CONTROLLED RELEASE SOCIETY

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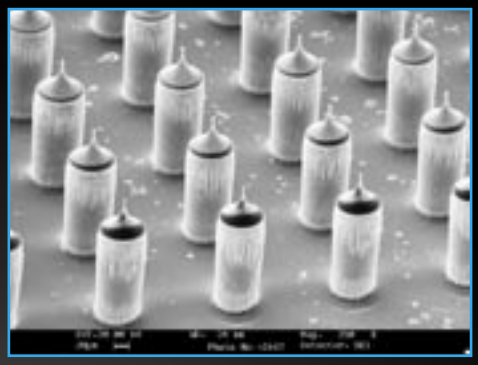
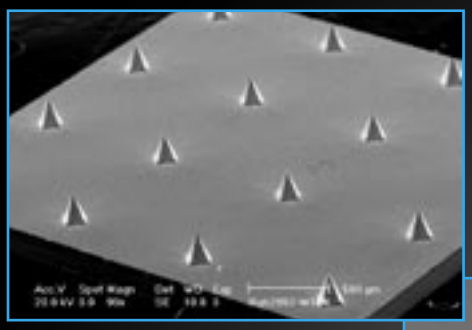
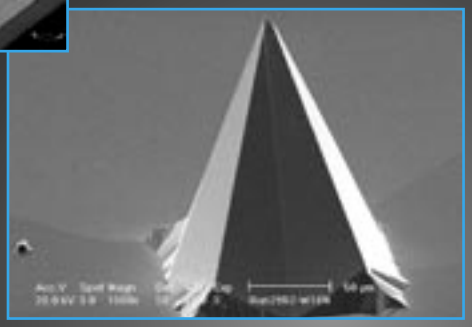
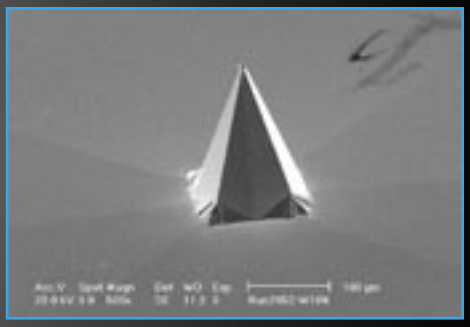
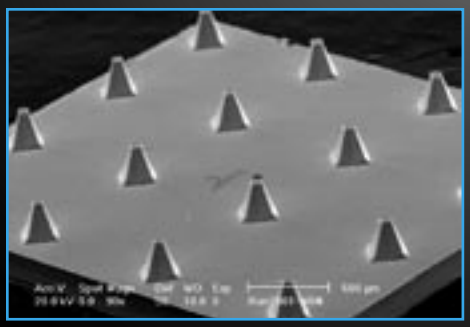
NEWSLETTER

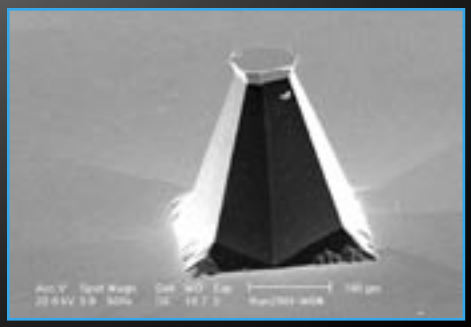












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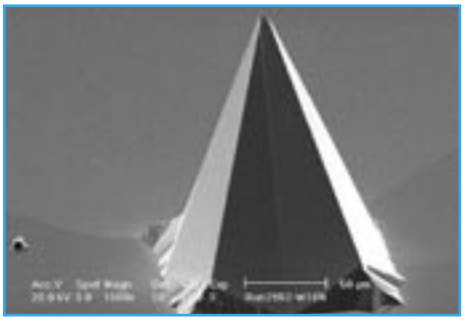

Microneedles presented by James Birchall during a recent UKICRS meeting.

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FROM THE *Editors*

by Bozena B. Michniak
IMDNJ-NJMS, USA

By now we are well into the new year and hopefully 2005 is going well for all of you professionally. Our new Editorial team is on board with Yvonne Perrie from Aston University in the United Kingdom, Steve Giannos as Industrial Editor, and Amy Lemmon as our new Managing Editor. We were sad to see Ijeoma Uchegbu leave the co-editorship at the Newsletter and we will miss her. I would like to take this opportunity to thank her for all the hard work during her tenure here and wish her well with all her new endeavors.

The abstract deadline is now past and we are preparing actively for the 32nd Annual Meeting & Exposition in Miami. An exciting program is being planned. Make sure to check out the PowerPoint™ slide show on the Website, http://www.controlledrelease.org/meetings/miami/index.cgi. The Plenary Sessions include three outstanding contributors, namely Sir Harold Kroto (University of Sussex, United Kingdom) addressing issues in nanotechnology, Robert Langer (MIT, US) on drug and tissue engineering, and Judah Folkman (Harvard University, US) on angiogenesis in cancer. Four mini Symposia have been planned and include: Bioinformatics Approaches to Drug Delivery and Targeting; Cell Culture Models of Biological Barriers; Molecular Targeting to Treat Disease, and Novel Characterization Tools for Drug Delivery Materials and Systems. The Soapbox and Pearls of Wisdom sessions are included again this year and I think we all look forward to the sunny Florida venue as well as a scientifically-stimulating conference this June. See you in Miami!!!

Meanwhile, in this issue of the Newsletter there are some interesting articles, namely one from Salvona Technologies, Inc. discussing the use of novel nanospheres providing a multi-component controlled release system, and Polytherapeutics, Inc. PharmaDur™ technology.

On another note, the CRS Newsletter strives to gather and present to you the best and most timely news in the drug delivery arena. I always notice how many new members join the Society and many of them are junior scientists. I am addressing the younger audience here, particularly the students, post docs, and junior scientists in academia and industry….. we would like to hear from you. Please think of some suggestions on areas of interest to you that could be covered in the Newsletter. We also need volunteers to submit reports from other professional conferences of interest to our CRS community and also full-length stories about completed research and development and the national and international accomplishments of our members. Email contributions to the CRS website and any comments/ suggestions to Bo Michniak at michnibb@comcast.net. Newsletter author guidelines are available at http://www.controlledrelease.org/publications/authorguide.cgi.

From the *President*

by Jennifer Dressman
Johann Wolfgang Goethe University, Germany

On behalf of the Board of Directors, I would like to extend our personal invitation to attend the Annual Meeting and Exposition to all CRS members. This year promises to be an active and progressive year for the CRS. We are actively building on our educational initiatives with special programming planned again this year for the Annual meeting as well as construction of the virtual library, which will be accessible to all members and is expected to be a rich source of information and visual aids. Further, through the efforts of our Local Chapter liaison, Ajit Singh, we will be establishing the infrastructure necessary to facilitate better information sharing among the local chapters.

Another important area of activity for the Board has been to take measures 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 professional and research goals. Art Tipton and the Finance Committee are working hard to optimize our cost/benefit ratio, while Joe Fix and the Marketing and Development Committee are continuing their efforts to expand our sponsorship.

Once again, we have a great program in place for the Annual Meeting & Exposition (please visit the CRS website at www.controlledrelease.org for more details) and, due to the attractive and easily accessible location, we are looking forward to a record attendance. ***Please register soon for the Annual Meeting and Exposition in Miami, Florida from the 18th to the 22nd of June.*** As most of you will have heard, Florida was pounded by several hurricanes in August/ September of 2004. However, we have been assured that our dates for 2005 are too early for tropical storms to pose a threat to our meeting.


Jennifer Dressman, President

Especially strong this year at the Annual Meeting will be the Exhibition, with most of the important players in the drug delivery and controlled release fields represented. A new benefit for attendees is the availability of lunch in the Exhibition area on both Monday and Tuesday. Please take the opportunity to eat lunch, browse the exhibits, surf websites or pick up email in the Internet café, and visit the recruiting booths to find out where the hottest jobs are being offered.

For those considering bringing the family to the Annual Meeting & Exposition, the convention hotel, the Fontainbleu Hilton, is an especially attractive destination, with its huge pool network and direct access to a gorgeous, sandy beach. Like last year, there will be a children's program available at the convention hotel.

We look forward to greeting you personally at the Annual meeting.

Wishing you all a productive and successful 2005.

Jennifer B. Dressman

Jennifer Dressman

From the Scientific Secretary

by Martyn C. Davies
University of Nottingham, United Kingdom

Martyn C. Davies, Scientific Secretary

The Controlled Release Society is again hosting the Annual Meeting and Exposition on a beautiful beach - specifically Miami Beach, Florida. Just reading the word "beach" makes me want to attend, especially with the cold, damp English weather outside! You'll want to attend, too, after you've read what's scheduled.

There were a flurry of abstracts that were submitted by the 31 January deadline. It does make the review, placement, and planning process an arduous and very important one. The Programme Chairs have their fingertips on the pulse of what's new and innovative and have designed an outstanding scientific meeting for you. Many thanks to Bioactive Programme Chairs Edith Mathiowitz, Claus-Michael Lehr and Jeff Cleland; Consumer & Diversified Products Programme Chairs Irv Jacobs and Cathy Ludwig; and Veterinary Programme Chairs Terry Bowersock and David Brayden on a job well done!

You'll want to arrive Friday night, so Saturday and Sunday you can network and attend one of the three Educational Workshops in Miami, which are: Colon Targeted Drug Delivery, chaired by CRS President Jennifer Dressman; Drug Eluting Stents: Clinical Need and Technology Solution, chaired by Syed Hossainy and Bob Falotic; and Micro and Nanoencapsulation: Formulation and Process, chaired by Chris Soper and Niraj Vasishtha.

The weekend continues with the Young Scientist Workshop, again ably organised by Mike Rathbone, along with Farid Dorkoosh, has a great range of speakers to educate and mentor the scientists of the future. On Sunday there will also be the Soapbox Sessions, the Releasing Technology Workshops, and the first of the Pearls of Wisdom Sessions, chaired by Hamid Ghandehari. The day closes with the Opening Reception in the Exhibit Hall.

CRS is honoured this year to have three internationally-renowned Plenary speakers who will engage the audience and share their expertise in Nanotechnology - Nobel Prize winning Sir Harry Kroto, Drug and Tissue Engineering: Past and Future - Robert Langer, and Angiogenesis in Cancer - Judah Folkman. CRS draws members from all over the globe, and the speakers you'll hear in June are no different; hailing from over a dozen nations.

Be sure to take part in one of the four Mini Symposia Monday-Wednesday. Mini Symposia presentations on Bioinformatics Approaches to Drug Delivery and Targeting, Cell Culture Models of Biological Barriers, Molecular Targeting to Treat Disease, and Novel Characterisation Tools for Drug Delivery Materials and Systems will peak your interest and cause much discussion.

For the Young Scientists, the Get Up-Get Educated Sessions on Monday and Tuesday are just what you're looking for. Mike Rathbone and the Education Committee are pleased to have Vince Lee and Steve Schwendeman presenting at these informative, get-the-day-started-off-right sessions.

The main scientific sessions boast over 25 invited speakers with many contributed papers. When you make your personal session choices in Miami consider the Combination Chemotherapy session. This is being co-sponsored by the International Liposome Society. Remember the joint Veterinary-Bioactive Materials session: Transdermal Delivery Challenges for Delivery in Human and Animal Health and the joint Consumer and Diversified Products-Bioactive Materials session Nanoparticle Technology. There truly is something for everyone at CRS!

The CRS is known for presenting new ideas and sessions at the Annual Meeting and Exposition, and 2005 will be the introductory year for the all new Industrial Session chaired by Susan Cady which should appeal to industrial CRS members with a bigger focus on the business of drug delivery. The Exhibit Hall will be crowded with the companies you want to see beginning Sunday evening through Tuesday afternoon. Plan carefully so you can do everything - attend oral and poster sessions, purchase equipment and services that are high on your wish list, and catch up with colleagues from around the world.

Mark your diaries now for the event of your summer - the 32nd Annual Meeting and Exposition of the Controlled Release Society.

CRS membership has many valuable benefits, and one of the best is the fact we can all register for the Educational Workshops and Annual Meeting and Exposition at reduced rates. The gold coast of Florida is where we'll be in June; see you in Miami! ▪

Scientifically Speaking

By Yvonne Perrie, Vincent Bramwell, Daniel Kirby, Anil Vangala, and Sarah McNeil
Aston University, United Kingdom

The Potential of Particulate Delivery Formulations for Protein Subunit Vaccines On Adjuvants and Delivery Systems

Emphasis upon particulate delivery systems for protein subunit vaccines is derived from increased safety in comparison to live vaccines and the need for enhanced immunological activity of often poorly immunogenic but otherwise promising vaccine candidates. In relation to the mechanism of adjuvant action of particulate delivery systems, there is the question of how the quality of the immune response relates to protection against a particular pathogen and, therefore, how this is or can be influenced by the delivery system. It is thought that induction of immune reactivity depends upon antigen reaching and being available in lymphoid organs in a dose-and time-dependent manner and that antigen that does not reach lymphoid organs is ignored by immune cells[1]. It has been suggested that antigen kinetics, load, and distribution are different for pathogens and model antigens and that this also contributes to the effective immune responses initiated against pathogens in comparison to a soluble antigen[2]. Facilitation of effective antigen delivery to draining lymph nodes is therefore potentially a highly desirable facet of candidate vaccine particulate delivery systems and biodistribution, including depot effect and antigen kinetics, likely play a highly important role in the mechanisms of adjuvant activity of particulate delivery systems (Figure 1).

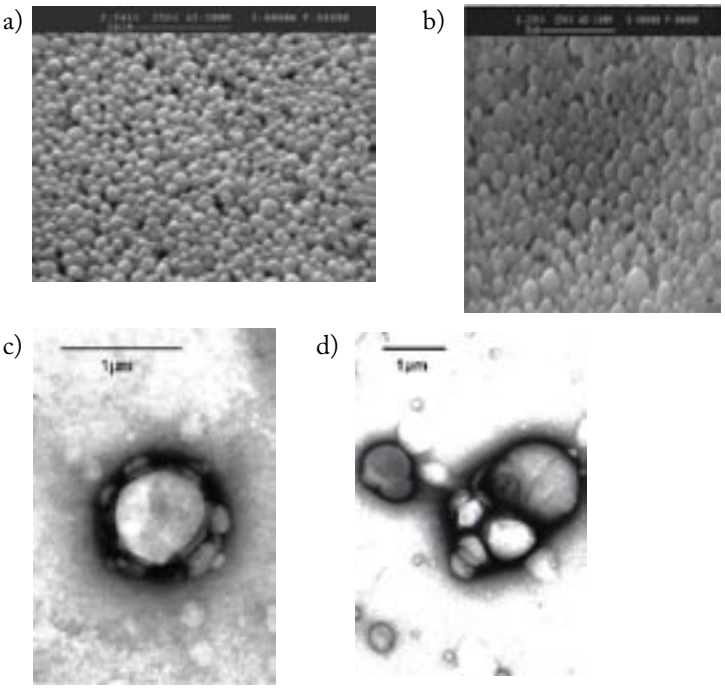

Figure 1. Examples of particulate delivery systems in vaccine design.
a) Scanning electron micrograph (SEM) of polycaprolactone microspheres formulated using water-in-oil-in-water (W/O/W) emulsion techniques, approximate size 1-2µm;
b) SEM showing similar microspheres formulated using PLGA;
c) Transmission electron micrograph (TEM) depicting a noisome prepared by the DRV method using the non-ionic surfactant, 1-Monopalmitoyl- rac-glycerol (Monopal);
d) TEM showing liposomes prepared, again by the DRV method, incorporating distearoyl phosphatidyl choline (DSPC) with cholesterol.

Despite the elucidation of Toll-like receptor (TLR) ligands from a diverse range of microbial sources[3], observations largely counter TLR involvement in the generation of immune responses by many adjuvants, including PLGA and other particle-mediated antigen delivery systems – it is thought that the range of receptors required would be unfeasibly numerous[4]. However, the use of co-adjuvants in delivery system formulation may facilitate the involvement of these pathways.

