CONTROLLED RELEASE SOCIETY

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NEWSLETTER

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Joke Bouwstra

Messages from the President and Immediate Past President

New Faces: Yvonne Perrie

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Biotherapeutics

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CONTROLLED RELEASE SOCIETY
NEWSLETTER
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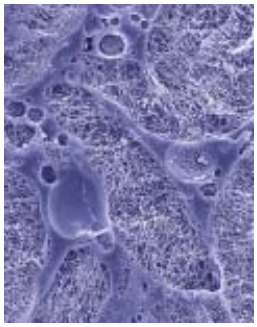
inthisissue

On the cover –



Cryo-SEM picture of Vernix caseosa.

Dedicated to the science and technology of controlled release and delivery and promoting education by releasing science to deliver a better future.

From the Editor

Ijeoma Uchegbu
University of Strathclyde, UK.

Another fine conference was had in Hawaii, I am sure that you will agree. The program organizers: Todd Becker, Terry Bowerstock, David Brayden, Martyn Davies, Anil Gaonker, David Grainger, Lisbeth Illum and Kazunori Kataoka should be well and truly congratulated. I particularly enjoyed the lecture given by Jane Lebowski on stem cells. Lebowski's work may one day make it possible to treat spinal cord injuries, giving hope to accident victims who might otherwise be confined to a less than optimum quality of life. How truly wonderful it must feel to know how profoundly your work may eventually help people. Life really is that simple.

Hawaii, as a venue lived up to its marvelous reputation. Well there was the beach, the beach and then the beach again. There is a lot to be said for sand and a temperature in excess of 25 degrees Celsius (78 degrees Fahrenheit in old money). Organization was as usual superb and the Polynesian entertainment gets my vote any day. I wonder if we could export the glamour of Polynesia to Miami next year. I hope you managed to get to one of the Pearls of Wisdom Sessions. Nanotechnology, is innovative and not the product of a clever rebranding exercise or so the audience felt at the "Nanotechnology: innovation or rebranding?" Pearls of Wisdom debate. Debaters, Sandy Florence and Kinam Park gave an excellent performance, because perform they did. If you could not make it to Hawaii, well there are always the pictures on page 4.

It is great to win awards and who doesn't long for one. The Controlled Release New Investigator Award is designed to spot new talent. Well here at the Newsletter we like to follow up our awardees and so Joke Bouwstra, a winner of the award in 1996 is profiled on page 19. Wow! What a career she has had since then. Working at a depth of a few tens of microns on the largest organ in the body – the skin, Bouwstra has been associated with a number of penetrating (excuse the pun) insights. Read all about her work on page 19.

This time of year sees the passing on of the Presidency and so we must say a fond farewell to Jim Anderson and a huge hello to our new president and the first woman president of the Society, Jennifer Dressman. Jennifer Dressman's inaugural address appears on page 3 together with Jim's farewell address. See you get two for the price of one. Who says we don't spoil you at the Newsletter.

Change they say is good, as good as a rest almost and it is with huge sadness that I announce my retirement from all things Newsletter. Time to give more to the day job, I am afraid. The Newsletter has changed for the better and that was my goal when I accepted the offer to co-edit. An excellent team remains in the shape of Bozena Michniak, Steve Giannos and new comer Yvonne Perrie. Yvonne's appointment will make the Newsletter even better and I am really happy to be leaving the Newsletter with such a capable team. Yvonne's profiles may be found on page 23. We also have a new Managing Editor, Amy Lemmon who takes over from Jaymie Griffin. Jaymie has since moved on to pastures new. Well it is ciao from me and see you soon from my colleagues Bo, Steve, Yvonne and Amy. Have a great read. ▪

The Controlled Release Society Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published three 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.controlledrelease.org.

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From the *Immediate Past President*

Dr. James Anderson

Honolulu had it all during the 2004 Annual Meeting & Exposition: sun, amazing science, visiting with international friends, outstanding science, surf, innovative science, networking opportunities, marvelous science, sand, wonderful science, a remarkable program, fantastic science, generous sponsors, superb science, and an outstanding exposition. Did I mention the science?

Mahalo "thank you" to everyone, presenter, participant, planner, sponsor, and exhibitor who made this year's Annual Meeting & Exposition a success. Special thanks to David Grainger, Lisbeth Illum, Kazunori Kataoka, Todd Becker, Anil Gaonkar, Terry Bowersock, David Brayden, and Martyn Davies for putting together a strong program and our major donors: ALZA, BASF, Banner Pharmacaps, Capsugel, Eurand, Guidant Corporation, and NOF Corporation.

As I pass the gavel to CRS's new President, Jenny Dressman, I reflect on some of the accomplishments of 2003-2004: our education initiative and renewing the Elsevier and ARDEL contracts. A special thanks to the Board of Directors who worked diligently in a team effort to improve all aspects of the society. With pride on what we accomplished, I look forward to being a part of the 2004-2005 initiatives President Dressman and the CRS community plan for releasing science to deliver a better future. I hope to see you in Miami, June 18 – 22, 2005. ■

From the *President*

Dr. Jennifer Dressman

Dear Colleagues

As you know, the CRS has a unique niche among scientific societies. Many associations in the medical field have close ties to and are highly influenced by professional groups; while others have a relatively narrow spectrum of interests. The CRS, by contrast, is run for and by scientists while maintaining a broad, interdisciplinary cross-section of membership. As such, we are uniquely positioned to be a leader in some of the most exciting and challenging developments of our time: to deliver genetic material efficiently and reproducibly into the cell, to bring the promises of biotechnology to reality in terms of therapeutics and to apply chronopathological and chronopharmacological concepts to the treatment of diseases, not only in humans but also in animals and plants. I am convinced that CRS members will be at the forefront with the breakthroughs necessary to achieve these goals.

What is CRS doing to support its members in their scientific endeavors? Our most important role is undoubtedly to offer our members a first-class annual scientific meeting. Martyn Davies and the Programming Committee put together a top-notch and of-the-moment scientific program for the Hawaii meeting and this year's team is well underway with plans for 2005. *Please mark your calendar now for the Annual Meeting in 2005, to be held in Miami, Florida from the 18th to the 22nd of June.*

A hallmark of CRS is our local chapter network, which provides many scientists working in controlled release access to CRS programming, even though it may be too tight financially for them to attend the Annual Meeting on a regular basis. In recognition of the high priority the CRS gives to its local chapters and local chapter members, I have appointed Ajit Singh (Chairman of Associated Capsules Group of Companies and a co-founder of the Indian Local Chapter) to serve as an *ad hoc* advisor to the Board of Directors, with the aim of catalyzing networks among the Chapters and communication of the Chapters with the Board. He will also be working to facilitate coordination of education activities between the Education committee and the local chapters.

The Education Committee itself, under the energetic and visionary leadership of Mike Rathbone, is working on a number of projects. In Hawaii the *Get up! Get educated!* program was launched and was extremely well received, with up to 100 early-bird scientists attending each of the sessions. Another initiative of the Committee is to establish a virtual library of resource material, including a visual aids library which will enable us to "borrow" slides to enhance our presentations, whether these are at the technical or the teaching level.

What must the leadership of CRS do to bring CRS to the next level of scientific excellence and member services? A key aspect is to ensure that the Society stays in good financial health. Only then can we invest in the infrastructure and programs that are important to assisting members achieve their research goals. Following in the capable footsteps of Susan Cady, Art Tipton and the Finance Committee are working hard to streamline costs, while Joe Fix and the Marketing and Development Committee are taking a pro-active stance, seeking to expand our sponsorship and exhibition programs.

This year promises to be an active and progressive year for the CRS. I think it is important to remember that we are building on a solid foundation passed on to us from previous Presidents and Boards, and I want to take this opportunity to thank both Jim Anderson and Sandy Florence, in particular, for their untiring presidential efforts in paving the way for the future of the CRS.

Wishing you all a productive and successful Fall.

Jennifer Dressman

Highlights of 2004 Ann

Congratulations CRS Awardees

Philipp Seib accepts the 2003 CRS - 3M Drug Delivery Systems Award

Sergio Capancioni accepts the 2003 CRS - Outstanding Veterinary Paper Award

Toaru Ooya accepts the 2003 CRS - Elan-NanoSystems Award

Cory Berkland accepts the 2004 CRS - Genencor Outstanding Consumer & Diversified Product Paper Award

Dr. Danny H. Lewis accepts the CRS - Nagai Innovation Award

Leslie Z. Benet accepts the Eurand Career Acheivement in Oral Drug Delivery Award

Walter A. Shaw accepts the 1st Place Eurand - Novel Approaches in Oral Drug Delivery Award

Antony D'Emanuele accepts the 2nd Place Eurand - Novel Approaches in Oral Drug Delivery Award

In-Hyun Lee accepts the 3rd PlaceEurand - Novel Approaches in Oral Drug Delivery Award

ual Meeting

Jack L. Koenig accepts the 2003 Jorge Heller Journal of Controlled Release Outstanding Paper Award

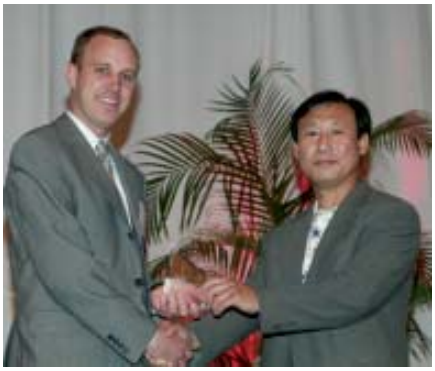
Jean-Christopher Leroux accepts the 2004 CRS - Young Investigator Award

Grand Prize Winner Kathryn Whitehead accepts the 2004 CRS-Capsugel Graduate/Postdoc Award

Manish Kumar Chourasia accepts the 2004 CRS - Capsugel Graduate/ Postdoc Award

Michelle Dawson accepts the 2004 CRS - Capsugel Graduate/Posrdoc Award

Sarah Lynn Tao accepts the 2004 CRS - Capsugel Graduate/Postdoc Award



Professor Kinam Park accepts the 2004 CRS - ALZA Founders' Award

Ronald J. Veršic accepts the 2004 CRS - Distinguished Service Award

Harlan Hall accepts the 2004 CRS - Distinguished Service Award

A Sincere Thank You to the Following Individuals

Jennifer Dressman accepts the president's gavel from James Anderson.

James Anderson congratulates David Grainger on a great 2004 meeting.

James Anderson congratulates Lisbeth Illum on a great 2004 meeting.

James Anderson congratulates Kazunori Kataoka on a great 2004 meeting.

James Anderson congratulates Todd Becker on a great 2004 meeting.

James Anderson congratulates Anil Gaonkar on a great 2004 meeting.

James Anderson congratulates Terry Bowersock on a great 2004 meeting.

James Anderson congratulates David Brayden on a great 2004 meeting.

Welcome 2004-2005 Volunteer Leaders

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Ijeoma F Uchegbu, University of Strathclyde, Glasgow, Scotland, UK
Arto Urtti, University of Kuopio, Kuopio, Finland

The Controlled Release Society sincerely thanks the following retiring volunteer leadership:

2003-2004 Retiring Board of Directors

James M. Anderson, President
Susan Cady, Treasurer

2003-2004 Retiring Board of Scientific Advisors

Avi/Abraham Domb
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Scientifically Speaking

Physico-chemical control of sub-10µm Particles via a novel crystal engineering approach

Robert Price and Sebastian Kaerger
University of Bath, UK

The requirement for controlling particle formation (crystal engineering) of active ingredients for the majority of medicines and drug delivery systems are mainly related to chemical issues, such as purity (impurities, solvent levels) and solid-state control of the crystal form and crystal habit. However, in a number of applications the physical and chemical properties of the particulates are critical in the overall stability, therapeutic and clinical performance of a pharmaceutical solid dosage form.

For example, in enhancing the solubility of active pharmaceutical ingredients for oral dosage preparations, particles less than 10µm are generally required to significantly increase the surface area-to-volume ratio. However, these particles generally exhibit poor flow properties and require significant formulation development for optimisation of powder handling and processing. In respiratory drug delivery, the particle size distribution of therapeutic aerosols is associated with the deposition pattern within the respiratory tract. The optimum particle size for respiratory delivery is 1-5µm. In addition to affecting flowability, the deaggregation and dispersion properties of therapeutic aerosols are critically related to the physico-chemical properties of the particles. This remains the key parameter in defining the efficiency and clinical performance of therapeutic aerosols.

The pharmaceutical issues pertaining to particles less than 10µm in diameter are associated with the hierarchy of physical forces influencing particulate interactions. These physical forces are not invariant with the size of the object on which they act. For particles greater than 10-100 µm in diameter, to objects as large as planets and galactic clusters, their interactive behavior is dominated by the force of gravity. However, below a critical size (~10-20µm) a particle would experience a range of physical forces that outrank the influence of gravity by several orders of magnitude. Hypothetically, such particles could be considered as effectively weightless in comparison to other forces they experience. For such a system, an external force would be required to deaggregate particles or to remove a particle from a surface.

The physical forces dominating such interactions are a composite of the ubiquitous van der Waals forces and dynamic capillary and electrostatic forces. Their specific influences are predominated by the surface properties of the interacting particles and not their bulk properties. The extent of particulate interactions is fundamentally governed by surface thermodynamic properties (surface free energies) and work of adhesion of interacting surfaces. Their influence can however be significantly modified by optimising the physical properties of particulates, including particle morphology and surface topography. Such modifications need to be directly related to minimising the available contact area between interacting surfaces. The smaller the contact area of interaction, the larger the separation distance between contiguous surfaces. This results in a significant decrease in particle adhesion. A macroscopic spherical morphology would, therefore, provide the optimum reduction due to its low surface-to-mass ratio. In addition to the macroscopic characteristics, the mesoscopic surface texture of the particles may significantly aid in reducing the available contact area and hence particle adhesion.

