CRS Delivering Bioactives

Newsletter

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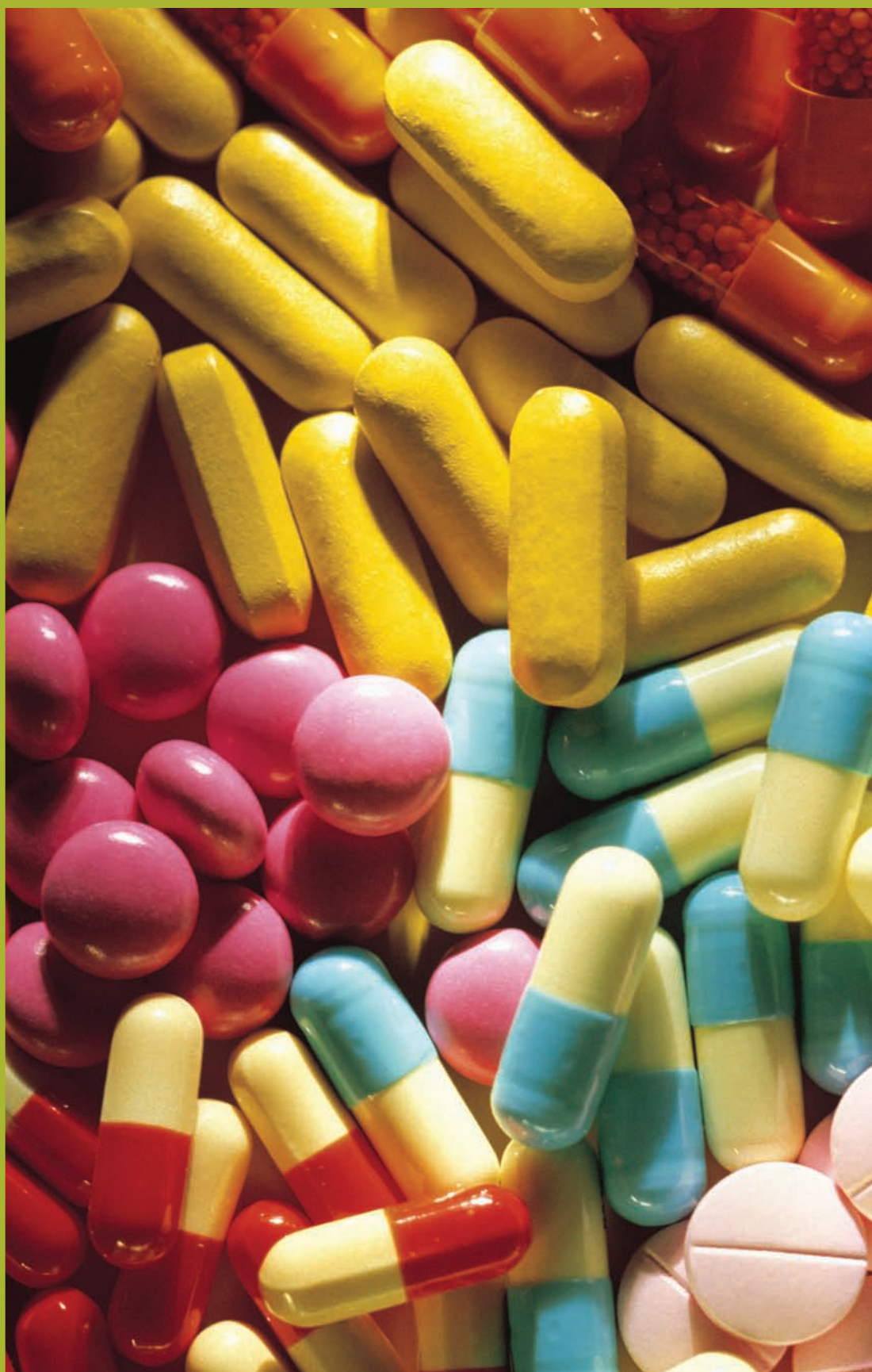

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CRS Newsletter

Delivering Bioactives

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

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Yvonne Perrie
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Aston Triangle, Birmingham, U.K.

Colonic Irrigation or Irritation: It Is All in the Title

Many of you will be reading this around or perhaps at the CRS Annual Meeting & Exposition, where this year we have had a bumper number of abstracts submitted. With so much research to review, how do we grab each others' attention and get our own research noticed? Indeed, in the new wave of measuring research by metrics, it is of vital importance that we get our papers noticed. So, how do we do it? One of the most important decisions is the title of the presentation.

It is often suggested that titles be limited to fewer than 10 words, not as a result of limited space but rather limited attention span. An article by Palladino and Handelsman (1) provides examples of "routine old boring titles." I dare not quote their examples as they are much too similar to many of my own titles. In a bid to create more exciting titles, they suggest using a colon. In defence of this strategy, they reference Dillon (2), who found that a colon was used in 72% of article titles and was associated with publishability, complexity of thought, and distinction of endeavour. This is a lot just from a colon! Others are also suggesting this strategy. In a recent column (3), James Hartley (Keele University, UK), suggests colons could be an imaginative way to improve citation counts and reports some interesting facts: the use of colonic titles in research papers is increasing; those working in the arts and social sciences like their colons (in titles); and within the science disciplines we also have different preferences for the use of colons, with single authors using colons more often than groups of authors.

The use of colons in a title has some key advantages. Clear punctuation and compound constructs in titles can provide immediate visual impact. By splitting the sentence into two sections, we can provide the primary information about the content more easily. Therefore, we can have text that attracts (e.g., "Colonic Interjection") followed by text that informs ("A Study of the CRS Poster Titles"). Palladino and Handelsman (2) also suggest we pose questions in titles, e.g., "Hair: Does It Matter?"—clearly this is short, snappy, to the point, and controversial with some.

However, not everyone likes colons in titles; some even accuse colons of being a fashion statement and demand their use be stopped. Indeed, I myself have fallen victim to such colonic purging. I recently was requested to irrigate the colon from the title of one of my CRS abstracts. The reviewer was very polite with the request, so we were happy to oblige. However, on further investigation into this topic—which appears a hotter debate than one might first think—I have decided to become colon retentive and continue to adopt a compound construction for titles. As you review the posters at the CRS meeting, note have many people have used a colon.

Best wishes and enjoy the meeting!

Yvonne Perrie

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Susan Cady
Intervet/Schering-Plough Animal Health, Yardley, PA U.S.A.

Over the past year the CRS Board of Directors has developed a new CRS strategic plan that specifies goals and objectives, along with current priorities for achieving these objectives. I would like to highlight some of our activities and the progress that has been made on some of the strategic initiatives that have grown out of these discussions:

Offering more satellite meetings is one of the key initiatives under Goal I—Promote high quality research in the science of delivery of bioactives. Two satellite meetings are planned for 2008, and the subcommittee is hard at work developing them. The first satellite meeting of 2008, "Multi-particulate Drug Delivery Systems: Challenges and Scope," was held in April in Orlando, FL. A special thanks to Chairs Ali R. Rajabi-Siahboomi, Colorcon, Inc., and Gurvinder Singh Rekhi, Elan Drug Technologies, who organized this successful meeting. The 2-day program featured presenters from 5 countries and attracted 70 attendees. The second satellite meeting of 2008, "Critical Variables in the *In Vitro* and *In Vivo* Performance of Parenteral Sustained Release Products" will be held in conjunction with the AAPS Annual Meeting on Saturday and Sunday, November 15–16, at the Georgia World Congress Center in Atlanta, GA.

Evaluating the feasibility of creating a CRS publications program is a key initiative under Goal III—Become the primary year-round information resource for the science of delivery of bioactives. In May, a meeting was held at CRS headquarters in St. Paul, MN, with the objective of defining the goals and objectives of the book publishing subsection of the initiative. Mike Rathbone has accepted the responsibility of chairing this important program. He is working with his advisory board on some new titles that will establish CRS books as quality must-haves for our members. Hopefully, they will also be seen as important works that the overall scientific community needs for its library collections. We know that it will take some time for editors and authors to write their chapters, but over the next 30 months we will watch their progress, and I look forward to seeing these in print and adding them to my reference collection. Hopefully, you will as well. If you have suggestions and ideas, please contact Jody Grider at CRS headquarters (E-mail: jgrider@scisoc.org; Tel: +1.651.994.3862).

Please take the time to look at the strategic plan in more detail on the website (www.controlledreleasesociety.org/about). There are many other activities currently underway, such as the Foundation scholarship program and the mentoring program.

As you review the strategic plan, are there initiatives you are interested in contributing to? Are there programs that you can contribute to and help the society, or some one who you can recommend? Please let me know, and I will get you the appropriate contact information. CRS needs and relies on its member volunteers to advance its efforts—please become one and see how your efforts can help make a difference to our society.

There are so many volunteers within our society who contribute to the various committee efforts. If there is a committee or initiative that you would like to learn more about or would like to participate in, please contact the committee chair or a CRS staff member to express your interest. The redesigned CRS website should be up and running before our annual meeting. Take a look and see if there is a committee in which you would like to participate.

As the staff and planning committees finalize the logistics for the 35th Annual Meeting & Exposition of the CRS in New York City, I hope that you plan to join us and actively contribute to the discussions and networking that make our meetings a special place to share experiences and learn about other areas within the delivery of bioactives. The networking, exhibitor interaction, and scientific exchanges might just contribute to that new project you are contemplating.

Looking forward to seeing you at the 35th annual meeting in New York City!

Susan Cady ■

Paediatric Medicines: Formulating a Solution

Dr. Daniel Kirby
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Aston University, Birmingham, U.K.

The formulation of safe, effective, well-tolerated children's medicines poses a significant challenge to the pharmaceutical scientific community, since in addition to the usual problems of formulation (e.g. solubility and chemical stability of the active), there exists a plethora of further difficulties involved in producing a "child-friendly" medicine.

For example, although solid oral dosage forms may be perfectly acceptable for the majority of adult patients, tablets or capsules may be inappropriate for children, particularly the very young; thus, alternative formulations are often required. In addition, taste is a greater determinant of whether the desired dose can be effectively delivered and also of medication compliance and, hence, therapeutic outcome for children (3). Indeed, recent results suggest that healthcare professionals—who encounter formulation issues on a daily basis—identify palatability as the greatest problem when administering children's medicines (Fig. 1; Kirby et al., *unpublished data*).

Added to this the varying pharmacokinetics of what is a heterogeneous population (it is often stated that children are not small adults [6], rendering extrapolation from adult data unsuitable), the problems associated with clinical trials (e.g. recruitment, available numbers, expense, ethics), and the financial viability of producing medicines specific to a small percentage of the market (≈15%), it is no surprise that there exists a severe lack of paediatric-specific formulations currently available.

Consequently, the use of medicines in an "off-label" (i.e. outside the terms of the marketing authorisation) or "unlicensed" (i.e. no license exists at all) manner is widespread, ranging from around 10% in primary care up to 90% in neonatal intensive care units (1,4). This practice, although necessary, effectively exposes paediatric patients, generally considered a more vulnerable population, to an increased risk of adverse events.

As such, paediatrics represents a neglected patient population, both in terms of clinical efficacy and safety data, as well as the availability of medical advances, including controlled release technologies.

In an attempt to tackle this critical issue, FDA (2002 Best Pharmaceuticals for Children Act) and, more recently, European (Regulation (EC) No 1901/2006) legislation has been implemented to encourage and (more so in the European case) necessitate studies, in order that, in the future, children will receive medicines that are both safe and acceptable. To make such studies worthwhile, there are financial incentives in terms of extensions to existing patents, whilst also recognising the need for research into off-patent medicines through the offer of market exclusivity for a specific paediatric formulation of a drug.

As part of the drive to improve the current situation, several initiatives have been set up to facilitate the growing demand for clinical research in the paediatric setting. Indeed, the World Health Organisation has recently launched a global campaign to "make medicines child size," and several member states in Europe have launched programmes to support further research in this field. One such venture is the UK Medicines for Children Research Network (UK MCRN), which incorporates a work stream—in collaboration with three UK academic centres—to focus specifically on the formulation aspects of children's medicines.

An area of particular concern is that of extemporaneous dispensing. Defined as the process of compounding of ingredients to prepare a medicine for an individual patient (5), the tendency in paediatrics is to convert a solid oral dosage form into a liquid oral dosage form through, for example, the crushing

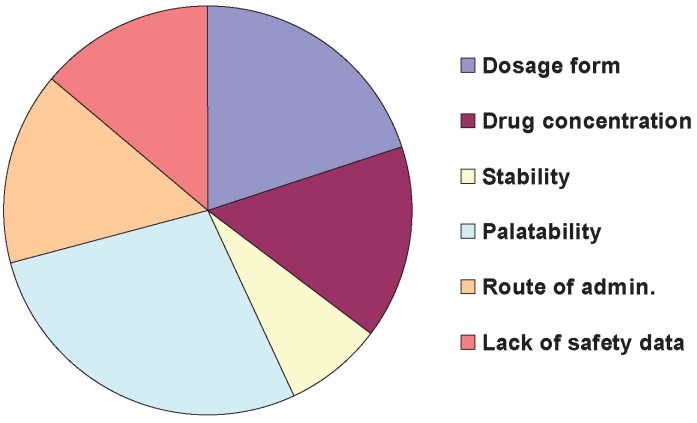
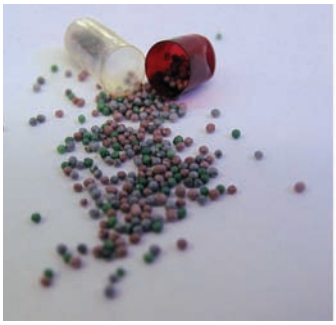


Figure 1. *Problems associated with children's medicines, as perceived by U.K. healthcare professionals. Self-completion questionnaires addressing possible formulation problems were distributed to paediatric healthcare professionals from hospitals within the West Midlands and Trent regions of the United Kingdom. The majority of responses were from nursing staff.*



of tablets followed by dispersion in a suspending agent. Although this may result in a more acceptable preparation for administration to a child and, as such, remains an essential part of paediatric therapy, there are several related risks. For example, halving of tablets, even when using commercially available tablet cutters, can lead to between 50 and 150% of the desired dose (2). In addition, the resulting formulations are rarely characterised for their pharmaceutical quality. For instance, shelf lives are often arbitrary figures defined with little or no evidence to support the physical, chemical, or microbiological stability of the preparations, whereas the crude suspensions invariably formulated may inhibit bioavailability or lack dosage uniformity, thus leading to potential under- or overdosing. In addition, the excipients employed in order to act, for example, as preservatives or to enhance organoleptic properties—notably ethanol, benzyl alcohols, and certain flavourings and sweeteners—may also pose potentially fatal toxicity and health-related risks, particularly in the very young. Additionally, problems concerning the availability of such preparations when transferring from secondary to primary care (7) further confirms that there is an evident and urgent need for further research within this field.

It seems obvious then that alternative, age-appropriate formulations are a research necessity. Indeed, paediatric medicines offer an opportunity to exploit existing and emerging technologies, particularly with regard to controlled release. For example, microencapsulation may be employed in taste-masking of a poorly tasting pharmaceutical active through, for instance, the production of granules or pellets (or micropellets) that may then be coated with a functional polymer (e.g. Eudragit®). A recent example of the use of such technology, incorporated into a novel device for paediatric use, is Grünenthal's Sip®-Technology for the delivery of antibiotics through a drinking straw.

In addition, the use of particulate delivery systems, such as liposomes, microspheres, or cyclodextrin complexes, have the potential to be utilised to improve the solubility, stability, and palatability of liquid dosage forms in particular, whilst also offering the potential for controlled release of the active ingredient. Further, there are several alternative dosage forms such as mini-tablets, chewable tablets, melts or oro-dispersable tablets (ODT), fast-dissolving films, powders for reconstitution, effervescent tablets, self-emulsifying drug delivery systems (SEDDS), and microemulsions, amongst others. Moreover, besides the oral route, there are distinct advantages in using, for example, suppositories that would negate the issues of taste, although they may pose problems with acceptability and compliance.

In summary, despite the current lack of available "child-friendly" formulations, recent directives and initiatives have set the agenda for improving the safety, efficacy and acceptability of paediatric medicines, and the onus is now on the scientific community to develop and exploit existing, emerging, and novel technologies to achieve the goal of better medicines for children.

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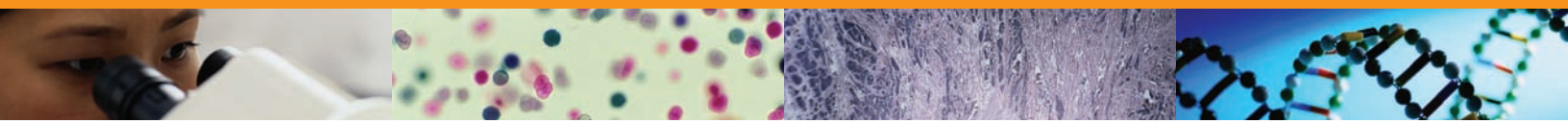

Encapsulation of Probiotics in Alginate Systems

Ming-Ju Chen[1] and Kun-Nan Chen[2]

Introduction

Probiotics can be defined as living microbial supplements that can improve the balance of intestinal microorganisms (1). Good probiotic viability and activity are considered essential for probiotics with maximum functionality. To benefit the consumer, a suggested minimum level for probiotics in food products is 10^7 CFU/mL (2) at the time of consumption. A major challenge associated with the application of probiotic cultures in functional foods is the retention of viability during processing. Moreover, since viable and biologically active micro-organisms are usually required at the target site in the host, it is essential that probiotics withstand the host's natural barriers, such as gastric transit.

Encapsulation has been investigated for its ability to provide protection of probiotic microorganisms in both food products and the intestinal tract. The selection of different types of coating materials usually depends on the functional properties of the microcapsules and coating process used. For dairy and food applications, probiotic encapsulation in food-grade porous matrices has been used most widely (3). Calcium alginate is favored above other supporting materials for encapsulating probiotics due to its simplicity, non-toxicity, biocompatibility, and low cost (4). Solubilization of alginate gel by sequestering calcium ions and releasing entrapped cells within the human intestines is another advantage. Furthermore, this ionically linked gel is thermostable over the range of 0 to 100°C. This article summarizes recent developments in the encapsulation of probiotics using alginate as a coating material.

Native Alginate

Alginate, a nature polymer, is a linear heteropolysaccharide of D-mannuronic and L-guluronic acids extracted from various species of algae. The functional properties of alginate as a supporting material are strongly associated with the composition and sequence of L-guluronic and D-mannuronic acids. Divalent cations such as Ca^{2+} preferentially bind to the polymer of L-guluronic acid (4). On addition of sodium alginate solution to a calcium solution, interfacial polymerization is instantaneous, with precipitation of calcium alginate in the form of beads, followed by a more gradual gelation of the interior as calcium ions permeate through the alginate systems. The size of the beads is generally dependent on the viscosity of the polymer solution, the diameter of the orifice, and the distance between the outlet and the coagulation solution. Concentrations of sodium alginate and calcium chloride used to form the beads vary between 1 and 3% alginate and 0.05 and 1.5*M* $CaCl_2$ (5–7). However, the use of alginate is limited by its inferior physical stability in the presence of chelating agents such as phosphate (8) and anti-gelling cations such as sodium and magnesium ions (9). The chelating agents share an affinity for calcium, which destabilizes the gel. Furthermore, a cross-linked alginate matrix system with a very low pH was reported to undergo a reduction in alginate molecular weight, causing faster degradation and release of active ingredients (10).

Treated Alginates Coated with Polycations

Coating alginate beads with polycations such as chitosan and poly L-lysine has been extensively studied in encapsulated probiotics (5,7–9,11). Chitosan-coated alginate capsules were produced by dropping an alginate solution into a mixture of calcium chloride and a chitosan solution (7). Since chitosan, poly-(2-amino-2-deoxy-β-D-glucopyranose), is a positively charged polyamine, this polymer forms polyelectrolyte complexes with alginate and produces polyanionic polymer membranes that do not dissolve in the presence of calcium chelators or anti-gelling agents.

Alginate poly-L-lysine microcapsules can provide good biocompatibility and have potential wide applications in the food industry (7). They are obtained by suspending alginate beads in a poly-L-lysine solution. This poly amino acid has a positive charge and forms a complex with surface alginate that increases the strength of microcapsules. Cui et al. (5) studied the bifidobacteria loaded in alginate poly-L-lysine microparticles and indicated that poly-L-lysine treatment greatly enhanced the survival of bifidobacteria during storage at 4°C.

Treated Alginates Coated with Prebiotics

Prebiotics are non-digestible food ingredients that can beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon (12). Several studies (13,14) have confirmed that incorporation of prebiotics and calcium alginate as coating materials provides better protection for probiotics in food systems and eventually in the intestinal tract, a result of proven synergy between the probiotics and prebiotics. Chen et al. (14) incorporated prebiotics as coating materials for probiotic microencapsulation and demonstrated that the addition of fructooligosaccharides, isomaltooligosaccharides, and peptides in the walls of probiotic microcapsules provided improved protection for active organisms. These probiotic counts remained at 10^6–10^7 CFU/g for microcapsules stored for 1 month and then subjected to a simulated gastric fluid test and a bile salt test.

Techniques for Probiotic Encapsulation

Spherical alginate beads can be produced using extrusion or emulsification techniques. Extrusion is the simplest and most

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common technique used to produce probiotic capsules with hydrocolloids, especially alginates (4,15). One of the major advantages of this method is that the viscosity of the fluid does not limit capsule generation (16). Furthermore, the biological matter can be treated at a lower temperature. Figure 1 shows the structure of alginate microcapsules prepared using extrusion. The microcapsules display spherical shapes, with groups of entrapped bacteria evident in the internal voids and surrounded by the matrix.