The major mechanisms of adjuvant activity postulated for particulate delivery systems are tabled below:

Table 1.
Particulate delivery systems: Mechanisms of adjuvant activity.

Mechanism of action	Delivery system
Up regulation of antigen presentation (signal 1)	Niosomes, PLGA[4]. Lipid vesicles[5].
Increased antigen uptake and localisation to lymph nodes	DRV liposomal DNA[6]. Liposome-encapsulated peptides[7]. Polymer micro- and nano-particulate delivery systems.
Cellular distress (signal 0)	Oil emulsions, surfactants, aluminium salts.
Depot effect	Oil emulsions, alum, gels, polymer based particulates, liposomes[7].

Oil emulsions, adjuvant vesicles (for example those used by Holten-Andersen et al. for the delivery of tuberculosis subunit vaccines[8]), liposomes, and niosomal delivery systems are all highly amenable to the inclusion of co-adjuvants that could increase mechanisms of adjuvant action to include TLR signalling. Evidence for the potential of this approach is highlighted by improved uptake by target cells facilitating enhanced activity of CpG motifs (that bind with TLR 9) mediated by liposomal entrapment[9] and a similar strategy for enhancing immune responses to intradermally administered dendritic cell targeted peptides[7].

Interestingly, the recent identification and interest in TLR function in host immune responses has led to the implication of these mechanisms in pathogen immune subversion such as TLR-induced immunosuppression (IL-10 release through TLR2), blockade of TLR recognition, and TLR-mediated induction of viral replication[10] in much the same way as invading organisms have been shown to

subvert other immune response elements that normally protect the host from succumbing to disease. Examples of these are the production of homologous cytokines or cytokine receptors, interfering with antigen presentation, and blocking apoptosis. In light of recent discoveries involving pathogen- associated molecular patterns (PAMPs) at least one of these mechanisms of immune evasion implicates TLR function. Therefore, the discovery and elucidation of TLR function has transformed the way in which we view the host-pathogen interface, giving a more comprehensive (if more complicated) view of immunological events and pathways. Pathways specifically involved in immune responses against complex pathogens such as *Mycobacterium tuberculosis* are mediated by a number of TLR interactions[11]. In addition to microbial interaction and intervention, a number of agents that can be used as adjuvants have been associated with specific TLR involvement in the initiation and qualitative direction of immune responses. A list of TLRs implicated in the function of specific adjuvants is listed in Table 2.

Table 2. *Selected adjuvants recognised by TLRs.*

Adjuvant / Moiety	TLR designation
dsRNA / Poly I:C (synthetic dsRNA analog)	TLR 3
Monophosphoryl lipid A (MPL) / Synthetic lipid A mimetics	TLR 4
ssRNA / Guanosine analogue, Loxoribine	TLR 7
CpG DNA motifs	TLR 9

Signal transduction events mediated by TLR molecules share a number of adaptor molecules both within the TLR family and with other immunologically important molecules (such as the IL-1 receptor and the TNF receptor superfamily) mediating intracellular signalling leading to crucial events such as dendritic cell maturation and inflammatory cytokine production[12] and implicating activation of NF-κB.

Continuing identification of TLR ligands and the involvement of specific moieties in immune activation via TLR-induced events has stimulated much research into the development of these moieties and their synthetic analogues as vaccine adjuvants[13] and, in addition, stimulation of TLRs in conjunction with other adjuvants (such as muramyl di-peptide (MDP)) can provide a synergistic effect.

Thus, delivery systems function in ways that can be perceived to be distinct from other adjuvants with a defined immunological interaction. In addition to this, there is an increasing body of research that supports the tenet that different mechanisms of adjuvant activity can engender additive or even synergistic effects. This includes the combination of delivery system technology with known TLR ligands as well as adjuvants that have other mechanisms of action, such as surface active agents. These recent developments validate and encourage the characterisation of the mechanisms of adjuvant action in order to elucidate the rational design of candidate vaccine formulations suitable for the delivery of protein subunit antigens and highlight the importance of the full evaluation of the increasing understanding of complex immunological interaction and pathways as an adjunct to, rather than a replacement of, our present understanding of carrier system technology for vaccine delivery. The potential of particulate delivery systems in vaccine design is comprehensively reviewed elsewhere[14].

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SPOTLIGHT:

Polytherapeutics, Inc.

by Kishore R. Shah
Polytherapeutics, Inc., USA

Topical application of therapeutic agents on the human body for either local or systemic activity has been practiced for ages. However, retention of the formulation at the site of application is a commonly experienced problem. Both mucosal and skin dosage forms are subject to natural removal from the site of application within varying periods of time. Instillation of drops of aqueous medications to eyes dramatically illustrates this problem. The short residence time severely limits drug bioavailability and the user's convenience and compliance. In order to address these and other issues a novel bioadhesive drug delivery system[1,2] (PharmaDur™), having unique controlled release properties, was developed at Polytherapeutics (PTI). The present author founded PTI and established an R&D laboratory in New Brunswick, NJ in 1997.

The mission of PTI is to conduct research and development of high value added and patent protected technologies and health care products targeted at meeting significant unmet or inadequately met customer/consumer needs to enhance their quality of life. The current focus of PTI is commercialization of its PharmaDur™ drug delivery technology, which is based on graft copolymers having a hydrophilic acrylic main chain containing carboxyl functionality and hydrophobic polystyrene graft chains (Figure 1). The PharmaDur™ copolymer that has been the subject of most of the development to date is poly(N,N-dimethylacrylamide-co-acrylic acid-co-polystyrene ethyl methacrylate). The copolymer exhibits microphase separation with a hydrophilic/hydrophobic domain system. The structural and morphological features of the copolymer determine its unique physical properties. It is water insoluble but can absorb ~ 20 times its weight of water in an aqueous environment to form a swollen hydrogel. The copolymer is not crosslinked; therefore, it is soluble in many organic solvents including pharmaceutical excipients and can be formed into desired shapes under the influence of heat and pressure.

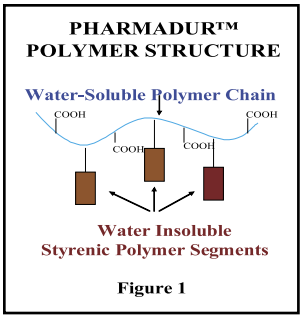

Figure 1

The copolymer exhibits a unique combination of bioadhesion and controlled drug delivery capability[3]. It can provide sustained release of both water-insoluble as well as water-soluble active agents for an extended period of time in the biological environment. Release profiles of water-insoluble clotrimazole (Figure 2) and water-soluble nonoxynol-9 (Figure 3) under sink conditions exemplify the drug delivery capability of the PharmaDur™ copolymer system. The duration of drug release can be tailored to occur within a period of hours to days, by judicious formulation variations, to satisfy the therapeutic requirements and patient convenience.

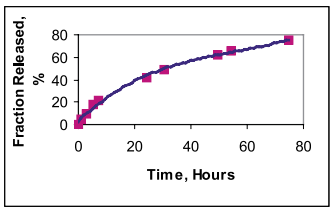

Figure 2: Clotrimazole release in 1:1

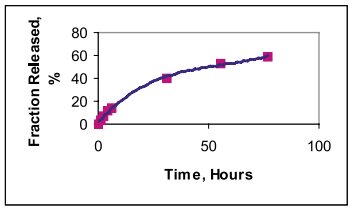

Figure 3: Nonoxynol-9 release in normal saline
PEG 400:Water solution

The copolymer forms very interesting vehicles in both aqueous as well as non-aqueous media for drug delivery. For example, a solution of the polymer in a non-aqueous water miscible solvent, such as lauryl lactate or ethoxy diglycol, forms a highly water-swollen but water-insoluble, mucous-like hydrogel upon equilibration in an aqueous environment. The in situ formed hydrogel exhibits a strong adhesion to the surface, such as mucosal membranes and skin, on which the gel formation occurs. Excellent bioadhesion of PharmaDur™ permits retention of its dosage forms for an extended period of time. The combination of the bioadhesion and its controlled release property is very useful in the development of formulations for mucosal drug delivery.

Although the polymer forms a water-insoluble hydrogel in water, it was discovered that the PharmaDur™ hydrogel can be homogenized to form a very stable dispersion, which is almost solution like and has a slight bluish haze. The copolymer appears to function as a polymeric emulsifier in such aqueous dispersions. Examples of compounds with which milk-like emulsions have been formed, without any added oil and/or surfactants, include steroids, miconazole nitrate, metronidazole, zinc oxide, and titanium dioxide. Thus, an aqueous dispersion of the copolymer provides a useful means for "solubilization" of water-insoluble drugs.

Bioadhesive PharmaDur™ copolymer has applications in mucosal (ophthalmic, vaginal, nasal, oral, and rectal), dermal, and transdemal drug delivery. Formulation of actives with PharmaDur™ can significantly improve performance of the active. The key areas of performance improvement consist in providing long-lasting effectiveness of the active (improve drug bioavailability) while minimizing or eliminating the toxic or undesirable side effects, and enhancing the user convenience/ compliance due to less frequent application needs.

Spotlight continued on page 18

Pharm News
Veterinary Controlled Release Activities at Miami 2005

by David Brayden
University College, Dublin

The veterinary committee has sourced two high profile speakers for the session entitled "*Transdermal delivery – Challenges for delivery to human and animal health.*" This continues the policy of joint programming for human and animal health researchers, which we began in Hawaii with our "*Human and animal models for peptide delivery*," symposium.

The first invited speaker is Dr. Gregory Glenn of the renowned Walter Reed Army Institute of Research and Iomai Corporation, Washington, DC. He will speak on the topic of non-invasive transcutaneous immunisation of mice and humans using topical application of ADP-ribosylating adjuvants and antigens. Dr. Glenn pioneered this technology and, amongst his numerous publications, has had a Nature paper on skin immunisation with cholera toxin. Since then, he has used non-toxic mutant toxins and a host of disease antigens. Recently his group obtained significant proof-of-principle immune data in man using heat labile enterotoxin and ETEC antigens on the skin. Their current work is to advance the hypothesis that skin immunisation with immunomodulators can increase subsequent responses to injected vaccines in subjects with a high vaccine failure rate. This could well have application to the elderly undergoing flu vaccinations or to cohorts of disease populations. Of interest to the vets is a paper by Dr. Glenn and his colleagues showing skin immunisation in a range of animal species (Hammond et al, 2000, Transcutaneous immunization of domestic animals: opportunities and challenges. Adv. Drug Deliv. Rev. 2000, 43(1):45-55).

The second speaker is Dr. Ron Baynes of the College of Veterinary Medicine at North Carolina State University. Dr. Baynes has experience using a swine skin model for testing transdermal uptake of both human and veterinary drugs. Together with his colleague, Jim Riviere, he also has an interest in the emerging field of assessment of the skin penetration of environmental and industrial plant-derived toxins, which has applications for the health of man and animals. Recently, Dr. Baynes published an important paper on how topical anti-parasitic avermectins penetrate the skin of a range of production animal species to different degrees and that this was largely dependent of the co-formulated excipients. This session will also be accepting selected transdermal podium papers from registrants interested in either human or veterinary applications.

At Miami, there will also be a social get-together of all attendees with an interest in veterinary controlled release. As in the past, this will be sponsored by Interag (New Zealand) and we are grateful for their continuing support. ▪

CRS 2005 Election

With over 20% of the 2005 membership participating in the election of the Controlled Release Society leadership, congratulations are offered to incoming Vice President, Susan Cady, and newly elected Board of Scientific Advisor members, Kazunori Kataoka and Thomas Rades.

The membership recognized the talents, contributions, and leadership skills of all the nominees, with close races for the positions. Thank you to Marcus Brewster, Syed Hossainy, and Rod Walker for your contributions to the Controlled Release Society, and your willingness to seek additional roles within the community.

The 2005-2006 Controlled Release Society Leadership is:

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PRESIDENT-ELECT: Randall Mrsny
VICE PRESIDENT: Susan Cady
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TREASURER: Arthur J. Tipton
MEMBERS-AT-LARGE: Jeffrey L. Cleland; Clive Wilson

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Jack J Burger	Alexander V Kabanov	Elka Touitou
Duncan Q M Craig	Kazunori Kataoka	Ijeoma F Uchegbu

To Jennifer Dressman, 2004-2005 President, and Mark Tracy and Arto Urtti, 2004-2005 Board Of Scientific Advisors, gratitude is extended for your dedication on fulfilling the mission of the Controlled Release Society in advancing the science and technology of chemical and biological delivery systems. Your contributions have made a great impact on the Society and will be felt for years to come.

Thanks are also extended to Nominations Committee members Jim Anderson, Sandy Florence, and Martyn Davies for the selection of outstanding candidates.

A Nanotechnology Delivery System for Oral Hygiene Products

by Adi Shefer and Sam Shefer, Salvona Technologies Inc., USA

Delivery of active ingredients for the prevention and treatment of periodontal diseases and delivery and sensory markers, such as flavors, onto the oral cavity has long been the target of the oral care industry. Periodontal disease, also known as pyorrhea or gum disease, is a major cause of tooth loss in adults. Tooth loss from periodontal disease is a significant problem beginning at about age 35, or even younger. It is estimated that about 4 out of 5 persons already have gingivitis and 4 out of 10 have periodontitis. 75% of the US population suffers from periodontal disease and this epidemic costs billions of dollars a year. The greatest single cause of periodontal disease is poor hygiene, indicated by the appearance of bacterial plaque and tartar (calcified plaque). It is believed that plaque and tartar are more sinister when they occur below the gum line than when they occur at or above the gum line.

Salvona Technologies Inc. developed a nanotechnology (Shefer A and Shefer S. D. 2003a, 2003b, 2004) that can be incorporated in conventional, over-the-counter oral care products to enhance the deposition of active ingredients and sensory markers onto the oral cavity and prolong their release over an extended period of time.

The nanotechnology is a multi-component system consisting of biodegradable, bioadhesive solid hydrophobic nanospheres encapsulated in a moisture or pH sensitive microsphere that effectively encapsulates one or multiple active ingredients and releases them in a consecutive manner, one after the other (Figure 1).

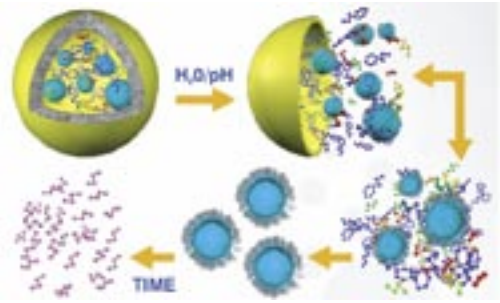

Figure 1: Salvona's multi component controlled release system. Change in pH or the presence of water disrupts the microsphere structure to releases the first encapsulated active and the bioadhesive nanospheres. The nanospheres provide prolonged release of the actives encapsulated within their structure over an extended period of time.

The multi-component delivery system confers many advantages over the above and other dispersion-based and particulate systems. All materials used are food or GRAS grade. Wide range of active ingredients, both hydrophilic and lipophilic actives, can be encapsulated in either the solid hydrophobic nanospheres, the water sensitive microsphere, or in both the nano and micro spheres. The combination of solid inner core with cationic exterior has enhanced stability and higher dispersibility in an aqueous medium. Altering either, or both, the inner solid core or the water sensitive matrix can manipulate the release rate of actives from the nanospheres. The nanospheres also have a lower risk of reaction of substance to be delivered with the vehicle than in emulsion systems because the vehicle is a solid inert material. Nanospheres are inherently more stable than structured vehicles such as lipospheres. Stability has become the major problem limiting the use of liposomes for controlled delivery, both in terms of shelf life and after administration.

The solid hydrophobic nanospheres have a positively charged surface that facilitates their adhesion onto the oral cavity (Figure 2). The bioadhesive properties of the nanospheres are attributed to the positively charged surfactant entrapped on the particle surface as the hydrophobic ends of the surfactants are embedded in the solid core and the hydrophilic ends are exposed on the surface of the nanospheres. The cationic surface can be comprised of cetylpyridinium chloride, a cationic surfactant that has anti-bacterial activity. The cationic surface is believed to attach to tooth surfaces via a complexing interaction between the cationic portion of the nanospheres and the proteinaceous portion of the tooth for predisposing the surface of the tooth to allow the nanospheres to adhere to the surface of the tooth.

