmaceuticals, Inc., a leader in combination drug/medical devices for the topical treatment of dermatological conditions, has been awarded the 2007 Frost & Sullivan North American Technology Innovation of the Year Award for its work in electrokinesis-enabled drug delivery. Frost & Sullivan, a global-growth consulting company, honored Transport at its annual North American Excellence in Healthcare Opportunities Awards Banquet, December 5, 2007, in Orlando, Florida.

Frost & Sullivan has recognized Transport with this prestigious innovation award for making "significant contributions in enhancing the delivery of topically applied dermatologic drugs." Transport's lead product, the SoloVir™ electrokinetic transdermal system (SoloVir™ ETS), may represent a significant breakthrough in the treatment of herpes labialis, also known as cold sores. SoloVir™ ETS enables the delivery of the company's novel 5% acyclovir gel formulation by means of electric current via a small, finger mounted, microprocessor-driven control unit with a single-use, unit-dose drug cartridge. This innovative design allows patients to safely

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self-administer the drug, exactly where, and when it is needed.

Dennis I. Goldberg, Ph.D., president and chief executive officer of Transport, comments on the award, "It is a great honor to receive this award from the respected Frost & Sullivan organization. I am pleased to accept this award on behalf of Transport and recognize the team that makes our unique drug/device combination products a reality. It's not just management and investors; it's the engineers, chemists, biologists, clinical development, regulatory and quality assurance experts who have contributed to our continued success. The convergence of all of these disciplines into a highly focused company is what distinguishes Transport Pharmaceuticals from the competition. It is gratifying to see the recognition for our innovation which is expected to bring significant contributions to patients afflicted with dermatology diseases and the physicians who treat them."

"Electrokinetic drug delivery has emerged as an alternative approach to overcome the limitations of, and to obviate the need for, hypodermic injection of many medications," states Pramodh Ishwarakrishnan, Frost & Sullivan industry analyst. "Transport Pharmaceuticals has achieved the noble distinction of creating a system which is poised to revolutionize the field of dermal drug delivery."

While Transport's initial focus is herpes labialis, future indications include onychomycosis, acne, actinic keratosis, keloids, warts, psoriasis, skin cancer, and medical aesthetic applications

New Drug Delivery Study Findings Reported by Scientists at Paul Brousse Hospital

Cancer Weekly via NewsEdge Corporation: December 6, 2007 – Fresh data on drug delivery are presented in the report "Modeling Oxaliplatin Drug Delivery to Circadian Rhythms in Drug Metabolism and Host Tolerance." According to recent research from France, "To make possible the design of optimal (circadian and other period) time-scheduled regimens for cytotoxic drug delivery by intravenous infusion, a

pharmacokinetic-pharmacodynamic (PK-PD, with circadian periodic drug dynamics) model of chemotherapy on a population of tumor cells and its tolerance by a population of fast renewing healthy cells is presented. The application chosen for identification of the model parameters is the treatment by oxaliplatin of Glasgow osteosarcoma, a murine tumor, and the healthy cell population is the jejunal mucosa, which is the main target of oxaliplatin toxicity in mice."

"The model shows the advantage of a periodic time-scheduled regimen, compared to the conventional continuous constant infusion of the same daily dose, when the biological time of peak infusion is correctly chosen. Furthermore, it is well adapted to using mathematical optimization methods of drug infusion flow, choosing tumor population minimization as the objective function and healthy tissue preservation as a constraint," writes J. Clairambault and colleagues, Paul Brousse Hospital. The researchers conclude, "Such a constraint is in clinical settings tunable by physicians by taking into account the patient's state of health."

Clairambault and colleagues published their study in *Advanced Drug Delivery Reviews* (Modeling oxaliplatin drug delivery to circadian rhythms in drug metabolism and host tolerance. *Advanced Drug Delivery Reviews*, 2007;59(9-10):1054-1068).