The emulsion technique has also been successfully used for encapsulating probiotics. The principle of this technique is based on the relationship between the discontinuous and continuous phases. The probiotics are essentially mixed into a solution of alginate (i.e., the discontinuous phase) and dropped into vegetable oil (i.e., the continuous phase) containing emulsifier (Tween 80) and surfactant (sodium lauryl sulfate) to form beads. The latter are harvested later by filtration. Emulsifiers can break up water and oil emulsions, thus preventing the spheres from coalescing before breaking up the emulsion. Surfactants can lower the surface tension in the coating matrix in order to reduce the size of the spheres. This technique provides both encapsulated and entrapped core materials and is easy to scale up for large-scale production. However, several studies have indicated that this technique may not be suitable for food products. The residual oil, emulsifier, and surfactant in the encapsulating material can affect the growth of live probiotics and interact with food components. In addition, the residual oil may damage the organoleptic properties and texture of the food products (17).

Survival of Encapsulated Probiotics

Gastrointestinal Conditions. Successful encapsulation of probiotics should provide profound survival of beneficial bacteria during its passage through the upper digestive tract to ensure that beneficial effects occur in the host intestines (18). Most studies have proven the advantages of encapsulating probiotics over free cells under *in vitro* gastric conditions. Chen et al. (19) found that the death rate of the probiotics in capsules decreased proportionally with an increase in alginate concentration (1–3%), bead size (1–3 mm), and initial cell numbers, when encapsulated *B. longum* was exposed to simulated gastric and intestinal juices. However, Hansen et al. (20) reported that small beads of <100 μm, compared with free cells, did not significantly protect probiotics in simulated gastric media. The effects of the simulated gastric fluid test (SGFT) on the outer structure of microcapsules observed by scanning electron microscopy (SEM) are shown in Figure 2. The microparticles retained their shapes, with smaller sizes and coarser surfaces after the SGFT. Hansen et al. (20) also found that the alginate microspheres retained their shapes and had smoother surfaces during exposure to simulated gastric juice at pH 2.0. A possible explanation for this observation is that treating the microparticles with a solution at pH 2 may cause some calcium to be displaced. After this treatment, surface calcium ions could not contribute anymore to the stability of the beads, resulting in smaller beads and smoother surfaces.

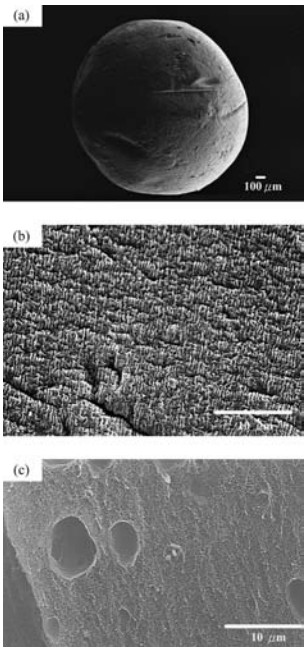

Figure 1. *Scanning electron micrograph of optimized B. bifidum microcapsules. (a) Whole microcapsule; (b) surface; and (c) cross-section.*

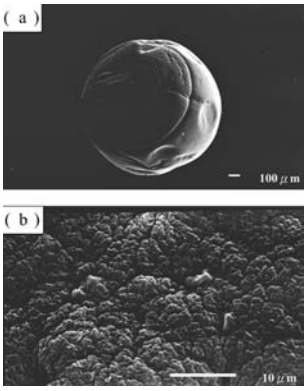

Figure 2. *Effects of SGFT on the outer structure of microcapsules observed by SEM. (a) Whole microcapsule; and (b) surface.*

Dairy Products. Encapsulation has been investigated for its ability to improve the viability of beneficial microorganisms in dairy products. Sheu et al. (21) studied the survival of culture bacteria in frozen desserts and indicated that the survival rate for *L. bulgaricus* in continuously frozen ice milk was approximated at 90% without a measurable effect on sensory characteristics when it was entrapped in calcium alginate. Kebary et al. (22) also reported that encapsulating *Bifidobacterium* spp. in alginate beads significantly improved its survival in frozen ice milk throughout the study's storage period. These findings encouraged further investigations on the incorporation of encapsulated probiotics in frozen desserts.

During the yogurt post-acidification stage (i.e., decrease in pH after fermentation) and storage at refrigerated temperatures, major cell death of probiotic bacteria routinely is experienced. Incorporating calcium-alginate beads into set yogurt formulations has been shown to provide better survival over an 8-week storage period compared with the survival of free cell counterparts (23,24). Desmond et al. (25) reported the viabilities and survival of both encapsulated *Bifidobacterium* spp. and *L. paracasei* in cheese for at least 6 and 3 months, respectively. In addition, acetic acid, a common metabolite of

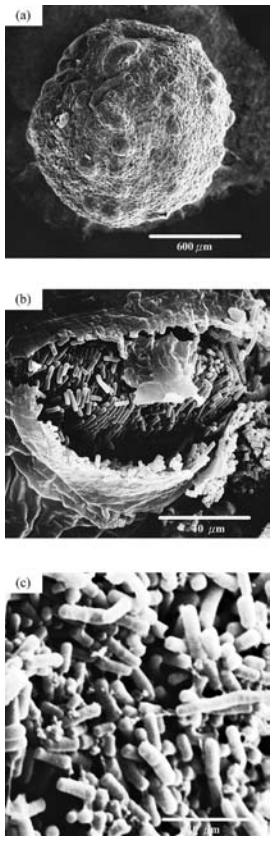

Figure 3. *Scanning electron micrograph showing the effect of the number of consecutive cultivations on microencapsulated probiotics. (a) Whole microcapsule; (b) surface; and (c) cross-section.*

Bifidobacterium spp. that is not preferred in dairy products, was not detected during ripening.

The following summarizes two major areas of applications of encapsulated probiotics in dairy products.

Continuous Cultivation

Alginate microcapsules, by virtue of their high degree of porosity, allow fast and easy diffusion of materials in and out of the alginate matrix. This is an advantage for the immobilization of live cells. Microbiological changes in alginate beads during consecutive cultivation showed a significant increase in cell counts (10^7–10^{12} CFU/g). SEM observations revealed that after 28 batch cultivations, the microparticles retained their shapes and surface morphology, with the probiotic bacteria distributed between the surfaces and interior of the microcapsules (Figure 3). These microcapsules produced by alginate offered a very high cell-retention capacity for microorganisms, even in the inner pores of the matrix. Growth and aggregation of cells in the voids resulted in complete filling of the outer and inner pores of the microparticles. An increase in cell counts with an increasing number of cultivations for fermented milk was also observed. Immediately after the addition of microcapsules to milk, the probiotics reached a concentration of 10^4 CFU/mL. This indicated that part of the microflora contained in the capsule was transferred to the milk. In a Kefir system, however, using encapsulated "kefir" cultures as the initial inoculum resulted in a lag period before the fermented milk reached normal cell population. It should be noted here that it is important to activate the encapsulated starter cultures before using them for cultivation.

Incorporation into Dairy Products

In the dairy industry, encapsulated probiotics can be used to accelerate cheese ripening, improve probiotic survival, and enhance their storage stability. Many dairy culture companies can design and manufacture, according to the customers' requests, microencapsulated ingredients that can synergistically provide benefits in the areas of nutrition, digestion, and immunity. Examples of such applications include yogurt, both set and stirred types, as well as cheese.

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Interspecies Differences Influencing Interspecies Extrapolations Part II of III: Interspecies Differences Influencing the Absorption of Oral and Parenteral Formulations

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Oral Drug Products

Interspecies diversity in gastrointestinal (GI) anatomy and physiology reflects the differences in their respective diets (1). The low fiber, high fat and protein diet of carnivores (e.g., dogs and cats) lends itself to a relatively simple colon but a well-developed small intestine (long villi). Pigs, as omnivores, possess a well-developed small intestine but have a more complex lower intestine to compensate for their diversified diet. The lower intestine of pigs also allows for dietary fiber fermentation. Herbivores have marked differences in GI physiology, as described below.

Understanding the physico-chemical properties of a compound (e.g., pKa, hydrophilicity) and the effect of formulation on product dissolution rate is critical when developing formulations that are intended to be used in more than one animal species. Marked interspecies differences in mean bile flow and composition can also affect drug solubilization and, therefore, drug absorption (2). Although rats and horses have no gall bladders, both species synthesize bile salts, and bile entry to the intestine occurs in a more or less continuous manner.

The GI physiology of four veterinary species is described below.

Horses. Due both to the highly variable pH of equine gastric contents (pH = 1.3–6.8, mean = 5.5) and the highly fibrous equine diet, drug absorption may be poor in much of the small intestine. This is particularly true for weak bases (where the higher pH will interfere with drug dissolution) and for drugs whose dissolution will be impaired by the decrease in diffusivity caused by the viscosity of ingested fibrous materials. Consequently, a large fraction of drug absorption in horses often occurs in the large intestine. Two other unique features of the equine GI tract are the lack of a gall bladder and a relative inability to vomit (3).

Equines are hindgut fermentors, with a small intestine whose fluid capacity is substantially less than that of the large intestine. Due to the poor absorption of the other nutrients released in the hindgut, equids need to consume food for about 18 hr per day to meet their nutrient requirements.

Ruminants. Because fermentation of fiber takes place proximal to the small intestine, the efficiency of nutrient absorption is markedly improved over that of the horse. This difference enables ruminants to reduce grazing time from the 18 hr per day associated with horses to only 6–8 hr per day (3,4). The rumen is a fermentation vat that can hold 100–225 L in cattle and 10–24 L in sheep and goats. It also contains approximately 150 billion microorganisms per teaspoon. The condition of the rumen reflects the environment necessary to maintain its microflora, including a temperature that ranges from 100 to 108˚F and between a pH of 5.8 and 6.4.

Few drugs, with the exception of sulfa drugs, can resist chemical degradation in the harsh environment of the abomasum of a ruminating cow. In contrast, drugs such as trimethoprim are degraded within the rumen.

Carnivores. Carnivores generally possess a relatively simple colon and a well-developed small intestine (long villi). Canine GI transit time is markedly faster than that of humans. Dogs tend to have a lower (fasting) basal acid secretion than do humans (5), leading to a higher pH, ranging between 1 and about 6. Conversely, following a meal gastric acid secretion rates in dogs exceed those of humans and slowly return to baseline, leading to a lower gastric pH compared with the postprandial human stomach. The higher pH found in the small intestine of dogs (versus that in humans) may result in better absorption of drugs that are weak bases.

Common veterinary animals that highlight the diversity in gastrointestinal anatomy—Jock the border collie (left) and a Hereford cow with her calf (right). Photos by Arlene McDowell.

For palatable formulations, the selection of a flavorant depends on the flavor and odor preferences of the intended targeted animal species. Cats are attracted to meat, fish, liver, and yeast flavors. Dogs are attracted to meat, liver, chicken, yeast, and sugars (6). Cats also have neither an attraction nor an aversion to sweet carbohydrates (7).

Parenteral Drug Products

The relative bioavailability of IM or SC dosage forms may not be comparable across animal species. Rather, numerous biological factors can influence absorption (e.g., absorptive area, injection volume, blood and lymph flow, exercise, local pH, ionic composition of extracellular fluids, drug or excipient binding to tissues, drug diffusivity through the formulation and injection site, and local drug metabolism [8,9]). Solubilized drug can also re-precipitate at the site of injection due to preferential absorption of the vehicle or the effect of local pH on drug solubility.

Interspecies differences in injection site also need to be considered, particularly with food producing animals, where sites are often selected on the basis of minimizing the loss of quality or residues associated with edible tissues.

Sustained Release (SR) Formulations

SR tablet formulations provide an important tool for enhancing patient compliance. Likewise, within veterinary medicine there is an ever-growing demand for long-acting products. However, the rapid GI transit time of dogs, along with the very strong crushing force of the canine stomach makes it difficult to formulate SR oral products (10). For this reason, the development of alternative gastric-retention systems may be particularly important in companion animal medicine, including gastro-retention devices, systems that lodge themselves in the stomach by altering their geometric configuration upon exposure to gastric fluids, and mucoadhesive systems.

With regard to parenteral products, an increasing number of veterinary dosage forms are being developed for prolonged (months) release. In these instances, parenteral formulations (e.g., microspheres, implants, *in situ* forming gels, lipophilic solutions, and suspensions) are of great interest. An upcoming review of the 2007 CRS Educational Workshop (Martinez, Burgess, Huynh, and Rathbone, to be submitted to the *Journal of Controlled Release*) will provide a synopsis of the interspecies considerations associated with the development of these formulations.

The final installment, "Interspecies Differences in Metabolism and Toxicology," will appear in the next *CRS Newsletter*.

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Back to Basics: 1. Tissue and Cell Culture

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This is the first in a series of articles introducing the basics of different research methods and techniques that may be required for the successful development and evaluation of controlled release technologies.

What Is Cell Culture and Why Do We Use It?
Cell culture is a technique whereby cells/tissues derived from either animal, human, or plant origin are isolated and grown within a controlled artificial environment. The simulated environment, if possible, should mimic the normal conditions found within the living organism from which the cells are derived. The cells should remain metabolically active, replicate, and grow in this environment. The use of cell culture studies, by application of *in vitro* cell cultures may provide solutions to *in vivo* challenges. Numerous studies covering an immense number of different topics and that have applied the use of cell culture have been conducted. Although the ultimate goal of these studies may vary, the basic cell culture technique is similar.

History and Recent Advances in Use of Cell Culture
The reported use of cell culture dates back to the early 1900s, when Harrison was able to successfully cultivate nerve cells *in vitro*. Following this revolutionary demonstration of cell isolation and growth outside the human body, Carrel and co-workers in 1911 were able to successfully culture embryonic and adult tissue cells, continually making great strides and contributions to cell culture, the development of various media and medium supplements, and the improvement of cell cultivation by use of cell culture flasks (1). Strangeways in 1919 demonstrated success using this technique. However, it was not until the 1940s and 1950s that sterilisation was used to avoid the risk of contamination of cell lines and tissue cultures. This was achieved by use of laminar flow hoods and antibiotics in the culture media.

A vast number of recent studies have used cell culture, illustrating the adaptive use of this technique within various areas of scientific interest. These have included studying the principles of cell biology, the effects of various classes of pharmacological agents on cells, vaccine production, immunology, aging, and nutritional studies, amongst others. For example, mononuclear cells have been isolated from blood samples of cancer patients and cultured *in vitro*. By activating these mononuclear cells in culture it was found that there was a reduction in the IL-2 response in breast cancer patients, with a depression of IL-2 levels correlating with the stage of the disease. Thus, measuring IL-2 production in breast cancer patients may contribute to their prognosis (2). Cell culture has also been used as an *in vitro* model to assess and measure the cellular and histological effects of smoking (3), and there are an extensive number of studies investigating the ability of various lipid-based vaccines to effectively transfect cells *in vitro* (4–7).

Essentials of Cell Culture
One of the main and most crucial challenges when working with cells in culture is keeping the cells healthy and alive. Prior to commencing any cell culture, the design and set-up of a cell culture laboratory must be addressed. This is vital in order to maintain a safe and efficient working environment. In order to avoid cross-contamination, individual work should be carried out separately either by area or time. In addition to the risks associated with cell contamination, the risks presented to the worker are also of utmost importance. As outlined in the "Biological Agents: Managing the Risks in Laboratories and Healthcare Premises" guidelines published by the Advisory Committee on Dangerous Pathogens (8), the risks associated with working with cell lines need to be considered prior to cell work being started. In particular the origin, source, and type of cell line must be taken into account.

Cell Culture: The Basics. There are a set of general procedures and rules that are used in cell culture, irrespective of the experimental purpose of the study undertaken. Primarily, it is essential that the laminar flow hood in which cell culture work is to take place be sterilised. Sterility is achieved by applying ultraviolet light (UV) to the working area for at least 10 min prior to use and subsequently by spraying the working area liberally with 70%, vol/vol, alcohol. Furthermore, it is critical that all surfaces and items within or introduced into the hood be kept completely sterile at all times.

I. Resuscitation of a frozen cell line
This initial step involves re-establishing the cell line or bringing the cells "back to life"! Cells are usually frozen in liquid nitrogen in order to maintain cell integrity over an extended period of time, and therefore, prior to any experimental procedures, the cells of interest must be thawed in a relatively quick but controlled manner to maintain their integrity. This procedure is usually carried out in four simple steps:

Preparation: Under sterile conditions, in the laminar flow hood, cell culture flasks should be prepared by adding the desired volume of the appropriate pre-warmed culture medium relevant for the cell line to be established. The outside of the

flask should be labelled, detailing the cell line, passage number, and worker's name and date.

Thawing: The cells should be removed from the liquid nitrogen storage tank, whilst wearing protective clothing to avoid contact with liquid nitrogen, and placed within a water bath set at the appropriate temperature (i.e., 25°C for insect cells and 37°C for mammalian cells), until the cells are fully thawed.

Sterilisation: The outside of the container in which the cells are kept needs to be sterilised, which should be done by wiping the outside with 70% alcohol. The container can then be placed in the sterile hood.

Growing: The cell suspension should be carefully transferred into the cell culture flask, containing pre-warmed medium, and placed in an incubator set at the appropriate temperature, with supply of the correct amount of CO_2.

II. Subculture of Adherent Cells

Cells will grow and adhere to the bottom of the tissue culture flask until they reach 90–100% confluence. Confluence is the point at which the cells cover the bottom of the flask completely (Figure 1). At this crucial stage, the cells must be subcultured/passaged to reduce the number of cells present. At this point replenishment of the "old" medium with "new," fresh medium and nutrients to enable the cells to continue growing over a longer period of time is essential. Cells will die if left to continue growing in overpopulated environments, due to lack of space and nutrients. (Note: the growth medium should be pre-warmed to the desired temperature for the cells prior to addition to the flasks).

Removal: The flask containing the relevant cells must be removed from the incubator and sterilised by careful spraying of the outside of the flask with 70% alcohol. The "old" medium is then removed and discarded as biological waste.

Detachment: Trypsin/EDTA solution should be added to the cells and then incubated for 5 min. To ensure that the cells have been completely detached from the flask, tap the side flask gently.

Figure 1. *Cell culture flasks containing growth medium with nutrients essential for cell growth, with cells adhering to the bottom of each flask.*

Dilution: The growth medium should be added to the flask to dilute the trypsin/EDTA solution. It is at this stage that the number of cultivated cells can be readily quantified as described below.

Washing: To remove trypsin from the cell solution, an optional washing step may be introduced. At this stage the cell suspension should be transferred to a sterile centrifuge tube and centrifuged to obtain a cell pellet. The supernatant (i.e., medium) should be removed carefully without disturbing the cell pellet. The cell pellet can be removed and then must be fully resuspended with fresh growth medium to maintain cell viability.

Growing: A portion of the cell suspension should be carefully transferred into a cell culture flask, containing pre-warmed medium and placed in an incubator set at the appropriate temperature, with a supply of the correct amount of CO_2 to permit continued growth.

III. Cell Quantification

Removal: 200 µL of the cell suspension to be quantified must be removed from the solution (II) under sterile conditions.

Staining: An equal volume of trypan blue solution is then added to this cell suspension and mixed thoroughly.

Counting: A 10-µL aliquot of this solution is added to each side of an haemocytometer (i.e., a thick glass microscope slide, with laser engraved grids) to determine cell counts, using the light microscope. Live cells are brighter and more visible than dead cells and, therefore, can be quantified.

IV. Cryopreservation of Cell Lines

Counting: Cells should be quantified (III) to determine the correct dilution and concentration of cells to freeze down (e.g., 4×10^6 cells/mL) for future use.

Washing: The cell suspension should be transferred to a sterile centrifuge tube and centrifuged to obtain a cell pellet. Under laminar flow the supernatant (i.e., medium) should be removed carefully without disturbing the cell pellet. The cell pellet should be resuspended fully with cryopreservation medium suitable for the specific cell line (e.g., 90% foetal bovine serum and 10% DMSO).

Splitting: Following suspension, the cell pellet should be separated into 1-mL aliquots and transferred into sterilised ampoules designed for cryopreservation. The ampoules should be fully labelled, stating cell line, passage number, date, and cell concentration prior to sealing.

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Freezing: The ampoules should be placed at –70°C overnight and subsequently transferred to a liquid nitrogen container for storage until the cells are required for use.

Following these steps should take you back to the basics of cell cultivation, harvesting, and evaluation. This article is intended to provide some of the basic and essential tools and instructions for effective use of cells and provide all potential cell culture users with a valuable starting point, so that when using microscopy your results will be as good as those depicted in Figure 2.

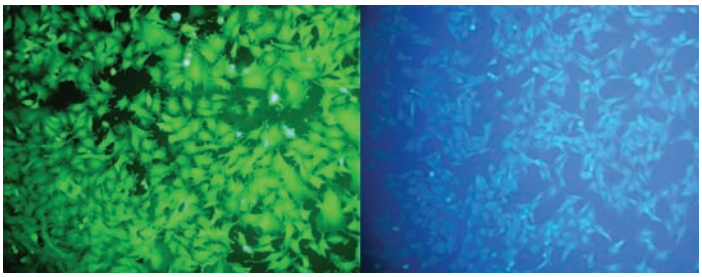

Figure 2. *Adherent bone-derived cells growing in in vitro conditions. (Photo courtesy of Dr. Richard M. Shelton and Dr. Jonathan Harris, Birmingham University, UK, and Prof. Yvonne Perrie and Dr. Alan Smith, Aston University, UK).*

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8th International Symposium on NDDS Organised by CRS Indian Chapter

The CRS Indian Chapter (CRS-IC) held its 8th International Symposium, "Advances in Technology & Business Potential of New Drug Delivery Systems," February 26–27, 2008, at the B.V. Patel PERD Centre, Ahmedabad, India.