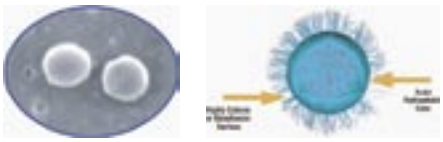

***Figure 2:** The left figure is a scanning electron microscope (SEM) image of the hydrophobic nanospheres released in response to moisture, magnified 10,000 times. The right figure is a schematic illustration of the nanospheres.*

There is general agreement that the junctional epithelium, which joins the tooth surface and the keratinized gingival oral epithelium, is a thin, non-keratinized tissue, lacking membrane-coating granules. The size of the nanospheres that are being released in response to moisture (0.01 microns to 0.5 microns) from the proposed multi-component delivery system are designed to take advantage of the anatomical features of the gingiva and adjacent tissues, as a site that can hold the nano-particles for a prolonged period of time.

Experimental and Product Performance

The oral cavity is lined by non-keratinized, stratified, squamous epithelial cells. This type of epithelial cells also lines other soft

tissue surfaces that include esophagus, vagina, and cervix. The HeLa cell line that we have chosen to use to determine the bioadhesive and mucoadhesive properties of the nanospheres is an epithelial-like cell line, originally derived from a carcinoma of the cervix. Since its origin, it has been one of the most widely studied cell lines. HeLa cells are cultured in Minimal Essential Medium (Eagles) with 10% fetal bovine serum. To test the adherence of nanospheres to the cell surface, HeLa cells have been plated at a density of 2 x 105 cells per dish (35 mm) in 2 ml medium. Three dishes are seeded for each data point. On the following day, the nanospheres have been dispersed in 1 ml medium. The medium in which the cells are cultured is aspirated and replaced immediately with the nanospheres-containing medium. The nanospheres were left to adhere to the cells by gravity for 5-, 15-, and 30 min. At each time point the medium is being aspirated, and the cells surface are gently rinsed twice with 2 ml medium (simulating rinsing the mouth following brush). Cells have been imaged immediately using an Olympus IX-70 inverted fluorescent microscope and Princeton Instruments Micromax cooled CCD camera.

The ability of nanospheres comprising the cationic surface to adhere to HeLa cultured cells is shown in Figure 3B and compared to that of nonionic nanospheres (Figure 3A). The specific adhesion of the cationic nanospheres to the HeLa cells is clearly evident and is significantly higher that that of the nonionic nanospheres. The results show that we can enhance deposition of the nanospheres by modifying their surface with bioadhesive cationic molecules.

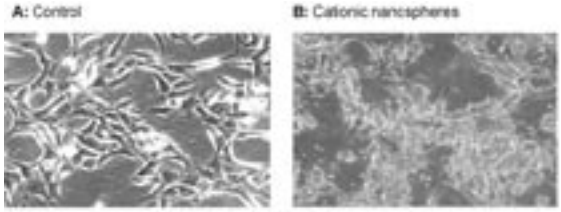

Figure 3: The left figure (A) is the adhesion of nonionic nanospheres that are not bioadhesive onto HeLa cell culture. The right figure (B) shows the adhesion of the cationic bioadhesive nanospheres onto HeLa cell culture.

The ability of the system to enhance the delivery and retention of active ingredients onto the oral cavity was studied in-vitro using saliva-coated hydroxyapatite disks (artificial teeth). The procedures for studying the uptake and retention of active ingredients onto saliva-coated hydroxyapatite disks (artificial teeth) have been described in literature (Comelli et al., 2002). An essential oil mixture containing 35.6% eucalyptol, 23.3% methyl salicylate, 16.3% menthol, and 24.8% thymol, was encapsulated in the nanospheres and the deposition of the free essential oil mixture onto the model tooth was compared to that of the encapsulated essential oils.

A solution comprising 1% of the free essential oil mixture was used as a control sample. 2% Polysorbate 20 were added to the solution to dissolve the essential oil mixture in the water. The percent of essential oil mixture deposited (the amount deposited divided by the amount applied) from a solution comprising 1% encapsulated essential oil mixture was compared to that deposited from the control sample.

0.5" diameter hydroxyapatite discs weighing about 400mg (Clarkson Chromatography, PA) were used as a tooth model; the surface area of one disc is equivalent to the average area of an adult size tooth. Human saliva was collected from volunteers and treated according to a protocol (Comelli et al., 2002) that inactivates salivary enzymes but maintains other proteins for surface adsorption. Briefly, the saliva were collected and centrifuged at 10 000g, 4˚C for 10 minutes. The supernatant was collected, heated at 60˚C for 30 minutes, and centrifuged again at 10 000g, 4˚C for 10 minutes. The saliva was aliquot and stored at –20˚C until use.

The adhesion experiments were performed by incubating hydroxyapatite discs with human saliva at 37˚C for 5 minutes prior to use. It is anticipated that salivary proteins contribute to the surface modification of teeth. Then, 1ml of 1% essential oils was added to the disc. Using cleaned tweezers, the disc was washed with 100ml of water three times, i.e., a total of 300 ml water, to simulate rinsing the mouth after brushing. The disc was transferred into a vial containing 1ml of acetone used to extract the essential oil mix that deposited on the tooth and assayed by gas chromatography. The experiment was repeated three times (n = 3) to obtain statistical parameters. The deposition data are presented in Figure 4.

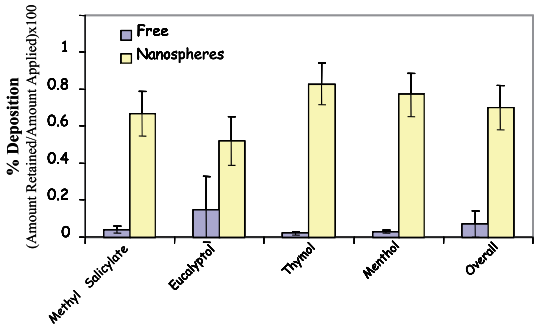

Figure 4: *Percent deposition of the free and encapsulated essential oil mix (total and the individual flavor ingredients) onto the model tooth.*

The percent deposition of the free ingredients onto the model tooth, in best-case scenario, is 0.1 % (see table 1), whereas that of the encapsulated ingredient is about 1%, i.e., 10 times more. Overall the nanospheres delivered 10 times more of the essential oil mixture compared to the free flavor. Flavor ingredients that are more water soluble, such as menthol and thymol, have very low deposition (about 0.03%). Encapsulation of these flavor ingredients enhances their deposition onto the model tooth, more than 20 times more.

Table 1: *Percent deposition of the free and encapsulated essential oil mixture (total and the individual flavor ingredients) onto the model tooth.*

Ingredient	Free	Encapsulated in Nanospheres
Methyl Salicylate	0.03% ± 0.01%	0.59% ± 0.20%
Eucalyptol	0.13% ± 0.09%	0.47% ± 0.22%
Thymol	0.04% ± 0.01%	0.99% ± 0.46%
Menthol	0.03% ± 0.01%	0.77% ± 0.38%
Total	0.23%	2.82%

C&DP continued on page 12

C&DP continued from page 11

The amount of essential oils that was retained on the model tooth over time was also studied. After the initial application of the 1% essential oil sample, different discs were extracted with acetone at 30, 60, and 90 minute time intervals to determine the amount of essential oil retained. The result shows (figure 5) that the amount of essential oils retained at 90 minutes is 10 times more than the sample treated with the 1% free oils. The result confirms that the nanospheres have the ability to extend the release of the flavor ingredients.

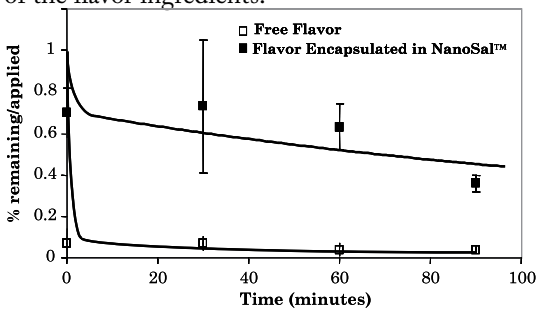

Figure 5: Retention of the free and encapsulated essential oil mixture (total) onto the model tooth over time.

The amount of menthol retain on the model tooth treated with the free essential oil mix after 90 minutes was 0.01%, whereas that retained on the model tooth treated with the encapsulated essential oil mix was 0.32 ± 0.06%, more than 30 times compared to the control. The amount of thymol retain on the model tooth treated with the free essential oil mix after 90 minutes was 0.03 ± 0.01% whereas that retained on the model tooth treated with the encapsulated essential oil mix was 0.61 ± 0.02%, again 30 times more.

Other Potential Applications

In addition to oral hygiene products, such as toothpaste, gels, chewing gum, the major other potential product applications for the nanosphere/microsphere system are baked goods, refrigerated/frozen dough and batters, tortillas and flat breads, processed meats, acidified dried meat products, microwavable entrees, seasoning blends, confectionery, specialty products, dessert mixes, nutritional foods, wellness products, health bars, dry beverage mixes, and many others.

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CReators
Controlled Release Education Articles on Technology Original Research and Science

From the Education Committee

Controlled Release Education, Research, and Industry in South Africa

by Rod B. Walker
Rhodes University, South Africa

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

Introduction
South Africa, as a relatively new democracy of 10 years, has several challenges with respect to delivery of health needs to the general population. Consequently, there is a need for undergraduate curricula in Pharmacy to change emphasis from sophisticated drug product design to focus on the provision of pharmaceutical services at a primary and public health care level. In this regard, the South African Pharmacy Council, a registered Education and Training Quality Authority, lays down the minimum requirements for a curriculum in Pharmacy and has its own Standards Generating Body. There are currently standards for Basic and Post-basic Pharmacy Assistants and for Entry Level Pharmacists with several other standards being developed. As a result of globalization, the shortage of pharmacists world-wide, and political changes, many South African trained pharmacists are leaving the country resulting in a major shortage of pharmacists in South Africa. Further, around 80% of the approximate 45 million populations rely on the public sector for their health care needs, and with an estimated 6 million deaths over the next 10 years likely to occur as a result of HIV and AIDs related diseases, the role of the pharmacist becomes even more important. Because of these factors there is a focus in South Africa on training pharmacists at an undergraduate level to deal with the fundamental issues rather than first world initiatives.

Nevertheless, topics in controlled, novel, and targeted drug delivery form an integral part of the undergraduate curriculum and more recently have gained popularity in many graduate programs in the country.

An additional factor affecting tertiary education is the recent restructuring of higher education in South Africa, which has resulted in mergers of several institutions, with the resulting uncertainty regarding the viability of several degree courses.

Education
Currently, there are eight institutions that offer a degree in Pharmacy in South Africa (Figure 1). Importantly, in the Southern African context there is only one other School of Pharmacy, which is located in Zimbabwe. Therefore, many institutions in South Africa are also training a large percentage of foreign students. The Bachelor of Pharmacy degree is a four-year program and currently there are 1700 students registered in all years in South Africa. Most universities offer postgraduate degrees by thesis only at the Master of Science and Doctor of Philosophy degrees. Recently, Rhodes University has started offering a PharmD degree. In addition, some universities offer Masters' degrees by a combination of course-work and thesis and others by course-work only. There are approximately 200 graduate students at pharmacy schools in South Africa.

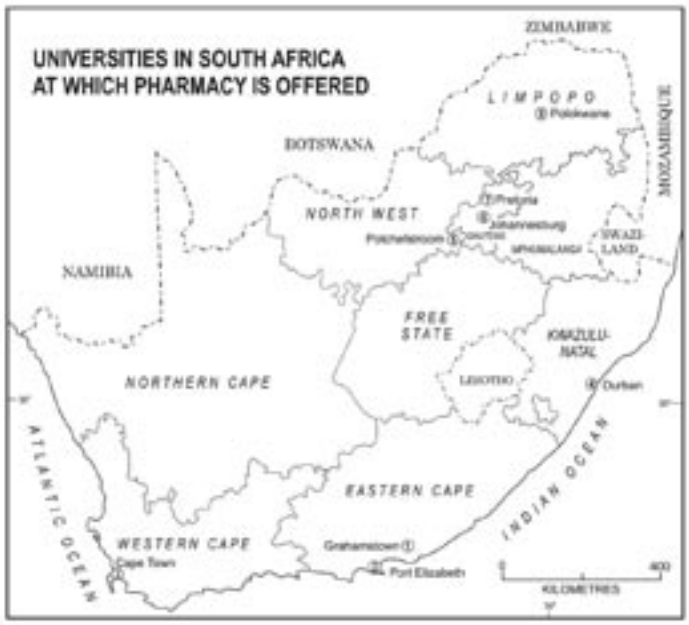

Figure 1. *A map of South Africa indicating locations at which Pharmacy is offered. 1. Rhodes University, 2.* University of Port Elizabeth, 3. University of the Western Cape, 4. University of Kwa-Zulu Natal Westville Campus, 5. Northwest University – Potchefstroom Campus, 6. University of the Witwatersrand, 7.** Medical University of South Africa (MEDUNSA) and Tshwane University of Technology, and 8. *** University of the North.*

* *Soon to be renamed Nelson Mandela Metropole University.*
** *MEDUNSA and Tshwane offer a joint course in pharmacy.*
*** *Soon to be renamed University of Limpopo.*

As a minimum requirement, all degree programs teach the fundamentals of controlled and novel drug delivery at the third or fourth year level. However the emphasis on aspects of novel drug delivery varies according to the interest and expertise of the staff teaching these courses.

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Education continued from page 13

Research Activities on Controlled Release in South African Universities

In terms of postgraduate training, there are several research groups in South Africa in which controlled and/or novel drug delivery research is being undertaken. These programs are partially funded by the National Research Foundation and the Medical Research Council in South Africa, but further substantive support is necessary to ensure major outputs can be achieved.

A summary of the academic staff at South African Universities and their areas of research interest in the area of Controlled Release (CR) dosage forms are listed in Table 1.

One of the major challenges facing these groups is to gain access to suitable funding to purchase specialized equipment and provide adequate funding for potential postgraduate students. A major difficulty for potential foreign postgraduates is the fact that, whilst not having to pay differential fees to attend universities in South Africa, they are in many cases not eligible for bursaries and scholarships as these are earmarked for South African students.

Pharmaceutical Industries Developing Controlled Release Dosage Forms

The pharmaceutical industry in South Africa is comprised of a combination of multi-national (innovator) and local (mainly generic) companies. Much of the manufacturing in South Africa is carried out by the generic industry, whereas many of the innovator companies no longer manufacture in South

Table 1. *Summary of Research in areas of CR at South African Universities*

Name	Area of Interest	University
Professor C Dangor	Sustained Delivery	University of Kwazulu Natal, Westville Campus
Professor P Danckwerts	Novel Delivery Systems	University of the Witwatersrand
Professor J Du Plessis	Transdermal drug delivery	Northwest University, Potchefstroom Campus
Ms G Enslin	Chitosans in drug delivery	Tshwane University of Technology
Professor T Govender	Mucoadhesive delivery systems	University of Kwazulu Natal, Westville Campus
Professor JM Haigh	Transdermal drug delivery	Rhodes University
Professor S Hamman	Chitosans in drug delivery	Tshwane University of Technology
Professor I Kanfer	Transdermal drug delivery	Rhodes University
Professor A Kotze	Chitosans in drug delivery	Northwest University, Potchefstroom Campus
Professor V Pillay	Polymers and Drug Delivery	University of the Witwatersrand
Professor P Vd Bijl	Transmucosal Delivery	[1]University of Stellenbosch
Professor RB Walker	CR/SR Formulation, Development, Assessment and Manufacture	Rhodes University

[1]University of Stellenbosch does not offer Pharmacy but has a Faculty of Medicine

Africa, but rather import and distribute their products. Recent changes in legislation, which has been promulgated to promote access to affordable medicines, may change the face of the pharmaceutical industry in the country. At present, there is no pharmaceutical company working on controlled release dosage forms. However, some university research groups are starting to invest in intellectual property and thus begin start-up drug delivery companies. Much of the research in the industries in South Africa is geared towards developing immediate release generic medicines only. However, there has been some interest in considering moving into the area of controlled release dosage forms.

