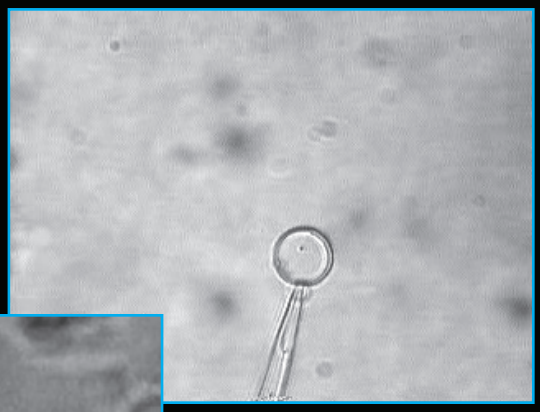
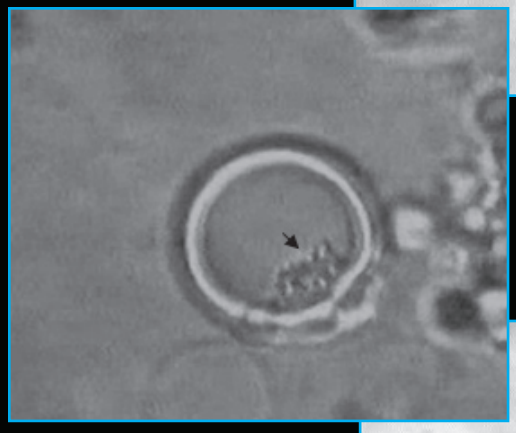
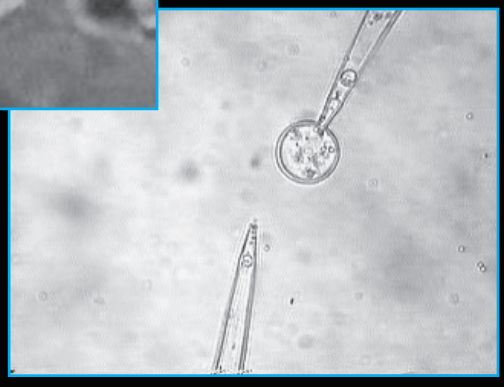
CONTROLLED RELEASE SOCIETY

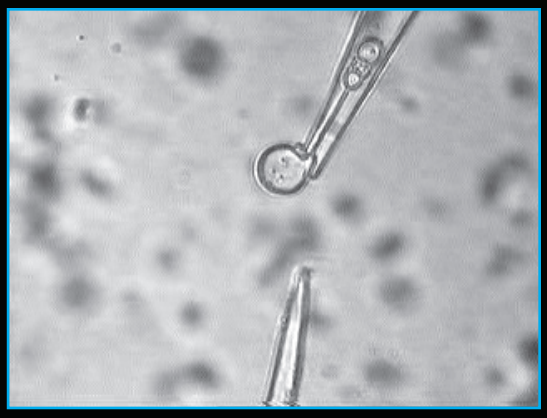
Volume 22•Number 3•2005

NEWSLETTER





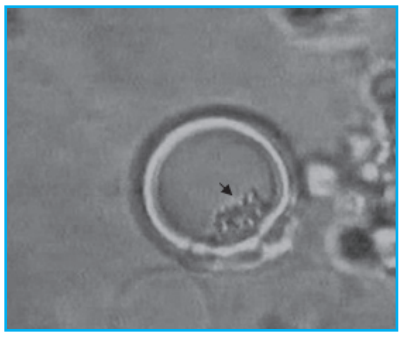




CONTROLLED RELEASE SOCIETY
NEWSLETTER
Volume 22 • Number 3 • 2005

inthisissue

On the cover –



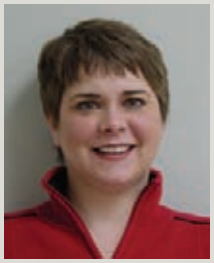
Flocculation of polystyrene microspheres inside an oligolamellar liposome on storage. Courtesy of Dr. B. Nassari and Prof. A. T. Florence, The School of Pharmacy, University of London.