The optimum physical characteristics of sub-10µm particles are shown in the scanning electron microscopy (SEM) image of the spores of a *vascellum pratense* fungus (Membranous puffball), Figure 1. While the spherical like nature of the respirable sized spores minimises the radius of contact between spores, the presence of nanometre (250-300nm) protrusions on the surface acts to further reduce the available contact area. To replicate this nanotechnology approach of nature to pharmaceutical particle engineering may be some time away!

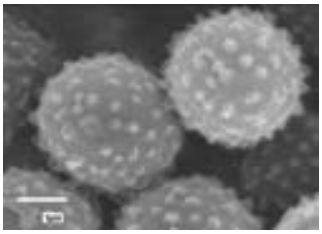


Figure 1: Scanning electron micrograph of the spores of a vascellum pratense fungus (Membranous puffball).

Over the past 10 years, both academia and industry have focused significant resources on crystal engineering techniques to improve the processing and handling of sub-10µm particles. However, there still remains the need to develop technologies which specifically address these physico-chemical requirements for controlling particulate interactions. This remains the critical limitation for the future development of these solid-state drug delivery systems. Meanwhile, the industry remains limited to the conventional secondary processing of crystalline material in fine tuning the particle size characteristics without any significant control of the surface characteristics and surface geometry of active ingredients.

Here, we report the use of a novel crystal engineering technology for generating sub-10µm crystalline particles in a single droplet to particle operation. The SACS (solution atomisation and crystallisation by sonication) process combines the use of an ultrasonic energy source with a novel collection system of highly supersaturated droplets for controlled particle formation and crystal engineering of low surface free energy drug particles [1]. The comparatively straightforward process, which is readily scaleable as a low cost batch or continuous process, is operated under atmospheric pressure and ambient conditions, with known solvents and no novel excipients. The process results in the formation of particles within a narrow particle size distribution with modulated control of particle morphology and topography with a low residual solvent content.

Scanning electron micrograph (SEM) images of paracetemol and sulfathiazole drug particles produced by the SACS process show the transformation of planar crystals formed via conventional solvent based crystallisation (SEM images not shown) to the curved surfaces of spherical crystalline particles (Figure 2).

Scientifically Speaking continued on page 23

Special Feature

BIOTHERAPEUTICS – FROM DRUG DISCOVERY TO DRUG DELIVERY

Steven A. Giannos
CRS Newsletter Industrial Editor, U.S.A.

Controlled release drug delivery – the route and dosage form in which drugs are administered - is undergoing an evolution in innovation as companies seek to capture the future promise of biotherapeutics and differentiate themselves in a competitive environment. As the list of biological drugs gaining regulatory approval grows, different technological approaches are being taken to deliver these drugs. Additionally, the demand for drug delivery technologies to protect products from generic competition is expected to expand the drug delivery market to nearly $89 billion by 2005 [1].

Non-invasive formulations delivered via the oral, pulmonary, nasal and transdermal routes will have higher sales than injected and implanted products since these fulfill unmet needs of less invasive and less painful treatment options, leading to higher patient convenience [1]. Businesses are also changing strategies to meet the challenges. These strategies can be broadly divided into three segments based on their technological approach: (1) exploitation of new or existing routes for drug administration, (2) the development of novel devices and (3) reformulation of a marketed drug compound [2].

Exploitation of new or existing routes for drug administration
The $30 billion biotechnology industry is already making a substantial contribution to pharmaceutical companies' top line growth, with over 100 FDA approved drugs and vaccines to its credit. Biological drug approval by the Food and Drug Administration (FDA) has been steadily rising since 1981, when the FDA first approved recombinant human insulin [3]. Over 30 biotechnology drugs and vaccines were approved in 2000 [4]. The number has now reached 'critical mass', presenting a growing opportunity for drug delivery firms to provide technical solutions to the challenges of macromolecular delivery. These challenges arise from a fundamental of physiology: after drugs enter the body they undergo the pharmacokinetic processes of absorption, distribution, metabolism and excretion (ADME).

Injection still remains the most effective way of administering therapeutics such as hormones, growth factors, monoclonal antibodies and vaccines. Delivering these drugs via more 'patient-friendly' routes than injection, while maintaining drug efficacy, is fast becoming the main concern of drug delivery. Among non-invasive delivery methods, one of the most promising approaches is pulmonary delivery. However, work is also being undertaken to deliver proteins by oral, transdermal, nasal and other mucosal routes [3-6].

As witnessed at the 31st Annual conference of the Controlled release Society, the development of established platforms continues, as well as new technologies emerging. Recent news bulletins have also publicized innovations in nasal, mucosal, transdermal (microneedles, microchips and spray emulsions), parenteral (injection), pulmonary

(inhalation) and oral drug delivery of therapeutic biologicals many of which are finding their way to the marketplace.

Development of novel devices

In the area of transdermals, several novel technologies are under development. Texmac Inc. (Charlotte, NC) has partnered with Nano Device and System Research Inc. ("Nanodes", Kyoto, Japan), in order to develop microneedles for clinical applications. Shown in Figure 1, these microneedles deposit functional substances, such as cosmetic powder or pharmaceutical drugs into human skin (epidermis or dermis layer). The microneedles are formed with materials of high water solubility. The microneedles can be made in a variety of sizes, based on the customer's preference and applications. Nanodes is the developer of the microneedle technology and Texmac is responsible for marketing and licensing the development and manufacturing to pharmaceutical and cosmetic companies in North American and European nations.

Figure 1. Close-up of Nanode's water soluble Micropile (microneedle) technology for drug delivery and cosmeceutical applications.

IGI, Inc. (Buena, NJ) along with Tarpan Therapeutics, Inc. (Buena, NJ) is developing parathyroid hormone fragment 1-34 (PTH (1-34)), which regulates cell differentiation and proliferation, for the treatment of skin disorders using IGI's Novasome delivery technology. Acrux (West Melbourne, Australia) is developing their *Patchless Patch*® delivery method as a liquid spray or aerosol formulation for forming a non-occlusive reservoir of drug and enhancer within the skin. The Acrux, Transdermal delivery systems, using their ACROSS® penetration enhancers provide an elegant alternative to traditional reservoir and matrix transdermal systems.

Novavax (Columbia, MD) is using novel delivery systems technologies to develop product candidates for the delivery of generic and non-generic drugs, peptides, proteins and oligonucleotides. Their product candidates are based on several patented platform technologies. Their micellar nanoparticles (MNPs) are non-phospholipid structures that can deliver a wide variety of ethanol based drugs and other therapeutic agents transdermally, without common side effects such as skin irritation. This technology is being used for Novavax's leading and soon to be marketed product *ESTRASORB*™ (estradiol topical emulsion) and the product candidate *ANDROSORB*™. Sterisomes™ is a depot delivery system comprised of 80% water, 15% drug and 5% lipid, capable of delivering a multitude of drugs. This technology is being used for Novavax's *ANDRO-Ject*™.

Nasal

Over the past few years, nasal drug delivery has gained renewed interest as an advantageous route for delivery. West Pharmaceutical Services (Lionville, PA) is developing the *ChiSys*™ technology as company's first branded drug delivery system. Based on a naturally occurring polysaccharide, chitosan, it is being evaluated as a non-irritant bioadhesive excipient for use in transmucosal delivery. *ChiSys*™ has been shown to increase the residence time of drugs when applied on mucosal surfaces, such as the nasal lining, thereby improving the bioavailability of drugs. The *ChiSys*™ technology has been licensed to several different companies for morphine, leuprolide, insulin, calcitonin and influenza vaccine.

Nastech Pharmaceutical Co., Inc., (Bothell, WA) is working on a phase I clinical trial to evaluate intranasal administration of human parathyroid hormone 1-34 (PTH1-34) in healthy subjects. PTH1-34 is a fragment of the naturally occurring human parathyroid hormone that is an important regulator of calcium and phosphorus metabolism Also, Nastech is investigating PYY3-36 (for peptide YY 3-36) for use in a nasal spray designed to deliver the natural, appetite-regulating hormone PYY directly to the bloodstream.

Oral/Aerosol

Among urgently needed applications of controlled release drug delivery systems are the delivery of biopharmaceuticals targeted specifically to the site of a tumor. Additionally, convenient oral/aerosol vaccine delivery systems are needed that can be easily distributed to a variety of populations in remote locales. Chrysalis Technologies (Richmond, VA) is developing the Aria™ technology - a soft mist aerosol platform for pulmonary drug delivery (Figure 2). West's ATOMist Delivery System is a proprietary hand-held device that uses electrostatic atomization to administer a highly efficient dose with a soft spray. A microdose of fluid can be delivered with a simple push of a button making the ATOMist device exceptional for adult, pediatric and geriatric applications.

Figure 2. Chrysalis Technologies' Aria™ (Functional prototype) portable inhaler for pulmonary drug delivery.

Acusphere (Watertown, MA) is focused on creating porous particles that are smaller than red blood cells. These microparticles can be used to deliver gases or these microparticles and nanoparticles can be used to deliver drugs to patients through various routes of delivery. The PROMAXX microsphere, produced by Epic Therapeutics Norwood, MA), is a protein-matrix drug delivery system that produces bioerodible protein microspheres in a totally water-based process. Multiple formulation options allow cost-efficient customization for specific applications. Cydex's (Lenexa, KS) Captisol (SBE beta-Cyclo-Dextrin) now for oral and pulmonary applications can also improve oral bioavailability by improving the solubility and dissolution, permeation and stability of drug compounds in oral solutions and solids.

Alkermes (Cambridge, MA) has developed two uniquely complementary platforms for drug delivery: ProLease and Medisorb injectable sustained-release technologies for both small and macromolecules. With release profiles lasting from days to months, each is designed to eliminate the need for frequent dosing. Another Alkermes product, AIR® Technology, is a proprietary drug delivery technology composed of dry powders ideally suited for delivery to the lungs. These microparticles are produced using many common excipients (sugars, amino acids, lipids) and have a geometric size in the range of 5 - 30 µm, with an aerodynamic size of 1-5 µm. The unique characteristics of these particles allow them to be used for both systemic and local delivery of small molecule, peptide, protein and other macromolecular drugs.

What's next?

The current research and development of novel biopharmaceuticals is leading to the development of non-viral gene delivery vehicles. Vical (San Diego, Ca), whose patented non-viral DNA delivery technology

Biotherapeutics continued on page 32

Pharm News

Vets Bite Back in Pearls Debate on Drug Delivery!

Dr. David Brayden (Veterinary Faculty, University College Dublin, Ireland) and Dr. Michael Rathbone (InterAg, New Zealand) debated the pros and cons of the topic "*Veterinary drug delivery is just human drug delivery on four legs*," respectively at a Pearls session at the CRS 2004 in Hawaii. This lively and entertaining exchange was chaired by Professor Rod Walker (University of Grahamstown, South Africa) in front of an appreciative audience of about 80 attendees. Brayden and Rathbone had discussed the debate in advance and their presentations reflected their efforts to coherently address the opposing arguments. This resulted in their talks containing mischievous cartoons of their opponent wearing the torsos of various types of animals!

In advancing the "pro" argument, Brayden approached the topic from several standpoints. Firstly, he conceded that there are known differences in pharmacokinetics and physiology between animals and man and that he wanted to move beyond that. Then, he also accepted that some devices needed to be tailored for veterinary-specific needs such as intra-mammmary injections, flea-collars and intra-vaginal delivery. At this point the audience thought that he was providing the "Con" argument! However, he then turned his argument around claiming that many human delivery systems are being adapted for, or are similar to, those being used in veterinary drug delivery and visa-versa. Examples included intradermal vaccination of cattle, skin patches of opiates for dogs and inhaled â adrenergic agonists in cats. A prime example of the similarity of the two types of human and animal delivery was the common type of design features of many current human gastroretentive devices and cattle intra-ruminal devices. The irony was that there was little contact between these groups of researchers and they appeared to have proceeded independently even though many of the principles were the similar. The same could be said of the many different types of intra-vaginal oestrogen-releasing systems used in humans and animals. In pointing out these similarities in what were admittedly selected examples, Brayden emphasised that he was not getting into which group was more innovative as it was not relevant to the debate. The more important point was that the examples showed that many similar-type devices worked equally well when *adapted* across a range of species. Brayden then argued that there is a lot of commonality between species in respect of the first principles of drug transport across biological membranes and also some basic mechanisms of metabolism. Subsequently, a case can be made that controlled release drug delivery researchers should be able to move relatively easily between veterinary and human and visa-versa. Finally, in support of the overall thesis, some stark facts were presented to the effect that much company-based veterinary drug delivery research is leveraged from human systems, that the majority of immediate- and controlled release drugs in the veterinary formulary are human-derived, and that the majority of recommended veterinary undergraduate pharmacology textbooks are entitled "human pharmacology." In summary, the "pro" argument was that, while there are notable exceptions, the majority of veterinary drug delivery systems were based on common inter-species transport models either derived from or developed in parallel with human systems.