U.S.-Based 3M in Talks with Indian Pharma Companies to License Tech Technologies

December 4, 2007 – U.S.-based \$23-billion diversified technology firm 3M is in talks with top domestic pharma companies to license drug delivery technologies. As a leading provider of asthma inhaler solutions to Indian companies, 3M plans to partner these firms in developing medicines that can be delivered through the skin (transdermal drug delivery). 3M expects its drug delivery division to be a future growth driver for its healthcare business in India. It wants to cash in on the recent trend among Indian pharma firms for innovative research, especially in drug delivery systems. The company is also exploring the option to conduct joint studies with Indian pharma firms. Talks have been initiated with the top 10

Indian pharma companies for transdermal drug delivery systems. According to Gautam Khanna, 3M India's vice president and head of healthcare, the firms are identifying molecules that can be delivered through their technology. Globally, 3M collaborates with pharma firms for product identification and pre-feasibility assessment until the commercialization of drugs. Its transdermal drug delivery solutions are for a wide variety of molecules, including vaccine, protein, and peptide.

3M, which is a global leader in inhalation drug delivery, manufactures more than 60 million metered dose inhalers each year. The company already works with a host of Indian firms for their asthma inhalers.

A Spoonful of Foam Helps the Medicine Go Down

In-PharmaTechnologist.com: November 29, 2007 – Is it a liquid? Is it a solid?... No, it's "foam-on-a-spoon." The drug delivery technology is a first of its kind, according to its makers at The Dow Chemical Company. And, its potential for the paediatric and geriatric markets is promising.

"A parent can deliver medicine to a child without worrying about the spilling and staining associated with typical coloured liquid medicines. The same is true for elderly patients and even pets that need medications," says The Dow Chemical Company Technical Services Leader Paul Sheskey. "Foam-on-a-spoon was developed to aid the dispensing of liquid preparations. Dow scientists were looking for a fast dissolving drug delivery system that would be easier to administer to people with difficulty taking tablets and capsules."

The foam-on-a-spoon (FOAS) drug delivery technology works by incorporating air into a liquid formulation using a foam dispenser. "When a foamed formulation is dispensed onto a spoon, the yield stress imparts to the fluid a significant spill-resistance," Sheskey said.

The company uses a foam dispenser made by Rexam Airspray, which is currently used in many applications, including hair, skincare, liquid soaps, and sun screens. Methylcellulose was used as the foaming agent. The technology itself is described by

Sheskey as a “natural progression” from the company’s foam granulation technology, which combines hypromellose with air to enhance tablet production while using less water than traditional wet granulation processing. “Potential advantages for this technology include product differentiation and line extension, convenience because no water is required, fast dissolution, and spill resistance,” Sheskey states.

The company has so far developed three prototypes using the active pharmaceutical ingredients (APIs) acetaminophen, diphenhydramine hydrochloride, and dextromethorphan hydrobromide, although Sheskey notes any API soluble in a liquid vehicle could be delivered this way. “Typical uses would include analgesics, cough-cold preparations, and allergy medications.” Sheskey says it is possible to look into developing a modified release profile for foam formulations, although the company was yet to investigate this.

FORMAC Pharmaceuticals Raises €1.7 Million to Launch New Drug Delivery Business

Market Wire via NewsEdge Corporation: November 7, 2007 – LEUVEN, Belgium – FORMAC Pharmaceuticals N.V. has raised €1.7 million (US\$2.4 million) to start up a new drug delivery business focused on the development of improved oral formulations of small organic drug compounds. FORMAC is a spin-off company from the University of Leuven (K.U.Leuven) based on four proprietary drug delivery technologies. The financing round was led by Allegro Investment Fund, Hunza Ventures, Gemma Frisius Fonds K.U.Leuven II, and Vinnof.

FORMAC will use its proprietary technology platform as a starting-point for the in-house development of improved delivery forms of generics and branded drugs of which the patent rights are near expiration. In parallel, FORMAC will provide access to its unique drug delivery technologies and pre-formulation skills in contract R&D and licensing collaborations with pharmaceutical companies.

FORMAC’s technology platform results from a long-term multi-disciplinary academic collaboration between the following K.U.Leuven research groups:

Department of Pharmaceutical Sciences (Prof. Guy Van den Mooter and Prof. Patrick Augustijns), Department of Microbial and Molecular Systems (Prof. Johan Martens), Department of Metallurgy and Materials Engineering (Prof. Jan van Humbeeck), and Department of Pathophysiology (Prof. Paul Rutgeerts).