Steven Giannos
Industrial Editor

Cathy Ludwig
Editor

Bozena Michniak
Editor

Yvonne Perrie
Editor



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Managing Editor

Vladimir Torchilin
President

Editors
Bozena Michniak & Yvonne Perrie

Industrial Editor
Steven Giannos

Thanks to members of the Publications Newsletter Subcommittee for helping with this issue: Martyn Davies, Jerome Barra, David Brayden, and Agis Kydonieus.

The Controlled Release Society Newsletter is the official newsletter of the Controlled Release Society. The newsletter is published three times annually providing scientific and technical information pertinent to the controlled release community and news about society and chapter activities. Members receive the newsletter via mail or online at www.controlledrelease.org.

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Contact register@controlledrelease.org regarding meeting registration.

Contact visibility@controlledrelease.org for information about exhibiting, advertising or other visibility opportunities.

Contact planner@controlledrelease.org for meeting program information.

FROM THE *Editors*

by Yvonne Perrie

The summer has gone, the students are back at University, and there is still plenty of paperwork outstanding which you promised yourself you would do over the summer break - but don't despair, here we bring you another CRS newsletter full of news and views; something to read over that well deserved cup of tea. In this issue we have lots of news and reports from the recent CRS conference in Miami, and I know we all say this every time, but the 32nd Annual CRS meeting in Miami really was the best yet. There was an excellent line up of presentations from a range of areas and it was difficult to decide which session to attend, a problem that continued into the evenings with events such as the Education Committee hosting a SPYS reception in parallel with the Vet reception. So be sure to look through the articles and photos to find out more on what's hot in the world of controlled release. Or you can just have a look to see if you can perhaps spot one of your colleagues badly dancing the night away at the Gala Dinner, a collection of scientists on the one dance floor is always worth a look.

However, if you are weary of hearing how good Miami was, do not despair. There is plenty more in this issue for you. We keep you up-to date with a round-up of the news from the field of controlled release, with a focus in this issue on recent transdermal patent applications, and we provide you a selection of the latest publications in veterinary controlled release research. As if that was not enough, there is also an article on parameter models for film-coating and a Scientifically Speaking article on Polysialic acids: who says PEGylation is the only way to give your drug stealth characteristics?

Other news from the CRS - our newsletter is now going out 4 times a year (rather than 3 if you were wondering) so this gives us more opportunity to feature more of your research; be you working in academia, government or industry, we have sections for you. So if I didn't already collar you in Miami, be sure to have a think about what you would like to submit. Guidelines for authors are on the CRS website or you could contact either my fellow editors at newsletter@controlledrelease.org or me directly at (y.perrie@aston.ac.uk). We are always happy to hear from you.

Wishing you all the best, and hoping to see you in Vienna in July 2006 if not before. ■

From the *President*

As we start the 2005-2006 year for the Controlled Release Society, there are a few people who need recognition for their contributions to Society during the 2004-2005 year.

Prof. Dr. Jennifer Dressman, thank you for your strong leadership of the Society. Your drive and have commitment the Society are greatly appreciated.

To Martyn Davies, Scientific Secretary, and the Program Committee, on behalf of the Society, I thank you for an outstanding program during the 2005 Annual Meeting and Exposition. You exceeded our expectations with the breadth and quality of the program.

The Education Committee, lead by Education Secretary Michael Rathbone, also deserves our thanks. They have shared their time and talents with us through the creation and introduction of the **Virtual Library**, and for organizing the Annual Meeting and Exposition *Young Scientist Workshop* and the *Get Up! Get Educated!* programs. Thank you.

Going forward

In this new millennium, pharmaceutical biotechnology will become increasingly important in all areas that improve the quality of living. Within this context, the role of the Controlled Release Society, which is the only international society covering all possible and imaginable areas of new formulations and new delivery systems of biologically active compounds, is unlikely to be overestimated.

Currently, the Society enjoys a well-deserved international reputation and unifies researchers representing related areas from all over the world. Our Annual meetings are among the most significant in biomedical sciences and the *Journal of Controlled Release* is among the highest rated journals in the field of experimental pharmacology. However, we must be prepared to meet the challenges of the future and continue to work hard to maintain our current level of performance. The field is ever-growing. Thus, there is room for improvement in all aspects of the Society.