In contrast, Rathbone took the stance that the title of the debate was a feeble attempt to demean the successes and achievements of his veterinary colleagues and launched into a trenchant defence of the independence and originality of veterinary drug delivery. With mock outrage, he refuted the suggestion that it was simplistic to suggest that two legs multiplied by two gave formulations fit for his four-legged friends. Early in the rebuff he offered an olive branch by showing a table of seven examples of human-to-animal switches for companion animals but used these examples to point out that these were limited examples appropriate for that (albeit very large) market. Rathbone expanded his argument by pointing out that the situation for production animals was quite different, since these systems had to be low cost, convenient and administered by an appropriate delivery route. Rathbone then argued that since animals have unique physiological and pharmacological differences to man, they required species-specific formulation and device-led research. The evidence for this was provided in the series of inventive ways that are required to dose controlled release drugs by the rectal route to elephants or oral route to giraffes! While Brayden had argued on the basis of common physiology (using selected examples of non-ruminants), Rathbone used the ruminant stomach as a way to illustrate the differences to man. He then argued that while skin patches had been used successfully in limited cases to deliver fentanyl to dogs and horses, in practice what the clients wanted for their animals were the cheaper and more practical pour-ons, spot-ons and flea collar-type systems. These systems were unique to the veterinary area. He then suggested, tongue-in-cheek, that his opponent did not really believe the "pro" argument at all by citing quotes from some of Brayden's publications in which he had emphasised that differences in veterinary pharmacokinetics and physiology meant that species individualization was required in formulation development. Overall, Rathbone presented the argument that veterinary drug delivery scientists had to be very creative and innovative to overcome species-specific considerations and boosted his argument by citing several examples from veterinary reproductive and anti-parasitic medicine where unique technologies had been specifically developed for animal use. The "con" argument therefore was that veterinary drug delivery was a creative field of research in its own right, with its own special challenges and solutions related to cost, device and veterinary needs and that it was not derived or directly leveraged from human drug delivery.

Overall, it was clear that both presenters cited a range of appropriate well-researched examples to suit their argument. Most participants acknowledged the areas of overlap and strongly advocated for more joint programming sessions at future CRS meetings.

The largely partisan veterinary audience ultimately voted against the motion, which meant that Mike Rathbone had to buy the beers! ▪

Spotlight *on Intelligensys*

by Elizabeth Colbourn, Intelligensys Ltd

Every day, an army of researchers add to the mountain of data being generated for drug formulation. But data itself has little inherent value; the mountain must be 'mined' for the nuggets of knowledge that will drive development forward. Faced with pressure to develop new products quickly and burgeoning amounts of data, achieving this by traditional means becomes increasingly difficult for the formulator. Fortunately, new computational approaches can leverage their efforts by *automatically* generating knowledge directly from data. When coupled with visualization and statistical validation, and robust optimization methods, these approaches provide powerful tools especially when integrated behind an easy to use computer interface.

Intelligensys has a mission of producing desk-top decision support software that enables its clients to formulate new products more quickly, and to more stringent quality standards, than ever before. Intelligensys software accelerates the client's ability to extract knowledge from their existing data, using artificial intelligence technologies, as models and as "if… then" rule statements.

Especially with new formulation types, where historical knowledge is not available, any technique that gives an edge in getting a new formulation to market more quickly has big advantages in establishing market position, and the Intelligensys software can. Provided the data are in electronic form (database or spreadsheet) they can be imported directly into the software, where models are developed to represent the cause-and-effect relationships linking inputs (ingredients and processing conditions) and measured properties. Model development is quick - typically a few minutes. Using the models, either for 'what if' predictions (changing ingredients or processing conditions and seeing how these affect properties) or for optimization is even quicker. Indeed, response is so quick that one of the company's clients has likened the software to "a knowledgeable colleague, whom you can bounce ideas off".

The modeling capability of Intelligensys's software is built upon neural computing. Originally designed in an attempt to mimic mammalian nervous systems, these methods are capable of 'learning' complex relationships within data and of representing these as usable models. Unlike statistics, neural computing methods do not require the formulator to make any assumptions about the model at the outset. Instead, they develop as complex a model as is needed to fit the data, and a process of 'validation' is used to ensure that the model fits only the underlying relationships and not the noise. In addition, neural networks can work successfully with large numbers of input variables, so it is not necessary to risk oversimplifying a problem in order to model it. As the reviews in the references show, a considerable number of papers in the published literature demonstrate that neural networks generally develop models that are at least as good as those obtained from statistical approaches.

More recent is the application of neurofuzzy computing, a novel technology that allows rules to be derived directly from data and that underpins the company's FormRules software. As the name suggests, neurofuzzy logic combines the adaptive learning capabilities of neural networks with fuzzy logic's ability to express complex concepts intuitively. Consequently, in addition to deriving simple models that highlight which variables are important in determining each property, neurofuzzy logic allows the models to be expressed as rules in the form IF (ingredient1) AND (ingredient2) THEN (property), with associated confidence levels. This immediately gives the researcher knowledge that can be used to focus future experiments in the right direction.

Neural computing does not provide the whole picture though. In its product INForm, Intelligensys integrates neural networks for modeling with genetic algorithms for optimization. Genetic algorithms, a method that uses a 'survival of the fittest' approach, can find the best solution in a multi-dimensional space far more effectively than can more traditional optimization approaches. The 'fitness' is assessed by how well the solution meets the objectives specified by the formulator and objectives are defined in INForm using fuzzy logic. So, the formulator can specify the properties that he wants (a specific release profile, for example) and the optimization will find the formulation that (within the specified ingredients and processing conditions) is most likely to provide them.

Intelligensys was founded in 1999 by industrialists with experience in pharmaceutical and chemical modeling, following discussions with Professor Ray Rowe, a pioneer in the application of artificial intelligence in pharmaceutical formulation. In parallel, Professor Rowe set up the PROFITS Group at the University of Bradford, UK. This special interest group consists of several pharmaceutical companies who provide funding for research into application of the techniques in exchange for a preview of how the technology can be applied, training in its use, and guidance in its implementation. Intelligensys has a close ongoing relationship with PROFITS and its client companies. Research currently being undertaken in collaboration with PROFITS includes investigating genetic programming as a new modeling tool for formulation, and the area of data mining in particular, extracting knowledge from disparate, but related, data sets. Technologies that are shown by PROFITS researchers to be useful to formulators are subsequently incorporated into new releases of Intelligensys software.

The company spent an initial 18 months developing its products, making its first sales in late 2000. Now Intelligensys software has been applied across a range of customers, from small pharmaceutical companies in Vietnam, to major multi-nationals like AstraZeneca, Pfizer and Schering. The company has its own software development effort, and has the reputation of being responsive to customer requests for enhanced functionality. ■

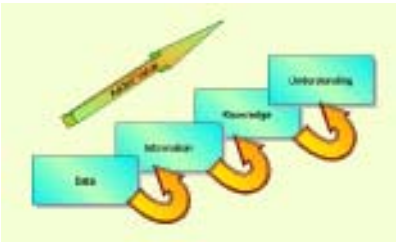


Figure 1. The problem: extracting value from data

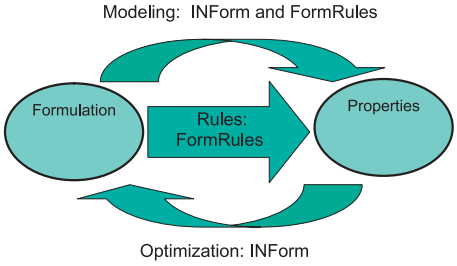


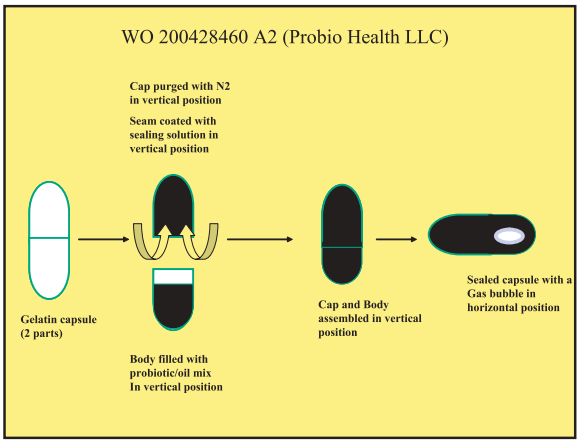
Figure 2. The solution: using intelligent software to extract models and rules

Microencapsulation & Controlled Release Nutraceuticals

by Jamileh Lakkis, Cadbury-Schweppes, Inc.

Microencapsulation and controlled release of nutraceuticals continued to dominate the consumer and diversified products patent literature this year. Topics ranged from controlled release of well-known nutraceutical actives such as probiotics, vitamins and minerals to less characterized plant extracts that can be co-administered with therapeutic drugs to enhance their bioavailability and/or reduce dosage levels. The following discussion highlights some of the innovative technologies and compositions that turned up in searching the patent literature the first 6 months of the year 2004.

Prebiotic and preservative uses in oil-emulsified probiotic encapsulations (Probio Health LLC) WO2004028460 A2. This invention describes stable compositions of probiotic bacteria suspended in edible oils. It also claims a unique anaerobic process for extending the shelf life of beneficial bacteria using novel nitrogen purge instant bonding, NPIB, technique (Figure 1). Using a two-piece gelatin capsule held in a vertical position, the lower cap is filled with the probiotic/oil slurry or emulsion while the top portion is flushed with nitrogen and sealed immediately with a polymer material. Rapid evaporation of the sealant carrier leads to instant bonding of the cap and body during capsule closing step. An interesting set of claims were concerned with classifying edible oils (olive, fish and soybeans) as prebiotic carriers, in addition to their role in lowering water activity and ability to reduce air diffusion. Other oils tested were claimed to have antibacterial activity, thus eliminating their effectiveness in such applications. Using this technique, it was claimed that shelf life of Lactobacillus casei increased up to 370% compared to their unencapsulated counterparts.



Delivery system useful for administration of biological components (Nutraceutix, Inc.) EP1429802. A unique gastric bypass delivery system in a predosage dry blend form is disclosed. The composition comprises essential components: 1) reduced moisture powder blends of probiotic active, 2) hydrophilic swellable polymer (gelatins or polysaccharides), 3) release-modifying agents, and 4) electrolytic agents. By sequestering water mobility, electrolytic agents can maintain a constant pH micro-environment in the vicinity of the microorganisms as well as providing means for their controlled hydration rate. The patented composition can be prepared via direct compression to form monolithic directly compressible tablets and capsules eliminating the need for coating or granulation steps that require addition of water to the composition.

Composite particles and method for preparing (Ferro Corp.) US 2004 0071781 A1). A method for producing composite particles using supercritical fluid extraction technique is disclosed. The process consists of co-dissolving a polymer and a biologically active material, emulsifying in a polar solvent to form an oil-in-water or water-in-oil-in-water emulsion. The composition is further contacted with a supercritical fluid (SCF) to extract the solvent. Removal of the solvent by the SCF from the emulsion supersaturates the medium with the polymer/active pair resulting in precipitating it out of solution with the active embedded into the polymer. By manipulating process conditions, the resulting composite particles can be recovered in the form of nano- or micro-composites spherical or needle shaped particles ~ 0.1 nm-10 microns.

Plant based agents as bioavailability/bioefficacy enhancers for drugs and nutraceuticals (Council of Scientific & Industrial Research) US20040121028 A1. This application discloses a method for isolating and purifying active fractions from

Microencapsulation continued on page 17

Strategies in Oral Drug Delivery 2005

January 9-13, 2005

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PROGRAM GOAL

A short course in the application of physiology, biochemistry and mass transport to oral drug absorption and dosage form design.

This course provides an in-depth focus on oral drug delivery, biopharmaceutics, methods for estimating and evaluating drug absorption, and strategies for achieving optimal drug delivery and absorption from the gastrointestinal tract. The course will include problem and demonstration sessions, and attendance will be limited to 70 participants to enhance interaction between faculty and students.

PRESENTED BY: DRUG DELIVERY Foundation

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Dissolution and Oral Absorption Evaluation

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Oral Delivery Systems: Formulation and Regulatory Standards

The Future: From Discovery to Regulation

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Microencapsulation continued from page 15

Cuminum cyminum plant with its intended use drug bioavailability enhancer for therapeutic drugs as well as nutraceuticals compositions. An effective ratio of bioenhancer:drug (0.1:300 w/w) is claimed to be beneficial in significantly reducing anti-TB drug dose while retaining drug's therapeutic effects.

Compositions based on vanilloid-catechin synergies for prevention and treatment of cancer (Purdue Research Foundation)US 6759064 B2. This invention describes methods and compositions for co-administering vanilloids and catechins (active components in tea) in a sustained release formulation at ratios that provide synergistic effects in treating primary and metastatic cancers in humans. Various modes of administration of the therapeutic compounds are disclosed, including dietary or nutritional supplements as well as therapeutic drug formulations. The vanilloid/catechins compositions are proposed as effective agents for blocking DNA transcription of a number of genes in cancer cell lines and in blocking transcription of nitric oxide (NO) synthase.

Tea polyphenol esters and analogs thereof for cancer prevention and treatment (University of South Florida) US 6713506 B2: This invention relates to polyphenol esters derived from green and black teas, and their analogs which are potent inhibitors of the growth of cancerous cells. The polyphenol esters are claimed to be highly effective in inhibiting chymotrypsin-like but not trypsin-like protease activity whereby tumor cells are arrested in G1 phase and selective apoptosis of cancerous cells are promoted. Examples of compositions of the invention for humans or veterinary use include edible compositions for oral administration such as solid or liquid formulations, capsules, tablets, and chewable formulations.