Concluding Remarks

Despite the challenges facing researchers and academics in the Pharmaceutical Sciences in South Africa, they have been productive in contributing to capacity development and the field of controlled release dosage forms for many years. Further evidence of their relative success can be measured by the collaboration between South African researchers with those in Belgium, Canada, France, Netherlands, New Zealand, United Kingdom, and the United States of America, amongst others. Future developments of interest to the CRS may include the establishment of a Local Chapter and ongoing support of the CRS Annual meetings. ■

Special Feature

Developing Child-Friendly Science: A Field Report

by Yvonne Perrie and Ruoling Guo
Aston Pharmacy School, United Kingdom

In a recent new initiative between local Universities and the City Education group, Birmingham 'Thinktank' Science Museum presented the first in a series of 'Meet the Scientist' sessions where University Researchers were asked to develop a one-day science programme for children from the region's primary schools (ages 6-11). As the first group to present a session, Yvonne Perrie and her research group presented a series of experiments which were tried and tested by 230 inquisitive and critical potential new scientists.

UK Science

This new push in the UK Midlands to get children involved in science early in their education is coming at a time when some areas of science are suffering from poor undergraduate uptake. This has contributed to science departments for Keele, Newcastle, and Exeter already being earmarked for closure[1]. Within the science disciplines, chemistry has suffered particularly from this fate with ten UK University chemistry departments having closed over the last decade resulting in chemistry student numbers falling by approximately 23% since 1997[2] precipitating the Royal Society of Chemistry to predict that at best 20, and at worst 6, chemistry departments will remain in 10 years time[3]. However, this may result in some departments developing new courses, with, for example the, number of pharmacy undergraduate places available in the UK continuing to rise, at potentially an unhealthy rate[4].

Science for fun

With an aim to help re-invigorate interests in science within younger students our mission from the 'Thinktank' was to deliver a series of interactive and fun experiments that would inspire, interest, and intrigue school children and positively introduce them to science. Working in a School of Pharmacy, we initially aimed to focus on science related to phenomena which influence the field of Drug Delivery/Pharmaceutical Sciences, however, as our experiments developed a few rogue, less directly relevant, but fun ones, emerged and were subsequently included.

The basic remit identified for our experiments were that, they should be quick to set up and deliver an outcome, this outcome should be both obvious and interesting, the experiment and the science should be effectively explained and managed at a ratio of about 1 'scientist' to 6 children, and they should allow, as much hands-on participation as possible. Various sources[5-9] were used to get ideas for experiments which we then manipulated to best fit our set-up within the museum space. A total of 8 experiments were presented to the school parties attending the museum, most of which were popular with the groups. However, two were not as popular as we had initially predicted. A few examples of the most popular ones are listed below.

'Giant Bubbles': By preparing a large stock of 'bubble solution' (Panel 1) a variety of experiments could be done with the students including providing different shaped bubble loops and challenging the students to make square bubbles. The asset of this experiment was that it could easily involve several participants and this remained the most popular practical throughout the day.

Panel 1
Bubble Solution:
320ml washing up liquid

30ml glycerol

3.8L tap water

Metal wire loops (or squares) wrapped tightly with wool to help absorb the solution and making films easier to create.

Leaving the bubble solution to age for at least a week helped improve efficacy.

Chemiluminescence:
1. Chilled luminal solution (0.23 g of luminol in 500 ml of a 0.10 M NaOH)
2. Chilled dilute bleach solution, 40 ml of laundry bleach in 400 ml of distilled water
3. Pour about 25 ml of each solution into a beaker and observe the glowing blue colour.

Figure 1: Anil Vangala shows Chemiluminescence in Action!

'Chemiluminescence': This lets the students mix two chilled solutions (luminol solution and dilute bleach solution; Panel 1) which when poured together produce a glow-in-the-dark blue light that lasts for several seconds (Fig 1).

'Invisible Ink': Using pH indicators, participants can write or draw using a cotton bud soaked in invisible ink (e.g. phenolphthalein solution) which is then revealed by spraying with e.g. ammonia (Fig 2); however, you have to be prepared for what the school children may write!

Figure 2: Habib Ali reveals some of the children's art.

Figure 3: Sarah McNeil shows some stacked solutions.

'Liquid Densities': This experiment, whilst taking slightly more patience from those involved, provides excellent visual results of how liquids have different densities. Simply by pouring in a range of decreasing density liquids into a graduated cylinder, a stacked layer of solutions can be formed by the children. Fig 3 shows 'stacked layers' of syrup, glycerine, washing-up liquid, coloured water, vegetable oil, and alcohol coloured for visual effect). Samples of various solids (e.g. a penny, candle wax, wood) can also be added to estimate their densities.

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Chapter Update

5th Annual Meeting of the Israeli Chapter of CRS (ICRS)

by Elka Touitou, President ICRS
The Hebrew University of Jerusalem, Israel

From left to right: Professor Franco Alhaique, Professor Elka Touitou (President, ICRS), and Professor Vladimir Torchilin (President elect, CRS)

This year the ICRS meeting brought together 221 attendees, among them invited speakers from abroad, scientists from academia and industry in Israel, a significant number of students, start-up companies, and regulatory offices' representatives. As usual, the ICRS Annual Meeting was filled with activities and sessions designed to give participants a chance to learn, socialize, and enjoy the surroundings. The topic of the conference was "Advances in drug delivery from carriers and devices". During the meeting, 58 papers covering a range of drug delivery related issues in the fields of pharmaceutics, chemistry, and biotechnology were presented. The 2004 Annual Meeting included keynote talks and oral and poster presentations.

Two keynotes were given by Prof. Vladimir P. Torchilin, President-elect of CRS, and Dr. Larry Brown from Epic Therapeutics, USA. Prof. Torchilin spoke on the topic of current approaches to intracellular drug delivery and Dr. Brown summarized the challenges and new tactics for administration of protein drugs. Other invited speakers from abroad were Prof. Franco Alhaique from the University of Rome, Dr. Vered Bisker-Leib from Baxter Healthcare Corporation, USA, and Dr. Daniel Bar-Shalom from Egalet, Denmark. The scientific program also included four selected students' oral presentations. The last session of the meeting was devoted to start-up companies' presentations on their research projects and achievements. The award committee selected the five most outstanding student presentations, who were: Biana Godin, Rivka Efrat, Ofra Benny, Inbar Freeman, and Irina Yudovin-Farber. Recipients of the first and second prizes received travel grants to the CRS 2005 Annual Meeting in Florida.

Dancers at the Gala Dinner

The Gala evening was an extremely successful event. It opened with the presentation of Awards honoring outstanding student poster presentations from the 2003 ICRS meeting. The awards ceremony was followed by dinner and dancing, which all who attended will fondly and pleasantly remember. The participants enjoyed the charming country atmosphere of Zichron Yaakov, the tasteful cuisine, good Israeli wine, and the lively and fun-filled dancing.

I would like to conclude by thanking our sponsors who helped to bring about this successful event: CRS, The Hebrew University of Jerusalem (HUJI), Yissum, The School of Pharmacy at HUJI, Agis Industries, Unipharm, Teva Pharmaceutical Industries, Ort Braude College, Alex Grass Center at the School of Pharmacy, David R. Bloom Center at the School of Pharmacy, Israeli Ministry of Science & Technology, Dexcell Pharma, Biodar, Trima Israel Pharmaceutical Products, NovaGali Pharma, Intec Pharma, Novel Therapeutic Technologies (NTT), and Wilhelm Rosenstein.

ICRS website: www.icrs.org.il ■

Report of Controlled Release Society Indian Chapter VIth International Symposium on Advances on Technology and Business Potential of NDDS

Amrita Bajaj, Secretary, CRS Indian Chapter
Padma Devarajan, UICT, India

The Controlled Release Society Indian Chapter organised the 6th International Symposium on Advances in Technology and Business Potential of New Drug Delivery systems February 18-19, 2005, at Hotel Tulip Star in Mumbai. The conference received overwhelming response from all over India and abroad. A galaxy of global experts constituted the faculty of the conference. Around 300 delegates participated from industry, regulatory bodies, and academia. The participants from the industry included personnel from R & D, QA, QC, and production, representing various levels in their organization. A total of 131 posters, representing high quality research work carried out in Indian universities, institutes, and industry, were presented at this conference

Sitting from left to right are Dr. Amrita Bajaj, Dr. Himadri Sen, Mr. Pankaj Patel, Prof Jennifer Dressman, Mr. Ajit Singh, and Dr. H.L Bhalla.

The inaugural function commenced with "SARASTWATI VANDANA" in true Indian tradition. Mr. Pankaj R. Patel, Chairman and Managing Director of Cadila Health Care and Zydus Group of Companies, India, presided as chief guest. Prof. Jennifer Dressman, President of CRS was the guest of honour. Mr. Patel talked of his vision for the Indian pharmaceutical industry, the flux in the industry due to the advent of the GATT era, and the possible role the industry could play globally. Prof. Dressman highlighted the role CRS plays globally during her inaugural talk. She also briefed the delegates on the programme highlights and topics to be covered at the 32nd Annual Meeting & Exposition of CRS, which is to be held in, Miami, Florida, in June 2005, and invited delegates to participate in the same. Prof. Bhalla, Chairman Scientific Committee and President Emeritus CRS Indian Local Chapter, welcomed the speakers and thanked all the guests, speakers, and delegates.

The scientific session started with Dr. Jennifer Dressman's lecture on "Prediction of the Intestinal Solubility of Poorly Soluble Drugs." During her talk she explained importance of solubility data in the formulation design and drug discovery and highlighted recent techniques for the same. The lecture was very illustrative and informative.

Prof. Crommelin, Utrecht University OctoPlus, Leiden, The Netherlands, delivered a lecture on "Impact of Biotechnology on the Design and Formulation of Drug Delivery Strategies." He focused on the business potential of various proteins and peptides, their delivery problems, and strategies to overcome these problems.

Dr. Vinod Labhasetwar, Associate Professor at the Nebraska Medical Center, Omaha, Nebraska, gave a talk on "Molecular Mechanism of Gene/Drug Delivery with Nanoparticles." He started with various issues associated with gene and protein delivery. He explained in detail the role of nanoparticles for intracellular drug delivery systems and problems like RES, endosomal uptake and strategies to overcome the efflux of drugs. He also touched on aspects of gene delivery using nanoparticles.

Dr. Gerrit Borchard, Vice President of Research at Enzon Pharmcaeuticals in New Jersey, gave a talk on "PEGylation of Antisense Oligonucleotides." He started his lecture with basic ideas about ologonucleotides, aptamers siRNA (RNAi) and CpG oligos, their delivery problems and how one can bypass this with PEGylation.

Dr. Chong-Kook Kim, Professor of Pharmacy in the College of Pharmacy, Seoul, Korea, spoke on "Thermoreversible Lipid-Based Drug and Gene Delivery Systems." The lecture was focused on solid lipid nanoparticles, their manufacturing optimization, pharmacokinetics and pharmacodynamics. He explained this with various examples of drugs like paclitaxel, clarithromycin, all trans retinoic acid, plasmid DNA and antisense oligonucleotide.

The last lecture of the first day was delivered by Dr. Vinod P. Shah, Senior Research Scientist, OPS/CDER/FDA, USA, on "Regulatory Requirements for Transdermal Drug Delivery Systems". He explained various biopharmaceutical considerations for TDS like bioavailability, pharmacokinetics, and established reproducibility sites for TDS. He illustrated this with various examples.

The second day started with the lecture of Prof. Y. Capan, Turkey, on "Nanoparticles Technology and its Pharmaceutical Applications." This was an overview of nanotechnology in drug delivery. He also explained brain targeting with NP and various technologies associated with cancer therapy, oligonucleotides, and targeted delivery for antibiotics.

Dr. Claus-Michael Lehr, Head of the Department of Biopharmaceutics and Parmaceutical Technology, Saarland University, Germany, spoke on "Pharmaceutical Nano-

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Journal of Controlled Release Highlights

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

The *Journal of Controlled Release* publishes papers in the field of controlled release of bioactive materials. The scientists who publish in the *Journal* represent a diverse group from many parts of the globe. The three papers highlighting upcoming publications were performed and authored at widely varying locations: China, Canada, and Belgium.

Fei and coworkers from the Chinese Academy of Sciences present recent findings on macrobranched cell-penetrating peptides for gene delivery. They created a unique peptide structure of varying molecular weight. These peptides were able to significantly increase DNA transfection capabilities *in vitro*.

Amsden and coworkers out of Canada report on a photocrosslinked biodegrable elastomer capable of sustaining the release of interferon-γ. This elastomer, prepared by UV-initiated crosslinking of end terminal acrylated *star*-poly(ε-caprolactone-co-DL-lactide), was able to release interferon-γ at a constant rate for 21 days. The biological activity of the drug was maintained at 83% of its original activity following release.

Improving oral delivery of poorly water-soluble drugs is the topic of a paper by Préat and coworkers (all from Belgium). They investigated self assembling block copolymers capable of forming micelles spontaneously. Using the drug risperidone, permeability through Caco-2 cell monolayers was increased due to an apparent increase in drug solubility. *In vivo* studies indicated that the self-assembling copolymers were capable of enhancing absorption and, overall, that these micellar formulations represent good candidates for oral delivery of poorly soluble drugs.

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The aqueous dispersions and emulsions of the copolymer upon drying on skin form an invisible and imperceptible hydrogel film ("Patch"), which is water-insoluble and exhibits a strong bioadhesion. It has been found in human studies that the formed hydrogel film is retained on skin for 24+ hours. The apparent conformability of the film to skin dynamics makes the copolymer particularly appealing for skin product applications (e.g. cream, lotion, or a gel) for 24-hour delivery of actives. Because the copolymer is very hydrophilic, it also helps to moisturize the skin, which is an added benefit. A cosmetically elegant and invisible "Patch", without the ugly and occlusive plastic film, is an attractive concept for transdermal delivery of drugs for systemic activity. Since the PharmaDur™ "patch" can be applied over a large area of skin, it can effectively be deliver drugs having high dosage or those with low skin permeability.

Polytherapeutics approach to commercialization of its unique PharmaDur™ technology is strategic alliances with other businesses. PTI's current alliances include the copolymer manufacturing and its marketing to cosmetic industry, product development and manufacturing, and licensing of the PharmaDur™ technology. Two skin care products, featuring PharmaDur™, were launched by a licensee (Secrets by Phyllis George LLC, New York, NY) in 2004. PTI's other key partnership is with a multi-national ophthalmic company for the use of PharmaDur™ as a delivery system in a proprietary drug product for the treatment of glaucoma.

For more information about PharmaDur™ contact the author at 732-448-1515.

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IntheNews

compiled by Steven Giannos
Industrial Editor, USA

Transport Announces Agreement with GlaxoSmithKline for European Rights to a Device/Drug Combination System for High-Potency Delivery of Acyclovir

Business Wire via NewsEdge Corporation : BIOWIRE2K FRAMINGHAM, Mass. & PHILADELPHIA--(BUSINESS WIRE)--Jan. 27, 2005--Transport Pharmaceuticals, Inc. (Transport) announced today that GlaxoSmithKline PLC (GSK) has signed a license and collaboration agreement for Transport's iontophoretic device/drug combination system for the delivery of acyclovir, an approved cold sore (herpes labialis) treatment. GSK received exclusive rights to market and sell the system in Europe, Australia, Latin America, and South Africa. Acyclovir 5% cream is marketed as an over the counter (OTC) product in these territories.

Under the terms of the agreement, Transport will receive an upfront license fee from GSK, as well as milestone and royalty payments. GSK will provide technical support and contribute to certain costs of the upcoming European Phase III clinical trials. To date, Transport has completed two double-blind, placebo-controlled Phase II studies.

Transport's oral herpes product delivers acyclovir, an approved treatment for cold sores, directly to affected skin at concentrations considerably higher than conventional topical formulations. This approach addresses the challenge of rapidly achieving clinically active concentrations of drug in the skin necessary to treat the virus - a barrier that limits the efficacy of available oral herpes therapies. In addition, Transport's product requires only one ten-minute application, compared with available formulations that require multiple applications each day for several days.