I extend a personal thank you to Jennifer Dressman, the 2004-2005 Board of Directors and Scientific Advisory Board. Their initiatives during the 2004-2005 year have positioned the Society to succeed in implementing a long-term multidirectional plan.

To achieve the strategic development the Society seeks, the following aims will be explored: 1. Increase public awareness of the Society's achievements, goals and challenges in the field via printed materials, public presentations and mass media. 2. Impact the community by increasing the Society's role in education. Currently, only a few courses on drug carriers, drug delivery, and drug targeting are offered within the programs of pharmaceutical education throughout the world. The Society via its university-associated members can improve this situation. 3. Increase the importance of the Society within the scientific community through its association with new fields, such as molecular biology, computer science and engineering. 4. Expand involvement in clinical medicine by attracting clinicians and new clinical fields. Currently, we already have experience with DNA and antisense therapy, and have just started our penetration into the huge diagnostic community. This activity should be continued. 5. Refresh our ideas and approaches by attracting input from more young scientists, clinicians and industrialists as well as attract other disciplines 6. Broaden international role for the Society through its activity in new geographic areas, such as Eastern Europe.

Vladimir Torchilin, President

Plans for Vienna are indicating that a strong program is in development. Many nanomedicine activities are going to be incorporated in the program. Watch for details over the next few months on our website at http://www.controlledrelease.org or via the member newsletter.

During the June 2005 Board of Directors meeting, the Board elected Ad Hoc Board Members Jennifer Dressman, Marketing Development, Michael Rathbone, Education Secretary, and James Anderson, Publishing Committee. These veteran society members will add a breadth of knowledge and experience to aid in the direction of the Society.

The Publishing Committee is a new committee to the Society. The charge for the committee is to work with our publisher, Elsevier, to produce books on controlled release.

As we move forward, we will continue to maintain the Society in a strong financial position and work on adding greater benefits to our membership. Contact me at president@woundheal.org to share your ideas for the Society. Together we will continue to make the Controlled Release Society the international choice for controlled release membership. ■

Highlights of 2005 Annual Meeting

Rainer Hoffmann Product through Science Award Robert Langer Presented by: Dr Hans Junginger of Naresuan University

Left to Right: Langer, Dressman, and Junginger

Calandra and Bhalla

Graduate Student/Post-Doc Outstanding Paper in Consumer & Diversified Products Paper Award Co-sponsored by Firmenich Winner: Amardeep Bhalla Presented By: Michael Calandra, Vice President of Firmenich

Burger and Dressman

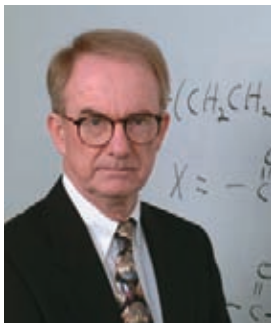
2005 Platinum Level Sponsor Award ICI Accepting This Award Is Jack Burger, Senior Scientist, Food Physics

Jorge Heller Journal if Controlled Release Outstanding Paper Award Co-Sponsored by: Elsevier Winner: Dennis E. Discher Presented by: Kim Briggs, Senior Publishing Editor, Elsevier

Briggs and Discher

Verma and Law

Outstanding Paper Awards Winner: Daya D. Verma Presented by: Deneen Law, Marketing Operations Manager Of 3M Drug Delivery Systems



Nagai Innovation Dr. J. Milton Harris

Innovative Aspects of Oral Drug Delivery and Absorption Graduate/Post-Doc Award Co-Sponsored by Capsugel Stefanie Hornung (Winner) Jason Vaughn (Honorable Mention) Stephan Motz (Honorable Mention) Kota Kodama (Honorable Mention) Presented by Dr. Jan Vertommen, Business Development Manager, Pfizer

Left to Right: Motz, Vaughn, Hornung, Kodama, and Vertommen

Brayden and Schmidt

Outstanding Veterinary Paper Award
Co-sponsored by PR Pharmaceuticals
Winner: David Brayden
Presented by: Dr. Paul Schmidt, Vice President, Pharmaceutical Research and Development, PR Pharmaceuticals