Compositions based on proanthocyanadin-catechin synergies for prevention and treatment of cancer (US 20040142048 A1): Methods and compositions for preventing or treating cancer comprising the co-administration of catechins and proanthocyanidins (prevalent in blue fruit extracts) into dietary or nutritional supplement or in therapeutic formulations are claimed. The disclosure is based, in part, on the discovery that ctaechins, and proanthocyanadins inhibit activity of a cancer specific protein, an isoform of NADH oxidase, specific to cancer cells (tNOX). The inhibition of tNOX results in the inhibition of cell growth, and ultimately, apoptosis of cancer cells whereas normal cells (which lack tNOX) are less affected. Thus, the invention provides a potent therapeutic composition with reduced or no adverse effects on normal, healthy cells. Sustained release compositions of this invention when administered to a human is claimed to maintain therapeutic circulating levels of caechins and proanthocyanadins at 10^{-7} M for at least 48 hrs in the sera. The levels are either circulating in the patient systemically or are localized onto the cell surface.

Bovine collagen and gelatins (Fibrogen, Inc.) US 20040018592 A1. An efficient approach for producing pure gelatin and collagen is disclosed. Uniqueness of this invention lies in two main characteristics: 1st) providing consistent supply of gelatins and collagens without the variability encountered in currently available materials used in controlled release applications & 2) providing pure material that is free of safety concerns associated with bovine spongiform encephalopathy (BSE). The method comprises three essential steps: (a) introducing at least one polynucleotide encoding bovine collagen, and at least one polynucleotide encoding post-translational enzyme for biosynthesis of collagen into a host cell, (b) culturing the host cell under conditions suitable for expression and (c) isolating the recombinant bovine collagen. Using recombinant bovine collagen construct and further isolation of the recombinant bovine gelatin; the process is claimed to provide the potential for producing gelatins and collagens specifically tailored and standardized for different applications and markets.

Nutraceuticals and method of feeding aquatic animals (Advanced Bionutrition Corp.) WO2004043140 A2. This invention describes a delivery vehicle for providing controlled release of bioactive agents (vitamins, minerals, proteins & nucleic acids) and live probiotic microbes to aquatic animals in the form of dry or wet beadlets. Binding of these actives to emulsified high-amylose starch and cross-linked alginates provides a means for their stability in the aqueous medium (ponds) and controlled release. The bioactive agents and live probiotic microbes can be prepared in the form of micro- or nano-particular beadlets.

Stable probiotic microsphere compositions and their methods of preparation (Cancure Corp.) WO 2004022031. This invention relates to viable and stable probiotic formulations for intestinal targeting made of double-coated microspheres. The composition comprises a core of one or more probiotic bacteria, microcrystalline cellulose (MCC) with a degree of polymerization from 165-365 and mean diameter from 45 to 180 microns, a disintegrant and a stabilizer. The mixture is extruded to form small segments, followed by spheronizing the segments and drying to form microspheres (primary coating). An enteric coating can be further applied to the microspheres (secondary coating) using fluid bed or other particle-coating techniques. The resulting probiotic microsphere is claimed to show no reduction in viable bacteria after one hour in simulated gastric fluid.

Complex coacervates containing whey proteins (NIZO Food Research) EP 1371410 A1. A method for providing whey protein based coacervation system is described. The disclosed complex comprises the combinatin of whey protein and active material to form an emulsion, followed by addition of a weak polyelectrolyte in conjunction with gum arabic. Complex coacervation is induced by adjustment of pH of the emulsion using weak acids (GDL) to < 5.2, hardening the shell using aldehydes or by enzymatic reaction. By cross-linking the coacervates, the core materials are claimed to be irreversibly retained in the capsules, a pre-requisite for effective taste masking applications. Claimed notable advantages of this composition include gelatin-free coacervation system that requires no heating steps.

Biologically active food additive (Pacific Fishing Industrial Research Center) RU 2222997 C1. This invention describes a preparation of biologically active food additive containing nucleoprotein complex (Tinrostim) isolated from soft roe of salmon fish and containing low molecular weight RNA (M. Wt. 100-300 kDa) in amounts of 75-80% with specified proportions of ascorbic acid and encapsulating promoting ingredients. The composition, in the form of tablets or capsules, is claimed to be effective for immuno-stimulation, anti-stress effect as well as capacity of activating mental and muscular performance.

Fat-protein encapsulation and protein fractionation (Lee) US 20040081725 A1: Disclosed s a method for encapsulating fat in animal blood protein matrix to form a free flowing powder with high payload and improved sensory properties. The process consists of solubilizing blood protein, incorporating fat into the solution, followed by homogenization. Heating the homogenized mixture to 55 deg C leads to the formation of a gel mass with entrapped fat droplets. Sequential bleaching using peroxides is claimed to be effective in eliminating the undesirable color of heat-treated blood proteins. ■

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People on the Move

Joke Bouwstra
Leiden/Amsterdam Center for Drug Research, The Netherlands

Joke Bouwstra received the CRS Young Investigator Award in 1996 for her work on transdermal drug delivery. Since then Bouwstra has continued to excel and today as Professor of Drug Delivery at the Leiden/ Amsterdam Center for Drug Research in the Netherlands, she leads a group of 15 scientists dedicated to studying the skin as a route for drug delivery.

Bouwstra received her M.Sc degree in Chemistry (cum laude) in 1980 from the University of Utrecht and her PhD in 1985 from the same institute. Bouwstra's PhD thesis was entitled, "Thermodynamic and structural investigations of binary mixtures". After this physical chemistry PhD, she turned her attention to applied research and entered the field of transdermal drug delivery. Bouwstra says that she loves this research area because it allows her to study both fundamental and applied concepts; the latter she carries out in collaboration with colleagues in the pharmaceutical industry. Bouwstra's research also allows her to work with PhD students, post-doctoral scientists and technicians, something that she enjoys very much.

When she started in the skin field at the end of the eighties, little was known about the organization of lipids in the skin and the role the lipid classes play in maintaining the skin barrier. This knowledge is very important in understanding the barrier function in normal and diseased skin. In order to get to the bottom of things, Bouwstra employed a plethora of biophysical and electron microscopy techniques to visualize the skin and elucidate the organization of skin lipids. She started off by providing evidence of the lipid organization in the skin of a number of species using *in vitro* techniques and has since moved on to an in depth study of the skin in man. This data gave Bouwstra considerable expertise, allowing her to study the ultrastructure of mammalian skin in both healthy and disease states. Simultaneously, using model systems based on isolated skin lipids, Bouwstra studied the role played by the various lipid classes and environmental factors, such as pH and temperature, on skin barrier properties. Quite recently, she has also found it possible to mimic skin lipid phase behavior using lipid mixtures prepared with synthetic ceramides. This research has been carried out in close collaboration with Maria Ponec from the Department of Dermatology in Leiden.

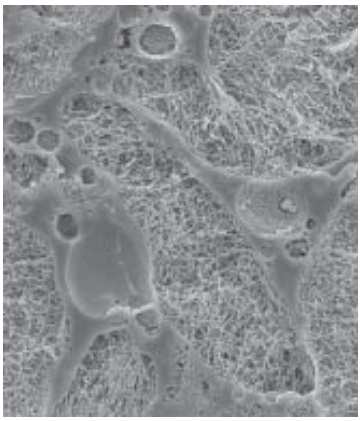

Figure 1: Cryo-SEM picture of Vernix caseosa, the creamy layer babies are coated with on delivery. The structure is very similar to that of the stratum corneum. Keratin is in the cells and the cells are swollen. This can be concluded from the darker regions between the keratin filaments.

Apart from delivery across the skin, the targeting of hair follicles is of great interest to Bouwstra, especially when delivering gene therapeutics and treating skin diseases, such as acne and alopecia. In Leiden these transfollicullar pathways have been studied *on-line* with one and two photon excitation microscopy.

Subsequently Bouwstra broadened her research by designing novel drug delivery systems to increase the transport of drugs across the skin. One of the approaches being used is vesicles based entirely on surfactants with special properties in terms of bilayer elasticity. With a combination of transport and *in vivo* visualization studies in man, the mode of action of these vesicles was demonstrated and her work showed that elastic vesicles rapidly enter the stratum corneum and accumulate in channel-like regions, thus transporting materials into the skin.

Bouwstra's interests stretch to the area of iontophoresis, particularly in as much as this electrical technique relates to the transdermal delivery of drugs with a small therapeutic window. The most important benefit to be derived from iontophoresis is its well-controlled transport rate, which may be carefully adjusted to patient requirements, enabling customized and programmed delivery. An example of candidate drugs suitable for delivery using this technique is the group of dopamine agonists used for the treatment of Parkinson's Disease. Both *in vitro* and *in vivo* transport studies are carried out at Leiden and these studies are conducted in pre-clinical and clinical settings. Bouwstra finds her work with patients an exciting challenge and her clinical experiences are made only possible by having good collaborators such as Professor Meindert Danhof of Leiden's Department of Pharmacology.

Bouwstra is currently working on two new projects. One is focused on the delivery of macromolecular compounds into the skin, such as vaccines. Technologies currently in use are microneedle arrays (collaboration with MESA$^+$, University of Twente). The delivery of vaccines to the skin is a relatively new research area with great potential. This area could have an important role to play in minimizing injection pain in children. Her second project involves the use of *in vitro* skin models reconstructed from either synthetic lipids or living cells. In these skin model studies Bouwstra collaborates with Dr Maria Ponec. Innovative delivery methods to promote skin repair processes will be tested using *in vitro* reconstructed skin models.

Bouwstra has published 156 peer-reviewed papers and 27 book chapters. She is also a co-inventor on 4 patents. Since 1996, she received over 7 million dollars in research grants. She is on the editorial board of several scientific journals and is local editor of the Journal of Investigative Dermatology. She has co-organized several conferences, among them: The Liposome Research Days, The 6th International Conference on Perspectives in Percutaneous Penetration and the Gordon Research Conference (focused on the barrier function of mammalian skin). She has co-edited a special issue of the journal, Proceedings in Investigative

Bouwstra continued on page 31

Chapter News

Indian Chapter Update

Controlled Release Society, Indian Chapter organizes Fifth International Symposium on "Advances in Technology and Business Potential of New Drug Delivery Systems"

Fifth International symposium on NDDS being inaugurated by Dr.D.B.Gupta, Chairman Lupin Ltd., sitting on the dais from left, Dr.Amrita Bajaj, Prof. Jennifer Dressman, Dr.Himadri Sen, Mr.Ajit Singh, Prof. David Triggle, Prof.H.L.Bhalla.

Rapid advances in the controlled release drug delivery area have resulted in an amazing 56% surge in the R & D expenses of pharmaceutical companies with controlled release interests. This increase in R & D expenditure is significant for the Indian economy because it shows that a new market is emerging and also is important when it is considered that the product patent regime will be effective in India from 2005. The science and technology surrounding new drug delivery systems (NDDS), the 5th International Symposium on "Advances in Technology and Business Potential of New Drug Delivery Systems" was organized by the Controlled Release Society, Indian Chapter (CRS IC), at the Sci-Tech Center, Mumbai on 16th - 17th February 2004. The symposium was cosponsored by SciTech Center, Lupin Ltd, Sun Pharmaceutical Industries, Colorcon Asia Ltd and Associated Capsules Group.

The symposium was inaugurated by Dr. D.B. Gupta, Chairman, Lupin Ltd., India, who emphasized the need for and market potential of NDDS. Mr. Himadri Sen, President of CRS IC, delivered the welcome address which highlighted the current areas of research in the field of NDDS. A presentation by Mr. Ajit Singh, Vice President, CRS IC, discussed the opportunities for exploitation of NDDS in India. Prof. David Triggle, State University of New York at Buffalo, presented a keynote paper on the influence of molecular biology on drug delivery. It was a privilege to have Professor Jennifer Dressman, President of the CRS, attend the symposium and address the audience. Professor Dressman of the Institute of Pharmaceutical Technology Biocenter, in Germany gave an overview of the activities and future plans of the CRS and also presented scientific papers on the development of *in-vitro* methods that predict *in-vivo* behavior of controlled release formulations. Professor Dressman's work showed that biorelevant dissolution tests could play a pivotal role in optimizing dosage form development and dosing conditions. She also discussed the strategies for dissolution enhancement of poorly soluble drugs by hot melt extrusion systems.

Dr. Vinod Shah of the Center for Drug evaluation and research, FDA, USA, discussed the regulatory aspects of NDDS with respect to safety and efficacy studies and the drug approval process. Dr. M. G. Kulkarni, of the Polymer Science and Engineering Group, National Chemical Laboratory, India, described the role of polymer architecture in developing commercial technologies for NDDS. He also discussed the design of non-infringing polymer architecture based on property performance relationships.

Dr. Gurvinder Singh Rekhi of Elan Drug Delivery Inc., USA, presented a talk on multiparticulate oral drug delivery systems along with their evaluation, IVIVC correlations and case histories. Dr. Amarjit Singh of Sun Pharmaceutical Industries Ltd., India, focused on targeted vesicular drug delivery systems. Dr Singh's presentation included some specific targeting principles such as the formation of a steric cloud around vesicles to control their distribution and the enhanced permeability and retention effects governing the accumulation of drugs in tumors. Dr Singh also shared his experience with H. pylori and anti-tumor targeting systems.

Dr. Nagesh Palepu of Hita Solutions, USA, presented a paper on the use of technologies designed for taste masking; chrono-modulation and gastro retention while Dr. Himadri Sen from Pharma Research and Regulatory affairs Department, Lupin Research Park, India, highlighted the intellectual property rights issues, regulatory approval process and the possibility of market exclusivity for patented drug delivery systems.

Mr. Manish Jain of Merrill Lynch, India, spoke on extended release and once daily formulations. He gave an overview of the market forces governing controlled and extended release formulations and their success in terms of sales, franchise growth and increased market share. Mr. Mark Pohl, a patent attorney from Pharmaceutical Patent Attorneys, LLC, USA, reviewed the various steps associated with the patenting process.