Left to right: Prof. H. L. Bhalla, emeritus president CRS-IC and chair of the Scientific Committee; Dilip Shanghavi, chief guest of the function and chair and managing director of Sun Pharma Industries Ltd., India; Prof. T. Nagai, guest of honour and chair of the Nagai Foundation, Tokyo, Japan; Prof. Leslie Benet, keynote speaker; Anant Thakore, co-chair of the Organizing Committee and chair of Anant & Co., India; and Dr. K. K. Singh, secretary of CRS-IC.

introduction on the centre and welcomed everyone on its behalf. Prof. T. Nagai, the guest of honour, released the first issue of the *Newsletter* of the CRS Indian Chapter. Prof. H. L. Bhalla introduced the participating dignitaries, and Prof. K. K. Singh, secretary of CRS-IC, proposed a vote of thanks. The scientific proceedings started with a keynote address, "Recent Advances in Biopharmaceutics: BCS and BDDCS," given by Prof. Les Benet. This was followed by as many as 15 invited talks by distinguished scientists from India and abroad. In addition, there was a special session on excipients, in which two representatives of excipient manufacturers discussed their products.

The symposium has increased steadily in strength, and this year there was significantly more participation from industry and academia. The symposium attracted more than 350 delegates and about 150 poster presentations. The concluding function was conducted by Prof. H. L. Bhalla. He announced the names of the winners of the 1st and 2nd place prizes for the Best Poster and gave the certificates and prizes to the candidates in his capacity as chair of the Scientific Committee. The 1st prize for Best Poster was awarded to Ritnesh Jain and Dr. V. B. Patravale. The 2nd prize was shared by Poonam Saraf and Prof. P. V. Devarajan and Pooja Sachan and Prof. K. K. Singh. Thereafter, Prof. Bhalla invited faculty members and interested delegates to express their opinions about the proceedings and make suggestions for improving the quality of future meetings. Many guests speakers from abroad praised the quality of the oral and poster presentations, as well as the hospitality and other arrangements.

Prof. Bhalla concluded the session by expressing his gratitude to all who made the symposium a grand success and declared the closing of the proceedings. ■

Attendees enjoy the technical program during the 8th International Symposium, "Advances in Technology & Business Potential of New Drug Delivery Systems."

2007 Meeting of the CRS Italian Chapter

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The 2007 Meeting of the CRS Italian Chapter took place in Rimini, Italy, on Thursday, June 14, as a satellite symposium of the 47th AFI Congress, the annual congress of the Italian Association of Pharmaceutical Industry. The joint AFI/CRS Italian Chapter symposium offered an excellent opportunity for Italian scientists and product developers working in the field of drug delivery to enhance cooperation between academia and industry.

According to the recently introduced trend, the CRS Italian Chapter contributed to the AFI congress by organizing a 1-day scientific session on drug delivery systems titled "Research and Development: New Technologies for Controlled Drug Delivery." The symposium was organized as a podium presentation/soap box, where both public and private institutions shared their knowledge, expertise, and scientific projects at the forefront of drug delivery and technological advances.

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Due to the large number of attendees, the symposium was divided in two parallel sessions. Chairs Prof. C. Caramella (Pavia University) and Dr. A. Tajana (AFI) welcomed the attendees and briefly introduced the aim of the meeting. A total of 61 speakers was involved—40 were representatives of 19 universities, and the remaining 21 were from industry. Each presentation had a time limit of 10 minutes and described research projects, know-how, and perspectives on exploitation in pharmaceutics.

Representatives from private companies showcased the strongly applicative target of their activities. Alpex Pharma, Flarer SA, IMA Dolida Dose Division, Farmatron, Bouty, Rofarma, Qualicaps, Cardinal Health, and APR presented a variety of projects involving oral delivery, ranging from multi-matrix systems for controlled drug release to film technology for oral dispersible tablets, lipid particles to chewable medications, and buccal to colon delivery.

The relevance of new industrial technologies for the development of oral therapeutic systems was highlighted by Pfizer and E-Pharma, which reported on innovative methods of industrial material processing, namely granulation and capsule filling.

Speakers from Valois, Chiesi, and Eratch emphasized the industry's interest in the development of inhalation drug delivery systems, while those from Monteresearch and Bouty presented projects on vaginal and transdermal delivery. Finally, Micro-Sphere, Sitec, Nanovector, Eurand, and Vitroscreen reported progress on micro- and nanotechnology know-how and applicability in the drug delivery field.

The university groups presented a variety of projects and evidenced their intense research activities in a broad and modern scientific scenario. The speakers presented projects highlighting the applicability of their research-efforts, ranging from micro- and nano-particles to mucoadhesive systems, ophthalmic to oral delivery, and bioconjugation to mathematical design.

After each session, in order to facilitate the exchange of information between speakers and audience, the various topics presented were discussed within smaller groups in a more informal atmosphere. Most participants enjoyed the interactive setup of the event and described the meeting as a professionally and socially rewarding experience.

During the evening assembly of the CRS Italian Chapter, the President Dr. Pedrani briefed the members on the formal procedure adopted in order to obtain the official status of the Association and announced the election of the Directive Council. Dr. Pedrani further reported on activities co-sponsored by the CRS Italian Chapter in 2007 (workshop on "Biotech Drug Development," March 7–8, Pavia; workshop on "Advances in Drug Delivery for Inhalation," April 23, Milan) and informed the audience about the CRS activities planned for the upcoming months. ■

New Zealand Chapter of CRS Holds 10th Formulation and Drug Delivery Conference in Dunedin

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Approximately 100 delegates gathered in Dunedin, New Zealand, for the 10th Formulation and Drug Delivery Conference in February of this year. With an additional day and more international speakers, the conference promised to be better than ever. Prof. Ian Tucker, dean of New Zealand's National School of Pharmacy and convenor of the Formulation and Drug Delivery (FDD) Research Theme at the University of Otago gave the opening address. He pointed out the interdisciplinary theme of this conference, with delegates having very diverse research interests, from pharmaceutical to immunological and agricultural. It is this interdisciplinary nature that has proven to be so successful over the years and given the opportunity for so many collaborative projects.

The first day kicked off with sessions on colloidal drug and vaccine delivery and solid-state issues in drug delivery. Prof. Jayne Lawrence from King's College in London was the New Zealand Chapter of CRS (NZCRS) keynote speaker, and she gave an excellent overview of the use of neutron scattering in the characterisation of colloidal systems. Various colloidal systems for vaccine and drug delivery are also investigated in the New Zealand, but due to lack of instrumentation, neutron scattering so far has not been a characterisation option. Hopefully this will change, and a collaboration can be established between Jayne Lawrence's group and the groups in New Zealand. The afternoon session started with a presentation by Dr. Robert Lancaster (University College, London, and formerly Pfizer), who gave the captive audience insight into the world of disappearing polymorphs and crystal structure

NZCRS Keynote Speaker Prof. Jayne Lawrence and Prof. Thomas Rades (NZCRS president).

Keynote Speaker Prof. David Jones and Dr. Natalie Medlicott (School of Pharmacy, Dunedin).

prediction based on his 30 years of experience in the solid-state area. Prof. Elisabeth Topp from the University of Kansas gave an interesting spin in the solid-state session with her presentation on protein stability in amorphous solids.

The theme of the second day was biological issues in drug and vaccine delivery. Having been a lecturer at the School of Pharmacy in Dunedin a few years back, the keynote speaker for this session was a familiar face to many attendees. Prof. David Jones (Queens University, Belfast) introduced us to the world of controlled release issues in medical devices and gave an excellent overview of how his research is trying to overcome release issues caused by encrustation, microbial biofilms, etc. by using drug-polymer conjugates, stimulus sensitive polymers, and facilitated drug diffusion from bioactive materials. David's talk was followed by a presentation by Prof. Claus-Michael Lehr (Univeristaet des Saarlandes, Saarbruecken) who gave an account of investigating the transport of nanoparticles across biological barriers, especially human skin and alveolar epithelial cells. The afternoon session was concerned with vaccine delivery before everyone got ready for the conference dinner. For the first time this year the conference organisers introduced a Limerick competition under the theme of formulation and drug delivery, and a group of postgraduate students won.

Because this was the 10th anniversary of the conference, things need to be bigger and better, and an extra day was dedicated to the veterinary session, this being of particular interest to New Zealand because of its big livestock industry and unique wildlife, which needs protection from pests. Dr. Marilyn Martinez from the U.S. FDA for Veterinary Medicine presented her views on factors that influence the gastric transit, solubility and permeability of oral dosage forms in dogs and pointed out that these differences have to be taken into account when developing medicines for dogs, while also highlighting the comparability issues between humans and dogs in clinical studies. Unfortunately Dr. Martinez could not give her presentation in person, but had to send over her slide show and present her findings over the phone. The next speaker, Dr. Hans-Juergen Haman from Bayer Health Care (Germany), did a great job in drawing our attention to the challenging task of developing controlled release topical formulations for animals. The limited variety of drugs, the special topical conditions of animals, and the necessary ease of application prove a great challenge for the formulation team.

Further presentations were concerned with drug delivery formulation for livestock animals and control of pest wildlife.

Before the closing remarks of the conference were given, the student prizes had to be handed out. As in every year, the competition was strong, and Dr. Robert Lancaster took the opportunity to congratulate all the students on their excellent efforts and made the comment that he envies them for their PowerPoint skills. Through the competition, the NZCRS recognises the student's research efforts and supports the attendance of students at the annual CRS meeting. The winners of this year's competition were Julia Myschik (School of Pharmacy, University of Otago), Bradley McLellan (University of Waikato), and Shakila Rizwan (School of Pharmacy, University of Otago). Since Julia had won the first prize already the year before and did not intend to go to New York, the prize money was deferred to the 2nd and 3rd place winners. So, see you in New York Bradley and Shakila.

Prize winners of the 2008 NZCRS student prize. Top: Julia Myschik; middle: Bradley McLellan; and bottom: Shakila Rizwan.

Attendees at the 10th Formulation and Drug Delivery conference in Dunedin.

The 10th anniversary of this meeting brought together a great variety of outstanding researchers; every day was filled with excellent presentations, and the extra day for the vet session was well received. The great momentum gained from this meeting will certainly be carried over to next year ,when the 11th meeting will be held in Dunedin. See you then. ■

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CRS Nordic Chapter Annual Meeting to Be Held in Tromsø, Norway

The 2008 Annual Meeting of the CRS Nordic Chapter will be held June 25–27 in conjunction with the 2nd Midnight Sun Meeting on Drug Transport & Delivery at the University of Tromsø, Norway. This 3-day meeting is meant to be a rather informal gathering of scientists who are interested in drug transport and delivery, from basic research to applied research and pharmaceutical development points of view. As in 2004, when the meeting was first held, the organisers expect about 100 participants from all over Europe (mainly Scandinavia) and from both academia and industry. The meeting will be hosted by the Drug Transport & Delivery-Group, Department of Pharmacy, University of Tromsø, with support from the Controlled Release Society Nordic Chapter. The meeting is strictly non-profit in nature.

The focus areas will be
- Drug solubility, analysis, prediction, and ways to overcome poor solubility
- Drug permeability, drug transporters, and permeability screening
- Drug delivery, nano drug carriers; and oral dosage forms

Each of the scientific sessions will be opened by a comprehensive talk given by a leader in the field, followed by a number of short oral communications selected from the submitted abstracts and complemented by a poster session and networking opportunities.

Speakers list:

Dr. Christel Bergström, Uppsala University, Department of Pharmacy, Screening Informatic Center
Dr. Matthias Brandsch, Martin-Luther-Universität Halle-Wittenberg, Biozentrum, Membrane Transport Group
Prof. Dr. Heike Bunjes, TU Carolo Wilhelmina Braunschweig, Inst. f. Pharmazeutische Technologie
Prof. em. Dr. Henning Gjelstrup Kristensen, University of Copenhagen, Faculty of **Pharmaceutical Sciences,** Dept. Pharmaceutics
Dr. Anna Lena Ungell, AstraZeneca R&D Mölndal, Discovery Drug Metabolism and Pharmacokinetics & Bioanal. Chemistry

Tromsø, the "capital" of northern Norway is easily reached by a 2-hour flight from Oslo. During the short yet intense summer, Tromsø is "the" starting point for excursions to the arctic.

For updated information please check the meeting homepage at http://uit.no/farmasi/4090/. ■

UKICRS Conference Review: 14th Annual Symposium 2008 Predicting Drug Delivery—Opportunities and Challenges

The 14th UKICRS Annual Symposium on "Predicting Drug Delivery—Opportunities and Challenges" was held at Merck Sharp and Dohme, United Kingdom, on Wednesday, January 23, 2008. The Symposium Organising Committee members were Dr. Leab Sek (Merck Sharp & Dohme), Dr. Abina Crean (University College Cork), Dr. Sarah Dexter (3M Health Care), and Dr. Majella Lane (School of Pharmacy University of London). The 14th UKICRS Symposium was highly successful, with approximately 85 registered delegates from the pharmaceutical industry and academia.

Dr. Shaun Fitzpatrick (Merck Sharp & Dohme) opened the morning session with a presentation titled, "Predicting Drug Delivery—An Industrial Perspective." The presentation highlighted the advantages and challenges associated with the development of oral controlled release dosage forms, including matrix and multiparticulate drug delivery systems. Multiparticulate extended-release delivery systems require relatively more complex developments and higher cost manufacturing techniques. In comparison, matrix extended-release delivery systems are cost-effective and simple to develop using readily available manufacturing technologies. The main limitation for this type of dosage form is the propensity to produce different blood exposure levels when taken with or without food. Whilst there are different *in vitro* techniques, such as USP Apparatus I and II and more recently Apparatus III and IV, available to predict formulation performance in humans, further developments in this area are required.

Dr. Cormac Taylor's (University College Dublin) presentation was titled, "The Hydroxylase Inhibitor DMOG Is Protective in a Murine Model of Colitis." Prolyl and asparaginyl hydroxylases are key oxygen-sensing enzymes that confer hypoxic sensitivity to transcriptional regulatory pathways, including the His studies investigating the effects of hydroxylase inhibition with dimethyloxalylglycine (DMOG) on Caco-2 intestinal epithelial cells *in vitro* (Caco-2) and in a dextran sodium sulphate (DSS)-induced model of murine colitis that demonstrates that hydroxylase inhibitors such as DMOG represent a new strategy for the treatment of inflammatory bowel disease.
Prof. Mark Cronin (Liverpool John Moores University) discussed "*In Silico* Prediction of Properties Relating to Dermal Drug

Delivery." For dermal delivery, there has been a considerable history of using QSARs to predict various aspects of skin permeability, using a variety of techniques to develop models. Typically most success has been achieved with the modelling of steady-state phenomena such as the permeability coefficient (K_p). This is because this type of data is most amenable to modelling. Some of the databases (e.g., the now classic "Flynn" data set and its updated versions) have been modelled by a variety of approaches, ranging from simple regression analyses based on hydrophobicity and molecular size to more complex models with non-linear methods. In other areas, *in silico* predictions can be made for other physico-chemical properties, such as melting point, aqueous solubility, vapour pressure, and Henry's law constant, with varying degrees of accuracy.

The presentation by Dr. Ben Forbes (King's College London) highlighted strategies for "Predicting Drug Delivery to the Lung." The factors determining the fate of an inhaled medicine include aerosolisation and particle deposition, dissolution, drug metabolism, transport by the mucociliary escalator, macrophage uptake, and transepithelial absorption. A number of *in vitro* systems are available to study the interaction of compounds and formulations with components of the respiratory tract, such as cell culture models of the respiratory epithelium and the isolated perfused lung.

The afternoon session was opened by an international guest speaker, Prof. Rod Walker (Rhodes University, South Africa), who provided an overview on "Paediatric Drug Product Development: Opportunities and Challenges." The presentation looked at paediatric drug product development and the various regulatory and technical hurdles that face scientists designing delivery systems for such patients. The opportunities that exist for novel delivery system design for this patient population and some examples were presented. Challenges for paediatric drug delivery in the developing world and the opportunities for innovation that arise from such challenges were also addressed.

Highlights of current postgraduate drug delivery research included Waleed Faisal (University College Cork) on "Investigations of Lycopene Absorption Mechanisms from the Gastro-intestinal Tract of the Rat." Daniel Wood (University of Hertfordshire) presented his research work on "Thermoenhancement of Percutaneous Drug Absorption." Sam Maher (University College Dublin) also presented his studies on "Increased Intestinal Permeability Induced by Melittin."

Left to right: Symposium chairs and presenters: Abina Crean, Mark Cronin, Daniel Wood, Leab Sek, Yvonne Perrie, Sarah Dexter, Michael Donaldson, Shaun Fitzpatrick, Rod Walker, Marc Brown, Ben Forbes, Sam Maher, and Waleed Faisal.

Prof. Marc Brown (University of Hertfordshire and MedPharm Ltd.) provided a comprehensive overview on "*In Vitro* Models for Optimising Ungual Drug Delivery." The presentation described the new generation of *in vitro* models and methodologies that are being used to 1) gain a more fundamental understanding of the barrier properties of the nail, 2) develop and optimise ungual formulations to aid the development of the next generation of topical ungual formulations, and 3) decrease the risk of failure when such medicinal products enter clinical evaluation.

Graduate presentation winner Sam Maher (left) and UKICRS Chair Yvonne Perrie (right).

Closing the symposium, Dr. Michael Donaldson (Stiefel Laboratories) spoke on "*In-Vivo* Models for Predicting Transdermal Delivery." The presentation highlighted *in vitro* techniques and *in vivo* models for predicting transdermal absorption and toxicity. In terms of measuring diffusion, there is a range of systems, several of which came online just recently; however, the simplest model is the nail swelling model, which assumes an increase in the weight of the nail is directly proportional to drug uptake. However, both Michael and Mark noted that new ethical procedures made it much more difficult to actually obtain nail samples, so even this method had limitations.

The UKICRS annual student award for Best Postgraduate Presentation was won by Dr. Sam Maher (University College Dublin) for his research on "Increased Intestinal Permeability Induced by Milittin." Nick Gower (University of Bristol), along with Dr. Paolo Avalle and Anna Midwinter from Merck Sharp & Dohme, won the Best Poster Award for their work on "The Use of NIR Spectroscopy to Study the Hydration of a Controlled Release Tablet."

The UKICRS Committee would like to thank all the speakers for their contributions in delivering an excellent program. The UKICRS Committee gratefully acknowledges Merck Sharp & Dohme as the main sponsor of the symposium and Aqualon and CRS for financial support. The committee would like to also thank the exhibitors at the symposium, including *Journal of Pharmacy and Pharmacology*, Eminate, Wyatt Technology, Horiba, and Oxford Instruments. ■

Why You Absolutely Have To Be There

Ijeoma F. Uchegbu
CRS Scientific Secretary, University of London, U.K.

It is not often that things work out so well as our planning for the 35th CRS Annual Meeting & Exposition, especially in the world of science, where success is often coloured by many less fruitful hours. I am pleased to tell you that the planning for the New York City meeting is proving to have a bit of a Midas touch about it. We have had more abstracts submitted than ever before for a meeting in the United States, have a cracking programme that offers topics spanning medicine counterfeiting, mental health therapies, and made-in-the-laboratory organs. We have programmed the sessions so you will be absolutely spoilt by choices when it comes to where to go and who to see, and honestly, if the enquiries we have had are any indication of the level of interest in our 35th Annual Meeting & Exposition, then we expect to welcome a huge gathering of the great and the greater to New York City. To insert one, and only one, cliché: can you afford to miss this?

We all know that the best deals are carried out over a cardboard cup of hot coffee, and so we have structured each day to allow for maximum networking. This has been done by allowing for many exhibition, as well as many more science, showcase hours, so you can learn something new, make new contacts, and meet up with old, and not so old, friends all under one roof! Now CRS makes it even easier for you to select your educational workshop, register for the annual meeting, and purchase your banquet tickets by providing online registration.

The CRS Annual Meeting & Exposition is unique in that it is not so large as to be absolutely overwhelming, in an "I cannot find my colleagues" sort of way, and yet is large enough to include a good sprinkling of scientists from the different disciplines in our science, as well as our friendly regulators. Our size and dedication to our members are some of our unique selling points.

Hilton New York. Photo by Ed Jacoby.

The CRS Annual Meeting & Exposition is a meeting that focuses exclusively on emerging technologies. We are passionate about new science, and I can tell you that the two days that Mark Tracy, Kam Leong, Martyn Davies, Teresa Virgallito, and I spent going through the abstracts were two of the most exciting days of 2008

Central Park. © Jeff Greenberg

for me, as the science being carried out by all of you is simply breathtaking. Some of the abstracts left me gasping an unspoken "why didn't I think of that?" Pure pleasure! We had a hard job selecting the very best for podium places. We did it in the end though, so you will get to hear some of our top scientists tell you about their ideas and how they validated them with good quality data. Some of the people I am anxious to hear speak are Shyh-Dar Li from the University of North Carolina, who is developing siRNA therapies for the treatment of cancer metastases, and Valentine Wascotte from the Université Catholique de Louvain, who is developing a non-invasive skin-based test for kidney disease. I could go on and on about the scientists who caught my eye, but we have limited space!

If you know of new scientists starting out who are wondering where to pitch their tents, this is the conference for them, as our knowledge gaps will be on display. Alternatively if you are a seasoned scientist looking to commercialise your endeavours, we have a healthy level of industrial attendees, in actual fact two halls full of industry exhibitors to choose from. If you happen to be one of a handful of thought leaders, you should attend, just to make sure that you are still a thought leader, if you catch my drift. Finally, if you are looking for technology to launch your next product, there is nowhere else on earth with pharmaceutical, consumer products technologies, and animal health all under one roof, and we all know that "borrowing" technology from one sector to service the other is a quick and easy way to out patent our intellectual property rivals.