Transport's platform is based on iontophoresis, a technology employing a low-voltage electrical charge to increase skin permeability in order to locally deliver medication through the skin. The company has developed a small, wireless computer-controlled electrode and medication applicator that will allow patients to self-administer topical drugs for a variety of indications.

Studies Show IGI's Novasome Microencapsulation Technology Improves Localized Delivery of H2 Antagonist for the Treatment and Prevention of Periododontal Disease

Business Wire via NewsEdge Corporation : BUENA, N.J.--(BUSINESS WIRE)--Jan. 27, 2005--IGI, INC. (AMEX: IG) announced that Boston University has applied for a patent for an invention using IGI Inc's patented Novasome® lipid microvesicles. The invention relates to a new method for the improved localized delivery of H2 antagonists for the treatment and/or prevention of periodontal disease. The described method involves topical administration of a H2 antagonist encapsulated with the Novasome® microvesicle delivery system. The Novasome®-based system is thought to lead to increased local absorption of the H2 antagonist and enhanced drug action. In an experimental study, the inventors have shown that topical administration of a preparation of the H2 antagonist, cimetidine, in Novasome® microvesicles prevented gingival inflammation and bone destruction in a rabbit periodontitis model. According to the inventors, Novasome® delivery of H2 antagonists could find applications in the management of inflammatory skin and other disorders.

Southern Research Institute spins out new for-profit drug delivery company, Brookwood Pharmaceuticals Inc.

Release Date: 1/26/2005 CHEMICAL BUSINESS NEWSBASE - PRESS RELEASE via NewsEdge Corporation : Southern Research Institute has launched a new for-profit company, Brookwood Pharmaceuticals Inc (Brookwood), spinning out the Institute's 30-year-old in-house drug delivery group, which focuses on the development of time-release formulations for pharmaceutical delivery. Brookwood recently acquired the Ohio-based external polymer manufacturing business of Alkermes Inc, and will operate that business as a Brookwood subsidiary called Lakeshore Biomaterials Inc. Brookwood initially will be wholly-owned by Southern Research Institute; both Brookwood and Lakeshore Biomaterials will be based in Birmingham, AL. Lakeshore Biomaterials will be a wholly-owned subsidiary of Brookwood. The group will primarily focus on long-acting parenterals, microparticles, implants, vaccine delivery, and clinical trial and commercial manufacturing, with much of the formulation work based on biodegradable polymers. Lakeshore Biomaterials will supply biodegradable polymers to new customers, support the long-term requirements of the external polymer customers previously supplied by Alkermes, and serve as a back-up supplier for Alkermes' internal polymer requirements. Brookwood Pharmaceuticals has formulation and scale up laboratories, clean rooms and a quality system that supports the manufacture of materials for clinical trials and market introduction.

6-Ketocholestanol improves skin permeation of 5-aminolevulinic

NewsRxDrugs via NewsEdge Corporation : 2005 JAN 28 - (NewsRx.com & NewsRx.net) The ability of 6-ketocholestanol to increase the skin permeation of the prodrug aminolevulinic acid (5-ALA) has been investigated. 6-Ketocholestanol was incorporated together with 5-ALA in four different formulations. Preparations used were a liquid solution/suspension of 5-ALA in buffer, 5-ALA in phospholipid liposomal formulations with and without gelating agent, and finally, a complex cream formulation also including phospholipids. Standard diffusion experiments of 5-ALA using Franz-type diffusion cells and porcine skin were performed, scientists in Austria report.

"Drug stability was monitored by analyzing the 5-ALA content in the different formulations over time and viewing the preparation for microbial contamination," said Barbara Gabriele Auner and colleagues at the University of Vienna. "The analysis of 5-ALA as a nonfluorescent probe was performed after chemical reaction, leading to a fluorescent derivative. The 5-ALA permeation through porcine skin was increased three-fold by 6-ketocholestanol in the cream formulation."

"The chemical stability of 5-ALA in the tested formulations was in the range of about 33 to 72% after an observation period of 28 days," reported Auner and her collaborators. "After that time point, microbial stability was no longer evident for formulations 2 and 3. Formulation 1 could be observed until day 34, and only formulation 4 showed a microbial stability over the whole observation period of 42 days."

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Auner and her co authors published their study in the *Journal of Pharmaceutical Sciences* (Influence of 6-ketocholestanol on skin permeation of 5-aminolevulinic acid and evaluation of chemical stability. J Pharm Sci, 2004;93(11):2780-2787).

For more information, contact Claudia Valenta, Institute of Pharmaceutical Technology and Biopharmaceutics, Centre of Pharmacy, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria. E-mail: Claudia.Valenta@univie.ac.at.

Sweet basil essential oils enhance transdermal drug delivery

NewsRxDrugs via NewsEdge Corporation : 2005 JAN 28 - (NewsRx.com & NewsRx.net) Scientists in Taiwan conducted a study to evaluate the essential oils from sweet basil (Ocimum basilicum, OB) as skin permeation enhancers to promote the percutaneous absorption of drugs.

"The *in vitro* and *in vivo* irritancy of the essential oils was also examined," noted J.Y. Fang and coauthors at Chang Gung University. "Terpenes with various carbon numbers (mono-, sesqui-, di-, and tri-) were identified in both the lower-polarity fraction (OB-1) and higher-polarity fraction (OB-2)."

"*In vitro* skin permeation and deposition of indomethacin were significantly enhanced after treatment with OB essential oils," test results showed. "The enhancing effect of OB-1 was greater than that of OB-2 in the *in vitro* permeation and *in vivo* cutaneous microdialysis analyses as well as in the plasma concentration of indomethacin."

"On the other hand, the *in vivo* study showed that OB-2 had a greater ability to retain the drug within the skin than did OB-1," according to the report. "Enhancement of the skin permeation of drugs by OB essential oils might be mainly due to improvement in the partitioning of the drugs to the stratum corneum."

"Both *in vitro* cell cultures (keratinocytes and skin fibroblasts) and *in vivo* transepidermal water loss showed no or only negligible irritation to skin by OB essential oils," the researchers concluded.

Fang and colleagues published their study in the *Biological & Pharmaceutical Bulletin* (Essential oils from sweet basil (Ocimum basilicum) as novel enhancers to accelerate transdermal drug delivery. Biol Pharm Bull, 2004;27(11):1819-1825).

For more information, contact J.Y. Fang, Chang Gung University, Graduate Institute of Natural Products, 259 Wen Hwa 1st Rd., Taoyuan 333, Taiwan.

OX26 shows promise as drug vector for brain capillary endothelial cells - Drug Delivery

NewsRxPainCNS via NewsEdge Corporation: 2005 JAN 17 - (NewsRx.com & NewsRx.net) -- A novel antibody may enable targeted drug delivery to brain capillary endothelial cells (BCECs). BCECs "express transferrin receptors," scientists in Denmark explained. In a study conducted by T. Gosk and coauthors at the University of Copenhagen, the "uptake of a potential drug vector (OX26, or anti-transferrin receptor antibody IgG2a) conjugated to polyethyleneglycol-coated liposomes by BCECs" was evaluated "using in situ perfusion in 18-day-old rats in which the uptake of OX26 is almost twice as high as in the adult rat."

"Using radio-labeling, the uptake of OX26 by BCECs after a 15-minute perfusion was approximately 16 times higher than that of nonimmune IgG2a (Ni-IgG2a)," the investigators found. "OX26 and OX26-conjugated liposomes selectively distributed to BCECs, leaving choroid plexus epithelium, neurons, and glia unlabeled."

"Ni-IgG2a and unconjugated liposomes did not reveal any labeling of BCECs," according to the report. "The labeling of BCECs by OX26 was profoundly higher than that of transferrin."

"Perfusion with albumin for 15 minutes did not reveal any labeling of neurons or glia, thus confirming the integrity of the blood-brain barrier," test results showed. "The failure to label neurons and glia shows that OX26 and OX26-conjugated liposomes did not pass through BCECs."

"The expression of transferrin receptors by endothelial cells selective to the brain qualifies OX26 as a candidate for blood-to-endothelium transport. A specifically designed formulation of liposomes may allow for their degradation within BCECs, leading to subsequent transport of liposomal cargo further into the brain," the researchers concluded.

Gosk and colleagues published their study in the *Journal of Cerebral Blood Flow and Metabolism* (Targeting anti-

transferrin receptor antibody (OX26) and OX26-conjugated liposomes to brain capillary endothelial cells using in situ perfusion. J Cerebr Blood Flow Metabol, 2004;24(11):1193-1204).

For additional information, contact T. Moos, University of Copenhagen, Panum Institute, Department of Medical Anatomy, Sect. B, DK-2200 Copenhagen N, Denmark.

Optimized liposomes deliver therapy to avascular tumor spheroids

NewsRxGeneTherapy via NewsEdge Corporation : 2005 JAN 13 - (NewsRx.com & NewsRx.net) The liposomal delivery of cancer therapeutics, including gene therapy vectors, is an area of intense study. "Poor penetration of liposomes into interstitial tumor spaces remains a problem, however. In this work, the penetration of different liposomal formulations into prostate carcinoma spheroids was examined," scientists in the United States report.

"Spheroid penetration was assessed by confocal microscopy of fluorescently labeled liposomes. The impact of liposomal surface charge, mean diameter, lipid bilayer fluidity, and fusogenicity on spheroid penetration was examined," said K. Kostarelos and colleagues, Johns Hopkins School of Medicine, Department of Radiobiochemistry.

"A variety of different liposome systems relevant to clinical or preclinical protocols have been studied, including classical zwitterionic (DMPC:chol) and sterically-stabilized liposomes (DMPC:chol: DOPE-PEG(2000)), both used clinically, and cationic liposomes (DMPC:DOPE: DC-chol and DOTAP), forming the basis of the vast majority of nonviral gene transfer vectors tested in various cancer trials."

"Surface interactions between strongly cationic vesicles and the tumor cells led to an electrostatically derived binding-site barrier effect, inhibiting further association of the delivery systems with the tumor spheroids (DMPC:DC-chol)," investigators noted.

"However, inclusion of the fusogenic lipid DOPE and use of a cationic lipid of lower surface charge density (DOTAP instead of DC-chol) led to improvements in the observed intratumoral distribution characteristics."

"Sterically-stabilized liposomes did not interact with the tumor spheroids, whereas small unilamellar classical liposomes exhibit extensive distribution deeper into the tumor volume. Engineering liposomal delivery systems with a relatively low charge molar ratio and enhanced fusogenicity, or electrostatically-neutral liposomes with fluid bilayers, offered enhanced intratumoral penetration."

"This study shows that a delicate balance exists between the strong affinity of delivery systems for the tumor cells and the efficient penetration and distribution within the tumor mass, similar to previous work studying targeted delivery by ligand-receptor interactions of monoclonal antibodies," researchers advised.

"Structure-function relationships from the interaction of different liposome systems with 3-dimensional tumor spheroids can lead to construction of delivery systems able to target efficiently and penetrate deeper within the tumor interstitium and act as a screening tool for a variety of therapeutics against cancer," they concluded.

Kostarelos and colleagues published their study in *International Journal of Cancer* (Binding and interstitial penetration of liposomes within avascular tumor spheroids. Int J Cancer, 2004;112(4):713-721).

For more information, contact G. Sgouros, Johns Hopkins School of Medicine, Department Radiobiochemistry, Division Nuclear Med, 220 Ross, 720 Rutland Avenue, Baltimore, MD 21205, USA.

BDSI's bioral drug delivery technology may reduce GI damage caused by NSAIDs and aspirin

Release Date: 1/11/2005 CHEMICAL BUSINESS NEWSBASE - PRESS RELEASE via NewsEdge Corporation : BioDelivery Sciences International Inc (BDSI) announced that, in laboratory testing, it recently applied its licensed and patented Bioral "nanocochleate" drug delivery technology to aspirin and traditional non-steroidal anti-inflammatories (NSAIDs) that are not selective COX-2 inhibitors. BDSI contracted with an independent testing laboratory to test its Bioral formulations of aspirin and other NSAIDs in a well-established animal model of inflammation. These proof-of-principle animal studies have demonstrated that encochleated NSAIDs enabled a statistically significant reduction in gastro-intestinal toxicity compared to standard formulations at clinically-relevant high doses of these NSAIDs and aspirin while providing comparable anti-inflammatory effects. BioDelivery Sciences International Inc is a biotechnology company that is developing and seeking to commercialise patented and licensed delivery technologies for pharmaceuticals, vaccines, over-the-counter drugs, nutraceuticals, and micronutrients.

Smart bombs developed to target cancer tumours

THE SCOTSMAN via NewsEdge Corporation, Release Date: 1/6/2005: It has been, revealed that tiny exploding capsules could be used to deliver cancer drugs directly to tumours without affecting healthy cells.

The almost invisible capsules could one day be used to deliver targeted chemotherapy directly to tumours, leaving adjacent body tissues unaffected by the treatment. Such a radical method of cancer therapy could soon spell an end to the debilitating and disfiguring effects of chemotherapy, which include hair loss, nausea, and temporary lack of nerve function.

The nanoscale capsules - under development by a team of researchers at the University of Melbourne in Australia, headed by Dr. Frank Caruso - are being designed to rupture inside the body when heated by a low energy laser pulse, delivering their payload exactly where it is needed.

As such, the powerful anti-cancer drugs would be rendered far more effective, and the side-effects less severe, if they could home in on a tumour and be delivered in a single burst. This would allow the drug to reach the concentrations needed to kill cancer cells while mitigating damage to surrounding tissues.

According to a report in the journal *New Scientist*, the new method of delivery involves enclosing the drug in special polymer capsules that are full of gold nanoparticles and attached to tumour-seeking antibodies. When these capsules are injected into the bloodstream the capsules will concentrate inside tumours. After enough capsules have gathered in the target region, a pulse from a "near-infrared" laser will melt the gold. As a result the plastic capsules are ruptured and the contents released in a specific location.

The capsules are invisible to the eye without the aid of a powerful electron microscope. Researchers make them by repeatedly adding the polymer to a suspension of drug particles that are roughly one thousandth of a millimetre wide until the polymer forms tiny spheres containing the drug payload. Gold particles that are six nanometers, or

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Patent Watch
TRANSDERMAL UPDATE

Priya Batheja, Rutgers; Debbie Persaud, UMDNJ-NJMS;
Bozena Michniak, UMDNJ-NJMS; & Agis Kydonieus, Samos Pharmaceutical, Inc., USA

We searched the patent literature for patents and patent applications published during the first half of the year 2004 and uncovered 151 patents and patent applications. From these, 32 were US issued patents and 51 US patent applications. There were also 22 European issued patents and 16 applications, as well as 30 world patents.

We only covered in this review the 32 US issued patents. Sixteen of these patents pertained to improved transdermal methods and devices and five to chemical enhancers. Another 11 used electrophysical techniques to increase the permeation of peptides and other drugs. Some of the more pertinent patents are discussed here.

The field of transdermal delivery was abuzz with activity during the first half of 2004 and some of the important events are covered below:

During the first six months of 2004, several transdermal activities of commercial and medical interest were announced. Several of these announcements pertained to the delivery of hormones to treat or prevent several diseases. P&G, Watson and Baylor College of Medicine announced the results of a 533-patient Phase III clinical trial for a testosterone patch for the treatment of Hypoactive Sexual Desire Disorder. The patch significantly increased satisfying sexual activity, sexual desire, responsiveness, and self-image. Acrux announced that it had licensed its Metered-Dose Transdermal System for Testosterone and Estradiol to Vivus Inc in the USA for the treatment of sexual desire and postmenopausal symptoms, respectively. Acrux had successfully completed Phase II studies for both products. Schering AG announced that the FDA had approved a dime-sized patch for the delivery of very low doses (14 micrograms/day) of estrogen for the prevention of osteoporosis; it also launched in the USA an estradiol/levonorgestrel patch for the control of postmenopausal symptoms. NexMed announced a 400-patient Phase III double-blinded clinical trial for its Femprox cream with patients that are diagnosed with female sexual arousal disorder. In a recent publication (Arterioscler. Thromb. Vasc.Biol. 23, 1671, 2003) it was shown that transdermal delivery of estrogen does not increase the activated protein C (APC) resistance and thus venous thrombosis beyond that of the placebo. Oral delivery of estradiol statistically increased the APC resistance.