Panel discussions were coordinated by Dr. Gopakumar Nair, of G.K.Nair Associates, India, and focused on the regulatory affairs and business opportunities associated with NDDS.
The scientific program was organized by Dr. Padma Devarajan, Mumbai University Institute of Chemical Technology, Dr. Sushma Mengi, C.U.Shah College of Pharmacy and Dr. Mangal Nagarsenker, Bombay College of Pharmacy. Poster sessions were coordinated by Dr. Vandana Patravale, Mumbai University Institute of Chemical Technology and Dr. Mala Menon, Bombay College of Pharmacy. A record number of 104 posters were presented and the first prize was awarded to Ali J*, Arora S., Ahuja A., Khar R.K., Faculty of Pharmacy, Jamia Hamdard, New Delhi for a presentation entitled Formulation and evaluation of Buccoadhesive compacts of Carvedilol. The second prize was shared by Khan I.A.* Patravale V.B., Mumbai University Institute of Chemical Technology, Mumbai for a poster entitled SMET'S: A novel fast release dosage form and Meshram R.N., * Bajaj A.N., Mengi S.A., Mittal S., C.U.Shah College of Pharmacy, Mumbai for work on Pancreatin Microspheres in combination with Gastric acid inhibitors and in vivo assessment using chronic Pancreatitis animal model for site specific delivery.

The conference highlighted the advances in drug delivery technologies and how these advances may be used to realize improved therapeutic and economic benefits. The conference also offered a new perspective on the current understanding of the field of controlled release. Drug companies manufacturing excipients and accessories used in the formulation of NDDS exhibited their products and interacted with the participants at the venue as a total of 235 delegates from industry and academia attended the symposium. The vote of thanks was offered by Dr. Amrita Bajaj, Secretary, CRS IC and the Annual General meeting of CRS IC was also held on the evening of 16th February.

Dr. Amrita Bajaj
Secretary, Controlled Release Society, Indian Chapter

Nordic Chapter Update

by M. Brandl and A. Bauer-Brandl, University Tromsø, Norway and K. Luthman, University Gothenborg, Sweden

July 1st to 3rd 2004, Institute of Pharmacy, Tromsø
A joint three-day meeting was held between the Drug Transport & Delivery Group at Tromsø University and the Nordic Chapter of the Controlled Release Society entitled "Midnight Sun Meeting on Drug Transport and Drug Delivery". The aim of the meeting was to discuss current knowledge on the challenges associated with drug transport and potential ways to improve drug delivery. The meeting had more than 80 delegates from all over Europe and beyond and was hosted by the University of Tromsø at the recently established Institute of Pharmacy.

The Drug Transport Session commenced with Professor Per Artursson (University of Uppsala) reviewing the state-of-the-art in a talk entitled, Cell Culture Models for Absorption Studies, followed by Dr. George Imanidis (University of Basle) describing his research group's attempts on a correlation of phospholipid membrane order and dynamics with solute permeability. Gøril Eide Flaten (University of Tromsø) presented a new approach for measuring drug permeability across phospholipid membranes and Dr. Till Bussemer (Aventis Pharma Deutschland GmbH, Frankfurt) summarised his group´s experience on in silico tools for the prediction of physicochemical and biopharmaceutical properties of drug candidates. After lunch Professor Bente Steffansen (Royal Danish Pharm. University Copenhagen) introduced the audience to the field of tailoring prodrugs to peptide transporters and Dr. Jon Våbenø (University of Tromsø) presented his project on dipeptidomimetics as pro-moieties for hPEPT1 targeted prodrugs. Professor Gert Fricker (University of Heidelberg) rounded up the drug transport session with a review of drug delivery across the blood brain barrier. Thereafter the audience were able to discuss 20 scientific posters as well as look at a small industrial exhibition on materials, instruments and services relevant to the field. The first day was concluded by a welcome reception on the sunny terrace of the institute with seafood snacks and local jazz music by "Skansens Fotvarmere", generously co-sponsored by Lipoid GmbH (Ludwigshafen) and Thermometric AB (Järfälla).

The Phospholipids Session commenced with a review by Professor Gerard Hornstra (University of Maastricht) on the health benefits of phospholipids containing n-3 fatty acids. Morten Moe (University of Tromsø) presented a paper on the complete lipid structure characterization by low-energy tandem mass-spectrometry. Dr. Jürgen Zirkel (Lipoid GmbH, Ludwigshafen) reviewed phospholipids in pharmaceuticals and related phospholipid products in terms of their quality aspects and regulatory requirements.

During the lunch break Professor Arto Urtti presented the Controlled Release Society Nordic Chapter´s mission and planned activities.

The afternoon session was dedicated to solids as dosage forms. Professor Göran Alderborn (University of Uppsala) started out by giving an overview of the compression behavior of agglomerates and its significance for tablet properties. The next speaker, Dr. Ingunn Tho (University of Tromsø), focussed on the preparation of pellets by extrusion/spheronisation, with an introduction to the challenges and possibilities of pectin as a new excipient for this technique. Thereafter, Marianne Hiorth (University of Oslo), introduced pellets for colon targeting by immersion coating the pellets with calcium pectinate and chitosan. Professor Michael Newton (Professor emeritus, London School of Pharmacy) extended the pellet subject by inviting the audience to share his decades of experience in extrusion / spheronisation, describing intriguing material behaviour which is yet not fully understood. He pointed out that a deeper and more systematic understanding of materials´ properties is not only of great scientific importance, but also necessary for development and commercialisation. However, Newton noted that it was increasingly difficult to get these aspects covered within the short-term goals connected with industrial funding. Anna Körner (University of Lund) took a close look at the interaction of polymer-matrix with water, exemplified by macrogols of different molecular sizes and the effect on dissolution. The session then moved on to a closer look at the solid state properties of drug substances, first with Dr. German Perlovich (Russian Academy of Sciences, Ivanovo, Russia) who described the differences between racemates and enantiomers exemplified by ibuprofen, going into detail on the crystal structures and into crystal lattice energies, both revealed by calculation methods and by experimentally measuring crystal sublimation energies. Secondly, Professor Adamo Fini (University of Bologna) reported studies on different salts of diclofenac and their effect on the release from solid dosage forms. The session was concluded by Dr. Peter Johansson (Thermometric, Järfälla, Sweden) who presented an overview of the usefulness of isothermal microcalorimetry in pharmaceutical research and quality control

Midnight Sun Meeting Organizers, Kristina Luthman and Martin Brandl. Not pictured: Annette Bauer Brandl, Einar Jensen, and Erik Loevaas.

Midnight Sun Meeting auditorium

In the evening the delegates met for a social gathering on top of the mountain "Storsteinen" enjoying an excellent conference dinner kindly co-sponsored by Clavis Pharma (Oslo), Weifa AS (Oslo), Polypure AS (Oslo) and PROBIO Nutraceuticals AS (Tromsø) as well as the University of Tromsø. A perfect day was rounded up by the breathtaking view over the snowy mountains of Kvaløy and Ringvassøy behind the Tromsø-sound glistening in the midnight sun.

The next day's morning session on Drug Delivery started with Professor Arto Urtti (University of Kuopio) detailing the mechanisms of DNA delivery with liposomal and polymeric systems, followed by Holger Grohganz presenting details of his project on the sustained release of the peptide hormone Cetrorelix from vesicular phospholipid gels. Various other aspects of liposomal drug carriers were discussed by Professor Gerd Bendas (Univ. Bonn): liposomal targeting of endothelial cells", Ann Mari Sætern (Univ. Tromsø): camptothecin-in-liposomes" and Dr. Heinrich Haas

Chapter News continued on page 31

NEW FACES

Yvonne Perrie

After obtaining her B.Sc degree in Pharmacy from Strathclyde University, Glasgow, Scotland (1994), and completing her one year Pharmacy pre-registration, Dr Perrie commenced her PhD, entitled "Liposomes as a gene delivery system", under the supervision of Prof G. Gregoriadis in the Centre of Drug Delivery Research, The School of Pharmacy, University of London. In 1998, she was appointed as a Post-Doctoral Research Fellow within the University of London investigating the application of non-viral gene-delivery systems to DNA vaccines. Dr Perrie then joined Lipoxen Technologies Ltd in 1999, a newly formed drug-delivery company, with the key responsibility of developing their DNA vaccine delivery platform. In September 2000, she was appointed to her current position as a lecturer in Pharmaceutics and Drug Delivery in Aston Pharmacy School, Aston University, Birmingham, UK. Currently her research is focused on three main areas: formulation engineering of vaccine adjuvant systems for both conventional and DNA-based antigens; strategic development of liposome-based systems for the delivery of biopharmaceuticals and nucleic acid-based therapies; and thirdly enhancing the solubility and delivery of poorly soluble drugs. Within her teaching responsibilities, Dr Perrie is also interested in enhancing and applying novel learning methods to Pharmaceutical Education.

Yvonne Perrie

In addition to her roles within Aston University, Dr Perrie is currently a Director of the Academy of Pharmaceutical Sciences (APS) where her responsibilities have included APS Newsletter Editor (2002-2004). She is also Secretary of the UK and Ireland Chapter of the CRS which currently boasts over 270 members and organises around two popular symposia a year. Further to these roles, Dr Perrie is now looking forward to her new position on the CRS newsletter which looks to be an exciting and interesting commitment. ■

Scientifically Speaking continued from page 9

Meanwhile, the nanometre scale roughness of the SACS produced particles further aids the reduction of the available contact area between contiguous surfaces. These alterations to the physical properties of sub-10µm particles may significantly alter interfacial interactions, leading to optimisation of powder handling and deaggregation properties of active pharmaceutical ingredients.

Conclusions

The development of the novel particle engineering SACS process may provide a key advance in the control and management of inter-particulate interactions of sub-10µm drug particles through modification of their macroscopic (particle size and shape) and mesoscopic (surface topography) physical properties.

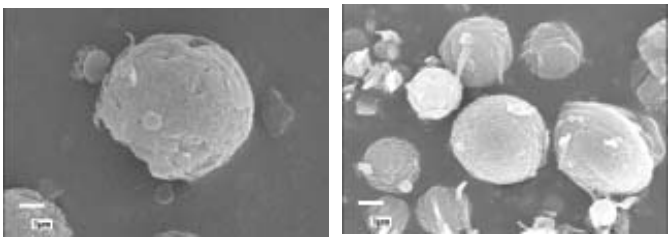

Figure 2a and 2b: electron micrographs of SACS processed (a) paracetemol and (b) sulfathiazole.

References

1. Kaerger, JS, Price, R. Processing of spherical crystalline particles via a novel solution atomisation and crystallisation by sonication (SACS) technique, Pharm. Res. 21: 372-381 (2004). ■

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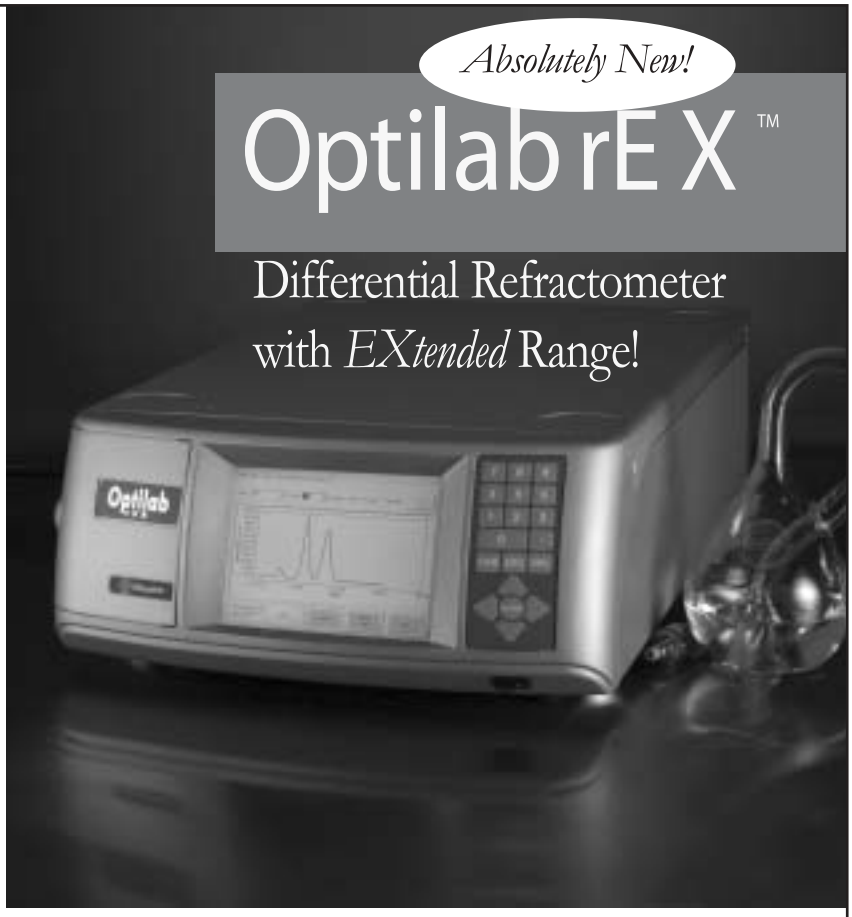

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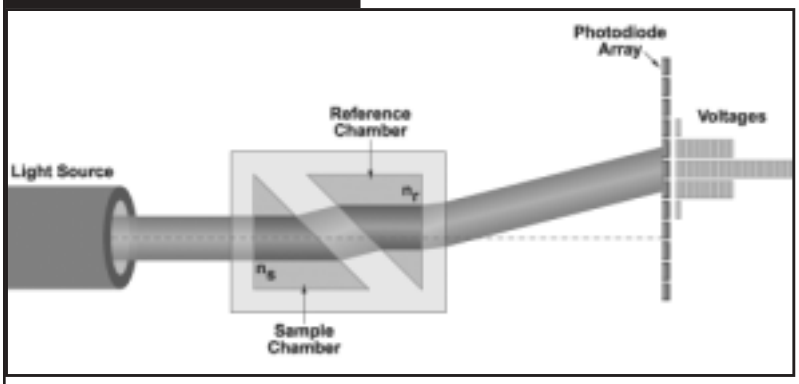

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InthetheNews

In the News
Development of GelSite drug delivery technology reported - Vaccine Delivery
NewsRxVaccines via NewsEdge Corporation : 2004 JUL 14 — At the 31st Annual Meeting of the Controlled Release Society (CRS), held in Honolulu June 12-16, DelSite Biotechnologies, Inc., a wholly owned subsidiary of Carrington Laboratories, Inc., (CARN), presented data describing properties of its novel GelSite polymer and the GelVac nasal powder vaccine delivery system.