Be sure to take advantage of your membership in the CRS and register now for the 35th CRS Annual Meeting & Exposition and an Educational Workshop at the member rates. Remember we want to see you and your work at the Hilton New York July 12–16! ■

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
AC Compacting LLC
Adhesives Research
Aicello Chemical Co., Ltd.
Alkermes Inc.
Allergan, Inc.
Almac Group
American Pharmaceutical Review
Aptuit
Aqualon, A Business Unit of Hercules Inc.
Asahi Kasei Chemicals Corporation
Avanti Polar Lipids, Inc.
Avantium Technologies
Aveva Drug Delivery Systems
Azopharma
Banner
BASF Corporation
Bilcare
Bio-images Research Ltd.
Bio-Lab Ltd.
Biovail Contract Research
Boehringer Ingelheim
Brookwood Pharmaceuticals
Buchi Corporation
Capsulution NanoScience AG
Catalent Pharma Solutions
ChemAgis USA, Inc.
ChemImage Corp.
CMA/Microdialysis
Coating Place, Inc.
Colorcon
Contract Pharma
Croda Inc.
Depomed, Inc.
Dermatrends, Inc.
Dissolution Technologies
DPT Laboratories
Drug Delivery Technology
Drug Discovery Today
DSM Biomedical
Duoject Medical Systems
DURECT Corp.
Eastman Chemical Company
Elan Drug Technologies
Elsevier
Erweka America Corp.
Eurand
FormuMax Scientific
Fuji Health Science
Gattefosse Corp.
Gaylord Chemical Corp.
Genzyme Pharmaceuticals
Glatt Pharmaceutical Services
Halozyme Therapeutics
Hanson Research
Hisamitsu Pharmaceutical Co., Inc.
IMA North America Inc.
Informa Healthcare Publishers
Innocore Technologies
Intertek MSG
Irvine Pharmaceutical Services
LCI Corporation
Lipoid LLC
Logan Instruments
LTS Lohmann Therapy Systems
Lubrizol
MedTRACK
Molecular Profiles
Mylan Technologies Inc.
NAL Pharma Ltd.
Nano Imaging Services
National Adhesives
Nisco Engineering AG
Nisso America Inc.
NOF Corporation
Northern Lipids Inc.
NovaMatrix/FMC BioPolymer
Noven Pharmaceuticals, Inc.
Oakwood Laboratories
OctoPlus NV
O'Hara Technologies
ONdrugDelivery
Oxford Instruments
Patheon Inc.
Pharmaceutical Profiles Ltd.
Pharmaceutical Technology
PharmaForm
Pharma Magazine
Pharma Polymers, Evonik Industries
Pharmatek Laboratories, Inc.
PharmCircle
Pharsight Corporation
Philips Research
PII
PolyMicrospheres-Advanced Nanotechnologies
Polymun Scientific GmbH
PURAC Biomaterials
Rohm & Haas Company
RTS Life Science
Samedan Ltd.
Scintipharma, Inc.
Shin-Etsu Chemical Co. Ltd.
Simulations Plus, Inc.
Skin Scientifica Inc.
Soliqs
SOTAX Corporation
Southwest Research Institute
Surface Measurement Systems NA
SurModics, Inc.
Sympatec, Inc.
Technology Catalysts International
Texture Technologies
Thermo Scientific
Varian, Inc.
Vector Corporation
XSpray Microparticles

Questions?

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What's on Board for the Future?

Selecting just the right venue for a CRS Annual Meeting & Exposition is something the Board of Directors takes quite seriously. It can be a daunting task when you consider CRS has members in more than 50 countries.

The Board and CRS headquarters staff work closely together to choose three or four potential locations for an annual meeting and exposition in any given year. One of the ways cities and countries are decided upon is by hearing from you. Members who attend an annual meeting and exposition are asked to complete and submit a survey at the conclusion of the summer's event. One of the questions asked on the survey is where would you like to see an annual meeting and exposition held? The answers are gathered, discussed, and considered when the CRS Board and staff are planning future meetings. The next time you're asked where you'd like CRS to meet, don't be shy, let your voice be heard, and tell your Society where you'd like to be in the future.

By using survey results, the Board and staff have learned that CRS members like attending annual meetings and expositions in Europe and going from one U.S. coast to the other. Because of the diverse membership of CRS, a variety of locales are always considered.

In an attempt to balance the wishes of members and the bank account at the same time, the CRS Board has selected the next three annual meeting and exposition locales. They are

36th CRS Annual Meeting & Exposition
July 18–22, 2009
Copenhagen, Denmark

37th CRS Annual Meeting & Exposition
July 10–14, 2010
Oregon Convention Center
Portland, Oregon U.S.A.

38th CRS Annual Meeting & Exposition
July 30–August 3, 2011
Gaylord National Resort and Convention Center
National Harbor, Maryland U.S.A.

These areas of the world were suggested by you, the members of the CRS, so we certainly hope to see you at each place when their time comes for the next CRS Annual Meeting & Exposition. Thank you for expressing yourselves! ■

Transdermal Update 2008

Priya Batheja,[1] Agis Kydonieus,[2] Diksha Kaushik,[1] and Bozena Michniak-Kohn[1]

We searched the literature for patents and patent applications related to transdermal delivery published during the calendar year 2007 and uncovered 288 such publications. Of these, 33 were issued US patents and 86 were US patent applications. There were also 83 World (WO), 72 European (EP), and 14 Japanese patent publications. It should be noted that many of these patents are counted more than once, since a patent application can be filed in the US, WO, and EP patent systems at the same time.

In this update we have reviewed mainly the US issued patents. Of the 33 issued patents, 10 pertained to electromechanically enhanced delivery and 23 to passive diffusion, including 8 for chemical enhancement. Some of the most pertinent publications and interesting highlights of this market are summarized below.

In September 2007 the FDA granted approval to Novartis for the Exelon patch containing rivastigmine, for the treatment of Alzheimer's disease. The patch can be applied to the back, chest, or upper arm and delivers 9.5 mg of rivastigmine over a period of 24 hr. Rivastigmine is a cholinesterase inhibitor that increases the activity of the neurotransmitter acetylcholine in the brain. The patch has been shown to reduce side effects such as nausea, vomiting, and other gastrointestinal side effects that are prevalent with the capsule form of the drug.

Separately, U.S. scientists at the University of South Florida have announced the development of a transdermal vaccine for Alzheimer's disease, which triggers the immune system to clear amyloid beta, a protein found in abnormal quantities in the brains of Alzheimer's patients.

In July the FDA also approved a spray developed by Acrux for the treatment of post-menopausal vasomotor symptoms such as hot flashes. The spray is a fast-drying formulation (45 sec) containing a naturally occurring estrogen (estradiol), an enhancing substance derived from sunscreen extract and a volatile solvent. The spray is applied to the inner forearm and it absorbed into the blood over a 24-hr period on a sustained basis. The product will be marketed in the United States by KV Pharmaceuticals.

Mylan also obtained approval for its generic fentanyl patch, which delivers 12 µg of fentanyl per hour. Mylan offers all five strengths of transdermal fentanyl, which is the generic version of Alza's Duragesic patch. During 2007, Lavipharm also obtained approval for its fentanyl generic patch.

[1] Laboratory for Drug Delivery, Rutgers-The State University of New Jersey, NJ, U.S.A.

[2] Samos Pharmaceuticals, LLC, Kendell Park, NJ, U.S.A.

In other developments, both Altea Therapeutics and Phosphagenics Ltd. have announced positive results for Phase I human studies with their topical insulin products. Altea is developing 12- and 24-hr transdermal patches to provide constant basal levels of insulin for people with type 1 or type 2 diabetes. In other Phase I developments, Transpharma Medical has announced positive results for the transdermal delivery of hPTH (human parathyroid hormone) for the treatment of osteoporosis. The 48-subject study was conducted to compare the tolerability and pharmacokinetics of hPTH patches to FORTEO (*Teriparatide*) (Eli Lilly) administered subcutaneously. Chrono Therapeutics also has announced positive results for their Phase I trial with their pulsative transdermal drug/device combination. The dose escalation trial showed statistically significant modulation and control of the dosing profiles. Finally, Acrux and Organon have announced a collaboration to develop and commercialize contraceptives, using Acrux's unique spray technology.

PASSIVE DIFFUSION

Methods and Devices for Transdermal Delivery

Abuse-Resistant Transdermal Dosage Form (3M Innovative Properties Company) US 7182955

A transdermal drug delivery device is described, where the device is capable of preventing abuse or misuse of substances such as narcotics or other agents. The active agent is present in a polymeric material that is in contact with the skin surface and may also contain additives such as penetration enhancers, antioxidants, etc. A barrier layer is present between the active reservoir and an adverse agent reservoir, which contains an antagonist to the active. On its other side, the adverse agent reservoir is connected to a porous medium that is in "fluid communication" with the proximal side of the active agent reservoir in contact with the skin. The antagonist is not delivered to the skin surface at a therapeutic level during intended use, but during attempted abuse, such as contact of the active agent with a liquid or its immersion in a liquid, the liquid also flows to the porous material, leading to release of the antagonist from the dosage form along with the abusable drug substance, thus preventing intended abuse.

Compositions and Methods for Transdermal Oxybutynin Therapy (Watson Pharmaceuticals, Inc) US 7179483

The present invention discloses methods and compositions for administration of oxybutynin, an anticholinergic used for treatment of overactive bladder and urinary incontinence, in ways that minimize associated adverse drug experiences such as dry mouth, dizziness, blurred vision, and constipation. The adverse effects are generally attributed to the presence and amount of active metabolites of oxybutynin, such as *N*-desethyloxybutynin,

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and are observed in a large number of patients to an extent that leads to treatment discontinuation. Embodiments of the invention include transdermal and topical dosage forms that specifically encompass each isomer for both oxybutynin and its corresponding metabolites, such that on administration the ratio of area under the plasma concentration-time curve (AUC) of oxybutynin to an oxybutynin metabolite is about 0.5:1 to about 5:1. The transdermal formulation may include permeation enhancers, anti-irritants, adhesion adjusters, and combinations thereof and has been shown to lower the mean AUC ratio of (R)-*N*-desethyloxybutynin to (R)-oxybutynin, resulting in greatly reduced amounts of the active metabolites of oxybutynin, while providing a therapeutically effective amount of oxybutynin. These formulations thus provide a significant advantage over oral administration of oxybutynin.

Drug Delivery System for Implantable Cardiac Device (Cardiac Pacemakers, Inc.) US 7201733

A responsive transdermal drug delivery system that can be incorporated into a cardiac device and can deliver the dose upon detection of a particular medical condition is disclosed. The implantable cardiac device, such as a cardiac pacemaker or defibrillator, can sense electrical activity occurring in a patient's heart and generate sensing signals that indicate the activity, such as arrhythmia or ischemia. With the help of a telemetry interface, the device can transmit radio frequency signals to the drug delivery device, which can be an electrically modulated transdermal drug delivery device affixed to the patient's skin. The drug delivery device consists of a microprocessor, memory, and a telemetry interface for receiving and demodulating radio signals received from the cardiac device. On receipt of the signals, it can deliver a pre-programmed quantity of the drug in a specific time period, leading to controlled drug delivery. The system can also be programmed to maintain a downloadable log of the sensed physiological variable and the amount of drug delivered by the device, which can provide feedback that can be used to formulate an optimum drug dosage schedule for the patient.

System and Method for Optimizing Tissue Barrier Transfer of Compounds (Transform Pharmaceuticals, Inc.) US 7172859

The present invention relates to high-throughput systems and methods to prepare a large number of single- or multiple-component formulation combinations at the same time and high-throughput methods to test the tissue (skin) transfer of such combinations. An embodiment of the invention describes an apparatus comprising a support plate, an array of samples on the plate, a membrane/tissue overlaying the array of samples, and a reservoir plate secured to a side of the membrane opposite the array of samples. The combinatorial high-throughput apparatus can be used to prepare and load samples, overlay the array of samples with a tissue specimen, secure the upper reservoir plate corresponding to the array of samples and fill them with a reservoir medium, and finally measure the concentration of each reservoir as a function of time to determine the flux of the actives across the membrane. Another embodiment of the invention also describes the ability to cut the tissue specimen to avoid lateral diffusion between wells and analyze the tissue specimen for defects or inhomogeneities. In addition, the system can also aid in processing samples by stirring, milling, filtering, centrifuging, emulsifying, lyophilizing, and reconstituting prior to assembly of the entire apparatus. The system typically can analyze at least 10 samples, and preferably more than 1,000 samples.

Transdermal Drug Delivery Device (Alza Corporation) US RE39588

A controlled release transdermal device for delivery of therapeutic agents is disclosed, whereby the device can provide diffusional drug delivery that prevents an initial burst of the drug, thus causing less irritation and providing delayed onset of drug administration. The delayed release is particularly beneficial in delivering drugs that have a tendency to irritate skin in large doses, such as benztropine, nicotine, and propranolol. The invention also claims a delivery device in which the therapeutic agent is converted from the stable form suitable for storage to the form suitable for delivery through the skin after the device is placed into its environment of use (in contact with the skin or mucosa). When placed in a biological environment, the moisture migrates into the system from the skin surface by osmosis or diffusion and passes through the adhesive layer and then to the activating means, where it mixes with an activating agent, preferably an acid or base stored in its anhydrous form. The acid or base forms an acidic or basic solution with the water, migrates into the salt drug reservoir, and converts the salt drug to its free form, which then passes freely through device layers and then through the skin. This invention has particular utility for the delivery of drugs that have a tendency to be unstable in their active forms but that are more stable as salts (sympathomimetic drugs such as terbutaline, salbutamol, and ephedrine). The device can also incorporate a rate-controlling membrane present between the activating agent and the drug reservoir that can serve to control the rate of hydration and diffusion of the activating agent, thereby controlling the delivery of the active drug.

A Method of Transdermal Drug Delivery Using Hyaluronic Acid Nanoparticles (University of South Florida) US Patent Application 20070036728

A method for the development of hyaluronic acid (HA) nanoparticles is presented, which is useful for the transdermal delivery of macromolecules, such as peptides, DNA, and other hydrophilic or hydrophobic molecules. The method of preparation of the HA nanoparticles comprises the steps of mixing HA and a hydrazide (oxalic acid) with a crosslinking agent (carbodiimide) in an aqueous solution, adding a non-polar organic solvent and a surfactant (sorbitan monostearate) to form an oil-in-water emulsion, and lowering the pH to allow intermolecular and intramolecular crosslinking. The nanoparticles are precipitated by the addition of alcohol.

Formulations for Amylin Agonist Peptides (Amylin Pharmaceuticals) US 7312196

A liquid pharmaceutical formulation is provided that comprises about 0.5–1.0% of an amylin peptide agonist, a buffer, a tonicifier or stabilizer, and a preservative. The formulation can be in liquid,

gel, or powdered form for delivery by several means, including transdermal drug delivery.

Enhancers for Transdermal Delivery

Composition for Transdermal and/or Transmucosal Administration of Active Compounds that Ensure Adequate Therapeutic Levels (Antares Pharma IPL AG) US 7214381

A pharmaceutical composition for transdermal and/or transmucosal delivery of diverse therapeutic agents via a gel or solution dosage form is disclosed. This system claims to have the potential for sustained and controlled delivery of actives ranging from hormones to other agents such as sedatives, anxiolytics, antihypertensive agents, and calcium regulators. This transdermal/transmucosal formulation entails a novel combination of various penetration enhancers that include 1) saturated fatty alcohols, saturated fatty acids, unsaturated fatty alcohols, and unsaturated fatty acids of formulae $CH_3(CH_2)_n$-CH_2OH, $CH_3(CH_2)_n$-CH_2COOH, $CH_3(C_nH_{2(n-1)})OH$, and $CH_3(C_nH_{2(n-1)})COOH$, respectively, wherein n is an integer between 8/22; 2) a ternary vehicle consisting of a C_1/C_4 alkanol, a polyalcohol, propylene glycol, and water; and 3) monoalkylether of diethyleneglycol. When the specific combination of lauryl alcohol and diethylene glycol monoethyl ether (Transcutol.RTM.P) are used to enhance composition, an adequate penetration enhancement factor and a sustained flux of the active agent is attained, thereby providing therapeutic, effective, controlled, and sustained levels of the active drugs by only once-a-day application of the formulation.

Drug Delivery Method by Enhanced Topical Application (CeramOptec Industries Inc.), US Patent Application 20070154536

A method of enhancing delivery of actives into human/animals via hair follicles is claimed that employs the use of a swellable formulation constituting biodegradable and bioactive polymers encapsulated in the form of microspheres or liposomes. The formulation is designed in such a way that it maintains the passage of actives by either 1) opening hair follicles and preventing them from collapsing; or 2) increasing the depth of the inner lumen of the hair follicles. This method claims to improve the flux of actives via hair follicles, causing localization of active in the tissues surrounding the hair follicles or under the skin and thereby leading to systemic delivery without skin surface modification. This novel system offers the advantage of increasing therapeutic effects of actives in the treatment of skin disorders and can also help in permanent removal of unwanted hair.

Mixture of Delivery of Low and High Molecular Weight Compounds (JRX Biotechnology, Inc.) US 7201919, US 7220427, US 7300666

A transdermal delivery system has been disclosed that is capable of delivering high molecular weight pharmaceuticals and cosmetic agents to the skin. This system comprises mainly three components: penetration enhancer, aqueous adjuvant, and an active. The penetration enhancer is a mixture of hydrophobic and hydrophilic domains, with the hydrophobic domain mainly containing animal- or plant-derived ethoxylated lipids and the hydrophilic domain ranging from alcohols to non-ionic solubilizers or emulsifiers. The aqueous adjuvants used in this system are water, *Aloe vera* juice, or other plant extracts. The therapeutic or cosmetic actives delivered through this system can consist of not only low molecular weight compounds such as NSAIDS (non steroidal anti-inflammatory drugs), capsaicin, boswellin, and antiviral compounds, but also extend to transdermal delivery of high molecular weight agents like collagen.

Penetration Enhancing and Irritation Reducing Systems (Cellegy Pharmaceuticals Inc.) US 7157097

A system capable of percutaneous enhancement of an active (preferably estradiol and its derivatives) is divulged, with the additional advantage of reducing the irritation associated with its transdermal or topical delivery. The formulation includes a therapeutic agent, a penetration-enhancing system, and a gelling agent and is maintained at a pH of 4–8. The pharmaceutical composition can vary from solutions, lotions, creams, and ointments to gels, aerosols, and patch devices. The penetration-enhancing system in this formulation is composed of a mixture of three components, namely a membrane fluidizer (oleic acid), a C_1–C_4 alcohol (ethanol, propanol, isoproponal, or their mixtures), and a penetration-enhancing alcohol (ethylene glycol, propylene glycol, butylene glycol, or their mixtures). The gelling agent incorporated in the formulation is usually selected from a group consisting of Carbopol® 1342, Carbopol® 940, Klucel®, and Klucel® HF. In addition to transdermal delivery, this system claims to possess mucosal penetration-enhancing effects.

Transdermal Administration of Nonsteroidal Anti-inflammatory Drugs Using Hydroxide-Releasing Agents as Permeation Enhancers (Dermatrends, Inc.) US 7244447

A method for enhancing the transdermal delivery of nonsteroidal anti-inflammatory drugs via a system involving hydroxide-releasing agents as a permeation enhancer is proclaimed. The formulation in this system is composed of a nonsteroidal anti-inflammatory agent, a hydroxide releasing agent, and a pharmaceutically acceptable carrier and can be prepared in several dosage forms, such as liquid, semisolid, or transdermal patch. The NSAID used in the formulation is a propionic acid derivative that is absorbed systemically upon transdermal delivery. The hydroxide releasing agent is an inorganic hydroxide such as sodium hydroxide or potassium hydroxide that releases free hydroxide ions in the presence of an aqueous carrier and subsequently improves the flux of the NSAID. The aqueous carrier may be natural moisture present at the skin surface or water accumulated due to the occlusive backing of the patch form. The method claims to minimize the probability of skin damage, irritation or sensitization associated with the application of the active and also shows suitability in enhancing the flux of NSAIDs across mucosal tissue.

Transdermal Update 2008 continued on page 26

Transdermal Update 2008 continued from page 25

ELECTROMECHANICALLY ENHANCED DELIVERY

Compositions for Electroporation (Pola Chemical Industries Inc.) US 7197359

A method for increasing percutaneous absorption is claimed that comprises composition of a drug, an electrolyte, and 5–0% of a polyhydric alcohol and menthol. The concentration of the drug to the electrolyte is adjusted so the osmotic pressure of the composition is lower than the osmotic pressure of physiologic saline, thereby elevating percutaneous absorption. The composition is applied to the skin, and voltage is applied by an electroporation device for a short period of time. The percutaneous absorption is enhanced for the remaining time of the treatment without further application of voltage. Propylene glycol is claimed as the polyhydric alcohol, and the optimum applied voltage is 300 V at a capacitance of 25 μF for 5 min.

Device for Enhanced Delivery of Biologically Active Substances (Intrabrain International NV) US 7200432

A method is described for the non-invasive transnasal or transocular iontophoretic delivery of a drug to the central nervous system (CNS) in an enhanced fashion and bypassing the blood brain barrier. The method comprises the following steps: 1) supplying the drug formulation proximate to the target region; 2) establishing an iontophoretic energy gradient between the drug supply and the target tissue; and 3) delivering the drug directly to and through a nervous system pathway to the target site without transiting through skin layers and vasculature, thus delivering the drug at higher rates.

Device for Transdermal Electrotransport Delivery of Fentanyl and Sufentanil (Alza Corporation) US 7302293

An iontophoretic device is described that comprises a switch that activates the device to deliver a dose of about 20–60 μg of fentanyl for a predetermined period of up to 20 min and then terminate said delivery. The iontophoretic control circuit allows up to 100 additional doses over a period of a day. The delivery of fentanyl and sufentanil is sufficient to induce analgesia in a human patient suffering from moderate to severe pain associated with major surgical procedures.

Methods of Monitoring Glucose Levels in a Subject and Uses Thereof (Animas Technologies, LLC) US 7228163

A method is presented for monitoring the effect of a pharmaceutical composition, such as one comprising pentamidine, saquinavir, quinine, or indomethacin, on the glucose levels of a subject receiving such a pharmaceutical composition. The method comprises the following steps: 1) iontophoretically extracting a glucose sample from the subject; 2) bringing the sample in contact with a sensor in the presence of glucose oxidase that reacts with glucose to produce hydrogen peroxide; 3) detecting and measuring hydrogen peroxide, which is specifically related to the concentration of glucose in the subject; and 4) comparing the glucose concentration values to the record of treatments with the pharmaceutical composition.