Vyteris, Inc. received FDA approval of its LidoSite patch, an iontophoretic patch delivering lidocaine and epinephrine through intact skin. LidoSite has been approved for use on normal intact skin to provide local analgesia that numbs the skin prior to administration of dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation.

Somerset Pharmaceuticals, a joint venture between Mylan and Watson, received an approval letter from the FDA on Emsam (its Selegiline transdermal system) for the acute and maintenance treatment of major depressive disorders. Schwarz Pharma and Aderis are developing a patch for once-a-day Rotigotine as a treatment for Parkinson's disease. Rotigotine is a novel dopamine D2 receptor agonist and it is presently in Phase III clinical trials. Eisai withdrew a new drug application for a transdermal formulation of Eperisone. The patch was designed as a muscle relaxant, but it did not demonstrate sufficient efficacy.

In March of this year, Janssen (J&J) announced that the US Courts upheld the validity of its Duragesic TM (Fentanyl transdermal patch) patent and ruled that a generic patch from Mylan infringed the patent; this action allowed the application of the additional 6-month period of pediatric exclusivity, until January 2005. Mylan immediately filed suit against FDA seeking to restore final approval for its generic Fentanyl transdermal system.

Watson's Oxytrol TM (oxybutynin patch) was approved for marketing in Europe by Belgium's UCB Pharma and in Canada by Paladin Labs. Also, Antares Pharma has completed a Phase I clinical trial in Germany for an oxybutynin topical gel.

Finally, Dow Corning and Rohm and Haas have formed a strategic alliance to address unmet needs in transdermal and topical drug delivery and other medical device applications. The alliance enables one-stop shopping for acrylic, silicone, and hybrid materials.

Given below are few summaries of the various patent developments in the field of electrophysical methods, devices/methods, and enhancers for transdermal delivery.

ELECTROPHYSICAL ENHANCERS

Controlled Heat-Induced Rapid Delivery of Pharmaceuticals (Lohmann) US 6756053 and US 6756052

A transdermal device is described that comprises a component that can increase local temperature and/or the local circulation of the blood in the skin so as to increase the permeation of pharmaceutical agents. The component is a rubefacient, a substance that can cause local skin irritation or reddening. Rubefacients claimed include pelargonic acid vanillyl amide, cayenne pepper oil resin, capsicum fruit extract, tincture of capsicum extract, and cayenne pepper. The increase in temperature is due to the increased circulation of blood in the local area only.

Methods and Apparatus for Improved Administration of Testosterone (Zars) US 6726673

The invention pertains to the increased delivery of androgens and more specifically testosterone and its derivatives by increasing the temperature of the patch and the patient's skin. The controlled heat from the heating device can adjust the rate of delivery of the androgen to mimic natural circadian patterns. A heating device described contains iron powder and activated carbon that oxidize when exposed to oxygen. A maximum temperature of 50 deg. C is claimed with a preferred range of 39 to 43 deg. C.

Method and Apparatus for Skin Absorption Enhancement (Matiolli Engineering) US 674 8266

Electrical pulses are applied onto the skin in a controlled way to increase absorption of a drug through the skin. In addition, mechanical vibrations can be applied to the skin to increase the absorption. The electrical pulses are provided to the skin through an array of electrodes disposed on a vibrating head plate. The mechanical vibrations are provided to the skin by the vibrating head plate. The electrical and mechanical vibrations are of the same frequency and phase to optimize permeation. The electrical pulses have a frequency of between 50 and 15000 Hz and peak voltage of 20 to 200 V. The frequency of the mechanical vibrations is between 10 and 200 Hz.

Method and Apparatus for Intradermal Incorporation of Microparticles Containing Encapsulated Drugs Using Low Frequency Ultrasound (Ultra-Sonic Technologies) US 6712805

A sonoporation method is disclosed for the transdermal delivery of a microparticles suspension containing microencapsulated drugs. The vessel containing the microparticles suspension has a porous membrane of 100 micron in diameter, which is in contact with the skin. The ultrasound horn is submerged in the microparticles solution. The ultrasound radiation is applied at a frequency (1 KHz to 5MHz), intensity (5 W/cm2 to 55 W/cm2), and a period of time (10 to 20 minutes), effective to generate cavitation bubbles which on collapsing transfer their energy to the skin causing the formation of pores with 1 to 100 micron in diameter. The ultrasound intensity is also effective in generating ultrasonic jets that are capable in driving the microparticles suspension through the porous membrane and the formed pores of the skin.

Transdermal Drug Delivery and Analyte Extraction (Transpharma) US 6711435 and US 6708060

A device for ablating the stratum corneum is presented comprising a plurality of electrodes in contact with the skin with the distance between electrodes being preferably between 0.01 and 0.1 mm. Electric energy is applied through the electrodes to induce an electric current to flow through the stratum corneum and to cause ablation of the stratum corneum in narrow channels. Preferably, an alternating current is applied with frequency between 1 kHz and 300 kHz. A second concept comprises a plurality of receiving electrodes and a driving electrode, which creates electrical contact with each receiving electrode sequentially, and applies current that is sufficient to ablate the stratum corneum.

Iontophoretic Drug Delivery (Birch Point Medical) US 6745071

A self-contained, pre-packaged iontophoretic device is claimed comprising a removable substrate onto which aqueous anode and cathode matrices are attached, isolated by water impermeable membranes, as well as the anode and cathode electrodes of the iontophoretic device. The removable substrate has at least one line to enable the prepackaged system to fold into itself, so as to associate the anode and cathode matrices to the anode and cathode electrodes respectively. Preferably, the cathode and anode matrices contain a fibrous material of cellulose, polyester or polypropylene, which is impregnated with a viscous gel made from solutions of polyvinyl pyrrolidone, polyvinyl alcohol, or carboxymethylcellulose among others.

Interface for Iontophoresis ((Hisamitsu) US 6743432

An interface for the delivery of proteins by iontophoresis is disclosed which comprises a membrane having a low adsorptivity for proteins, wherein the membrane is a hydrophilized fluororesin, a hydrophilized polysulfone, or a hydrophilic cellulose derivative. Polymers claimed include polyfluoroethylene, polyvinylidene fluoride and ethylene/vinylidene copolymer, all of which have also a hydrophilic moiety. Preferred embodiments of

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six billionths of a metre in diameter, are then added to the mix, together with the antibodies which will target the tumour and a lipid polymer that forms an outer layer.

In laboratory tests, the capsules were ruptured by a ten nanosecond pulse from a near-infrared laser. Because of the nanostructure of the gold particles, the pulse is enough to melt them at a much lower temperature than normal, without damaging the precious drug payload. The report said: "In clinical use, the laser would be able to penetrate a few millimetres of tissue. It could be shone through the skin, or be beamed inside the body through an endoscope."

Dr. Caruso said he believed the key innovation of the research had been in making the particles react to a laser that is harmless to the body. He told *New Scientist*: "The [amount of] infrared energy needed to rupture the capsules is well within safety limits and is way below that used to remove tattoos."

At present, chemotherapy is what is known as a systemic therapy, meaning the drugs affect the whole body by going through the bloodstream. The treatment is effective against cancer cells because the drugs interfere with rapidly dividing cells. However, chemotherapy has side-effects because cancer cells are not the only rapidly dividing cells in the body. The treatment's systemic nature means the drugs have access to all such cells, even those necessary for the body's continued good functioning.

Nanoscale drug delivery could make the prospect of chemotherapy much less worrying to many cancer sufferers.

Corautus Genetics Announces Publication of Gene Therapy Approach to Vascular Disease Using Stents in Circulation

PR Newswire via NewsEdge Corporation: ATLANTA, Jan. 6 /PRNewswire-FirstCall/ -- Corautus Genetics Inc. (Nasdaq: VEGF) announced today the publication of preclinical results of the company's gene transfer technology administered via drug-eluting stents. In a separate project, Corautus' technology is currently being tested in a Phase IIb trial known as GENASIS ("Genetic Angiogenic Stimulation Investigational Study"), which is enrolling up to 404 patients with Class III or IV angina in approximately 25 cardiac medical centers in the United States. In the GENASIS trial, defined doses of Vascular Endothelial Growth Factor-2 (VEGF-2) in the form of naked DNA plasmid, a non-viral vector, are delivered to diseased heart muscle tissue via the Boston Scientific Corporation Stiletto(TM) endocardial direct injection catheter system.

In the preclinical study reported in the journal *Circulation* (Vol. 110, No. 1, pp. 36-45), a team of researchers under the direction of Dr. Douglas W. Losordo, Chief of Cardiovascular Research at Caritas St. Elizabeth's Medical Center in Boston, tested VEGF-2 gene transfer in an animal model of stent thrombosis. The results demonstrated for the first time that VEGF-2 could be delivered to blood vessels using drug-eluting stents and that this delivery led to accelerated growth of healthy endothelial cells while reducing pathological thickening of the artery ("neointima formation," or scarring) associated with restenosis.

In addition to his role in the preclinical research of VEGF-2, Dr. Losordo is the national principal investigator for the ongoing GENASIS trial. Dr. Losordo commented, "Local drug delivery by drug-eluting stents has already been shown to be a useful strategy for the prevention of restenosis. However, the current strategies share the liability of impairing endothelial recovery and increasing the associated risk of stent thrombosis. Our results demonstrate the possibility of therapeutic local gene transfer using a stent platform technology and that VEGF-2 gene-eluting stents may be effective in the prevention of restenosis by accelerating, rather than inhibiting, endothelial recovery."

Richard E. Otto, President and CEO of Corautus, stated, "We believe this demonstrates a growing body of evidence from preclinical and clinical studies that VEGF-2 gene transfer is a broadly enabling approach to the treatment of cardiovascular disease. The results published from this preclinical work with drug-eluting stents by Dr. Losordo and his team indicate another potential application using VEGF-2 that may benefit a large patient population. Results from early-stage clinical trials of patients with severe coronary artery disease have also been encouraging in reduction of the severely limiting symptoms of refractory angina. Based on these clinical findings, we initiated in September 2004 the largest angiogenesis trial currently ongoing in the United States."

TransPharma Medical and Teva Sign Development, Distribution and Supply Agreement to Develop and Commercialize Unique Transdermal Drug Delivery System

Business Wire via NewsEdge Corporation: LOD, Israel--(BUSINESS WIRE)--Jan. 5, 2005-- TransPharma Medical Ltd., the Israeli-based drug delivery company that develops unique transdermal drug delivery platforms, announced that it has signed a long-term development, distribution, and supply agreement with Teva Pharmaceutical Industries Ltd., one of the top 25 pharmaceutical companies and one of the leading generic pharmaceutical companies in the world. The two companies will jointly develop transdermal drug delivery systems for up to five selected molecules.

"This agreement has great significance for our company as well as for the drug delivery industry in general," said Dr. Daphna Heffetz, CEO of TransPharma. "With our unique Transdermal delivery platform and Teva's reputable pharmaceutical abilities and market presence, this strategic partnership has the potential to bring to the market an innovative system that enables transdermal delivery of complex drugs such as high molecular weight proteins."

The undisclosed financial terms of the partnership are expected to yield long-term value for both partners. Under the agreement, Teva will, worldwide, exclusively market each transdermal drug delivery system and will pay TransPharma milestone payments, royalties, and development costs. The development process will be carried out in cooperation between the two companies. TransPharma is also in contact with other companies for developing transdermal drug delivery systems for other molecules not included in the Teva-TransPharma agreement.

"Teva is pleased to enter into this partnership. Transdermal delivery of therapeutic proteins has always been an important objective, which may provide patients with a convenient replacement to injections," said Dr. Aharon Schwartz, Teva's Vice President of Strategic Business Planning & New Ventures. "We believe that with TransPharma's technology, Teva will be able to bring to the market added value biogenerics."

TransPharma has modified and applied medically proven RF cell ablation technology

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Biotechnology: Perspectives for Drug Targeting, Gene Delivery, and Tissue Engineering." He emphasized the novel application of atomic force microscopy (AFM) in the delivery system and imaging of nanotechnology. The lecture was informative with various applications of AFM, its perspectives for drug targeting, gene delivery, and tissue engineering.

Dr. David J. Brayden, University College of Dublin, Ireland, gave a talk on "In vitro Intestinal Epithelial Models for Polymer Adherence and Drug Transport." He explained various cell lines used for drug transport and correlation with intestinal sacs. He discussed various case studies with respect to drug transport.

Dr. Francesco M. Veronese, Department of Pharmaceutical Sciences-Padua University, Italy, gave a talk on "Peptide and Non-peptide Drug PEGylation for Improved Therapy." He explained in detail aspects of PEGylation for delivery of biotech and other drug molecules.

Dr. Tony D'Emanuele, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, United Kingdom, gave a talk on "Prodrugs and Nanocarriers: Use of Dendrimer Nanocarriers to Enhance Oral Bioavailability." He explained polymer architecture of dendrimers. He showed use of dendrimers conjugated with drugs for increased solubility and increased transport through cell membrane.

Dr. Karsten Cremer, Founder and Principal of Pharma Concepts GmbH, Switzerland, focused on the business aspects of drug delivery systems in his talk on "Advances in Oral Drug Delivery Technologies for Life Cycle Management." He explained the rationale for oral drug delivery technologies for life cycle management.

He also discussed various technologies for orally disintegrating dosage forms like Durasolv, Flashdose, Oraquick, Advatab, Zydis and the advantages of one over the other.

The last session was an interactive session. Dr. Himadri Sen, President of the CRS Indian Local Chapter and President of Pharma Research and Regulatory Affairs, Lupin Ltd., India joined Dr. Cremer on the dias and interacted with the delegates on various issues.

The poster sessions provided an insight into the on going research in drug delivery systems in India. It was highly appreciated by one and all and stimulated intense interaction and interest. The best poster awards went to:

1. Malik R., Misra A., Venkatesh K. S., Tondwal S
   Pharmaceutics Division, Central Drug Research Institute, Lucknow.
   Advanced Centre for Electronic Systems, Indian Institute of Technology, Kanpur.
2. Shah K. A, Patravale V. B.
   University Institute of Chemical Technology, Mumbai.
3. Raghuwnshi Dharmaendra and Kanaujia Parijat.
   Dr. Harsingh Gour University Sagar, India.

In addition to the posters, some exhibitors displayed the novel excipients and machinery used in the dvelopment and manufacture of NDDS.
The symposium was cosponsored by Controlled Release Society, Associated Capsules, Lupin Ltd, Sun Pharmaceuticals, and Colorcon Asia Ltd.

Overall, CRS-2005 nurtured a lot of interaction between academia-industry and government agencies and was a great success! ■

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'Dancing Raisins': This is a very easy experiment for the children to do at home. Firstly, show the group how raisins are denser than water and therefore sink in a beaker of water. Then place the raisins in a solution of lemonade (or baking soda and vinegar). In this case, the raisins will rise to the surface due to the carbon dioxide gas adhering to them. When the raisins reach the surface, the gas is released and subsequently the raisin sinks again.

Summary
Children have always been recognised as the strongest critics; therefore, if we can stimulate them with science and they can appreciate the basic principle behind an experiment then we can hopefully help engender interest for the science disciplines. Whilst the outlined experiments above are clearly aimed at a younger age group, many such similar experiments can be re-developed for use within lecture-based educations helping perhaps to further engage our undergraduates in lectures during our courses and provide additional motivation within learning (and teaching).

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9. http://library.thinkquest.org/10429/high/indexh.htm ■

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to develop a unique way to accurately and safely create micro-channels in the skin's outer surface and enable transdermal delivery of drugs that cannot be delivered using previously existing technologies.