The results reported continue to demonstrate the inherent advantages, flexibility, and uniqueness of the GelSite polymer, which has led the company to the development of ways to improve nasal and injectable drug delivery systems.

One set of data described the interactions of the GelSite polymer with different salts in solution and in gels, which are important for designing successful protein and peptide delivery platforms. The second presentation described studies showing that GelVac formulations conferred sustained antigen release and significantly increased serum IgG and lung IgA responses against inactivated influenza antigen in animal models.

The GelSite polymer is a proprietary, naturally occurring, high-molecular-weight charged polysaccharide that possesses a unique combination of chemical and functional properties, making it an ideal platform for delivery of proteins and peptides. GelSite is water-based and is capable of in situ gelation, i.e., changing to a gel upon contact with bodily fluids. The GelSite polymer is the basis for the company's GelVac intranasal powder vaccine delivery system.

Irish pharmaceutical company enters oral drug-delivery market
NewsRxVaccines via NewsEdge Corporation: 2004 JUL 14 — Merrion Pharmaceuticals, Inc., has entered the $25 billion oral drug-delivery market. The company will develop its own products and seek collaboration and licensing opportunities with pharmaceutical and biotechnology partners. Merrion was founded by Growcorp, an Irish life sciences venture capital group, to enable the acquisition of a comprehensive portfolio of drug-delivery assets from Elan Corp., plc. Michael J. McKenna, PhD, an experienced biopharmaceutical executive, has been chosen as Merrion's CEO.

Merrion has acquired a wide range of oral-delivery systems for use as enabling technologies for biotechnology products and as life cycle management tools for the pharmaceutical industry. The company's technology platforms include: penetration enhancers that improve the absorption of oral drugs through the gastrointestinal tract; gastroretentive technology to provide extended release of drugs from the stomach; and targeting molecules to enable oral vaccine delivery and to target drugs to the brain. Merrion has four products currently in phase I clinical testing.

Established in 2004, Merrion is a privately held, specialty pharmaceutical venture focused on novel, oral drug delivery. The company develops and manufactures technologies to meet the growing needs of the pharmaceutical and biotechnology industries. The technologies were originally developed by the Elan Biotechnology Research Center, which was founded in Dublin in 1994. Merrion's worldwide headquarters are in Wilmington, North Carolina. The company's R&D and manufacturing operations, Merrion BioPharma, Ltd., are located in Dublin, Ireland.

Treasure Mountain Holdings Announces It has Entered Into a Merger Agreement With Vyteris, Inc.
PR Newswire via NewsEdge Corporation: SALT LAKE CITY, July 8 / — Treasure Mountain Holdings, Inc. (OTC Bulletin Board: TMHI) announced today that it has entered into a definitive merger agreement with Vyteris, Inc., a privately held company. Under the terms of the merger agreement, a wholly owned subsidiary of Treasure Mountain will merge with and into Vyteris, upon which Vyteris will become a wholly owned subsidiary of Treasure Mountain. Under the terms of the merger agreement, it is contemplated that after Treasure Mountain takes certain post-closing actions, stockholders of Vyteris will own approximately 98.4% of Treasure Mountain's common stock. Under the terms of the merger agreement, upon closing, the directors and officers of Vyteris will become the directors and officers of Treasure Mountain.

The merger agreement is subject to several conditions, including the completion of a pending financing by Vyteris, approval of Vyteris' stockholders, satisfactory completion of due diligence and the receipt of fairness opinions by the board of directors of both Treasure Mountain and Vyteris. There can be no assurance that these conditions will be satisfied or that the merger will be consummated.

Vyteris, a Delaware corporation headquartered in Fair Lawn, New Jersey, has developed and produced a pre-filled, active transdermal drug delivery system that delivers drugs through the skin comfortably, without needles. On May 6, 2004, Vyteris received approval from the U.S. Food and Drug Administration to commercially launch its first product, the LidoSite(TM) Topical System. LidoSite is a topical delivery system indicated for use on normal intact skin to provide local anesthesia for needle stick procedures such as injections and intravenous therapies as well as superficial dermatological procedures. Vyteris has not yet begun commercial sales of its LidoSite product.

pH-sensitive toxins find application in vaccines and drug delivery - Vaccine Development
NewsRxVaccines via NewsEdge Corporation: 2004 JUL 7 — pH-sensitive toxins are finding application in vaccines and drug delivery. pH-sensitive toxins are secreted by bacteria and reach the cytosol of eukaryotic target cells by complex mechanisms involving receptor binding, membrane interaction, and translocation across a cell lipid membrane. Membrane interaction and ability to reach the cytoplasm have been used respectively to present proteins at the cell surface and to transport foreign peptides or DNA into the cytoplasm. The first approach is used in anticancer vaccination and the second in inducing a major histocompatibility (MHC) class I presentation of exogenous peptides or proteins," scientists in Belgium report.

"A brief overview of the use of toxins themselves for targeting cancer cells is also presented," said Veronique Cabiaux at the Free University of Brussels. "Altogether, the data suggest that pH sensitive toxins have a huge potential for surface presentation or cytosol transport of biomacromolecules and that many ways could still be explored to develop new strategies in vaccination or therapeutic methods."

Cabiaux has published a review article on the subject in Advanced Drug Delivery Reviews (PH-sensitive toxins: interactions with membrane bilayers and application to drug delivery. Advan Drug Delivery Rev, 2004;56(7):987-997).

Dermatrends announces patent related to transdermal delivery of broad category of amine drugs
CHEMICAL BUSINESS NEWSBASE - Minneapolis, MN, July 7: Dermatrends Inc has received a US patent that covers the method of using bases to enhance the permeation of amine drugs across the skin. The patent is the eleventh granted to Dermatrends, all related to its breakthrough technology in the field of transdermal patch drug delivery. It covers the very wide drug category of amine drugs, which includes a variety of compounds used to treat conditions ranging from Alzheimer's disease, to enlarged prostate, to acid reflux disease. To date, prescription drugs used in the treatment of these diseases have been available primarily in oral delivery format. Dermatrends' new US patent number 6,719,997 covers the use of hydroxide releasing agents with amine drugs. In its application, Dermatrends demonstrated that its base hydroxide-releasing agent was able to increase flux rates, or permeation. Widely prescribed amine drugs include donepezil and galantamine HBr, both used to treat Alzheimer's disease, and also the compounds tamsulosin, finasteride and dutasteride, all of which are used in the treatment of enlargement of the prostate. Another class of amine drugs includes proton

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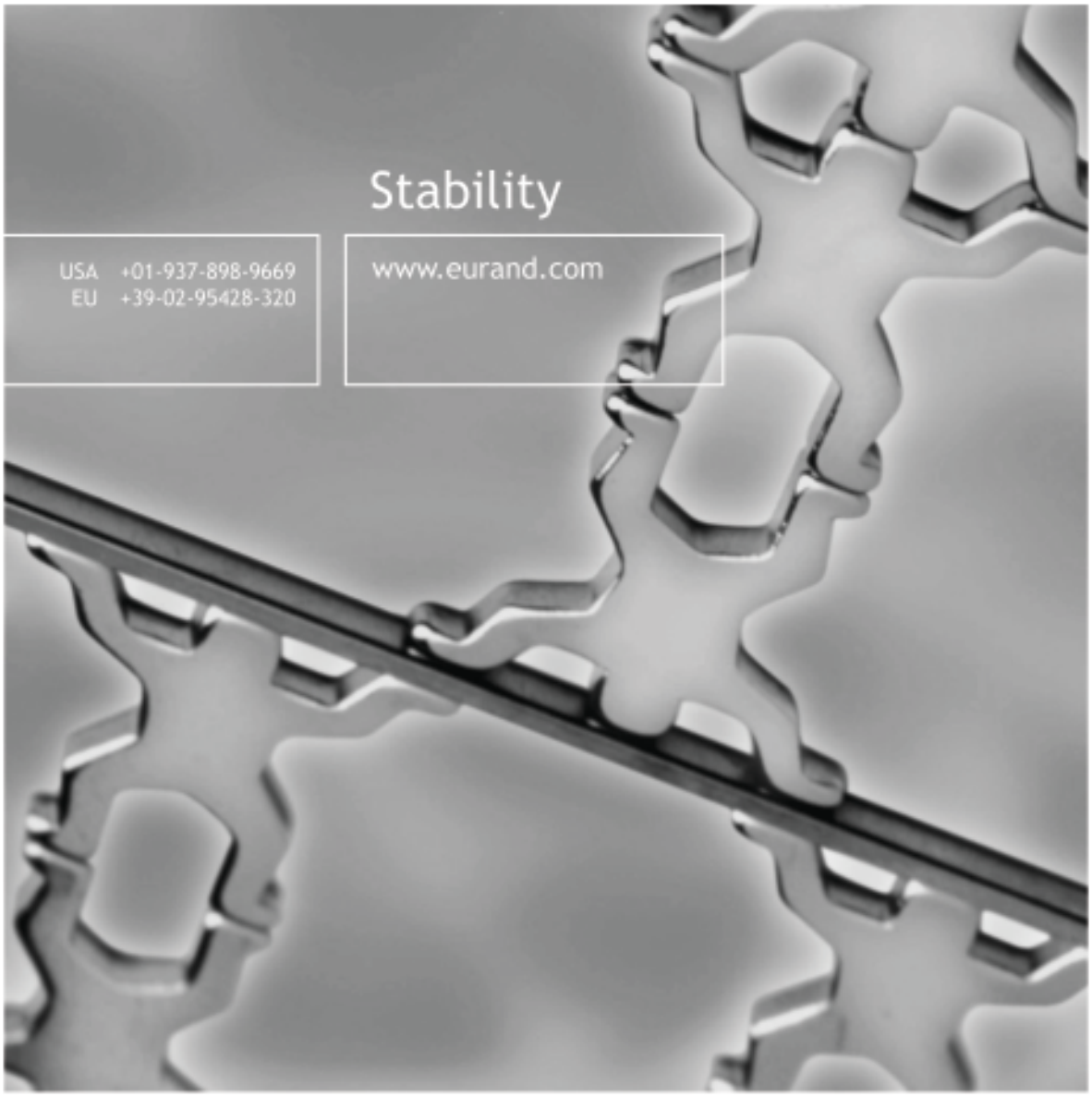

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pump inhibitors such as omeprazole, rabeprazole and lansoprazole, which are used to treat a form of acid reflux disease. Amine drugs also include compounds commonly used for pain relief, antidepressants, and amphetamines such as Ritalin. Dermatrends is currently working with pharmaceutical partners to bring its technology to consumers. Dermatrends Inc is a privately held medical research and development company based in Minneapolis, MN, with scientific laboratories in San Diego, CA.

DURECT Announces Positive Clinical Results With Its ORADUR(TM) Sustained Release Oral Gel-Cap Technology
PR Newswire via NewsEdge Corporation: CUPERTINO, Calif., July 6 — DURECT Corporation (Nasdaq: DRRX) announced the advancement of its ORADUR™ sustained release oral gel-cap technology (formerly referred to as the SABER™ oral gel-cap technology) with positive human clinical results for Remoxy™. Remoxy is a novel long-acting oral formulation of oxycodone based on DURECT's ORADUR technology under development by Pain Therapeutics, Inc., which is targeted to decrease the potential for drug misuse or abuse. On June 29, 2004, Pain Therapeutics announced the results of studies conducted in human volunteers in the United Kingdom to confirm Remoxy's anti-abuse properties and to assess the drug's pharmacokinetics.

Ultrasound could be used to get drugs to tumors - Drug Delivery
NewsRxCancer via NewsEdge Corporation: 2004 JUL 6 — Ultrasound scans might be most familiar for getting a peek at a developing fetus, but the technology could also be used to treat cancer. A partnership between the University of California (UC) Davis, Siemens Medical Systems and ImaRx, Inc., funded by a U.S. National Cancer Institute grant, will study ways to deliver drugs to tumors using focused ultrasound.

The plan is to put cancer-fighting drugs into tiny capsules that are injected into the bloodstream and can be steered to a tumor using ultrasound. Once there, the capsules target the tumor through antibodies or other molecules coating the capsule surface. They can also be burst open with a focused pulse of ultrasound.

"The idea is to locally concentrate the drug," said Katherine Ferrara, professor and chair of biomedical engineering at UC Davis and principal investigator on the grant. Many cancer drugs have toxic side effects. By concentrating the drug capsules in the tumor, the total dose of drug affecting the rest of the body can be reduced, she said.