Transdermal or Transmucosal Drug Delivery Device (Hisamitsu Pharmaceutical Co. Inc.) US 7200433

An iontophoretic transdermal or transmucosal delivery device is disclosed in which an energy pattern controller is configured to enable the drug delivery device to provide energy through 1) a combination of a pulse-depolarized type and a direct current and pulse type; 2) the pulse-depolarized type supplying repetitive pulses and discharging a residual charge during a pulse resting period; and 3) the pulse type supplying repetitive pulses, wherein the types of energization are conducted sequentially. It is claimed that the device gives excellent drug permeability with low irritation and reduced power consumption.

Device for Manipulating a Needle or Abrader Array and Method of Use (Becton Dickinson and Company) US 7186235

A microneedle device and a method for delivery of a drug are disclosed that comprise 1) a bottom wall having a planar outer surface with a plurality of 10-μm to 1.5-mm microneedles extending outward and having a length of 100–250 μm; 2) side walls and a top wall defining a reservoir for said substance to be delivered; 3) a device-manipulating member that is deformable and attached to at least one wall and extending beyond said wall; and 4) the manipulating member is a handle allowing one to hold the device and apply pressure on at least one of the walls to dispense said substance from the reservoir. It is claimed that the device avoids or eliminates excess pain and discomfort normally caused as a result of microbraders or microneedles entering the epithelial layers beneath the stratum corneum.

Functionalized Microneedle Transdermal Drug Delivery Systems, Devices and Methods (Gregory A Smith) US Patent Application 20070078376

Iontophoretic devices and methods are disclosed for transdermally delivering therapeutically active agents through an array of microneedles. The method provides for microneedles formed on a substrate, said substrate, and needles being functionalized with functional groups such as alkoxysilanes. Optionally, an iontophoretic assembly is provided in which the active electrode assembly comprises an active agent reservoir wherein the surface-functionalized substrate is positioned between the active electrode assembly and the skin.

Microneedle Drug Delivery Device (Georgia Tech Research Corporation) US 7226439

A simple device with a plurality of hollow microneedles is provided that allows delivery of drugs at clinically effective rates, with minimal damage, pain, or irritation to the tissue. The device comprises a substrate to which the plurality of microneedles is attached and a reservoir containing the drug, which is in communication with the microneedles. The reservoir can be made of deformable elastic material, so the amount of drug delivered can be selectively altered by compressing the reservoir. The reservoir can also be a syringe or a pump connected to the substrate.

Interface for Transdermal Drug Administration Device (Hirotoshi Adachi et al.) US Patent Application 20070123837

A microneedle transdermal delivery device is provided that can apply a drug to the skin evenly from a plurality of projections through the skin. The device comprises a flat plate with a plurality of two dimensionally arranged conical or pyramidal projections and a plurality of openings capable of delivering the drug, which are respectively arranged in correspondence with the projections. The flat plate can be made of metal or ceramic, and the ratio of the openings to the projections can be 1:1 to 1:2, respectively.

Devices for Transcutaneous Delivery of Vaccines and Transdermal Delivery of Drugs and Uses Thereof (Iomai Corporation) US Patent Application 20070088248

A system for disrupting the skin is disclosed that comprises a mask and a disrupting member mechanically coupled to the mask, wherein said mask has an opening and it contains a fastener (PSA) to secure the mask to the skin and said disrupting member is capable of being passed over the opening to disrupt the exposed skin. The disrupting member can be a metal or a ceramic abrasive made up of metal blades or protrusions capable of cutting grooves in the skin. Macromolecules, including antigens and vaccines, can be delivered through the disrupted skin area.

Intradermal Incorporation of Microparticles Containing Encapsulated Drugs Using Low Frequency Ultrasound (Ultra-Sonic Technologies, LLC) US 7232431

An apparatus and method of sonoporation of the skin are disclosed for the intradermal delivery of a microparticle suspension. The microparticles can have a diameter of 0.1 to 50 μm and can be liposomes, polymeric spheres, and biodegradable particles. The tip of an ultrasound horn applies ultrasound radiation to the microparticle suspension to generate cavitation bubbles, causing pores to be formed in the skin of the patient. The ultrasound radiation (1–30 kHz) intensity and distance from the skin are also effective in forming ultrasonic jets driving the microparticles through the formed pores into the skin. The ultrasound radiation is applied at a frequency other than the resonant frequency of the microparticles to avoid rupturing them. ■

People in the News

Compiled by Steven Giannos
Industrial Editor

Profs. Patrick Stayton and Allan Hoffman Start PhaseRx, a New Seattle Biotech Company Formed for Delivery of siRNA and Other Macromolecules

PhaseRx Inc. is a new Seattle biotechnology startup company focused on developing novel approaches to the delivery of siRNA and other macromolecules. On February 28, 2008, they announced the closing of their initial institutional financing, totaling $19 million. The financing was led by ARCH Venture Partners, 5AM Ventures, and Versant Ventures.

PhaseRx was formed by Robert Overell of Foundation BioVentures together with co-founders Profs. Patrick Stayton and Allan Hoffman from the University of Washington's Department of Bioengineering; Prof. Oliver Press, MD, of the Fred Hutchinson Cancer Research Center's Clinical Research Division; and Dr. Paul H. Johnson, the company's chief scientific officer. The company has exclusively licensed novel polymer technology from the University of Washington that was developed by the Stayton and Hoffman laboratories, in collaboration with the Press laboratory. This technology enables the effective intracellular delivery of siRNA. Pat Stayton and Allan Hoffman are long-time members of the Controlled Release Society. Hoffman received the CRS Founders Award in 2007.

Altea Therapeutics Appoints Dr. Richard H. Guy to Its Scientific Advisory Board

Business Wire: February 13, 2008 – ATLANTA, Ga. – Altea Therapeutics has announced that Dr. Richard Guy, professor of pharmaceutical sciences and the head of the Department of Pharmacy & Pharmacology at the University of Bath, has joined the company's Scientific Advisory Board.

"Richard Guy is a leading scholar in the field of transdermal drug delivery. We are thrilled to welcome him as a member of our scientific advisory board and look forward to his close association with our scientists as we develop our proprietary transdermal patch technology, the PassPort System, designed for the efficient delivery of drugs that normally would need to be administered by needle injection, including proteins, carbohydrates and water-soluble drug salts," said Dr. Eric Tomlinson, president and CEO for Altea Therapeutics.

"Altea Therapeutics has recently made several significant advances in the transdermal delivery field," said Prof. Guy, who added "The PassPort Transdermal Delivery System has the potential to expand the classes of drugs that can be painlessly delivered from a skin patch. I look forward to working with the scientific team at the company."

Dr. Guy's principal scientific achievements are in the areas of characterizing the function of the skin barrier for drug absorption, enhancement of percutaneous absorption, iontophoresis, noninvasive bio-sensing of blood glucose and other analytes, and the prediction and assessment of skin penetration and topical bioavailability. Dr. Guy has published more than 250 peer-reviewed articles and more than 70 book chapters and has co-authored one book and co-edited seven others. He is also a co-inventor on 10 patents. Dr. Guy received a M.A. degree in chemistry from Oxford University and a Ph.D. degree in pharmaceutical chemistry from the University of London. He has held academic posts at the University of California, San Francisco and the University of Geneva. Dr. Guy serves on the editorial advisory boards of numerous journals, including the *European Journal of Pharmaceutics and Biopharmaceutics* and *Diabetes Technology & Therapeutics*. He is a past president of the Controlled Release Society and is an advisor to several companies in the pharmaceutical, cosmetic, and biotechnology industries. Dr. Guy is an elected Fellow of the Academy of Pharmaceutical Scientists, Great Britain, the Royal Society of Chemistry, the American Association of Pharmaceutical Scientists, and the American Association for the Advancement of Science.

David W. Grainger Joins *Drug Delivery* Journal as Co-editor-in-Chief

PRNewswire: January 22, 2008 – NEW YORK, N.Y. – David W. Grainger, Ph.D., has joined the *Drug Delivery* Journal as Co-editor-in-Chief. *Drug Delivery*, published by Informa Healthcare, a leading content provider of pharmaceutical science information for the academic and industrial communities with peer reviewed coverage of basic research, development, and application principles at molecular, cellular, and higher levels.

Dr. Grainger, currently professor and chair of the Department of Pharmaceutics and Pharmaceutical Chemistry in the College of Pharmacy at the University of Utah, is an internationally respected and award-winning professor and scholar in the drug delivery and biomedical device fields. His new appointment seeks to guide the journal's overall direction within the drug delivery community as this field evolves and integrates with emerging science and technology. It also signals an invitation for new high-quality manuscripts now being accepted for consideration for publication in *Drug Delivery*.

"Dr. Grainger's new position as Co-editor-in-Chief of *Drug Delivery* signifies an exciting new direction for us," says Carolyn Honour, vice president and publishing director, Informa Healthcare, Pharmaceutical Science. "Dr. Grainger's expertise

offers a fresh perspective on current research and development[s] in this area and should establish a new era of leadership for a journal that carries a tradition of delivering quality articles to the scientific community." *Drug Delivery* publishes original research, critical reviews, book reviews, and industry announcements, such as patent updates, literature alerts, and news of important events.

"I'm really excited and challenged about my new role at *Drug Delivery*," declares Dr. Grainger. "I'm looking forward to attracting, acquiring-and publishing-the highest quality and most impacting research articles to help advance and disseminate the work being done in this field."

Dr. Grainger, a past member of the Scientific Advisory Board and annual symposium chair for the Controlled Release Society, holds many advisory panel positions within the industry. Among the many honors he has received is the PhRMA Foundation's Excellence in Pharmaceutics Award (2005) and the Society for Biomaterials' Clemson Award for Basic Research in Biomaterials (2007). He earned his Ph.D. degree in pharmaceutical chemistry from University of Utah. ■

Welcome New Members

Mohammad J. Abdekhodaie
Tiffany S. Adams
Prafulla Agrawala
Remigius U. Agu
Denize Ainbinder
Adam W. G. Alani
Courtney Anderson
Samantha N. Andrews
Shabbir Anik
Yasutaka Anraku
Elias M. Assaad
Rania M. Badr
Misuk Bae
Lisa M. Bareford
Bhavesh Barot
Guillaume Bastiat
Nicolas Bertrand
Sarah M. Betterman
Shrikant A. Bhonsle
David Blaser
Miriam Breunig
Luis Brito
David Brown
Aneta J. Brud
Vanessa Bunjes
Alexander Burghardt
Fulden Buyukozturk
Gerard D. Byrne
Gregoire Cardoen
Camilla Cervin
Prerona Chakravarty
Tamim Chalati
Lipika Chatterjee
Abhishek Chaudhary
Jun Chen
Weiliam Chen
Xiaoming Chen
Ji Cheng
Peiwen Cheng
Vinay Chhatre
Chiao-Hsi Chiang
Youngil Cho
Ji S. Choi
Leonard Y. Chu
Judith Cohen
Gemma Coombs
Philippe Couckuyt, Sr.
David C. Coughlan
John Cowley
Yen Cu
Pieter R. Cullis
Dongmei Cun
Bolivar Damasceno
Nilanjana Das
Elise Dauphin
Elisangela A. De Moura Mendonca IV
Edward DiAntonio
Thomas A. Diezi
Priscila M. D'Mello
Fred Donelson
Rakesh Dontireddy
Gerard G. M. D'Souza
Dominique Duchene
Gulengul Duman
Paul S. Egee
Hoda M. Elgendy
Mahmoud Elsabahy
Christine A. Falabella
Yassin Farag
Ryan D. Fell
Richard E. J. Forster
Todd P. Foster
Madurai G. Ganesan
Jessica Garbern
Sonia Gervais
Sarah L. Goh
Gaurav Goyal
Jacob Grunwald
Xiaochen Gu
Sevgi Gungor
Qiongyu Guo
Jyoti Gupta
Raghavendra Gupta
Vivek Gupta
Neslihan Gürsoy
Manhee Han
Oshrat Harush-Frenkel
Simon Heuking
Peter T. Higuchi
Martin Holzer
Dave Horton
Md. Sharif Hossain
Melissa D. Howard
Yi-Ling Huang
Jeesun Hwang
Lim Hyun Ju
Tomoko Ida
Annabel Igonin
Michael Jay
Steven Jay
James G. Jin
Markus Johnsson
Lene Jorgensen
Reena Joseph
Alexandra P. Kafka
Praveen Kandi
Nobuya Kaneko
Johanna Kanzer
Takeshi Kasuya
Yurie Katayama
Erik Kaunisto
Diksha Kaushik
Rizwan Kazmi
Catherine A. Kelly
Hanieh Khalili
Elena Khazanov
Jae D. Kim
Jongoh Kim
Akihiro Kishimura
Szymon Kobierski
Iryna Kravchenko
Sarah Kuechler
Neeraj Kumar
Masanori Kuramoto
Aikaterini Lalatsa
Les L. Lawrence
Jang W. Lee
Moonseok Lee
Mirko Leonhardt
Jian-Xin Li
Jinjiang Li
Ming Li
Ning Li
Hsiang-Fa Liang
Charlie Lin
Hung-Yin Lin
Wen J. Lin
Yuh-Jing Lin
Anthony Listro
Julian B. Lo
Michiel Lodder
Xiuling Lu
Steven MacLellan
Madhu Madan
Claire E. Madden-Smith
Srinivas Madduri
Karla E. Madrigal
Parth D. Mair
Vincent Malaterre
Kuldip R. Malhotra
Radhakrishna K. Maroju
Enrico Mastrobattista
Saori Matsushita
Paul Mawson
Jaroslaw Mazgalski
Clare McCoy
Colin McCoy
Christopher W. McDaniel
Joseph McGonigle
Ángel E. Mercado-Pagán
Gioconda Millotti
Masafumi Misaki
Ritu Mishra
Kanjiro Miyata
Erwin Mombarg
Cheol Moon
Jeffrey W. Moore
Stephanie J. Mudd
Claudia Mueller
Tatsuya Murakami
Yuki Murase
Narasimha S. Murthy
Senthil Murugappan
Susanne Muschert
Julien Namur
Charlene Ng
Hemin Nie
Akihiro Nishi
Kayoko Niwata
Adwoa Nornoo
Kevin P. Nott
Mohamed M. I. Nounou
Makoto Oba
Katsuyuki Okubo
Tomoyuki Omura
Martin O'Neill
Mohammad Othman
Dawn L. Padfield
Susanne Page
Safak Paker-Leggs
Jayanth Panyam
Punit Parejiya
Hyoun-Hyang Park
Fathima Patel
Sanjay Patel
Sarsvatkumar B. Patel
Elizabeth Pearson
Chiranjeevi Peetla
Cary Percy
Glen Perera
Diana Peykova
Pemakorn Pitukmanorom
Veronique Preat
Samuel R. Pygall
Ronny Reinberg
Zhongxu Ren
Shakila B. Rizwan
Qian Ru
Duangkamon Sakloetsakun
Rajesh Salkar
Henelyta Santos Ribeiro
Jennifer L. Sarafolean
Mark Saunders
Michalakis Savva
Andrew J. Sawyer
Nanette Schulte
Curtis Schwartz
Manali Shah
Milin N. Shah
Alireza Shalviri
V. Prasad R. Shastri
John N. Shell
Margarita Shumilov
John Simons
Skuli Skulason
Sohee Son
Matthew E. Staymates
Alina Stefanache
Magdalena Stevanovic
Kinjal Suchak
Hiroshi Suzuki
Deborah Sweet
Janos Szamosi
Seiichi Tada
Hikaru Taira
Nakanishi Takeshi
Dov Tamarkin
Jiansheng Tang
Chandan M. Thomas
Potta Thrimoorthy
Fredrik Tiberg
Sandip B. Tiwari
Tu Hao Tran
Ya Tsz A. Turner
Frank Van de Manakker
Sunil Vandse
Albert Van Hell
Maria D. Veiga
Bhavna Verma
Anja Vetter
Ana Vila
Stephan G. Von Eggelkraut-Gottanka
Nagesh A. Wagdare
Anne J. Wandrey
Lin Wang
Yuhua Wang
Rob Ward
Alan L. Weiner
Xiaoguang Wen
Charlotte C. Williams
Hywel D. Williams
David Woolfson
Shy C. Wuang
Yuanyuan Xie
Peisheng Xu
Yoshihito Yaginuma
Motoo Yamasaki
Bruce Yan
Tatsunobu Yoshioka
Jerry C. Zhang
Wen Zhang
Mingxing Zhou
Ting Zhu
Christian Zimmer
Fatema Zohra
Hadasa Zuckerman

In the News

Compiled by Steven Giannos
Industrial Editor

MAY 2008

Investigators at University of Iceland, Faculty of Pharmacy, Publish New Data

Drug Week via NewsEdge (NewsRx.com): May 8, 2008 – A report, "Topical Drug Delivery to the Posterior Segment of the Eye: Anatomical and Physiological Considerations," has been recently published in *Pharmazie*. According to recent research from Iceland, "Drug delivery to the posterior segment of the eye is important for potentially treating various disorders in the retina, choroid, vitreous humor and optic nerves. Due to anatomic membrane barriers and the lacrimal drainage it can be quite challenging to obtain therapeutic drug concentrations in the posterior parts of the eye after topical drug administration."

"Since the membrane barriers cannot be altered with non-invasive methods invasive methods such as direct drug injection into the vitreous humor and subconjunctival, subtenons capsule or suprascleral injections are gaining popularity. However, invasive methods can cause discomfort for the patient and can also lead to complications that are even more serious than the disease being treated. Alternatively, novel ophthalmic formulations can be developed that specifically target topical drug delivery to the posterior segment of the eye. Anatomical and physiological barriers in the eye are reviewed as well as the theoretical model of passive drug diffusion from the eye surface into the eye. It is shown that enhanced drug delivery through conjunctiva/sclera to retina can be obtained by formulating lipophilic drugs as hydrophilic drug/cyclodextrin complex solutions," write T. Loftsson and colleagues, University of Iceland, Faculty of Pharmacy.

The researchers conclude, "Optimization of the delivery system by formulating the drug as a low-viscosity aqueous drug/cyclodextrin complex suspension results in sustained high concentrations of dissolved drug in the tear fluid which further increases the targeted drug delivery to the posterior segment." Loftsson and colleagues published their study in *Pharmazie* (Topical Drug Delivery to the Posterior Segment of the Eye: Anatomical and Physiological Considerations. Pharmazie, 2008;63(3):171-179).

Cambridge Consultants Offers Fast Track to Phase I Clinical Trials for Inhalable Drugs with Development Support for Conix

Drug Week via NewsEdge (NewsRx.com): May 8, 2008 – Cambridge Consultants (www.cambridgeconsultants.com) demonstrated a series of technology developments and services for its Conix inhalable drug delivery technology at the Respiratory Drug Delivery Conference in Scottsdale, AZ, for companies looking to accelerate their move into Phase I clinical trials for their inhalable drugs. Conix offers a low cost threshold previously not available with traditional inhaler technology developments.
The company met with pharmaceutical and medical device companies during the RDD Conference to demonstrate and discuss a series of technology developments and support services surrounding the Conix inhaler platform. The inhaler is based around a novel "reverse flow cyclone" and contains no moving parts or propellants. The inhaler can be made from a single piece of plastic, where it would cost just 4¢ to manufacture in high volume (5 million per annum). The unique swirling action within the patented cyclone provides an extremely effective de-agglomeration process, enabling a large percentage of the drug to be delivered efficiently into the lung. In-house tests with existing formulations from mass market asthma and COPD inhalers have shown that the drug separation mechanism is so efficient that it is up to 40% more effective than many inhalers on the market today.

PharmaDerm to Expand Product Offerings with Purchase of Vectoris Pharma—Newly Acquired Technology Allows for Oral Delivery of Insulin

Drug Week via NewsEdge (NewsRx.com): May 8, 2008 – ICBS Limited (ICBS) (Pink Sheets:ICBT) – PharmaDerm, an international pharmaceutical venture between ICBS, McCoy Enterprises, and Connell Associates, has announced that they have acquired Vectoris Pharma, a company that has developed an oral insulin, Perosulin®. Perosulin® is a needle-free, non-inhaled insulin delivery technology.

PharmaDerm will commercialize Vectoris Pharma Corporation's proprietary platform drug delivery technology for trans-mucosal drug delivery. The technology involves the use of a suspension of large macro-molecular drugs, such as insulin, to facilitate systemic delivery via the buccal membrane. The oral mucosa provides a convenient route for macro-molecular delivery of active agents. "Looking ahead in the development of this needle-free platform technology, we envision the immediate development of buccal delivery of insulin followed by pain products such as fentanyl," states Joe Connell, COO of PharmaDerm. "We will focus our efforts on equipping military and emergency personnel with a convenient, accurate, multiple-dose and needle-free atropine."

PharmaDerm will be focused on licensing, developing, and commercializing of Perosulin®. PharmaDerm will work with the U.S. Food and Drug Administration (FDA) and The Health Protection Branch of Canada to gain regulatory approval of Perosulin® for commercialization.

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Study Data from Johnson & Johnson Update Understanding of Drug Delivery

Drug Week via NewsEdge (NewsRx.com): May 8, 2008 – Current study results from the report "Supersaturating Drug Delivery Systems: Effect of Hydrophilic Cyclodextrins and Other Excipients on the Formation and Stabilization of Supersaturated Drug Solutions" have been published. According to recent research from Belgium, "Supersaturating drug delivery systems (SDDS) utilize two important design elements in their preparation including converting the drug of interest into a high energy state or other rapidly dissolving form to facilitate the formation of supersaturated drug solutions and providing a means for stabilizing the formed supersaturated solution such that significant drug absorption is possible from the gastrointestinal tract. This has been referred to as a 'spring' and 'parachute' approach."