“Drug delivery is a booming business and FORMAC intends to become one of the key players in this industry,” says Laurens G. Theunis, chief executive officer of FORMAC. “This investment will allow us to rapidly advance our internal programs towards clinical development and to gradually expand our global commercialization activities.”

“We were impressed with the enormous scientific and commercial potential of FORMAC’s technology platform,” says Geert Everaert, managing partner of Allegro Investment Fund and chair of FORMAC. “FORMAC’s new approach to drug development will allow pharmaceutical companies to enhance R&D productivity as well as to address the need for better and safer medicines.”

Thinsol™, a Novel Oral Ingestible Film Composition Delivery System, Takes the Heat Out of Manufacturing

Marketwire: November 6, 2007 – MONTREAL, Canada – Paladin Labs Inc. (TSX: PLB), a leading Canadian specialty pharmaceutical company, has submitted a patent application for its novel oral ingestible film composition delivery system, Thinsol™. Thinsol™ is a water-based, enzymatically digested carboxymethylcellulose (CMC-enz) film that is suitable for the rapid delivery of pharmaceutical and nutraceutical active ingredients.

Thinsol™ may offer significant advantages over current edible film technologies. BioEnvelop’s™ research has determined that use of the Thinsol™ delivery technology allows for the development of products that others may not be able to formulate in a film strip format, such as products that are heat-sensitive and those that require high drug loads on each strip.

Specifically, Thinsol™ can accommodate active ingredients in a quantity of up to

60% of the overall weight of the film, allowing for development of a film strip containing over 100 mg of active ingredients. Currently, the largest amount of active ingredients in a commercial film strip is 60 mg.

In addition, unlike most film strip technology, Thinsol™ does not require heat during the manufacturing process. Using Thinsol™, films can be dried at low temperatures from sources such as hot air or infrared technology, which allows for greater product opportunities for drugs that are heat-sensitive or labile.

“Thinsol™ is fast dissolving, it leaves no residue in the mouth, being a water-based system, there is no need for the use of alcohol or other solvents during its production and it can be dried at low temperatures,” says Etan Jagermann, chief operating officer of BioEnvelop™. “This technology opens up a whole new source of product opportunities for BioEnvelop™.”

The film can dissolve in 5–30 sec, but BioEnvelop R&D Director Eve Belanger adds that the strip could be formulated to take longer to dissolve. “If we needed, we can increase [dissolution] to one minute. Some drugs are better absorbed when they take longer to dissolve in the mouth,” she said. “The drugs used could be either soluble or insoluble.”

So far the companies have done trials with proteins, herbal extracts, oils, and caffeine. Belanger adds that the strips could be formulated to taste like peppermint or chocolate and could even use an encapsulation technology to hide the bad taste of the drugs.

Altea Therapeutics Announces Positive Clinical Results for Its Basal Insulin Transdermal Patch in Patients with Type 1 Diabetes

Business Wire via NewsEdge Corporation: October 30, 2007 – ATLANTA, Ga. – Altea Therapeutics has achieved sustained and steady basal levels of insulin in patients with type 1 diabetes using a small transdermal patch delivering recombinant human insulin in a cost-effective manner. These results were

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presented at the SMi 8th Annual Diabetes Conference held in London, UK. To date, Altea Therapeutics has clinically studied the basal insulin transdermal patch in over 90 healthy subjects or people with type 1 diabetes. Results show transdermal delivery of insulin that achieves therapeutic levels in people with type 1 diabetes equivalent to subcutaneous injections of currently marketed long-acting insulins.

“A transdermal patch providing steady basal levels of insulin for people with type 1 and type 2 diabetes provides numerous unique clinical and commercial benefits in what is the fastest growing segment of diabetes care,” states Dr. Eric Tomlinson, president and CEO of Altea Therapeutics. “A basal insulin transdermal patch, based on the Company’s proprietary PassPort™ Delivery System, could help overcome the significant compliance and safety problems associated with the repeated need for insulin injections. By meeting specific concerns expressed by patients that refuse or avoid insulin injections, the basal insulin transdermal patch has the potential to enable a wider acceptance and earlier introduction of insulin therapy that can lead to improved management of diabetes.”