This enables a wide variety of small molecules, biotech drug molecules, vaccines, and other macromolecules, specially formulated in patches, to pass through the skin barrier at therapeutic levels and into the systemic circulation. This patented technology is employed in TransPharma's drug delivery system, ViaDerm®, which enables painless, low-cost, user-friendly drug delivery through the skin. Suitable for home use, it consists of a reusable battery-operated handheld device and a patch containing a drug. The system has been proven in pre-clinical and clinical trials to improve the administration of a wide variety of molecules, including proteins and other macromolecules.

For more information, visit the company's website at www.transpharma-medical.com.

CONTACT: TransPharma Medical Ltd. Shlomit Weisblum, +972-9-9514666 or +972-54-2031974 shlomit@idancom.com

Aerosol technology set for wider use in medication delivery

NewsRxDrugs via NewsEdge Corporation : 2004 DEC 31 - A breakthrough technology that enables liquid medication to be inhaled through the lungs with as much as 90% efficiency and used in a recently launched medical device is set to be more widely used for a range of liquid and dense suspension drugs.

Cambridge (U.K.) based The Technology Partnership (TTP), Europe's leading independent technology development and licensing company, has announced it is working with a number of international companies to commercialize its electronic aerosol technology.

Called TouchSpray, this technology is the basis of the new eFlow Electronic Nebulizer revealed recently by PARI (headquarters in Starnberg, Germany), a developer of aerosol delivery and pharmaceutical formulation development.

TTP also announced a further breakthrough of its TouchSpray technology called 'Reverse Taper TouchSpray', which enables fluids containing very dense suspensions of insoluble compounds to be administered using an inhaler device.

The TouchSpray technology has significant implications for the treatment of chronic respiratory conditions such as asthma, cystic fibrosis, chronic obstructive pulmonary disease, and other similar conditions. However, it also has implications beyond this that will allow pharmaceutical companies to deliver other more delicate compounds and formulations using the more convenient and comfortable inhalation route.

The technology is a breakthrough in that it enables a bioavailability as high as 90% of the inhaled medication delivered to the lung. This compares with only 20-30% typically delivered using conventional 'Metered Dose Inhaler' (MDI) technology.

This significantly enhanced efficiency means physicians would be able to prescribe smaller doses of medication and for dramatically shorter treatment times. An additional potential advantage is the reduction of unwanted side-effects that result from ingestion in the stomach or intestine.

Andrew Sant of TTP commented on the significance, "For new drugs that cannot be administered as a pill, inhalation is by far the preferred delivery route. TouchSpray is a huge advance in that a number of new drugs, including those with large, fragile molecules, can now be delivered successfully via inhalation.

TouchSpray aerosol technology will open up unrivaled new possibilities for the delivery of medication for respiratory and systemic conditions, as well as in atomizing difficult suspension drugs."

Contact lenses deliver drugs to eye

pharma Technologist.com, Jan. 1, 2005 - Researchers in Singapore have developed a novel way of delivering drugs into the eye – loading them into contact lenses.
At present, most ophthalmic drugs are delivered via eye drops, but it is estimated that 95 percent of the activity of medication delivered in this way is lost as the eye drops mix with tears and drain into the nasal canal. This can also cause side effects. Now, researchers at Singapore's Institute of Bioengineering and Nanotechnology (IBN) claim to have solved this problem by developing polymeric contact lens material that can be loaded with active compounds.

Using an *in situ* micro-emulsion polymerisation process, Drs Edwin Chow and Yang Yi-Yan were able to incorporate drugs within a nanostructured polymer matrix. To do this, they used a bi-continuous micro-emulsion as a medium to prepare the drug-loaded contact lens material. This material is ideal for biological and biomedical applications, as it is compatible with human skin cells and corneal epithelial cells, and is also permeable to gases, water, and components of the tear fluid.

Chow, the lead scientist in the project, said: "This process involves combining oil-based monomers, water, and a polymerisable surfactant."

Using the approach, the surfactant binds the monomers and water to create a clear mixture. A specific dose of drugs is added and the combined mixture is then poured into a lens mould. When this mixture is hard, the resulting lens is full of tiny nanometre-sized channels, through which the drug can slowly diffuse onto the surface of the eye.

"This cross-polymerisation of organic components in a bi,continuous micro-emulsion can be initiated readily using either heat or ultraviolet light. Using this simple process, one can easily fabricate transparent and mechanically strong contact lens material in the form of sheets or ophthalmic moulds," according to Chow. Because the lenses are made in a one-step process, cost of manufacturing is kept low, he added.

Another advantage of using these contact lenses over other ophthalmic drug delivery systems is that the drug delivery rate can be controlled and remains effective over longer periods of time. "We can control the flow of the drugs by varying the width of the channels. This can be done by changing the constitution of the mixture that makes up the lens material," said Chow.

IBN is currently looking for partners to commercialize the lens materials and said it has already received enquiries from several contact lens companies. The technology could be used to deliver medication for a range of eye diseases, including glaucoma, a leading cause of blindness that is currently difficult to treat.

Chow noted that the technology allows different types of eye medication to be incorporated into the lens' mixture, and initial studies suggest that glaucoma medications, antibiotics, and anti-inflammatory drugs would all be suitable for delivery in this way.

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the invention include an interface membrane, which is less than 300 micron in thickness, with porosity between 60% and 90%, pore size less than 20 micron and a protein adsorptivity of less than 10 micrograms/cm2.

DEVICES/METHODS

Film-forming agent for drug delivery and preparation for percutaneous administration (Pacific Corporation) US 6750291

A non-sticky film-forming agent for transdermal delivery is described to have superior elasticity, flexibility, and adhesion properties to the skin. The polymer is a blend of polyurethane and an addition polymerization polymer having a carboxylic acid derivative as a functional group. The polyurethane provides flexibility due to low glass transition temperature and allows free body movement for high elasticity. The unique blend shows better adhesion properties without phase separation.

Apparatus for the transdermal treatment of Parkinson's disease (Neuroderm Ltd.) US 6746688

The invention pertains to the transdermal delivery of levadopa to treat individuals suffering from Parkinson's disease. The delivery system includes a container connected to a patch. The formulation and the drug (Levadopa alkyl ester) are kept separately and mixed before administration. The delivery system maintains the stability of the formulation and provides continuous penetration of drug through the area of the skin under the patch, avoiding the usual fluctuations of levadopa in the body.

Transdermal delivery devices containing polydiorganosiloxane polymers to regulate adhesive properties (Watson Pharmaceuticals, Inc.) US 6730318

The transdermal system consists of a matrix type patch, which adheres to the skin and uses an effective amount of a polydiorganosiloxane polymer fluid as an adhesion-adjusting agent. The polymer fluid incorporated into the pressure sensitive adhesive regulates the adhesive strength and does not cause irritation or ulceration upon removal. Also, the device adheres to the skin just long enough to accomplish its purpose and does not leave a significant amount of residue on the skin.

Cutaneous administration system (Hewlett-Packard Development Company, L.P.) US 6723077

The invention pertains to the cutaneous delivery of bioactives using a jet dispenser. The jet dispenser works similar to inkjet technology used in printing, and sprays the active through a spacer onto a cutaneous target. The device contains a controller that has the capacity to respond to changes in multiple drug regimens, thus customizing the delivery to the patient. The dispenser can act as an electromechanical patch and can serve to provide long-term or extended delivery of the drug.

Compositions for efficient release of active ingredients (The Proctor & Gamble Company) US 6716441

The invention consists of an oleaginous composition that effectively releases hydrophilic skin care ingredients, such as vitamins, hexamidine, truacetin, and phytic acid, in their active forms. The formulation also incorporates a barrier protectant with good staying power on the skin. Such protectants include fatty acids, fatty alcohols, animal oils, and animal fats. The protectant coats the skin to protect the skin against direct contact with bodily exudates as well as penetration by moisture or irritants. The invention provides continuous release for long lasting benefits and could be applied topically with the help of canisters, sticks, aerosol dispensers, and web substrates including pads, bandages, wipes, absorbent articles, etc.

Transdermal therapeutic systems having improved stability and their production (LTS Lohmann Therapie-Systeme AG) US 6699498

The invention consists of a Transdermal Therapeutic System (TTS), which delivers an active agent and at the same time minimizes its oxidative degradation during storage. This is achieved by using only those formulation constituents, which are substantially free of hydroperoxides. The recipe consists of ingredients in unique proportions, such that they have a peroxide number (PON) of not more than 20, preferably with particular preference not more than 5. Reducing substances disclosed include sodium sulfite and sodium hydrogen sulfite in lower alcoholic concentrations.

System and methods for local intradermal treatment (Masters) US 6696078

The invention pertains to the transdermal delivery of single/multiple pharmaceutical agents for local intradermal treatment of a dermal invasion/injury by an identified pathogen, which is carried by an identified vector. The system could be used by individuals at high risk of being infected with a pathogen after dermal injury. The invention uses a patch containing a mixture of a penetration enhancer, a macrolide antibiotic and a tetracycline antibiotic and is applied to the site of dermal injury where it targets the pathogen before inoculation.

Transdermal delivery of an anti-inflammatory composition (Dickson) US 6689399

The invention pertains to the use of capsacinoid in conjunction with a primary amine, such as glucosamine in a high concentration. The two ingredients act synergistically to provide pain relief from joint and muscle pain. This method claims to provide prolonged relief without adverse events such as burning and itchy sensations normally associated with topical capsaicin administration. It can also be used to treat joint/muscle pain associated with an inflammatory response.

Titratable dosage transdermal system (Euro-Celtique, S.A.) US 6682757

The system involves a multiple-patch unit that is connected along borders. The patches provide systemic delivery of a therapeutic agent in dosages that are proportional to the number of units applied. Each patch unit contains a firm backing layer and a drug layer containing the therapeutic agents.

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The material could also be modified to produce self-lubricating contact lenses to relieve the discomfort of contact lens wearers suffering from dry eyes, while other potential applications include loading wound-healing drugs in the lenses to treat corneal wounds, or as a means of modifying the lens material for use in vision correction.

The researchers are now conducting *in vivo* studies in laboratory animals, in order to understand the detailed pharmacokinetics of drug release with their lenses.

Liposomal encapsulation improves efficacy of L-dopa

NewsRxPainCNS via NewsEdge Corporation: 2004 DEC 27 - (NewsRx.com & NewsRx.net) "Parkinson disease is a neurodegenerative disease and its symptoms are relieved" by administration of LD, which is converted by neuronal aromatic L-amino acid decarboxylase (AADC), restoring dopamine (DA) levels in surviving neurons," scientists in Italy explained.

In order to minimize unfavorable side effects, A. Di Stefano and colleagues at G. D'Annunzio University studied new dimeric LD derivatives, as potential prodrugs for Parkinson therapeutic treatment.

"To improve the bioavailability of the synthesized prodrugs, they were encapsulated in unilamellar liposomes of dimiristoylpho sphatidylcholine (DMPC) and cholesterol (CHOL)," the investigators said. "*In vivo* microdialysis was used to monitor the striatal LD and DA concentrations after i.p. administration of new delivery systems."

"Bioavailability evaluation was performed by means of the HPLC-EC method," according to the report. "The striatal levels of LD and DA were remarkably elevated after i.p. administration of liposomal formulation of prodrug (+)-1b ([(O,O-diacetyl)-L-dopa-methylester]-succinyldiamide)."

"This formulation showed about 2.5-fold increase in the basal levels of DA in dialysate rat striatum, suggesting that liposomal formulation of (+)-1b significantly increases LD and DA concentrations with respect to equimolar administration of LD itself or free prodrug (+)-1b," the researchers concluded.

Di Stefano and coauthors published their findings in the *Journal of Controlled Release* (Evaluation of rat striatal L-dopa and DA concentration after intraperitoneal administration of L-dopa prodrugs in liposomal formulations. J Control Release, 2004;99(2):293-300).

Additional information can be obtained by contacting A. Di Stefano, Universita G. D'Annunzio, Dipartimento di Scienze del Farmaco, Via Vestini 31, I-66100 Chieti, Italy.

Method for prolonged pulmonary insulin delivery

NewsRxDiabetes via NewsEdge Corporation : 2004 DEC 27 - (NewsRx.com & NewsRx.net) -- Encapsulation of insulin-cyclodextrin complex in PLGA microspheres is a new approach for prolonged pulmonary insulin delivery.

"The insulin administration by pulmonary route has been investigated in the last years with good perspectives as alternative for parenteral administration. However, it has been reported that insulin absorption after pulmonary administration is limited by various factors. Moreover, in the related studies one daily injection of long-acting insulin was necessary for a correct glycemic control," scientists in Brazil report.

"To abolish the insulin injection, the present study aimed to develop a new formulation for prolonged pulmonary insulin delivery based on the encapsulation of an insulin: dimethyl-beta-cyclodextrin (INS:DM-beta-CD) complex into PLGA microspheres," said Marta Maria Gontijo de Aguiar and collaborators at the Federal University of Minas Gerais and the University of Sao Paulo. "The molar ratio of insulin/cyclodextrin in the complex was equal to 1:5. The particles were obtained by the w/o/w solvent evaporation method. The inner aqueous phase of the w/o/w multiple emulsion contained the INS:DM-beta-CD complex."

"The characteristics of the INS:DM-beta-CD complex obtained were assessed by 1H-NMR spectroscopy and circular dichroism study," reported the investigators. "The average diameter of the microspheres prepared, evaluated by laser diffractometry, was 2.5311.8 micron and the percentage of insulin loading was 14.761.1. The hypoglycemic response after intratracheal administration (3.0 IU/kg) of INS:DM-beta-CD complex-loaded microspheres to diabetic rats indicated an efficient and prolonged release of the hormone compared with other insulin formulations essayed."

Aguiar and associates published their study in the *Journal of Microencapsulation* (Encapsulation of insulin-cyclodextrin complex in PLGA microspheres: a new approach for prolonged pulmonary insulin delivery. J Microencapsul, 2004;21(5):553-564).

For additional information, contact Armando da Silva Cunha Jr., Laboratory of Pharmaceutical Technology, Federal University of Minas Gerais, Av. Antonio Carlos, 6627 CEP: 31270010-Belo Horizonte-MG, Brazil.

West Pharmaceutical Services Concludes Drug Delivery Strategic Review

PR Newswire via NewsEdge Corporation : LIONVILLE, Pa., Dec. 27 /PRNewswire-FirstCall/ -- West Pharmaceutical Services, Inc. (NYSE: WST), the global market leader in closure systems and syringe components for use with injectable drugs, today announced that it has signed a definitive agreement to sell a substantial majority interest in its drug delivery business to a new company formed by Warburg Pincus to facilitate the acquisition. Closing is expected to occur early in 2005.

The drug delivery business will operate from West's facility in Nottingham, England, and will employ all of the division's employees at that location. Drug Delivery operations at West's Lionville facility will wind down following the transaction. Approximately 30 jobs will be eliminated and the Company has notified affected employees.

In June of 2004, the company announced that it would conduct a strategic review of its drug delivery business, and that it intended to complete that process by the end of 2004. The company's drug delivery division will be classified as a "discontinued operation" in the company's subsequent financial reports, including its clinical services business, which the company will continue to operate while it is held for sale or other disposition. The ownership interest in the new company will be accounted for on a cost basis.

Donald E. Morel, PhD, West's Chairman and Chief Executive Officer, commented, "I am pleased that we have completed the strategic review of options for the Drug Delivery Division and are able to announce this transaction on our original schedule. This agreement will result in significant new funding for the drug delivery technologies in partnership with world-class financial sponsors who understand the market for these technologies, allowing us to participate in the ultimate success of the business

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ENHANCERS

Transdermal drug delivery system for anti-inflammatory analgesic agent comprising diclofenac diethylammonium salt, and the manufacturing method thereof (Samyang Corporation) US 6723337

The invention pertains to the use of diclofenac diethylammonium salt as an anti-inflammatory analgesic agent in a transdermal delivery system. A matrix layer enhances the penetration and adhesion of the drug due to a non-aqueous acrylic polymer used as an adhesive constituent. A non-ionic surfactant and terpene serve as absorption enhancers. The addition of a dissolution assistant to the above makes it possible for more amount of drug to be available for absorption.