"The current effort is designed to assess materials which may affect properties in SDDS. To this end, a series of excipients was tested in a co-solvent/solvent quench method to assess their ability to attain and maintain supersaturation for a group of 14 drug development candidates. The approach focused on hydrophilic cyclodextrins including hydroxypropyl-beta-cyclodextrin (HPbetaCD) and sulfobutyl-beta-cyclodextrin (SBEbetaCD). Various rheological polymers and surfactants were also included in the study. Consistent with previous investigations, the pharmaceutical polymers, as a class, had minimal effects on the extent of supersaturation but tended to be good stabilizers while the surfactants tended to provide for the greatest degree of supersaturation but the formed systems were poorly stable. This study found that hydrophilic cyclodextrins, especially SBEbetaCD, gave superior results in terms of attaining and maintaining supersaturation," write M. E. Brewster and colleagues, Johnson & Johnson.

The researchers conclude, "A knowledge of the behavior and performance of excipients in this context can be useful in designing solid oral dosage forms for difficult-to-formulate drugs and drug candidates." Brewster and colleagues published their study in *Pharmazie* (Supersaturating drug delivery systems: Effect of hydrophilic cyclodextrins and other excipients on the formation and stabilization of supersaturated drug solutions. Pharmazie, 2008;63(3):217-220).

Study Data from Y. Chen and Colleagues Update Understanding of Drug Delivery

Drug Week via NewsEdge (NewsRx.com): May 1, 2008 – According to recent research from Wuhan, People's Republic of China, "A new self-microemulsifying drug delivery system (SMEDDS) has been developed to increase the solubility, dissolution rate and oral bioavailability of vinpocetine (VIP), a poor water-soluble drug. The formulations of VIP-SMEDDS were optimized by solubility assay, compatibility tests, and pseudo-ternary phase diagrams analysis."

"The optimal ratio in the formulation of SMEDDS was found to be Labrafac:oleic acid: Cremophor EL: Transcutol P=40: 10:40: 10 (w/w). The average particle diameter of VIP was less than 50 nm. In vitro dissolution study indicated that the dialysis method in reverse was better than the ultrafiltration method and the dialysis method in simulating the drug in vivo environment. [Compared] with VIP crude drug power and commercial tablets, (-)VIP-SMEDDS caused a 3.4- and 2.9-fold increase in the percent of accumulated dissolution at 3 h. Further study on the absorption property of VIP-SMEDDS employing in situ intestine of rats demonstrated that VIP in SMEDDS could be well-absorbed in [the] general intestinal tract without specific absorption sites. In addition, the developed SMEDDS formulations significantly improved the oral bioavailability of VIP in rats. Relative bioavailability of (-)VIP-SMEDDS and (+)VIP-SMEDDS increased by 1.85- and 1.91-fold, respectively, in [relation to] VIP crude powder suspension," write Y. Chen and colleagues.

The researchers conclude, "The mechanisms of enhanced bioavailability of VIP might contribute to the improved release, enhanced lymphatic transport, and increased intestinal permeability of the drug." Chen and colleagues published their study in the *Biological & Pharmaceutical Bulletin* (Biological & Pharmaceutical Bulletin, 2008;31(1):118-125).

APRIL 2008

Aradigm Announces Data Show No Occurrence of Primary Lung Cancer in Patients Treated with AERx® Insulin Diabetes Management System (iDMS)

Business Wire via NewsEdge: April 30, 2008 – HAYWARD, Calif. – Aradigm Corporation (OTCBB:ARDM) has announced that review of the clinical data by Novo Nordisk, with whom the company had a collaboration for inhaled insulin, revealed no occurrence of primary lung cancer in patients inhaling insulin using the AERx® insulin diabetes management system (iDMS). AERx iDMS uses an aqueous formulation of insulin delivered by a hand-held electronic inhaler. Review of the clinical trial data for AERx iDMS revealed no cases of primary lung cancer in either the 2,307 patients treated with AERx iDMS or the 1,218 patients treated with comparator treatments.

Additionally, no treatment-related histological changes were seen in the lungs of rats following a 6-month exposure period or in monkeys exposed for a 9-month period. Furthermore, quantitative evaluation of proliferating cells in the lungs of the animals in these studies revealed no difference in proliferation between the treatment and control groups. Such cell proliferation assays are used to assess the potential for abnormal cell growth, which may be a precursor for lung cancer.

Based on analysis of market data from Business Insights and Wolters Kluwer PHAST, Aradigm believes that the market for inhaled treatments of chronic respiratory diseases is estimated at approximately $20 billion and growing at over 10% per year. "Treatments of respiratory diseases by inhalation have proven to be valuable to millions of patients with asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis," states Igor Gonda, Ph.D., the company's president and CEO. "Aradigm remains strongly committed to development of a

pipeline of inhalation therapies to help patients with severe respiratory diseases."

Novo Nordisk previously announced the termination of its Phase 3 clinical trials for fast-acting inhaled insulin delivered via AERx iDMS. Novo Nordisk stated they were not terminating the trials because of any safety concerns. The latest review by Novo Nordisk was in response to an announcement made by Pfizer Inc. on April 24, 2008, that it has updated the product labeling for Exubera®, a diabetes treatment inhaler that delivers dry powder formulations containing insulin as the active ingredient, to include a warning about lung cancer cases observed in patients who received Exubera® in its clinical program. Pfizer reported that in the clinical trials, 6 of 4,740 patients using Exubera® developed lung cancer compared with 1 of 4,292 patients in the control arm. The labeling update by Pfizer further stated that all patients who developed lung cancer had a prior history of cigarette smoking and that there were too few cases to determine whether the development of lung cancer was related to the use of Exubera®.

Lux Biosciences' Presentations at ARVO Highlight Both Topical and Polymer Delivery Technologies Targeting Chronic Inflammatory Ocular Diseases

Business Wire via NewsEdge: April 28, 2008 – JERSEY CITY, N.J. – Next generation polymer technologies for the controlled delivery of drugs and tailor-made product concepts for topical delivery to the eye offer major market opportunities for new and/or improved treatments for a variety of chronic inflammatory ocular conditions, states Lux Biosciences, Inc., a privately held biotechnology company specializing in the field of ophthalmic diseases. Company scientists and collaborators presented data on a proprietary topical product and new bioerodible polymer/drug approaches for the treatment of dry eye and other inflammatory eye diseases at the 2008 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), in Fort Lauderdale, FL.

"Some 15 - 20 million people in North America and Europe are affected by chronic inflammatory diseases of the eye, which include such conditions as dry eye, keratoconjunctivitis, blepharitis and uveitis," states Ulrich Grau, Ph.D., Lux Biosciences president and chief executive officer. "Lux has licensed Isotechnika, Inc.'s next generation calcineurin inhibitor, voclosporin, for ophthalmic indications - the oral form of which (LX211) is currently in phase 3 clinical development in uveitis. By combining this molecule with innovative delivery technologies, such as mixed micelles or bioerodible polymers, we can deliver therapeutic concentrations of drug directly to the eye in a targeted and sustained fashion, offering the potential to greatly improve treatment for these widespread ocular conditions."

Prof. Ashim Mitra and colleagues from the University of Missouri, Kansas City, in collaboration with Lux Biosciences, presented a poster on the development of a clear, mixed micellar formulation product (LX214) for the treatment of dry eye syndrome and other potentially relevant ocular diseases.

Prof. Joachim Kohn and colleagues from the New Jersey Center for Biomaterials of Rutgers, The State University of New Jersey, and Lux Biosciences also gave an oral presentation on the development of a bioerodible insert for ocular delivery of voclosporin. The inserts under investigation were created from polymers selected from a large combinatorial library of bioerodible polyarylates and polycarbonates developed by the Rutgers University researchers and licensed to Lux Biosciences for ophthalmic use. When formulated with a drug, inserts employing these polymers exhibit a new hybrid mechanism of drug release that is capable of sustained drug delivery from 6 to 24 months. As such, these drug/polymer combinations have potential clinical implications for the treatment of a variety of immune-mediated ophthalmic conditions. The prototype implants are very small, owing to the fact that the active ingredient is very potent. More information can be found on the company's website at www.luxbio.com.

Studies from S. K. Jain and Co-researchers in the Area of Diabetes Published

Diabetes Week via NewsEdge (NewsRx.com): April 24, 2008 – According to recent research from Sagar, India, "In spite of encouraging results of alternative parenteral dosage forms, the problems of type I diabetes and insulin delivery remain a challenging area of research. Glucose responsive liposomes (GR) containing encapsulated insulin and GOD were prepared using defined molar ratios of DPPE Egg PC, cholesterol and any of three different fatty acids viz. oleic acid (GR-O1 & GR-O2), palmitic acid (GR-P1 & GR-P2), stearic acid (GR-S1 & GR-S2)."

"The control formulations include a non-glucose responsive liposome (PS-L; no GOD) and non-pH-sensitive liposome (NP-L; no pH-sensitive component). The GR formulations showed a marked aggregation at pH 6.8-6.4 and a glucose concentration dependent permeation and destabilization. In vitro, insulin release was 21-31% within 0.5 h at 100 mg/dL glucose incubation and was doubled (52-62%) at 250 mg/dL; the release was slightly higher with the formulations of 2 molar ratios of fatty acids. Following s.c. injection, the GR formulation showed higher responses to reduce blood glucose (percentage of initial is expressed) and were found to be 40-50% compared to control formulations (PS-L; 61% and NP-L; 67 +/- 5.5%)," write S. K. Jain and colleagues.

The researchers conclude, "Nonetheless, tailoring of controlled release and long circulating forms of this carrier system may improve its potential." Jain and colleagues published their study in the *Journal of Drug Delivery Science and Technology* (Journal of Drug Delivery Science and Technology, 2007;17(6):399-405).

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New Drug Development Data Have Been Reported by J. Woo and Co-authors

Cancer Weekly via NewsEdge (NewsRx.com): April 24, 2008 – "A conventional, cholesterol-containing liposome formulation of cisplatin has demonstrated insignificant activity in clinical trials, due in part, to insufficient release of encapsulated content following localization within solid tumors. For this reason, the development of a triggered release liposome formulation is desirable," scientists in Vancouver, Canada, have reported.

"In this report, cisplatin was encapsulated into lysolipid-containing thermosensitive liposomes (LTSL) using a novel technique, which relies on the equilibration of cisplatin across the liposomal membrane at temperatures above the gel-to-liquid crystalline phase transition temperature (T-C) of the bulk phospholipid. Mild heating and drug loading into LTSL did not induce morphological changes of the liposomes. In vitro data demonstrated that >95% of encapsulated cisplatin was released from LTSL within 5 min following mild heating at 42 degrees C, while <5% was released at 37 degrees C. Under similar conditions, lysolipid-free thermosensitive liposomes exhibited 70% release of cisplatin at 42 degrees C, and cholesterol-containing liposomes exhibited negligible drug release at 42 degrees C. The pharmacokinetic profiles of LTSL- and TSL-cisplatin indicated that these formulations were rapidly eliminated from circulation (terminal t(1/2) of 1.09 and 2.83 h, respectively)," write J. Woo and colleagues.

The researchers conclude, "The therapeutic utility of LTSL-cisplatin formulation will be based on strategies where hyperthermia is applied prior to the administration of the liposomal drug - a strategy similar to that used in the clinical assessment of LTSL-doxorubicin formulation." Woo and colleagues published their study in the *International Journal of Pharmaceutics* (International Journal of Pharmaceutics, 2008;349(1-2):38-46).

Celator® Pharmaceuticals Successfully Uses Nanoparticles to Administer Hydrophobic Drug Combinations

Cancer Weekly via NewsEdge (NewsRx.com): April 24, 2008 – Celator Pharmaceuticals has reported results on a novel approach designed to deliver drugs that are incapable of dissolving in water (hydrophobic drugs) in nanoparticles to enhance and control drug circulation. These findings allow the company to combine hydrophobic drugs such as paclitaxel with other anti-cancer drugs, based on the company's proprietary CombiPlex technology™. The results were presented in a poster presentation at the American Association for Cancer Research meeting in San Diego.

CombiPlex technology™ is a drug ratio technology platform that represents a new approach that identifies a ratio of drugs that will deliver a synergistic benefit, locks the desired ratio in a drug delivery vehicle, and maintains the ratio in patients, with the goal of improving clinical outcomes.

To date, Celator has utilized liposomes to deliver synergistic drug combinations to treat cancer. Hydrophobic drugs such as paclitaxel are not amenable to this form of delivery because they detach from liposomes almost immediately after injection. Celator scientists report that they were able to generate a library of hydrophobic paclitaxel conjugates incorporated into nanoparticles. In preclinical testing, these nanoparticles were shown to circulate in the blood for more than 24 hr, allowing the drug to accumulate selectively in solid tumors where it can then be released and exposed to tumor cells.

According to the research findings, the ability to optimize paclitaxel conjugates could make it possible for higher drug levels to be maintained in plasma for extended periods, which is associated with superior preclinical antitumor efficacy when compared with drug delivery involving paclitaxel at its maximum tolerated dose. In addition, preclinical studies involving a drug conjugate of paclitaxel and gemcitabine co-formulated into nanoparticles showed that a synergistic ratio of the two drugs circulating in plasma was maintained for more than 24 hr after intravenous injection.

Echo Therapeutics and Cato BioVentures Sign Right of First Offer Agreement for Dermatology Products and Transdermal Drug Delivery Technologies

Canada Newswire English via NewsEdge: April 21, 2008 – FRANKLIN, Mass. – Echo Therapeutics (OTC Bulletin Board:ECTE) has announced that it has signed a dermatology product and transdermal drug delivery technology right of first offer agreement with Cato BioVentures, the venture capital affiliate of Cato Research, a global contract research and development organization. The agreement grants Echo exclusive rights of first negotiation to all dermatology product and transdermal drug delivery technology opportunities identified or acquired by Cato BioVentures.

"This agreement expands our long-standing strategic relationship with Cato BioVentures and Cato Research and enables us to leverage their deep industry access to a wide range of business development opportunities in our core focus areas," states Patrick Mooney, M.D., Echo's chair and CEO. "Cato is familiar with our core transdermal platforms–AzoneTS™ for drug reformulation and the Symphony tCGM System for non-invasive continuous glucose monitoring–and understands our model to leverage those platforms internally and with product and technology acquisition opportunities that fit our model."

Zelos Therapeutics and Aegis Therapeutics Announce Collaboration for Intranasal Delivery of Zelos' ZT-031

Business Wire via NewsEdge Corporation: April 16, 2008 – WEST CONSHOHOCKEN, Pa., and SAN DIEGO, Calif. – Zelos Therapeutics, Inc. and Aegis Therapeutics LLC have announced the signing of a collaboration agreement for the development of an intranasal spray formulation of the proprietary parathyroid hormone (PTH) analog ZT-031 (Ostabolin-C™, cyclic PTH-(1-31)). Under the collaboration, which is exclusive across the PTH field, Zelos will utilize Aegis' patented Intravail® permeation enhancer technology to develop an intranasal version of ZT-031 for the treatment of osteoporosis and other bone diseases. A subcutaneous formulation of ZT-031 has already successfully completed a 12-month Phase 2 clinical trial in the treatment of osteoporosis.

EyeGate Pharma Initiates Phase I Study of EyeGate® II Delivery System

Market Wire via NewsEdge Corporation: April 14, 2008 – WALTHAM, Mass. – EyeGate Pharma, a privately held, specialty pharmaceutical company using iontophoresis technology to safely and non-invasively deliver therapeutics into the front and back of the eye for treating serious ocular diseases, has announced the initiation of a Phase I clinical study designed to assess the safety and tolerability of the non-invasive EyeGate® II ocular drug delivery system in up to 95 healthy adult volunteers. This is a single-center, randomized, single-masked, comparative-group safety and tolerability study of a range of single iontophoretic dose levels with a citrate buffer via the EyeGate®® II delivery system. For more information, visit www.eyegatepharma.com.

MannKind Stumbles in Fallout From Exubera

in-pharmatechnologist.com: April 14, 2008 – MannKind has suspended its search for a potential partner for its inhaled insulin product Technosphere in the wake of the news of Exubera's possible cancer risk. The company still believes its treatment has potential but given the current cynicism over the inhaled insulin market has decided not to search for a partner at this time.

In its statement MannKind states, "At this time, we believe that we will be unable to achieve an appropriate valuation for Technosphere Insulin until Phase III data are available that confirm our belief in the safety and efficacy of Technosphere Insulin."

MannKind is relying on good Phase III data for their inhaled insulin treatment to reassure investors, the pharmaceutical community, and the public of the safety of their product. The trial is due to finish later this year, but the concern is that the credibility of inhaled insulin is damaged beyond repair.

Many financial analysts have already written off the inhaled insulin market following the news about Exubera. However, MannKind believes its Technosphere Insulin has been more thoroughly tested than Exubera, with a two-year carcinogenicity study in rats showing that the product was well tolerated after daily inhalations for 104 consecutive weeks.

Iomai and Merck & Co., Inc. Evaluate Use of Iomai Immunostimulant Patch

Vaccine Weekly via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Iomai Corporation (NASDAQ:IOMI) has announced that it has signed an agreement with Merck & Co., Inc. to conduct proof-of-principle preclinical studies evaluating the use of the Iomai needle-free immunostimulant patch.

Merck has first option to negotiate an exclusive license. These preclinical proof-of-principle studies will be conducted using an undisclosed Merck vaccine. Iomai recently announced results of a 500-person Phase 1/2 trial in which a clinically relevant adjuvant effect was observed when a version of the immunostimulant patch was administered in combination with an injected vaccine for pandemic influenza, and data from a prior European trial demonstrated the ability of the immunostimulant patch to boost the immune response of the elderly who receive an injected seasonal influenza vaccine.

The Iomai approach uses a potent adjuvant applied to the skin through a patch that is affixed over the site of the injected vaccine. Once the patch is applied, the adjuvant passes into the skin, targeting cells called Langerhans cells. These specialized skin cells carry the adjuvant into the lymph nodes, where it works to boost an individual's immune response to the vaccine. This proprietary approach is known as transcutaneous immunization (TCI).

Last year, the Department of Health and Human Services (DHHS) awarded Iomai a $128 million contract to fund the company's development of a dose-sparing patch for use with a pandemic influenza vaccine, and that contract is currently funding the Phase 1/2 pandemic influenza trial. The patch being used in that program is similar to the one that will be used in the Merck collaboration, with the same adjuvant and delivery system.

Research from Center for Drug Evaluation and Research Yields New Findings

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Research findings, "Lipid Excipients and Delivery Systems for Pharmaceutical Development: A Regulatory Perspective," are discussed in a new report. "The use of lipid-based dosage forms for enhancement of drug absorption or delivery has drawn considerable interest from pharmaceutical scientists. The unique characteristics of these dosage forms, however, present significant challenges to pharmaceutical industry and regulatory agencies in many ways," researchers in the United States report.

"For example, safety assessment is necessary when the use of a new lipid excipient is considered. An important question for lipid formulation is whether the drug remains in solubilized form along the gastrointestinal (GI) tract after it is administered. Certain lipid excipients and surfactants have been reported to change intestinal permeability or interfere with enzyme/transporter activity, thereby affecting drug bioavailability. The potential influence of biopharmaceutical and/or pathophysiological factors on the drug or lipid excipient(s) needs to be explored. For a complex lipid-based dosage form, the conventional in vitro dissolution methods may not be appropriate for predicting in vivo performance in view of the convoluted GI processing of the lipid vehicle and formulation. Of paramount importance is to identify any gaps in the scientific understanding of lipid-based dosage forms so that regulatory issues can be addressed. More mechanistic studies should be encouraged to facilitate a better understanding of the pharmaceutical characteristics of lipid formulations and complex interactions between lipid excipient, drug and physiological environment. This review discusses some regulatory considerations in the use of lipid excipients and delivery systems for pharmaceutical

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development," write M. L. Chen and colleagues, Center for Drug Evaluation and Research.

The researchers conclude, "Implications in the regulatory determination of pharmaceutical equivalence, bioequivalence and therapeutic equivalence are also illustrated." Chen and colleagues published their study in *Advanced Drug Delivery Reviews* (Lipid Excipients and Delivery Systems for Pharmaceutical Development: A Regulatory Perspective. Advanced Drug Delivery Reviews, 2008;60(6):768-777).

Study Results from Tabriz University of Medical Sciences, Drug Applied Research Center

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Scientists discuss new findings in life sciences in "Swellable Elementary Osmotic Pump (SEOP): An Effective Device for Delivery of Poorly Water-Soluble Drugs." "A new type of elementary osmotic pump (EOP) tablet for efficient delivery of poorly water-soluble/practically insoluble drugs has been designed. Drug release from the system, called swellable elementary osmotic pump (SEOP), is through a delivery orifice in the form of a very fine dispersion ready for dissolution and absorption," scientists writing in the *European Journal of Pharmaceutics and Biopharmaceutics* report.

"SEOP tablets were prepared by compressing the mixture of micronized drug and excipients into convex tablets. Factors affecting the release of drug from the SEOP tablets containing a poorly water-soluble drug, indomethacin, have been explored. The release behaviour of indomethacin from different formulations of this dosage form was studied at pH 6.8 for a period of 24h. The formulations were compared based on four comparative parameters, namely, D(24h) (total release after 24h), t(L) (lag time), RSQ(zero) (R square of zero order equation) and D%(zero) (percentage deviation from zero order kinetics). The drug release profile from osmotic devices showed that the type of polymer in the core formulation can markedly affect the drug release. The results showed that concentration of wetting agent in the core formulation was a very important parameter in D(24h) and release pattern of indomethacin from SEOP system. Increasing the amount of wetting agent to an optimum level (60mg) significantly increased D(24h) and improved zero order release pattern of indomethacin. Increasing concentration of caster oil (hydrophobic) in the semipermeable membrane of the device or hydrophilic plasticizer (glycerin) in coating formulation markedly increased t(L) and decreased D(24h). The results also demonstrated that aperture size is a critical parameter and should be optimized for each SEOP system. Optimum aperture diameter for the formulations studied here was determined to be 650microm for zero order release pattern. t(L) and D%(zero) were dramatically decreased whereas D(24h) and RSQ(zero) increased with increasing the aperture size to optimum level," write J. Shokri and colleagues, Tabriz University of Medical Sciences, Drug Applied Research Center.