Wilding and Perrett

Career Achievement in Oral Drug Delivery (Eurand)
Winner: Dr. Ian Wilding (right)
Present by: Dr. Stephen Perrett (left), Corporate Technology Director at Eurand International

Outstanding Pharmaceutical Paper Award
Co-sponsored by CyDex, Inc.
Winner: Amit Jain
Presented by: Joe Fix, President, Cydex, Inc

Jain and Fix

Novel Approaches in Oral Drug Delivery
Present by: Dr. Stephen Perrett, Corporate Technology Director at Eurand International
Jongbin Lee (United States of America), Honorable Mention
Jules Jacob (United States of America), First Place

Lee, Perrett, and Jacob

Scott and Hashida

Founders Award
Mitsuru Hashida (winner)
Presented by: Drew Scott, Director, Business Development, ALZA

Young Investigator Award
Dr. Mark R. Prausnitz

Meeting Round-up

32nd Annual Meeting & Exposition of the Controlled Release Society

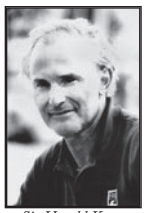
By Yvonne Perrie
Aston Pharmacy School, United Kingdom

Once again the CRS conference committee organised an excellent programme for us in Miami with a range of sessions catering for all and including Controlled Release of Flavors and Food ingredients, Vaccines, Tissue Engineering, Advances in Process Technology, and Cell Culture models. The education committee had obviously been very busy and had organised a range of sessions for anyone under the 40 (however I do not believe proof of age was required). The education committee have provided a full round up of these events including their 'Get Up! Get Educated' sessions which ran at 7am on Monday and Tuesday. Probably with good hind-sight we were not asked to 'get up and educated' on Wednesday morning after the CRS banquet where much dancing was undertaken by many.

Robert Langer

Other highlights included the excellent range of plenary speakers - Robert Langer, Judah Folkman and Sir Harry Kroto all of whom gave very insightful and interesting presentations. Robert discussed the 'gene therapy bottleneck', and attributed gene therapy as an area of much excitement and disappointment but he noted effective delivery systems could still enable these systems to improve, in particular with many of the new polymer systems which were becoming available. Judah presented a very interesting report on tumour angiogenesis. In particular, he demonstrated how controlling the rate of drug delivery can change the pharmacological action of a drug. This was nicely demonstrated by some work he did with aesthetic gases which can have an aesthetic or analgesic action depending on their rate of delivery. On Wednesday, Sir Harry took us on a NanoSpace Odyssey, and discussed the role of nanotechnology but stressed this is just a new perspective for chemistry. He noted the diverse range of applications these new nanostructures had from electrical conductors to drug release technology, but currently our lack of expertise in this area limits their fantastic potential. He also noted the work that the Vega Science Trust was doing (www.vega.org.uk). This is a non-profit trust which broadcasts science programmes over the internet for free. These are produced by experts in science and engineering and he called upon us all to visit, use and expand this excellent resource

M. Judah Folkman



Sir Harold Kroto

Perhaps one of the most unusual highlights of the meeting was the awards ceremony which opened with a group of Salsa Dancers, which at 8am was a bright and loud way to start the day. Indeed most of the audience rather enjoyed watching the reaction of those people on stage who were located particularly close to the dancers. Many of the awardees are featured in the photo's shown on page 4, amongst them, Dr David Brayden was noted to have made a clean sweep of the Vet Research related awards.

Other events included the Pearls of Wisdom which hotly debated if non-injectable vaccines should be a low priority in Vaccinology, this session is reviewed in our Pharm news section. In the parallel Pearls session, the planning for a University spin-out company were debated by Ian Wilding (Pharmaceutical Profiles) and Clive Wilson (Biomaterials), with Clive arguing that a lifestyle approach can provide for a more considered balance between enjoying the experience and return of investment. In the C&DP Pearls of Wisdom session, Harlan Hall (Coating Place Inc., USA) presented his case that there were more advantages and less disadvantages to providing contract research services, as opposed to supplying contract manufacturing/ development services, citing high capital requirements, high regulatory costs and danger of obsolence as some of the disadvantages of contract manufacturing. Sam Shefer (Salvona, USA) presented the opposing position that providing research services has it's disadvantages as well.