Transdermal administration of pharmacologically active amines using hydroxide-releasing agents as permeation enhancers (Dermatrends, Inc.) US 6719997

The invention involves administration of a pharmacologically-active amine in combination with a hydroxide-releasing agent as a penetration enhancer. The hydroxide-releasing agent is used in predetermined amounts that increases the flux of the drug and does not cause any damage. Also, the use of the agent makes it unnecessary to convert the acid addition salt to the free amine base before incorporation into the transdermal delivery device.

Formulations for the transdermal administration of fenoldopam (Alza Corporation) US 6699497

Fenoldopam, administered along with a permeation enhancer, provides for the sustained release of the drug at an effective rate to provide treatment for hypertension, congestive heart failure, or acute renal failure. The system uses a reservoir containing Fenoldopam to maintain therapeutically effective levels. Also disclosed are methods to improve the compliance of patients by providing compositions, devices, and methods for the transdermal administration of Fenoldopam at an effective rate.

Hyaluronate lyase used for promoting penetration in topical agents (Esparma GmbH) US 6719986

Hyaluronate lyase obtained from microbial fermentation is used as a penetration enhancer. The formulation consists of an agent composed of the hyaluronate lyase and a hydrophilic medicament in different galenic formulations. Due to the unique origin of the enzyme, the formulation does not lead to skin irritation even after several hours of exposure. The invention also includes colloidal carrier systems and can be used to treat skin diseases or functional disorders of the skin. ■

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without committing further capital. This, in turn, will focus management on building the long-term growth and profitability of West's pharmaceutical systems businesses." Company's website http://www.westpharma.com.

Novel *in vitro* model of blood-cerebrospinal fluid barrier developed

NewsRxPainCNS via NewsEdge Corporation : 2004 DEC 20 - (NewsRx.com & NewsRx.net) The BCSFB "plays a key role in the influx and efflux transport of drugs and endogenous substrates in the cerebrospinal fluid (CSF)," scientists in Japan noted.

"To clarify the molecular mechanism of the BCSFB transport system, a new *in vitro* BCSFB model, i.e. an immortalized rat choroid plexus epithelial cell line (TR-CSFB)," was "established from transgenic rats harboring a temperature-sensitive simian virus 40 large T-antigen gene," in a study conducted by K. Hosoya and coauthors at Tohoku University.

"TR-CSFB cells grow well at 33 degrees C because of activation of the temperature-sensitive large T-antigen," the collaborators explained. "These cells have a polygonal epithelial cell morphology and express typical choroid plexus epithelial cell markers, such as transthyretin (TTR) and Na+, K+-ATPase, as well as the transporters, system A and ABCC1/mrp1."

"The localization of Na+, K+-ATPase, and the transport direction of system A, are polarized in TR-CSFB cells as is the case *in vivo*," test results showed. "TR-CSFB cells exhibit L-proline and L-glutamic acid uptake activities and may reflect the CSF-to-blood efflux transport functions involving these amino acids *in vivo*."

"Using TR-CSFB cells, we found for the first time that oatp3 is expressed at the BCSFB," according to the report. "TR-CSFB cells appear to be a useful *in vitro* model of the BCSFB for the study of drug transport, BCSFB transporters, and the regulation of BCSFB functions," the researchers concluded.

Hosoya and colleagues published their study in *Advanced Drug Delivery Reviews* (A new *in vitro* model for blood-cerebrospinal fluid barrier transport studies: an immortalized choroid plexus epithelial cell line derived from the tsA58 SV40 large T-antigen gene transgenic rat. Advan Drug Delivery Rev, 2004;56(12):1875-1885).

For more information, contact T. Terasaki, Tohoku University, Graduate School of Pharmaceutical Sciences, Department of Molecular Biopharmacy and Genetics, Aoba Ku, 6-3 Aoba, Sendai, Miyagi 9808578, Japan.

Drug delivery system with EDTA is safe intravaginal barrier

NewsRxWomensHealth via NewsEdge Corporation : 2004 DEC 23 - (NewsRx.com & NewsRx.net) -- A female-controlled drug delivery system (FcDDS) containing sodium dodecyl sulfate as a microbicide, ethylenediaminetetraacetic acid (EDTA) as a synergistic microbicide, and lactic acid as a pH modulator is biocompatible and a safe intravaginal barrier device against sexually transmitted diseases, University of Missouri pharmaceutical researchers report.

B.K. Warrier and colleagues evaluated "the host response of the vagina to the FcDDS … through biocompatibility tests including cell viability, estrogenicity, and cytotoxicity assays on HeLa cervical cells and NIH:Ovcar-3 ovarian cells. Gel electrophoresis and reverse transcriptase polymerase chain reaction assays on HeLa cervical cell lines were also performed to elucidate the effects of EDTA on the expression of particular proteins of interest."

The research team reported, "The results of the cell viability test showed no significant difference in viability of cells upon exposure to EDTA at concentrations less than 0.035% that was reported to exert spermicidal activity. EDTA at concentrations less than 0.035% did not cause any cytotoxicity."

"The results of reverse transcriptase polymerase chain reaction analysis revealed that EDTA induced the expression of a 67-kDa protein in HeLa cells, which was identified as elastin binding protein (a part of the elastin receptor complex)," the scientists said. They concluded, "This work has demonstrated that FcDDS containing EDTA is biocompatible and safe to be used as an intravaginal barrier device."

Warrier and coauthors published their study in the *Journal of Biomedical Materials Research*: Part A (Biocompatibility of components of a female controlled drug delivery system. J Biomed Mater Res Part A, 2004;71A(2):209-216).

For more information, contact C.H. Lee, University of Missouri, School Pharmacy, Division Pharmaceutical Science, Department of Pharmaceutical, 5005 Rockhill Rd., Katz Bldg 108, Kansas City, MO 64110, USA.

OptiNose takes nasal delivery to a higher level

In-pharmatechnologist.com, 21/12/2004 - Norwegian drug delivery specialist OptiNose has raised €4.5 million in a new financing that will support the development of its nasal delivery system, designed to hike efficiency over current devices. The financing comes at the end of a busy year for the company, which established a UK subsidiary and completed its first Phase I clinical trial of a product based on its technology.

OptiNose was founded in 2000 to commercialize a novel technology designed to dramatically increase the efficiency of nasal drug delivery, and open up this route to a wider range of therapeutic agents. Nasal delivery is of interest to drug developers as it can provide good systemic absorption, and OptiNose claims that its technology can rival intravenous administration in its speed of action.

The main limitation with nasal delivery is that the main approach to improving penetration of the drug – using smaller particles – heightens the risk that the drug could be deposited in the lungs. But OptiNose has developed a system that isolates the nasal passages and prevents this from happening.

The firm's bi-functional delivery system relies on two elements of the nose's anatomy. Firstly, during exhalation the soft palate closes, cutting off the nasal passages from those of the lung. Secondly, once the soft palate is closed, a passage opens between the two nostrils to create a common nasal airway.

OptiNose has addressed these two anatomical factors with its drug delivery device. The inhaler is inserted into one nostril by a sealing nozzle as the subject blows into a mouthpiece. The combination of closed soft palate and sealed nozzle creates an airflow which enters one nostril, travels through the common pathway and exits through the other nostril, with no deposition in the lung.

By altering the conformation of the device – for example, by partially blocking the exit of the airflow, OptiNose can target drugs to specific regions of the nasal passages, such as the adenoids, sinuses, middle ear, or even the olfactory bulb – providing a means

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of delivering drugs directly to the central nervous system.

The company is initially focused on improving the delivery of generic medicines, and the new funding will enable the development of further versions of the device, including a multi-use device to better satisfy the needs of some potential partners.

"By combining our delivery technology with selected off patent drug substances we can create combination products with safety and efficacy profiles that transcend the performance of ordinary nasal sprays," said OptiNose CEO Helena Djupesland.

She noted that the device is suitable for single or multi-dosing of both liquid and powder formulations, with either topical or systemic action. Areas where nasal delivery is of particular interest include obesity, vaccines, rescue medications such as morphine, epilepsy, and panic attacks, as well as obvious targets such as sinusitis and rhinitis.

The company recently published a study showing there is no lung deposition with the bi-directional technology and will be publishing its Phase I trials results – using the device to deliver a neuroactive compound - in 2005.

Kalam to Open Sun Pharmaceutical's Latest R&D Center

(President Kalam to inaugurate R&D facility at Tandalja)
INDIA BUSINESS INSIGHT
via NewsEdge Corporation : Sun Pharmaceuticals Ltd (SPL), Vadodara, Gujarat, is setting up a huge research and development centre.
President APJ Kalam will be inaugurating the 200,000 square foot R and D facility at Tandalja on 14 Dec 2004. Sun Pharma has called it a new threshold in its initiative in drug discovery innovation. The facility is claimed to be one of a kind in Gujarat and will be dedicated to research in process chemistry, dosage form development, and novel drug delivery systems. The R and D facility spread across16 acres has modern laboratories for a dedicated team of 325 newly recruited scientists. The team would soon be strengthened with the addition of 125 pharmaceutical researchers. The fully-equipped laboratories for biological and analytical development would focus on pharmacokinetics, tissue culture, and screening. Sun Pharma is the fifth largest pharmaceuticals company in the country. It has 33 patents in drug delivery and reverse engineering and has 331 filings for approval.

Noven Issued U.S. Patent for Transdermal Delivery of ACE Inhibitor

MIAMI--(BUSINESS WIRE)--Dec. 16, 2004--Noven Pharmaceuticals, Inc., a leading developer of advanced transdermal drug delivery technologies and prescription transdermal products, today announced that it has been issued a new U.S. patent.

U.S. Patent No. 6,805,878, entitled Transdermal Administration of ACE Inhibitors, is effective through the year 2021. The patent relates to a method for delivering a therapeutically effective amount of enalaprilat, the pharmaceutically active form of the drug enalapril, by means of transdermal drug delivery systems (patches). Enalapril is an angiotensin-converting enzyme (ACE) inhibitor generally indicated for the treatment of hypertension and other heart conditions.

"Our science and legal teams continue to work to expand our intellectual property portfolio," said Robert C. Strauss, Noven's President, CEO & Chairman. "We currently hold over 30 U.S. and over 180 foreign patents, and more than 130 patent applications are pending worldwide."

Novel semicrystalline films developed for drug delivery

NewsRxBlood via NewsEdge Corporation : 2004 DEC 16 - (NewsRx.com & NewsRx.net.) Semicrystalline films of poly(vinyl alcohol) (PVA) were prepared by annealing amorphous PVA films at temperatures above the glass transition temperature of 85 degrees C, thus allowing the macromolecules to form crystallites, which stabilized the films and made them behave as if they were chemically cross-linked.

"Films were prepared by casting a 15% aqueous PVA solution onto glass slides and annealing them at temperatures ranging from 90 to 120 degrees C at 15 to 90 minutes. The degree of crystallinity of the dry films was measured by differential scanning calorimetry," scientists in the United States report.

"As the annealing time increased," wrote N.A. Peppas and coworkers, "the degree of crystallinity increased lip to a maximum value of about 48%. Swelling studies were performed by placing the films in deionized water at 37 degrees C until they reached equilibrium, typically in 3 to 4 days.

"The water uptake was inversely proportional to the degree of crystallinity. Poly(acrylic acid) (PAA) and poly(ethylene glycol) (PEG) were blended with PVA in amounts of 15 and 25 wt% to add desirable properties to the ensuing films. Annealing studies showed that the addition of PAA decreased the crystallinity of the films while introducing pH sensitivity."

"Swelling studies of the PAA/PVA blends were performed in phosphate buffer solutions at varying pH levels. The studies showed that increasing pH from 3 to 6 caused an increase in the swelling of the films. Annealing studies also showed co-crystallization of PEG and PVA and molecular interactions between the molecules," researchers said.

The authors concluded, "These films exhibit excellent properties for drug delivery applications due to their stability, lack of toxic leachable compounds, and high swellability."

Peppas and colleagues published their study in the *Journal of Drug Delivery Science and Technology* (Semicrystalline poly(Vinyl alcohol) films and their blends with poly(Acrylic acid) and poly(Ethylene glycol) for drug delivery applications. J Drug Deliv Sci Technol, 2004;14(4):291-297).

For more information, contact N.A. Peppas, University Texas, Department Chemical Engineering, 1 University Station, C0400, Austin, TX 78712, USA. ▪

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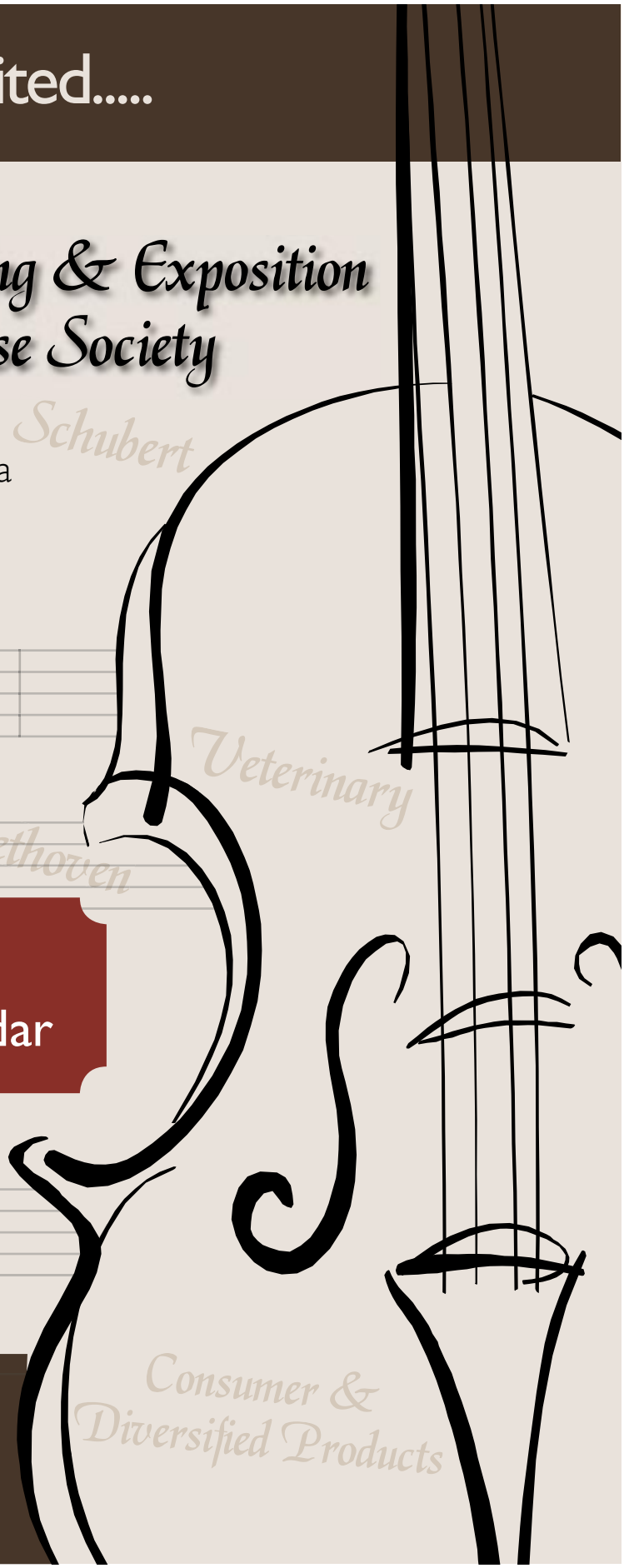

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Issue 3 deadline
July 18, 2005

Calendar of events

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

Third Annual Nanomedicine and Drug Delivery Symposium
September 25-27, 2005
University of Maryland, Baltimore
Baltimore, Maryland, USA
www.pharmacy.umaryland.edu/nanomedicine/

MIT, Kyoto University, CRS, Japanese Soc. for Drug Delivery Systems 8th US-Japan Symposium on Drug Delivery Systems
December 18-23, 2005
Westin Maui Resort & Spa
Maui, Hawaii, USA
cjbeal@mit.edu
http://web.mit.edu/langerlab
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Pharmaceutical Sciences World Congress
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www.fip.org/PSWC/index1.htm

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34th Annual Meeting of the Controlled Release Society
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35th Annual Meeting of the Controlled Release Society
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