The researchers conclude, "This study also revealed that optimization of semipermeable membrane thickness is very important for approaching zero order kinetics." Shokri and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (Swellable Elementary Osmotic Pump (SEOP): An Effective Device for Delivery of Poorly Water-Soluble Drugs. European Journal of Pharmaceutics and Biopharmaceutics, 2008;68(2):289-297).

Investigators at Pharmaceutical Research Center Zero in on Life Sciences

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Current study results from the report "Reduced Food-Effect and Enhanced Bioavailability of a Self-Microemulsifying Formulation of Itraconazole in Healthy Volunteers" have been published. "Self-microemulsifying drug delivery systems (SMEDDS) represent a possible alternative to traditional oral formulations of lipophilic compounds. This study was designed to compare the oral bioavailability and food-effect of SMEDDS of itraconazole (ITRA-GSMP capsule containing 50mg itraconazole) to that of the currently marketed formulation (Sporanox capsule containing 100mg itraconazole)," investigators in Korea report.

"Eight healthy volunteers received Sporanox or ITRA-GSMP capsule in the fasted state or after a high-fat diet on four separate dosing occasions with a 2-week washout period. Blood samples were collected and analyzed. After administration of the ITRA-GSMP capsule, AUC0-24 and Cmax were 1.9- and 2.5-fold higher in the fasted state and 1.5- and 1.3-fold higher in the fed state, respectively, than those of the Sporanox capsule. Moreover, ITRA-GSMP capsules yielded more reproducible blood-time profiles than Sporanox capsules. Food had a marked effect on itraconazole absorption from the Sporanox capsule, whereas the influence was less pronounced for the ITRA-GSMP capsule," write J. S. Woo and colleagues, Pharmaceutical Research Center.

The researchers conclude, "Collectively, our data suggest that a new self-microemulsifying formulation may provide an alternative oral formulation for itraconazole with improved oral bioavailability and reduced food-effect." Woo and colleagues published their study in the *European Journal of Pharmaceutical Sciences* (Reduced Food-Effect and Enhanced Bioavailability of a Self-Microemulsifying Formulation of Itraconazole in Healthy Volunteers. European Journal of Pharmaceutical Sciences, 2008;33(2):159-165).

Drug Delivery Study Findings from P. P. Constantinides and Colleagues

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Researchers detail new data in drug delivery in "Advances in Lipid Nanodispersions for Parenteral Drug Delivery and Targeting." According to a study from the United States, "Parenteral formulations, particularly intravascular ones, offer a unique opportunity for direct access to the bloodstream and rapid onset of drug action as well as targeting to specific organ and tissue sites. Triglyceride emulsions, liposomes and micellar solutions have been traditionally used to accomplish these tasks and there are several products on the market using these lipid formulations."

"The broader application of these lipid systems in parenteral drug delivery, however, particularly with new chemical entities, has been limited due primarily to the following reasons: a) only a small number of parenteral lipid excipients are approved, b) there is [an] increasing number of drugs that are partially or not soluble in conventional oils and other lipid solvents, and c) the ongoing requirement for site-specific targeting and controlled drug release. Thus, there is [a] growing need to expand the array of targetable lipid-based systems to deliver a wide variety of drugs and produce stable formulations which can be easily manufactured in a sterile form, are cost-effective and at least as safe and efficacious as the earlier developed systems. These advanced parenteral lipid-based systems are at various stages of preclinical and clinical development which include nanoemulsions, nanosuspensions and polymeric phospholipid micelles."

"This review article showcases these parenteral lipid nanosystems and discusses advances in relation to formulation development, processing and manufacturing, and stability assessment. Factors controlling drug encapsulation and release and in vivo biodistribution are emphasized along with in vitro/in vivo toxicity and efficacy case studies. Emerging lipid excipients and increasing applications of injectable lipid nanocarriers in cancer chemotherapy and other disease indications are highlighted and in vitro/in vivo case studies are presented," write P. P. Constantinides and colleagues.

The researchers conclude, "As these new parenteral lipid systems advance through the clinic and product launch, their therapeutic utility and value will certainly expand." Constantinides and colleagues published the results of their research in *Advanced Drug Delivery Reviews* (Advances in Lipid Nanodispersions for Parenteral Drug Delivery and Targeting. Advanced Drug Delivery Reviews, 2008;60(6):757-767).

Monash University, Victorian College of Pharmacy, Publishes Research

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – New investigation results are detailed in a study, "Enhancing Intestinal Drug Solubilisation Using Lipid-Based Delivery Systems," published in *Advanced Drug Delivery Reviews*. According to recent research from Parkville, Australia, "Lipid-based delivery systems are finding increasing application in the oral delivery of poorly water-soluble, lipophilic drugs. Whilst lipidic dose forms may improve oral bioavailability via several mechanisms, enhancement of gastrointestinal solubilisation remains argueably the most important method of absorption enhancement."

"This review firstly describes the mechanistic rationale which underpins the use of lipid-based delivery systems to enhance drug solubilisation and briefly reviews the available literature describing increases in oral bioavailability after the administration of lipid solution, suspension and self-emulsifying formulations. The use of in vitro methods including dispersion tests and more complex models of in vitro lipolysis as indicators of potential in vivo performance are subsequently described, with particular focus on recent data which suggests that the digestion of surfactants present in lipid-based formulations may impact on formulation performance," write C. J. Porter and colleagues, Monash University, Victorian College of Pharmacy. The researchers conclude, "Finally, a series of seven guiding principles for formulation design of lipid-based delivery systems are suggested based on an analysis of recent data generated in our laboratories and elsewhere." Porter and colleagues published their study in *Advanced Drug Delivery Reviews* (Enhancing Intestinal Drug Solubilisation Using Lipid-Based Delivery Systems. Advanced Drug Delivery Reviews, 2008;60(6):673-691).

Study Findings Reported by Researchers at Novartis

Biotech Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Research findings are discussed in a new report, "The Potency of the Adjuvant, CpG Oligos, Is Enhanced by Encapsulation in PLG Microparticles." According to a study from the United States, "The objective of this work was to evaluate the potency of the CpG containing oligonucleotide encapsulated within poly(lactide-co-glycolide), and coadministered with antigen adsorbed to poly(lactide-co-glycolide) microparticles (PLG particles). The formulations evaluated include, CpG added in soluble form, CpG adsorbed, and CpG encapsulated."

"The antigen from Neisseria meningitidis serotype B (Men B) was used in these studies. The immunogenicity of these formulations was evaluated in mice. Poly(lactide-co-glycolide) microparticles were synthesized by a w/o/w emulsification method in the presence of a charged surfactant for the formulations. Neisseria meningitidis B protein was adsorbed to the PLG microparticles, with binding efficiency and initial release measured. CpG was either added in the soluble or adsorbed or encapsulated form based on the type of formulation. The binding efficiency, loading, integrity and initial release of CpG and the antigen were measured from all the formulations. The formulations were then tested in mice for their ability to elicit antibodies, bactericidal activity and T cell responses," write P. Malyala and colleagues, Novartis.

The researchers conclude, "Encapsulating CpG within PLG microparticles induced statistically significant higher antibody, bactericidal activity and T cell responses when compared to the traditional method of delivering CpG in the soluble form." Malyala and colleagues published their study in the *Journal of Pharmaceutical Sciences* (The Potency of the Adjuvant, CpG Oligos, Is Enhanced by Encapsulation in PLG Microparticles. Journal of Pharmaceutical Sciences, 2008;97(3):1155-1164).

Report by L. Chen and Co-researchers Describes Recent Advances in Controlled Release

Biotech Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – According to recent research from Changchun, People's Republic of China, "This paper presented a new

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approach for preparing a new type of slow-release membrane-encapsulated urea fertilizer with starch-g-PLLA as biodegradable carrier materials."

"By solution-casting and washing rapidly with water the urea was individually encapsulated within the starch matrix modified by L-lactide through in situ graft-copolymerization. The release behavior of urea encapsulated in the films was studied, and [the] following conclusions were achieved: (1) the introduction of hydrophobic PLLA reduced the swellability of [the] starch matrix and decreased the release rate of urea; (2) the urea release rate could be controlled from several hours to 1 day by adjusting the graft efficiency; (3) scanning electron microscopy revealed that the urea encapsulated within the starch matrix was uniformly dispersed in the form of tiny cell and the urea encapsulated in the modified starch film released through a diffusion mechanism," write L. Chen and colleagues.

The researchers conclude, "Therefore, the modified starch products for controlled release could be expected to have widely potential application in agriculture industry as fertilizer carrier." Chen and colleagues published their study in *Carbohydrate Polymers* (Carbohydrate Polymers, 2008;72(2):342-348).

Researchers at Zhejiang University, College of Pharmaceutical Sciences, Release New Data

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – New investigation results are detailed in a study, "Solubility-Modulated Monolithic Osmotic Pump Tablet for Atenolol Delivery," published in the *European Journal of Pharmaceutics and Biopharmaceutics*. "A method for the preparation of monolithic osmotic pump tablet was obtained by modulating atenolol solubility with acid. Tartaric acid was used as solubility promoter, sodium chloride as osmotic agent and polyvinyl pyrrolidone as retardant agent," investigators in Hangzhou, People's Republic of China, report.

"Ethyl cellulose was employed as semipermeable membrane containing polyethylene glycol 400 as plasticizer. The formulation of atenolol monolithic osmotic pump tablet was optimized by orthogonal design and evaluated by similarity factor (f(2)). The optimal monolithic osmotic pump tablet was found to be able to deliver atenolol at the rate of approximate zero-order up to 24h, independent of release media and agitation rate," write L. Liu and colleagues, Zhejiang University, College of Pharmaceutical Sciences.

The researchers conclude, "The approach of solubility-modulated by acid-alkali reaction might be used for the preparation of osmotic pump tablet of other poorly water-soluble drugs with alkaline or acid groups." Liu and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (Solubility-Modulated Monolithic Osmotic Pump Tablet for ateNolol Delivery. European Journal of Pharmaceutics and Biopharmaceutics, 2008;68(2):298-302).

New Biopharmaceuticals Research Reported by Scientists at University College

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Scientists discuss new findings in biopharmaceuticals in "Biopharmaceutical Challenges Associated with Drugs with Low Aqueous Solubility—The Potential Impact of Lipid-Based Formulations." "The percentage of new chemical entities synthesized with low aqueous solubility and high therapeutic efficacy is growing, this presents major challenges for the drug delivery scientists. The role of physicochemical properties in identification of suitable drug candidates for oral lipid-based delivery systems is discussed," investigators in Cork, Ireland, report.

"A knowledge of the interplay of physicochemical and biopharmaceutical drug properties with the physiological environment of the gastro-intestinal tract (GIT), as a prerequisite to successful formulation design, is reviewed. The importance of excipient selection with an emphasis on bioactive excipients is stressed," write C. M. O'Driscoll and colleagues, University College.

The researchers conclude, "The need for more examples of in vitro-in vivo correlations as a means of maximizing the development potential and commercial future for lipid-based formulations, and, promoting confidence within the industry for these delivery systems is highlighted." O'Driscoll and colleagues published their study in *Advanced Drug Delivery Reviews* (Biopharmaceutical Challenges Associated with Drugs with Low Aqueous Solubility—The Potential Impact of Lipid-Based Formulations. Advanced Drug Delivery Reviews, 2008;60(6):617-624).

Reports from Kyoto University Describe Recent Advances in Solid Cancer Therapy

Cancer Weekly via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Data detailed in "Anti-tumor Effect of All-Trans Retinoic Acid Loaded Polymeric Micelles in Solid Tumor Bearing Mice" have been presented. "All-trans retinoic acid (ATRA) polymeric micelles were developed for parenteral administration. The distribution characteristics and antitumor activities of ATRA polymeric micelles were evaluated after intravenous administration to mice bearing CT26 solid tumors," scientists in Kyoto, Japan, report.

"ATRA incorporated in poly(ethylene glycol)-poly(benzyl aspartate) block copolymer was prepared by the evaporation method. The levels of [3H]ATRA in blood and tissue including tumor were determined by measuring the radioactivity after injection into mice. The tumor volume and the survival of the mice were determined to assess the anticancer activity. The delivery of ATRA by polymeric micelles prolonged the blood circulation and enhanced the accumulation of ATRA in the tumor tissue compared with the administration of free ATRA. Tumor growth was significantly delayed and the survival time of mice was prolonged following the treatment by ATRA polymeric

micelles demonstrating the improved anticancer activity of ATRA," write N. Chansri and colleagues, Kyoto University.

The researchers conclude, "Polymeric micelles are a promising and effective carrier of ATRA in order to enhance tumor delivery and they have a promising potential application in the treatment of solid tumors." Chansri and colleagues published their study in *Pharmaceutical Research* (Anti-tumor Effect of All-Trans Retinoic Acid Loaded Polymeric Micelles in Solid Tumor Bearing Mice. Pharmaceutical Research, 2008; 25(2):428-434).

New Drug Delivery Research from Silpakorn University, Department of Pharmaceutical Technology

Drug Week via NewsEdge Corporation (NewsRx.com): April 10, 2008 – Researchers detail new data in drug delivery in "Development of Time-, pH-, and Enzyme-Controlled Colonic Drug Delivery Using Spray-Dried Chitosan Acetate and Hydroxypropyl Methylcellulose." According to recent research from Nakhon Pathom, Thailand, "A colonic drug delivery with a new concept based on a combination of time-, pH-, and enzyme-controlled system was developed. Spray-dried chitosan acetate (CSA) prepared from low molecular weight chitosan was characterized."

"A combination of CSA and hydroxypropyl methylcellulose (HPMC) was used as new compression-coats for 5-aminosalicylic acid (5-ASA) tablets. Factors affecting in-vitro drug release, i.e. % weight ratio of coating polymers, enzyme activity, pH of media, and excipients in core tablets, were evaluated. The tablets compression-coated with HPMC:CSA at 60:40 and 50:50% weight ratio providing lag times [of] about 5-6h were able to pass through the stomach (stage I, 0.1N HCl) and small intestine (stage II, pH 6.8, Tris-HCl). The delayed release was time-and pH-controlled owing to the swelling with gradual dissolving of CSA and HPMC in 0.1N HCl and the less solubility of CSA at higher pH. After reaching the colon (stage III, pH 5.0, acetate buffer), the dissolution of CSA at low pH triggered the drug release over 90% within 14h," write J. Nunthanid and colleagues, Silpakorn University, Department of Pharmaceutical Technology.

The researchers conclude, "Furthermore, the degradation of CSA by beta-glucosidase in the colonic fluid enhanced the drug release while adding the disintegrant or the osmotic agent in the core tablets would affect the drug release." Nunthanid and colleagues published their study in the *European Journal of Pharmaceutics and Biopharmaceutics* (Development of Time-, pH-, and Enzyme-Controlled Colonic Drug Delivery Using Spray-Dried Chitosan Acetate and Hydroxypropyl Methylcellulose. European Journal of Pharmaceutics and Biopharmaceutics, 2008;68(2):253-259).

MARCH 2008

Acusphere Licenses Hydrophobic Drug Delivery System to Cephalon for $10 Million

Business Wire: March 31, 2008 – WATERTOWN, Mass. – Acusphere Inc. (NASDAQ: ACUS) has announced that it has signed an agreement to license the intellectual property rights to its Hydrophobic Drug Delivery System™ (HDDS) for oncology applications, along with the rights to AI-850, its formulation of paclitaxel, to Cephalon, Inc., in exchange for a cash payment of $10 million.

"We are very pleased with the terms of this transaction, which establishes a strong value for part of our technology platform that is at an early stage of development," states Sherri C. Oberg, president and CEO of Acusphere. "We are confident that Cephalon is the right partner for one application of this important technology, given its strong focus on oncology. Just six months ago, we announced that AI-850 was a potential bio-equivalent to the one of the fast-growing anti-cancer drugs, Abraxane®. This transaction confirms the potential for our technology in the oncology arena, which is one of many potential applications for our HDDS technology."

Frank Baldino, Jr., chair and CEO of Cephalon, states, "Cephalon has a growing oncology business with a deep and diverse portfolio of marketed products and pipeline compounds. The addition of the HDDS technology, and AI-850 in particular, will build on our expertise and expand our oncology portfolio."

Abuse-Resistant Oxycodone Primed for Clinical Trials

in-pharmatechnologist.com: March 30, 2008 – IntelliPharmaCeutics is ready to move into full-scale clinical trials with a once-daily oral formulation of oxycodone based on the company's ReXista abuse- and alcohol-resistant technology.

A drug delivery specialist based in Toronto, Canada, IntelliPharmaCeutics has successfully completed a pilot clinical study with its controlled-release version of oxycodone, the notoriously abuse-prone opioid analgesic whose appeal to addicts has earned it the monicker "hillbilly heroin." The study found that the ReXista formulation of oxycodone was bioequivalent in a single dose to two doses of the reference drug, Purdue Pharma's Oxycontin.

IntelliPharmaCeutics' ReXista formulation of oxycodone is designed to resist abuse by oral ingestion when the drug is crushed or chewed, by injection when it is combined with solvents, or by nasal application when oxycodone is crushed or powdered. It also guards against the entire daily dose of oxycodone being released when the drug is taken with alcohol "in any quantity," IntelliPharmaCeutics notes. This problem is "so serious with some opioid drugs, such as hydromorphone, that their use has been limited or curtailed by the FDA," the company adds.

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The goal of the pilot clinical trial was to compare the pharmacokinetics of ReXista oxycodone in a single 40-mg dosage form with 20-mg of Oxycontin given twice daily under fasted conditions. The outcome was that the ReXista product demonstrated sustained-release pharmacokinetic activity, with blood plasma concentrations at clinically significant levels over a 24-hr period, IntelliPharmaCeutics reports. The company plans to release detailed results of the pilot trial after further study and analysis. "With these results in hand, we will certainly move rapidly to advance the development into a full clinical trial program," comments Chief Executive Officer Dr. Isa Odidi.

Inhaled TB Vaccine Shows Promising Results

in-pharmatechnologist.com: March 20, 2008 – Animal studies reveal that we may be on the road to creating the first inhaled vaccine for tuberculosis, with results showing the vaccine to be at least as effective as the injected form. The inhaled vaccine, which takes the form of a fine powder, would be easier to administer in third world countries, as it does not require needles, syringes, or water, and it does not need to been refrigerated during transport.

The vaccine, developed by researchers at Harvard University and tested by scientists at the University of North Carolina at Chapel Hill, is based on the Bacille Calmette-Guérin (BCG) vaccine commonly used throughout the world, which takes the form of weakened *Mycobacterium bovis* cells from the cow form of TB.

In the injectable form these cells are freeze dried, to preserve the cells in a weakened but living state during storage and transportation before use. However, vaccines prepared in this way need to be refrigerated throughout transportation, and it must be mixed with water to be able to administer the vaccine through an injection, making it impractical to administer under the conditions of the developing world.

An inhaled dry-powder vaccine would solve some of these problems, as delivery through an inhaler is non-invasive and does not require water. "The vaccine is stable and can be transported and stored without refrigeration. In addition, the ease associated with simply inhaling the vaccine makes it suitable for delivery in any location without risk of contamination," says Tony Hickey, University of North Carolina. However, until now it had been hard to create a powder with fine enough particles to safely administer directly to the lungs. The team solved this by using special additives and a spray-drying process, where the cells are sprayed through heated gas to create a dry powder before storage.

When tested on animals the results seem very promising, with better results for the inhaled vaccine compared with the injected vaccine. "After delivering the vaccine to the animals and then exposing them to infectious micro-organisms only 1 per cent survive in the lungs of animals immunised by the pulmonary route while 5 per cent survive in those treated with the usual injection," states Hickey. However, he remains cautious as to how these results will translate to humans.

U.S. Team Claims a First in Nanovalves for Drug Delivery

in-pharmatechnologist.com: March 19, 2008 – A team of nanotechnologists and chemists based in the United States has created a novel nanovalve that could be used to deliver medications according to the pH environment in the body. The approach is novel because the nanovalve is capable of functioning in an aqueous environment under physiological conditions, in contrast to older conformations that were only stable while immersed in organic solvents. Eventually, the aim of the project is to develop a structure that can pass into cells and respond to the very small differences in pH that occur in diseased and healthy tissues, allowing the release of therapeutically active agents only in diseased cells. Scientists at the University of California, Los Angeles, NanoSystems Institute modified the surfaces of porous, dye-filled nanospheres, creating stem-like structures. On top of this primary scaffolding, the team stacked a series of cucurbit[6]uril units (molecular baskets formed from repeated glycouril that have a characteristic "squashed pumpkin" formation), creating—at neutral to acidic pH—a mechanically-interlocking pseudorotaxane architecture that blocks the nanosphere pores, thereby preventing the release of a test agent, a dye called rhodamine, held within.

When the local pH is moved into the basic range, the intramolecular bonds holding the structure in place are weakened, causing the nanosphere pores to open and the dye to be released, while maintaining the structures' overall 2D-hexagonal formation. The team used luminescence spectroscopy to measure the release of the dye, confirming via absorption analysis that for every 15 mg of the particles an average of 3 mmol of dye was released.

In effect, the researchers have created a supramolecular conformation that acts as a controllable molecular valve that is stable in an aqueous environment. The research team, under the leadership of J. Fraser Stoddart and Jeffrey I. Zink, state that although the aqueous-stable nanovalve represents a significant breakthrough in nanomolecular architecture, further work needs to be undertaken to fine tune the process. The technology is described in a paper published in the German journal *Angewandte Chemie*.

Lilly Declines to Inhale with AIR Insulin Program

in-pharmatechnologist.com: March 11, 2008 – The prospects for a viable market in inhaled insulin therapies are looking markedly thinner after Eli Lilly pulled the plug on its joint development program with drug delivery specialist Alkermes for AIR Insulin. Lilly is taking an estimated $90–120m charge ($0.05–0.07 per share) to earnings in the first quarter to terminate development of the inhaled insulin incorporating Alkermes' proprietary AIR pulmonary technology. The decision scraps a seven-year effort that has seen Lilly recruit thousands of diabetes patients for clinical trials. It comes only weeks after Novo Nordisk dropped its own AERx inhaled insulin system from late development, at a cost of DKK1.3bn ($0.267bn), having concluded the product was unlikely to offer significant clinical or convenience benefits over insulin injections with pen devices.