UC Davis researchers led by Ferrara will carry out preclinical studies on the system. Siemens Medical Systems will design and build the imaging equipment, including developing ways to direct pulses of ultrasound to a three-dimensional volume. ImaRx, Inc., of Tucson, Arizona, makes the capsules for drug delivery.

QLT to broaden with acquisition of Atrix
CHEMICAL BUSINESS NEWSBASE - CHEMICAL AND ENGINEERING NEWS, June 30: Biotechnology company QLT is to acquire Atrix Laboratories in a share and cash transaction valued at $855 M. QLT has one approved drug, Visudyne. Atrix has Eligard (leuprolide acetate), approved for prostate cancer, and also brings with it the Atrigel sustained-release drug delivery system. Two other Atrix products are expected to reach the market in 2005: a sustained-release version of Eligard, and Atrisone, a topical acne product. Atrix had sales of $50 M in 2003 and has strategic alliances with companies including Pfizer, Novartis, and Aventis. It is expected to be profitable in 2004. Although QLT says it has branched out into dermatology, oncology, and urology, industry observers say the company is under pressure in its core area of ocular disease because of new drugs under development at Eyetech Pharmaceuticals, Genentech, and elsewhere.

OctoPlus Grants SurModics Access to Two Biodegradable Polymer Families for Medical Device Applications
PR Newswire via NewsEdge Corporation: LEIDEN, The Netherlands, June 29 — OctoPlus, a drug delivery and development company, announced today that it has granted SurModics, Inc. (Nasdaq: SRDX), a leading provider of surface modification and drug delivery solutions to the medical device industry, an option to acquire an exclusive license to two novel classes of biodegradable polymers for use in the site specific delivery of drugs from medical devices. The agreement is an important step for OctoPlus to accelerate the proliferation of its proprietary polymer platforms, through SurModics, in the development of drug eluting medical devices, for example, drug eluting stents.

The two polymer families covered under this agreement are PolyActive(TM) and OctoDEX(TM), which are currently under pre-clinical and clinical evaluation by OctoPlus for use as pharmaceutical drug delivery products. PolyActive(TM) is a biodegradable multiblock polymeric drug delivery system based on two well-known polymers. Its biodegradability, extensive safety record and tunable release properties make it an excellent choice for the controlled release of proteins and hydrophobic small molecule drugs. In particular, PolyActive(TM) has been used in thousands of patients as part of two FDA approved products, and has an existing FDA Master File. OctoDEX(TM) is a delivery system for the controlled release of proteins and large particles such as liposomes and antigens and is based on cross-linked dextran microspheres. OctoPlus recently reported successful completion of Phase I studies for a sustained release formulation of human growth hormone based on OctoDEX(TM).

DURECT Corporation and NeuroSystec Corporation Announce Exclusive Agreement to Develop Treatments for Certain Inner Ear Disorders Including Tinnitus
PR Newswire via NewsEdge Corporation : CUPERTINO, Calif., and VALENCIA, Calif., June 21 — DURECT Corporation (Nasdaq: DRRX) and NeuroSystec Corporation ("NeuroSystec"), a privately held company located in Valencia, CA, announced the signing of an exclusive agreement to develop, market and sell products for the treatment of certain inner ear disorders including chronic tinnitus (ringing in the ears). Under the agreement, DURECT granted to NeuroSystec exclusive worldwide rights to develop and commercialize products designed for the treatment of tinnitus and to improve post-operative recovery and tolerance of surgical implantation of cochlear devices using specified DURECT proprietary drug treatment methods and drug delivery technologies to deliver precise doses of appropriate medications directly to the middle or inner ear.

"DURECT's portfolio of innovative otologic drug treatment methods and drug delivery technologies and the groundbreaking tinnitus research already conducted by DURECT and its collaborators provide a compelling reason to believe that we will one day be able to offer an effective treatment for the millions of patients in the US and abroad who suffer constantly with this debilitating disease," stated Alfred E. Mann, Chairman of NeuroSystec. "Tinnitus is truly an unmet medical need affecting millions of people. We are very excited to work with DURECT to develop the first promising therapy under this agreement," added Dr. Stephen McCormack, President and CEO of NeuroSystec.

"Alfred Mann brings to this collaboration his impressive track record of vision and success at other companies he has founded such as Advanced Bionics, Minimed, Pacesetter, and Mannkind. We are delighted to have the opportunity to collaborate on such an innovative and meaningful venture with Mr. Mann, Dr. McCormack and their team at NeuroSystec," stated Felix Theeuwes, Chairman and Chief Scientific Officer of DURECT. "This collaboration demonstrates the strengths of DURECT's pharmacological research capabilities, as well as the breadth of applications for DURECT's drug delivery technologies, and we anticipate will create products that will offer hope to millions of tinnitus sufferers around the world," added James E. Brown, DVM, President and CEO of DURECT.

Antares Pharma Announces DPT Laboratories, Ltd. is Preferred Supplier of Transdermal Gel Technologies
PR Newswire via NewsEdge Corporation : EXTON, Pa., June 16 — Antares Pharma Inc. (OTC Bulletin Board: ANTR) and DPT Laboratories, Ltd. today announced a letter agreement between the companies whereby DPT will become the preferred development and manufacturing organization for Antares Pharma's transdermal gel products for clients referred to DPT by Antares Pharma.

Commenting on this agreement, Dr. Roger G. Harrison, CEO and President of Antares Pharma, said, "Initiation of this agreement

In the News continued on next page

meets one of our stated milestones for 2004. We believe that this arrangement will provide our current and future partners with an assured source of quality products for clinical evaluation and commercialization and will also encourage our future partners to view Antares Pharma as a company that can offer research, development and manufacturing of transdermal gel products. DPT was chosen based on their proven capability in this field, our positive experience in working with them and a shared belief in the value of opportunities for transdermal gel products."

Paul Josephs, Vice President of Sales and Commercial Operations for DPT, commented, "Antares Pharma is clearly one of the leading companies in promoting the use of transdermal gel technology as a viable alternative to other routes of delivery. As a leading supplier of gel products to the market, we look to these kinds of relationships to enable us to assure continuity in the value chain from development to production. We look forward to developing further business relationships of this kind."

Spherics, Inc. Begins Phase I Clinical Trial with Spherazole(TM), Bioadhesive-Based Itraconazole
PR Newswire via NewsEdge Corporation: LINCOLN, R.I., June 14 — Spherics, Inc. today announced it has started a Phase I clinical trial for Spherazole(TM) (itraconazole) an oral formulation of the antifungal agent that incorporates Spherics' proprietary bioadhesive technology. The study is the company's first clinical trial to evaluate the potential of its bioadhesive delivery technologies to improve the profile of itraconazole and other drugs.

Janssen's itraconazole, registered as Sporanox(R), is a widely used antifungal agent with estimated annual worldwide sales of over $500 million. An improved dosage form of itraconazole utilizing Spherics' technology can potentially offer unique benefits in terms of release rate control, reduced variability, improved safety profile and elimination of fasted-fed differences.

"Spherics has made great progress in advancing its oral delivery technologies and in building a pipeline of drugs where we can add substantial therapeutic value," said Ze'ev Shaked, Ph.D., President and CEO of Spherics. "This study is the first of several clinical trials we expect to begin in the coming months to establish the broad utility of Spherics' technology." The company's development pipeline includes oral formulations of Nanotaxel(TM) oral paclitaxel formulation, and other super generic drugs that can potentially benefit from applying Spherics' delivery approach.

Conor Medsystems and Biotronik Agree to Develop Bioabsorbable Drug Eluting Stent
PR Newswire via NewsEdge Corporation: MENLO PARK, Calif. and BULACH, Switzerland, May 27 — Conor Medsystems, Inc. and Biotronik AG today announced that they are entering into collaboration for the research and development of bioabsorbable drug eluting stent technologies. The new technology will combine Biotronik's unique absorbable metal stent (AMS) with Conor Medsystems' novel vascular drug delivery stent platform, enabling tailored drug release kinetics for the treatment of restenosis and other vascular disorders. Financial terms of the agreement were not disclosed.

"Through this exciting R&D partnership with Biotronik, we hope to develop what may be the first drug eluting absorbable metal stent platform," said Frank Litvack, M.D., chairman and Chief Executive Officer at Conor Medsystems. "This collaboration brings together Conor Medsystems' insight into next generation drug eluting stent technology with Biotronik's absorbable metal stent materials to spearhead an important new vascular technology breakthrough and a potentially significant contribution to the field of cardiovascular treatment."

Conor Medsystems' stent platform, designed for use in vascular drug delivery applications, consists of hundreds of non-deforming reservoirs that house and protect the drug, providing up to six times the drug dose capacity compared to surface-coated stents. The reservoirs are the key to tailored release kinetics for controlled drug release and targeted delivery, including spatial and directional control. The reservoirs have the capability to release a broad spectrum of drugs and polymers — including lipophilic and hydrophilic compounds and biologics. In addition, the Conor Medsystems stent can deliver multiple drugs with independent release rates and directionality. The company's novel COSTAR(TM) cobalt chromium paclitaxel drug eluting stent is currently under clinical investigation in multiple international clinical trials.

Biotronik developed its absorbable magnesium alloy stent (AMS) as an alternative to conventional metal stenting and to other absorbable polymer stents under development, which have limitations with recoil properties.

Novacaps Delivery System makes difficult combination drugs possible.
Chemical Business Newsbase, TAMPA, FL, May 27 - Innercap Technologies, Tampa FL, announces its multi-phase, multi-compartment capsule drug delivery system. The proprietary Novacaps delivery system accommodates otherwise incompatible pharmaceutical agents, solid or liquid, in a single-dosage, combination product. Surging worldwide interest in such combination formats is evidenced by the FDA's recent initiative to advance the development of single-dosage forms for delivery of multiple HIV/AIDS drugs. With the Innercap delivery system, therapeutic entities that have never been combined before can be administered together, via an oral or a suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This approach maximizes bioavailability and, at the same time, addresses patient-compliance problems that often plague multi-drug regimens. The Novacaps delivery system can be used for all therapeutic classes such as immunologic, cardiovascular, neurologic, psychiatric, oncologic, and pain management. Innercap Technologies is located in Tampa, FL. ■

CReators Controlled Release Education Articles on Technology Original Research and Science

From the Education Committee

Designing Controlled Release Formulation – A design project for chemical engineering seniors at Northwestern University

Professor Harold Kung, Northwestern University, USA

An education initiative was organized by Dr. Avinash Thombre, CRS Education Committee that involved exposing twelve seniors in chemical engineering at the Northwestern University, USA, to the principles of controlled release science and technology.

For ten weeks from January 5 to March 10, 2004, twelve seniors in chemical engineering at Northwestern University (Evanston, Illinois USA), working in three teams of four, explored the application of chemical engineering to controlled release drug delivery for their senior design project. A senior design project is part of their requirement for an undergraduate degree, and these students chose to expand their horizon in this new area not taught in a traditional chemical engineering curriculum. More specifically, the project was titled: "*Nothing to sneeze at - Design of a Controlled Release Pharmaceutical Formulation*". The teams were asked to design the dosage form based on pharmacokinetic principles and investigate several controlled release technologies such that the new formulation would require less frequent dosing and, thereby, improve patient convenience and compliance. They were to consider three different controlled release technologies (e.g., hydrophilic matrix tablets, osmotic tablets, coated multiparticulates filled in capsules, etc.) and recommend a development program for the new release formulation.

The project was formulated by Dr. Avinash Thombre at the Groton Laboratories of Pfizer Inc. (Groton, Connecticut USA), working together with Professor Harold Kung, the author. The project involved elements of both product and process design. The students were required to formulate specifications for their products in order to maintain a certain concentration of active ingredient in the plasma, a conceptual process to manufacture the product, and a development program to gather needed information for a complete process design.

Since few students had the background on drug delivery, an adequate introduction and a supply of relevant literature information were critical. This was accomplished in a lecture by Dr. Thombre on the steps in drug discovery and formulation. The lecture was supplemented with substantial reading materials, which were made available to the students in the library. Throughout the 10 weeks, the student teams met regularly with the instructor, and Dr. Thombre served as a resource person.

Based on their feedback, the students enjoyed the challenge of diving into a completely new field. They were pleasantly surprised that what they learned in chemical engineering kinetics and reactor analysis could be applied to analyze the uptake and distribution of drug in the body. Perhaps the most interesting part of the project was the challenge associated with the design of the release method. Initially, the students treated the project just like any standard textbook problem. They aimed at understanding the standard release technologies and analyzed the performance of each of these methods. However, with some prompting, they began to be innovative, and designed new methods that could best achieve the target specifications.

Overall, the students enjoyed their experience. They felt that they had learned a lot in the ten weeks. The instructors felt the same. Designing a controlled release method proved to be a highly educational topic. ■

CRS Education Committee sponsors inaugural symposium at Kings College London

Adam Watkinson, King's College London, UK

The CRS Education Committee jointly sponsored a half-day symposium held at the School of Pharmacy, Kings College London, UK on 4th March entitled "Industrial Perspectives on Drug Delivery". The aim of the symposium was to educate and raise awareness of controlled release science and technology to newly graduating pharmacists.

It is widely acknowledged that currently there is a worryingly low number of pharmacy graduates entering post-graduate education and the pharmaceutical industry in general. This may be due, in part, to increasing levels of student debt and the perception of rapid and high levels of remuneration for graduate pharmacists in community pharmacy relative to that available in other sectors. There therefore exists a need to inform, educate and raise awareness of the rewards that a career in the pharmaceutical industry can bring to newly graduating pharmacists.