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

Foamix Acquires Rights to Dual-Chamber Aerosol Foam Technology

PR Newswire via NewsEdge Corporation: October 29, 2007 – NESS ZIONA, Israel – Foamix Ltd., a specialty pharmaceutical company focused on the development of topical foam products, has licensed the exclusive worldwide rights for a dual-chamber aerosol device from Wella AG. With its brands in hair care and cosmetics, Wella has been part of The Procter and Gamble Group since 2003. “Combination pharmaceutical products are becoming a prominent component of topical therapy, as demonstrated by acne

medications combining benzoyl peroxide with antibiotics and retinoids, psoriasis drugs combining Vitamin D analogs and steroids and anti-pigmentation drugs that combine steroids, hydroquinone and retinoids; however, due to compatibility constraints, creating a stable combination product with reasonable shelf life is a challenge. This license will enable us to incorporate two or more active agents in the same pharmaceutical product, with no stability concerns,” states Foamix CEO Dr. Dov Tamarkin. “We are committed to continuing progress at the forefront of topical therapy, and our ability to develop stable, safe and effective combination drugs will provide added value for Foamix and for our industry partners,” he adds.

According to the license agreement, Foamix has the exclusive rights to use the dual-chamber device for all topical and intra-vaginal drug products requiring prescription. The financial terms of the agreement were not disclosed. The device is protected by US Patent 6,305,578, EP 1075325 and JP Patent 2000-600768. Foamix has its own patent applications, covering a broad spectrum of foam vehicles and drugs that can be incorporated in this device. ■

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Dora Akunyili, National Agency
for Food and Drug Administration
and Control, Nigeria
*Combating Counterfeit Medicines in
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Rakesh Jain, Massachusetts
General Hospital & Harvard
University, U.S.A.
*Normalization of Tumor Vasculature
and Microenvironment by
Antiangiogenic Therapies: From
the Bench to the Bedside and Back*



Raymond T. Bartus, Ceregene Inc.,
U.S.A.
*The Development of AAV-Neurturin
(CERE-120) as a Novel
Neurorestorative Therapy for
Advanced Parkinson's Disease: From
Concept to Clinical Trials and Beyond*



Thomas Tuschl, Rockefeller
University, U.S.A.
*Mechanisms of Mammalian
Small-RNA-Mediated Gene
Regulation*



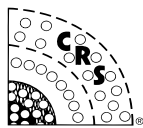
Mark E. Davis, California Institute
of Technology, U.S.A.
*Nanoparticle Cancer Therapeutics:
From Concept to Clinic*



Jackie Ying, Agency for Science,
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*Nanostructure Processing of Advanced
Biomaterials and Biosystems*

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calendar of events

who...what...where...when

13th Arden House European Conference

March 31-April 2, 2008
Royal Pharmaceutical Society of
Great Britain
London, UK
[www.rpsgb.org/worldofpharmacy/
events](http://www.rpsgb.org/worldofpharmacy/events)

CRS Satellite Meeting: Oral Multi-particulate Drug Delivery Systems: Challenges and Scope

April 3-4, 2008
Embassy Suites Orlando Lake
Buena Vista
Orlando, Florida, USA
[www.controlledreleasesociety.org/
main/meetings/](http://www.controlledreleasesociety.org/main/meetings/)

2nd Asian Pacific ISSX Meeting

May 4-7, 2008
Shanghai, China
www.issx.org

Particles 2008 - Particle Synthesis, Characterization, and Particle-Based Advanced Materials

May 10-13, 2008
Wyndham Orlando Resort
Orlando, Florida, USA
[http://nanoparticles.org/
Particles2008/](http://nanoparticles.org/Particles2008/)

35th Annual Meeting of the Controlled Release Society

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Hilton New York
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CPT2008

July 27-August 1, 2008
Québec City Convention Centre
Québec City, Québec, Canada
www.cpt2008.org/

World Congress of Pharmacy and Pharmaceutical Sciences 2008

August 29-September 4, 2008
Basel, Switzerland
www.fip.org

EUFEPS Workshop Opportunities and Challenges in Vaccine Delivery

September 15-17, 2008
University of Geneva
Site d'Archamps, France
[www.eufeps.org/document/_con.
html](http://www.eufeps.org/document/_con.html)