In an earlier update on the AIR Insulin program, which prefigured Lilly's announcement by revealing that the company was "evaluating its business case for AIR Insulin" and was expected to "make a decision to discontinue the program in the next week," Alkermes indicated a willingness to continue with the Phase III program regardless of Lilly's commercial intentions.

"While Lilly may elect not to commercialize AIR Insulin, Alkermes believes that the Phase III safety and efficacy trials should be completed," it states. "Data from these studies will provide patients, physicians and the scientific community with long-awaited and important data for the evaluation of new diabetes medications." Whether Alkermes has the resources to carry on development of AIR Insulin without an immediate partner should emerge once the company has taken a closer look at its options.

'Nested' Nanoparticles Increase Efficiency of Drug Delivery

in-pharmatechnologist.com: March 6, 2008 – A "matryoshka doll" filled with drugs could be the missing link that finally allows nanomedicine to fulfill its potential. University of Texas researchers believe that by encasing their drugs in a series of nanoparticles they can produce a highly targeted treatment that bypasses the body's immune defenses, which have typically plagued other nanotechnology therapies.

These defenses protect the body from foreign bodies that enter the bloodstream, including therapeutic nanoparticles. The different levels of attack include enzymes in the blood that corrode the particles and microphage cells that actively attack and destroy the particles and remove them from the bloodstream. The drug must then penetrate the vessel walls to reach deep inside the tumor. These defenses are so effective that on average just one out of every 100,000 drug molecules actually end up in the area they were meant to be targeting. In the past it has been difficult to find particles that could both penetrate these "biobarriers" and effectively find and target the correct tumor cells.

Mauro Ferrari's multistage delivery system overcomes these defenses using a series of nanoparticles, contained one inside the other. As it passes through each barrier the drug sheds a shell to reveal a new particle that is best suited to the next line of immune defense. "Silicon is fully biodegradable to a rate that can be carefully controlled, and the degradation products are harmless and produced in quantities much lower than the average dietary intake. In addition, we know how to manufacture its size, shape, and charge density to a great variability - as used in the microelectronics industry," explains Ferrari.

Once in their desired position, the silicon particles can release quantum dots or carbon nanotubes—both of which act as contrast agents for imaging applications. The carbon nanotubes can also be stimulated to produce heat, which itself could be used as a therapy. These particles can also be used to deliver other therapeutic agents, to achieve high concentrations within the tumor without needing to increase the actual dosage of the drug. Ferrari is currently investigating the possibility of using the particles to deliver short interfering RNA (siRNA) molecules that could silence messenger RNA within a tumor cell to stop it reproducing. Ferrari presented his research in the March issue of *Nature Biotechnology*.

MicroDose and Merck Agree to $32M for DPI Deal

in-pharmatechnologist.com: March 5, 2008 – Merck & Co has signed a $32m deal to evaluate MicroDose Technologies' dry powder inhalation technology in the delivery of some of its respiratory product lines. MicroDose's DPI system has already attracted interest from several major pharmaceutical firms, including Switzerland's Novartis. It is a handheld, low-cost, breath-activated device that utilizes piezo electronics to deliver compounds and is suitable for both small or large molecule therapeutics and for local and systemic applications.

The administration of pharmaceuticals through the respiratory tract is one of the most established methods of drug delivery. The large surface area and associated blood supply make the lungs an ideal means of rapidly disseminating medications. At present, conditions such as asthma and chronic obstructive pulmonary disease are routinely treated using aerosolized inhalable medications, as opposed to the many injectable treatments that are also available.

Scott Fleming, senior vice president, marketing, of MicroDose, states, "This agreement to bring innovative inhalation products to market is a positive milestone in the continued growth of MicroDose and represents further validation of our DPI technology." Soren BoChristiansen, general manager of Merck's bone, respiratory, immunology, and endocrinology franchises, echoes these thoughts, commenting," through this agreement Merck has gained access to a novel delivery technology that has the potential to facilitate the administration of and ensure patient compliance with drug treatments targeting the lungs."

FEBRUARY 2008

Novozymes and Upperton Move Nanoparticles Toward Commercialization

in-pharmatechnologist.com: February 21, 2008 – Denmark's Novozymes has renewed and extended its collaboration with U.K.-based biotech Upperton Limited on a drug delivery system that exploits the natural binding properties of recombinant protein nanoparticles to improve compound targeting and bioavailability. The new agreement focuses on the commercial exploitation of the companies' jointly owned rP-nano technology, which Upperton will use to generate nanoparticles from recombinant proteins expressed in Novozymes' proprietary yeast-based system.

The current focus is on drug and gene delivery, for example, cancer therapeutics, vaccines, DNA/iRNA, pulmonary delivery or localized delivery for wound-healing/topical applications. The scope could also extent to *in vitro* diagnostics and personal care products.

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U.K. Team to Use Nanoparticles to Improve Brain Drug Delivery

in-pharmatechnologist.com: February 20, 2008 – A nanoparticle-based delivery system is being developed in the United Kingdom as a potential means of bypassing the blood-brain barrier and improve the treatment of central nervous system diseases such as brain cancer. One example of such work is research being conducted by scientists at the University of Portsmouth, in the United Kingdom. The three-year project, which is funded by a £451,000 ($880,000) grant from the Biotechnology and Biological Sciences Research Council, is using polymer-based nanoparticles to modify a naturally occurring peptide capable of creating temporary openings in the blood-brain barrier, allowing for improved drug delivery.

Project leader Dr. Eugen Barbu and colleagues will develop particles of approximately one-thousandth the width of a single human hair that are able to both breach the blood-brain barrier and act as a delivery container for the medications. Dr. Barbu explains that the team has chosen to work with natural polymers due to their lack of toxicity and ability to biodegrade.

Prof. Darek Gorecki, who will be working alongside Dr. Barbu, states, "the BBSRC thought it was worth investing half a million pounds because though other scientists are studying ways of penetrating the blood brain barrier, this idea of using modified natural polymers is novel." He cautions however that the work is still at an experimental stage and is unlikely to have a direct impact on drug delivery for some time. Prof. Gorecki adds, "we are hoping that by using modified polymers working in various ways we can generate a temporary opening in the cells of the blood brain barrier and allow drugs to be delivered straight to the brain." The hope is that in the future such a nanoparticle-based delivery approach can improve the delivery of therapy for a broad spectrum of brain disorders ranging from stroke to Alzheimer's.

Fentanyl Patches Recalled Over Leakage Risk

in-pharmatechnologist.com: February 20, 2008 – Concerns have been building across North America about the safety of transdermal patches for delivering the highly potent narcotic analgesic fentanyl. Both brand-name and generic companies selling fentanyl patches have recalled some of their products voluntarily due to the risk of a potentially life-threatening manufacturing defect.

The problems emerged when PriCara, a division of Ortho-McNeil-Janssen Pharmaceuticals, said all lots of 25 µg/hr Duragesic (fentanyl transdermal system) CII patches sold by PriCara in the United States, as well as all 25 µg/hr fentanyl patches sold as an authorized generic by Sandoz in the same market, were being recalled voluntarily "as a precaution" from wholesalers and pharmacies. The action was taken in co-operation with the U.S. Food and Drug Administration (FDA). The patches involved all had expiry dates of December 2009 or earlier and were all manufactured by Alza, the drug delivery specialist that, like PriCara, is part of the Johnson & Johnson group.

All 25 µg/hr fentanyl patches manufactured by Alza and sold in Canada—by both Janssen-Ortho as Duragesic and by Ranbaxy as Ran fentanyl transdermal system patches, under an October 2006 licensing and supply agreement between Janssen-Ortho and Ranbaxy Pharmaceuticals Canada—were also taken off the market. The Canadian regulatory authority, Health Canada, issued a public health advisory warning against use of the affected patches. Another company that has taken precautionary measures over potential defects in fentanyl patches is one of PriCara's generic competitors, Actavis.

The company has voluntarily recalled 14 lots of fentanyl transdermal system CII patches sold in the United States by its subsidiary Actavis South Atlantic LLC. The lots in question were manufactured for Actavis on contract by Corium International. The recalled lots "may have a fold-over defect which may cause the patch to leak and expose patients or caregivers directly to the fentanyl gel," Actavis states, adding that it was "unaware of any injuries resulting from this issue."

Targeted Nanoparticles Open Up Cartilage to Drug Delivery

in-pharmatechnologist.com: February 19, 2008 – A novel delivery system that converts the structure of cartilage "from a barrier into a reservoir" could provide an answer to the challenge of administering and maintaining drugs in avascular tissue. Modified polymeric nanoparticles developed by researchers at the École Polytechnique Fédérale de Lausanne in Switzerland and the University of Massachusetts in the United States were found in animal studies to accumulate in an extracellular matrix (ECM) of articular cartridge at concentrations of up to 72 times more than non-targeted nanoparticles, remaining in the matrix without statistically significant clearance for up to 96 hr.

As Jeffrey Hubbell et al. point out in a paper published in *Nature Materials*, delivering drugs to cartilage for purposes such as treating early degradation in osteoarthritis is usually hampered by poor bioavailability due to the lack of vascularized tissue and the dense ECM, which acts as a barrier to entry.

The avascularity of cartilage tissue favors regional administration of the drug within the joint space rather than into the systemic circulation. However, compounds are rapidly cleared from the synovial fluid into the lymphatic system, accounting for the low bioavailability and raising the possibility of adverse systemic effects. The researchers sought to overcome these obstacles by developing particles that would be small enough to enter the cartilage matrix, as it is dynamically compressed during normal movement, and would display sufficient affinity for a cartilage ECM component to be retained there. Targeting of the cartilage matrix "is likely to be an important factor in future pharmaceutical approaches for the treatment of osteoarthritis," they suggest.

West Pharmaceutical and Nektar Formally Sever Exubera Ties

in-pharmatechnologist.com: February 19, 2008 – West Pharmaceutical Services has formally announced the end of its Exubera relationship with the product's developers, Nektar Therapeutics. The contract manufacturer, whose Tech Group division was jointly responsible along with the United Kingdom's Consort Medical for manufacturing the inhaled insulin device, says it will now be reimbursed for facility, inventory, raw materials, and personnel costs "at levels that are consistent with the company's previously announced expectations."

In November, Nektar's Exubera commercialization partner Pfizer agreed to pay Nektar $135m in compensation for unexpectedly pulling the Exubera device from the market due to poor sales. It also agreed to hand over its commercial interest and regulatory filings for the product. Nektar still has faith in the product's ability to sell and is seeking a new partner for the troubled device.

The repercussions of Pfizer's dramatic Exubera exit from the market have been gradually filtering through to the West, with the company preparing to restructure its affected Tech Group contract manufacturing unit.

Anti-AIDS Gel Disappoints, Failing to Prevent HIV Infection in Study of African Women

Associated Press WorldStream via NewsEdge Corporation: February 18, 2008 – The first anti-AIDS vaginal gel to make it through late-stage testing failed to stop HIV infection in a study of 6,000 South African women, disappointed researchers have announced. The study was marred by low use of the gel, which could have undermined results, they state. Women used it less than half the number of times they had sex, and only 10% said they used it every time as directed.

Scientists are still analyzing the results to see if this made a difference. They also plan more tests on a revamped gel containing an AIDS drug that they hope will work better. The gel used in the current study did prove to be safe, however, and researchers called this a watershed event. But for now, the effort is the latest disappointment in two decades of trying to develop a microbicide—a cream or gel women could use to lower their risk of getting HIV through sex. A female-controlled method is especially needed in poor countries where women often can't persuade men to use condoms.

A year ago, scientists stopped two late-stage tests of a different gel after early results suggested it might raise the risk of HIV infection instead of lowering it. The new study tested Carraguard, a microbicide developed by the nonprofit, New York-based Population Council. It contains carrageenan, which comes from seaweed and is widely used in the food and cosmetics industries as a gel, stabilizer, and thickening agent. Lab, animal, and early human tests suggested it might prevent HIV and other sexually spread infections. The latest study was done from March 2004 through March 2007 in Gugulethu, Isipingo, and Soshanguve, all in South Africa.

The Population Council hopes to start tests this year of a revamped Carraguard containing an experimental AIDS drug, MIV-150. The group also has studies under way on a contraceptive version of the gel, Carraguard plus hormones.

Study Results from J. J. Sun and Colleagues Broaden Understanding of Drug Development

Drug Week via NewsEdge Corporation (NewsRx.com): February 14, 2008 – "In recent years the interest of sustained drug delivery into [the] inner ear [has been] promising, at the same time a great deal of novel oral drugs using biodegradable vehicles have been produced to achieve sustained drug release. The aim of this study was to use biodegradable vehicles to release dexamethasone in the round window membrane application," investigators in Beijing, People's Republic of China, report.

"Dexamethasone gels composed of alginate and chitin were prepared and the release-permeating profiles were studied using a reproducible in vitro apparatus. A longer-period time course was simulated using the parameters acquired in this study. The data obtained in this study was compared with those of other studies in intratympanic drug delivery, and an appropriate initial dosage was extrapolated. The combination of alginate and chitin could efficiently restrict dexamethasone diffusion and the time course suggested a sustained drug concentration within 24 hours. A higher initial dosage was estimated to achieve a stable therapeutic concentration in vivo," write J. J. Sun and colleagues.

The researchers conclude, "The combination of alginate and chitin could be used as [a] vehicle for sustained release of dexamethasone in intratympanic application." Sun and colleagues published their study in the *Chinese Medical Journal* (Chinese Medical Journal, 2007;120(24):2284-2289).

Patch Instead of Pills Makes Living with Alzheimer's Disease Easier

CNW: February 12, 2008 – DORVAL, QC – For the first time, Alzheimer's patients and their caregivers will have the visual reassurance of continuous delivery of a medication through the skin. Now there will be no pills to remember, no pills to swallow, and no worries about medication being taken properly. The Exelon® patch (rivastigmine), for the symptomatic treatment of mild to moderate Alzheimer's disease, is now available in Canada.

While Alzheimer's disease is a chronic condition, for which long-term treatment should be a primary goal, statistics show that approximately 50% of patients stop treatment with oral cholinesterase inhibitors (including Exelon®), the group of drugs typically used to treat the early and middle stage symptoms of Alzheimer's disease, after only six months. Some

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patients simply forget to take their pills, have trouble swallowing them, or have difficulty with side effects and stop their medication, which can cancel out any treatment benefits. The patch optimizes the way the medication is distributed throughout the body and allows patients to reach and maintain the maximum effective dose of medication with three times less reported side effects compared with Exelon® capsules.

The Exelon® patch was designed with compliance in mind, and preference study results show that the patch was chosen over Exelon® capsules by more than 70% of Alzheimer's caregivers as a method of drug delivery. The patch provides visual reassurance that medication has been administered, reducing some of the burden associated with caring for a loved one affected by Alzheimer's disease.

Rhode Island Researcher Working on New Kind of Skin Patch

NewsEdge Corporation: February 1, 2008 – WARWICK, R.I. – A researcher who helped develop a popular mosquito-killing device now is working on a way to take the sting out of medical treatments by creating a new skin patch for administering prescription drugs. Emma Durand was chief technology officer at American Biophysics Corp. in North Kingstown, once considered the fastest-growing private company in the United States. American Biophysics and its mosquito-sucking yard protector were once toasted by the national news media and had gained a key retailing ally in home-improvement goliath Home Depot.

But disputes among American Biophysics investors doomed the company, which ultimately filed for bankruptcy protection. The onetime poster child for Rhode Island technology firms was sold last year to a company in Pennsylvania. The demise of American Biophysics left Durand with a lot of knowledge about how human skin works, but no way to apply it. Enlisting the aid of two partners with experience in polymer manufacturing, Durand has developed a way to enhance transdermal patches—medicated adhesive pads that are placed on the skin to deliver specific doses of medication through the skin and into the bloodstream.

"Patches really give doctors a degree of control they can't get with oral medications," states Durand, who now heads Isis Biopolymer Inc., a Warwick startup company she founded this year. Durand is president and chief technology officer. The twist Durand and her research team put on the technology is developing a way to attach medications to a paper-thin, flexible, printed circuit that monitors and controls dosages. The patches are 0.002 of an inch thick.

Using computer software, doctors can set the dosages for up to three medications that are absorbed into a gel on the underside of the patch. A patient profile would alert the doctor to allergies or potentially harmful interactions with a person's active prescriptions. A doctor would e-mail a prescription to a drugstore, where a pharmacist would transfer the dosing information via a hand-held control to the wireless patch. Once programmed, the patches can deliver the medications for up to 7 days before being replaced. Before being discarded, the doctor can use a wireless scanner to determine how much of the medication was dispersed into a patient via the patch's weak electrical current.

Almost all prescription medications can be put into a form that can be made into a patch. However, drug patches do have shortcomings, the NIH notes on its website: the adhesives can irritate the skin, and the pads can come loose when moistened as people shower or sweat. Durand and her research team, Michael Jordan and Miao Yong-Cao, have worked on adhesives that would reduce those problems.

Dr. Edward Iannuccilli, formerly the chair of Rhode Island Hospital and currently a professor at Brown Medical School, recently joined the Isis Board of Directors and its Medical Advisory Panel. Iannuccilli noted that the multidrug regimens of elderly patients are difficult for medical professionals to monitor. "What I liked about Durand's idea is that there is the quality and compliance assurance of what she's doing," he says. "This is a way to have safety and compliance."

Vyteris Announces Redirection of Business to Focus on Peptide Delivery

Business Wire: February 1, 2008 – FAIR LAWN, N.J. – Following the successful results of a completed Phase 1 clinical trial demonstrating that Vyteris' patented Smart Patch transdermal technology can deliver a peptide molecule in humans without the use of needles, Vyteris, with approval from its Board of Directors, has redirected its business to focus on the development of peptide delivery using its Smart Patch technology. The company also states this redirection will allow for the further development of small molecule delivery using its technology as well.

Given the significant opportunity within the peptide/small molecule arena, the company will de-emphasize its marketing efforts related to its LidoSite product. As a result, the company will immediately reduce its workforce by approximately 32 employees that were solely or partially dedicated to LidoSite. "While we continue to believe LidoSite can benefit venipuncture, dermatology, rheumatology and oncology practices and improve overall patient experience, we believe greater opportunities for success for Vyteris exist with biotechnology companies as well as large pharmaceutical companies, as they continue to search for new and innovative ways to improve their product portfolio," states McIntyre.

JANUARY 2008

Generex Biotechnology Awarded New European Patent

Prime Newswire: January 28, 2008 – WORCESTER, Mass. – Generex Biotechnology Corporation (NasdaqCM:GNBT – News) has announced that the European Patent Office has granted the company a new European patent, "Mixed Micellar

Delivery System and Method of Preparation.'' The patent will be validated in 11 European countries, including the United Kingdom, France, and Germany. The patent contains process and formulation claims to a pharmaceutical formulation for delivery through the mucosal membranes.

The company's flagship product, oral insulin (Generex Oral-lyn™), which is available for sale in Ecuador for the treatment of patients with Type-1 and Type-2 diabetes and which was approved for sale in India in October 2007, is in various stages of clinical development around the world. For more information, visit www.generex.com.

Bioadhesive Technology Aids Transmucosal Drug Delivery

in-pharmatechnologist.com: January 28, 2008 – BRIDGEWATER, N.J. – The Transdermal business group of National Adhesives has launched the PROLOC™ bioadhesive drug delivery system, a new bioadhesive technology that provides the means to deliver drugs locally or systemically from various mucosal absorption sites on the body. According to National Adhesives officials, several successful clinical trials have been completed to support the delivery of drugs across the mucosa using this novel technology. These clinical trials include successful delivery via buccal, vaginal, ocular, and nasal absorption sites.

PROLOC™ is a proprietary technology providing superior bioadhesive properties with the capacity for high drug loading. The proprietary process, which does not create a new chemical entity, incorporates a USP-grade polysaccharide and polycarboxylated polymer and is effective as a sustained or controlled release preparation with an active agent. The system is fully erodable and can be utilized as a powder, compressed into a tablet, or cast as a film.

PROLOC™ is effective for both localized and systemic therapies. It facilitates transmucosal drug delivery, providing a convenient means for rapid and direct local or systemic absorption and onset of therapeutic effects, allowing lower dosages, and resulting in fewer side effects. More information is available by contacting PROLOC@nstarch.com. ■

Calendar of Events

2008

35th Annual Meeting of the Controlled Release Society

July 12-16
Hilton New York
New York City, New York U.S.A.
www.controlledreleasesociety.org

MIT: Advances in Controlled Release Technology: Polymeric Delivery Systems for Pharmaceuticals, Proteins and Other Agents

July 21-25
MIT Campus
Cambridge, Massachusetts U.S.A.
http://web.mit.edu/mitpep/pi/courses/controlled_release_technology.html

CPT2008

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

Advances in Tissue Engineering

August 13-26
Rice University
Houston, Texas U.S.A.
http://tissue.rice.edu/

World Congress of Pharmacy and Pharmaceutical Sciences 2008

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

EUFEPS Workshop Opportunities and Challenges in Vaccine Delivery

September 15-17
University of Geneva
Site d'Archamps, France
www.eufeps.org/document/_con.html

NanoDDS '08 Nanomedicine and Drug Delivery Symposium

October 18-19
University of Toronto
Toronto, Canada
www.nanodds.org/template_view.cfm?PageID=1

2009

The 36th Annual Meeting of the Controlled Release Society

July 18-22, 2009
Copenhagen, Denmark
www.controlledreleasesociety.org/main/meetings

World Congress of Pharmacy and Pharmaceutical Sciences 2009

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

2010

The 37th Annual Meeting of the Controlled Release Society

July 10-14, 2010
Oregon Convention Center
Portland, Oregon U.S.A.
www.controlledreleasesociety.org/main/meetings

CRS Delivering Bioactives

Controlled Release Society
3340 Pilot Knob Road
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United States of America