As part of its remit for promoting education on controlled release science and technology to undergraduate and post-graduate students, the CRS Education Committee jointly sponsored a symposium held at the School of Pharmacy, Kings College London, UK. The half-day symposium was held on 4th March and was entitled "Industrial Perspectives on Drug Delivery". It included presentations from five leading industrialists with backgrounds in different areas of drug delivery. The speakers who kindly provided their time were Adrian Davis (GSK), Mike Hannay (IVAX), Dave Howlett (PharmaDelivery Solutions), Paul Gellert (AstraZeneca) and Ian Wilding (Pharmaceutical Profiles).

The areas of drug delivery that were covered included the topical, transdermal, pulmonary and oral routes and an overview of how these can be assessed in man. In addition to discussing the challenges of each of these routes of drug delivery from an industrial angle, the speakers used their time to inform the audience in a more general manner about what working in the industry was like.

The symposium was attended by approximately 40 students from the final year Drug Delivery Elective and was very well received. In subsequent feedback sessions many students commented on how interesting and useful the afternoon had been and even suggested widening the audience to include more of their final year colleagues. The symposium will be held again next year and may be expanded to a whole day, possibly including a chance for the students to present their course work either as posters or as short oral communications.

The symposium was organized and chaired by Adam Watkinson (Strakan Pharmaceuticals) who is a member of the CRS Education Committee and a visiting professor at King's College London and Marc Brown (Senior Lecturer in the Pharmacy Department, King's College London and Drug Delivery Elective Course Leader). The organizers gratefully acknowledge the sponsorship provided by CRS, Strakan Pharmaceuticals and MedPharm Ltd. ■

Patent Watch

By Ijeoma F. Uchegbu, University of Strathclyde, UK

A number of drug delivery patents have been granted over the last 12 months and a snap shot of this innovation is given below.

IMPLANTS AND DEVICES

Berkley Advanced Biomaterials (US 6,767,550) have patented an implantable hydroxyapatite based material for the controlled delivery of anti-cancer and gene therapeutics. The hydroxyapatite material is bioresorbable making it ideal for site specific controlled delivery.

A catheter capable of delivering drugs using ultrasonic energy (US 6,723,064) has been patented by Advanced Medical Applications, USA. The catheter is attached to an ultrasonic transducer and is capable of delivering drugs and ultrasonic waves to a patient's blood vessels for example.

A transdermal drug delivery device with improved storage stability (US 6,660,295) has been patented by Alza Corporation. This device is designed for non occlusive application and is contained within a sealed pouch together with a stabilizer such as a dessicant or oxygen scavenger.

LIPOSOMES

Liposomes for the oral delivery of drugs and bearing an enteric coating (US 6,759,058) have been patented by Western University, USA. These liposomes, which consist of phospholipids and an enteric coating material, are said to have enhanced gut stability and improved oral delivery parameters.

New amphiphiles which enhance the stability of liposomes are disclosed by Nutrimed Biotech, USA (US 6,699,499). Said amphiphiles consist of a hydrophilic unit or polymer and two or more hydrophobic units attached at spatially distinct regions. Liposomes bearing such amphiphiles may be used to deliver a range of bioactives.

OTHER PARTICULATES

A patent for the use of porous particles for pulmonary drug delivery (US 6,740,310) has been granted to the Massachusetts Institute of Technology, USA. Particles have a mass density of, for example 0.4 g cm^3 and a size of about 5μm. Particles containing a bioactive agent and made from a variety of biodegradable materials may be easily aerosolised for delivery to the respiratory tract.

The Massachusetts Institute of Technology, USA has also been granted a patent for stimuli responsive delivery particulates (WO 2004/056311). In response to endogenous stimuli the cross linked polymer particle degrades to release the bioactive agent contained within.

A method for the microencapsulation of DNA using solvent extraction (US 6,743,444) has been patented by the Microbiological Research Authority, UK. Microparticles are designed for the oral administration of DNA for vaccine or therapeutic purposes.

POLYMERS

Hydrogels formed form macromers comprising at least 4 polymeric blocks (US 6,639,014) have been patented by Alza Corporation, USA. Of the 4 polymeric blocks at least two must be hydrophobic and at least one hydrophilic. Macromers may be cross-linked to form hydrogels by a variety of means. The hydrogels may be used to coat tissues or to deliver drugs.

Nektar Therapeutics, USA has patented the use of multi-arm block copolymers for drug delivery (US 6,730,334). Each multi-arm polymer must have at least 3 copolymer arms covalently attached to a central unit and each of the copolymer arms comprises an inner hydrophobic and an outer hydrophilic segment. The central core and the inner hydrophobic segments of these multi-arm polymers may be used to entrap hydrophobic bioactives for their controlled release.

A patent for drug delivery polyamino acid vesicles (US 6,576,254) has been granted to the University of Strathclyde, UK. Polyamino acids bearing at least one hydrophobic and at least one hydrophilic group assemble into polymeric vesicles in the presence of cholesterol. These polymeric vesicles may be used for the delivery of a number of bioactive agents. ■

Journal of Controlled Release Highlights

by David. R. Friend
MicroDose Technologies, Inc., U.S.A.

Three papers being published shortly in the *Journal of Controlled Release* address interesting new developments in the field. The first paper reports on the drug release mechanisms of drug-loaded biodegradable stent matrices. The recent commercial success of drug coated metal stents may be expanded by the alternatives presented. Biodegradable stents offer some advantages over metal stents as noted by Venkatraman and coworkers who studied the ability of novel biodegradable stents composed to polylactides and poly(lactide-co-glycolide)s to release the drugs paclitaxel and rapamycin *in vitro* in a controlled manner.

Patches for drug delivery have traditionally been restricted to transdermal and buccal formulations. Recently however efforts to use this approach to improve oral delivery of macromolecules have been made. Whitehead *et al*. report the preparation and testing of a unidirectional intestinal patch capable of delivering insulin orally. The patches (about 2 mm in diameter and 500 μm thick) were designed to adhere to intestinal epithelium by using a combination of several known mucoadhesive polymers. *In vivo* observations suggest the patches are capable of adhering to the intestines of rats and can promote absorption of insulin through intestinal epithelium.

Lim and coworkers at the University of Utah are studying the use of regulatable fusion proteins capable of controlling the subcellular localization of plasmid products (for gene therapy). Using a ligand-based approach, it was possible to control trafficking of specific proteins into the cell nucleus in a dose dependent manner. The overall goal of this work is to develop a bi-directional on/off switch for control of subcellular targeting of therapeutic proteins. ■

Bouwstra continued from page 19

Dermatology and in 1998 she received the Heinz Maurer Preis fur Dermatologische Forschung. 12 PhD awards have been made based on the research carried out in Bouwstra's group. Despite being a prolific researcher, Bouwstra also enjoys teaching and as such she teaches physical pharmacy and transdermal drug delivery to students on the Leiden Biopharmaceutical Sciences course. Bouwstra also runs undergraduate practical classes in Drug Delivery Technology.

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6. Grams YY, Whitehead L, Cornwell P, Bouwstra JA. On-line visuatlization of dye diffusion in fresh unfixed human skin. Pharm. Res. 21: 851-859 (2004).
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Chapter News continued from page 21

(Munich Biotech, Neuried): *p*artition of Paclitaxel in Cationic Liposomes. After lunch, Professor Ijeoma Uchegbu (University of Strathclyde) gave an overview of the drug Delivery Opportunities arising from pharmaceutical nanotechnology. Dr Hendrik Fuchs (Charité, Berlin) showed how they successfully designed novel cleavable immunotoxins, targeted against squamous carcinoma cells. The final presentation was by Dr. Gerhard Pütz (University of Freiburg) who outlined to the audience how the apheresis-techniques may be used for elimination of liposomes from the blood.

At the end of the meeting an independent jury honoured Gerhard Pütz for the "best oral contribution given by a young scientist". The prize for the "best poster presentation" went to Leide Cavalcanti, Oleg Konovalov, (both European Synchrotron Radiation Facility, Grenoble France), Iris Torriani (State University of Campinas, Brazil) and Heinrich Haas (Munich Biotech AG, Neuried, Germany) for their contribution titled "Molecular organization of the hydrophobic anti-cancer drugs paclitaxel and ellipticine in lipid bilayer membranes"

The attendants´ feedback was enthusiastic and emphasized that besides experiencing the world´s northernmost university and the arctic summer, they mainly enjoyed the broad range of current pharmaceutical topics covered and the relaxed atmosphere of the meeting. A series of Mid-Summer Meetings on Drug Transport and Drug Delivery are planned by the research institutes in Scandinavia and the CRS Nordic Chapter. Professor Bente Steffansen announced that the Royal Danish Pharmaceutical University in Copenhagen would host the next meeting in the summer of 2006. ■

Biotherapeutics continued from page 11

is based on an important discovery that muscle tissues can take up polynucleotide genetic material, such as DNA or RNA, directly, without the use of viral components or other delivery vehicles, and subsequently express the proteins encoded by the genetic material for periods ranging from weeks to more than a year. In addition, Vical is developing other formulation and delivery technologies, including the use of lipid molecules, synthetic polymers called poloxamers, and other approaches, to enhance DNA expression or increase the immune response in DNA vaccine applications.

Recently, researchers at Chiron (Emeryville, CA) designed antigen delivery systems using charged polylactide co-glycolide microparticles. The polymeric microparticles with encapsulated antigens have become well established in the last decade as potent antigen delivery systems and adjuvants. Chiron has recently shown that an alternative approach involving charged polylactide co-glycolide (PLG) microparticles with surface adsorbed antigen(s) can also be used to deliver antigen into antigen-presenting cell populations.

Novavax's Novasomes™ are non-phospholipid vesicles: proprietary structures, made from amphiphiles, in which drugs or other materials can be encapsulated for delivery into the body topically or orally; currently being licensed as adjuvant carrier systems for a variety of vaccines. Alza Pharmaceuticals Corp. (Mountain View, CA) is using the company's Stealth liposome technology to deliver the anticancer agent Doxil (doxorubicin HCl) intravenously to tumor cells [7].

Two other areas showing promise are chronopharmaceutics and pulsatile controlled release. PULSYS™, an oral drug delivery technology being developed by Advancis Pharmaceutical Corp. (Germantown, MD), enables once daily pulsatile dosing. Amoxicillin PULSYS is designed to deliver amoxicillin at lower dosages over a shorter duration of therapy in a once-daily formulation. Advancis' preclinical studies demonstrated improved bactericidal effect for amoxicillin when delivered in a pulsatile fashion versus standard dosing regimens, even against resistant bacteria.

MicroCHIP's (Bedford, MA) innovative microchip delivery system, Figure 3, is being developed for use in the areas of pharmaceuticals, diagnostics, animal health, food and nutrition, and consumer products. Their patented technology is based on tiny silicon or polymeric microchips containing up to hundreds or thousands of micro-reservoirs, each of which can be filled with any combination of drugs, reagents, or other chemicals. Complex chemical release patterns of proteins, hormones, pain medications, and other pharmaceutical compounds can be achieved by opening the micro-reservoirs on demand using preprogrammed microprocessors, remote control, or biosensors.

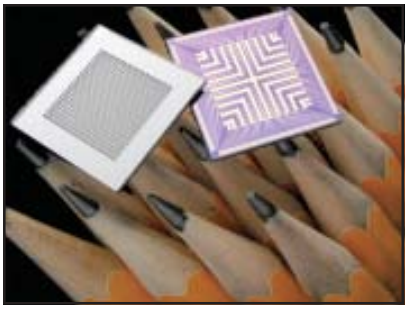

Figure 3. MicroCHIPS technology. The silicon chips contain reservoirs capped by noble metal membranes that open when electronically activated.

NanoMed is focused on using its core platform technology to develop novel nanoparticle-based advanced drug delivery systems that target drugs and vaccines to specific cells and tissues for the treatment of infectious diseases, neurodegenerative diseases, and cancer. A potential blockbuster application of NanoMed's core platform technology will be to deliver drugs to the brain. NanoMed has obtained in-situ blood-brain barrier (BBB) transport of two different types of nanoparticles (in four separate studies) with no adverse effects at the BBB and with uptake comparable to existing central nervous system (CNS) therapeutic agents [8].

Biotechnology, in its many current and potential applications, is the outcome of a revolution in the biological sciences that will affect every aspect of human existence. The applications of biotechnology are broad and have already brought impressive results in agriculture, human health and environmental concerns. The development of new drug delivery technologies, whether inhaleable, oral or transdermal, are offering noninvasive approaches to parental biotherapeutics. With several pulmonary insulin products currently in late stage human clinical trials, inhaleable systems are leading the market. Microneedles present an elegant and painless way to deliver medications through the skin. Gene delivery and nanotechnology, while still in their infancy, are showing great promise in the development of advanced delivery systems and the growth of this industry. We have much to look forward to in the upcoming years.

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   West Pharmaceutical Services, Inc.: www.westpharma.com
   Nastech Pharmaceutical Company, Inc.: www.nastech.com
   Chrysalis Technologies, Inc.: www.chrysalis-technologies.biz
   Acusphere, Inc.: www.acusphere.com
   Epic Therapeutics, Inc.: www.baxterdrugdelivery.com
   Cydex, Inc.: www.cydexinc.com
   Alkermes, Inc.: www.alkermes.com
   Vical, Inc.: www.vical.com
   Chiron Corporation: www.chiron.com
   Alza Corporation: www.alza.com
   Advancis Pharmaceutical Corp.: www.advancispharm.com
   MicroCHIPS, Inc.: www.mchips.com
   NanoMed Pharmaceuticals, Inc.: www.nanomedpharm.com ■

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