Overall it all added up to yet another excellent CRS conference leaving all attendees looking forward to Vienna next year. ■

CRS Miami Meeting 2005 Lunch-With-Experts Session

By Chun Wang
University of Minnesota, US

The idea behind 'Lunch with an expert' came after Chun Wang attended an American Society of Gene Therapy conference in 2004 and they had a series of sessions called meet-the-experts. This year's experts included: Robert S. Langer, Elazer R. Edelman, Kam W. Leong, Derek O'Hagan and Vincent H. L. Lee. Over 50 graduate students and/or young scientists were invited to have lunch with one of the above experts.

When asked for her opinion Melanie Walsh, one of the invited 'Lunch with the Expert' participants commented, "As I am new to the controlled release field, I was delighted to have the opportunity to meet Kam Leong at the CRS 'lunch with the experts' session at the 2005 CRS conference, Miami Beach. Arranging to have lunch with Dr. Leong was as simple as replying to an e-mail, picking up a free lunch box and arriving at his table. Dr. Leong was very open and welcoming and after introducing himself, he asked everyone at our table to tell him a little about ourselves (they were nine of us present in total). He showed an interest in our work and even stayed a little beyond the allotted lunch time. I thoroughly enjoyed this experience and hope that it will be continued at future CRS meetings."

Mazen El-Hammadi (University of Strathclyde, UK) had the pleasure to attend lunch with Vincent Lee. He reports: During the few days before the "business lunch meeting" I was very excited and looked forward to making the most of it. For someone like me, just about to take first step in my future profession, it felt like a great chance. At the lunch table we gathered- 7 young scientists as well as the expert - Vincent. We were from 7 different countries from all over the world but shared the same interest and desire to listen to and learn from an expert with a long history and big experience. The fact that we come from a diversity of backgrounds was quite interesting - industry, academia, PhD students, post-doctors, chemists and pharmacists. "Lunch with an expert" was a brilliant idea. Although, the one-hour lunch duration was not enough to discuss all the interesting issue. However, it was a good and easy opportunity for meeting important people and learning from them. ■

Soapbox Session: Emerging Drug Delivery and Biotech Companies

By Steven A. Giannos
Industrial Editor

Six years ago at the 26th Annual CRS Conference in Boston, Drs. Eyal Ron and Philippe Dor started the Soapbox Sessions, intending to provide a platform for the identification of new ideas and potential collaborations within the controlled release field. Sponsored this year by Molecular Profiles, these fast-paced 5-minute presentations introduce both emerging and established technology-driven businesses and allow them to present their technologies, products, and services. The Soapbox Sessions are a huge success at the Annual conference, and this year was no exception

Miami's Soapbox Session was the largest yet, with a total of 38 presentations. According to Dr. Eyal Ron, Co-Chair of the sessions, the time slot Sunday afternoon was expanded 30 minutes before and after, in order to accommodate an additional fifth session for the ever-increasing number of presentations.

After a brief opening by Dr. Ron, Dr. Nikin Patel, CEO of Molecular Profiles, welcomed all the presenters and members of the audience to the afternoon forum, then gave an overview of the Soapbox Session. Dr. Ron continued with the guidelines for the participants and their presentations and the history of the Soapbox Session.

At the first Session in 1999, Drs. Ron and Dor had no idea what to expect or how the Soapbox Session would be received. Happily, the Session was a complete success. The small meeting room could barely accommodate the overwhelming response, and it was "standing room only" until the end of the afternoon. Since that first Session, Eyal and Philippe have been co-chairing the Soapbox Session, enabling companies with new drug delivery technologies as well as new companies with novel controlled release technologies to have "their 5 minutes of fame." ■

Soapbox Session *continued on page 33*

CRS Education Committee Activities at the 2005 CRS Annual Meeting, Miami Beach, Florida

By Roderick B Walker, Rhodes University, South Africa
Michael J Rathbone, InterAg, New Zealand
Sevda Senel, Hacettepe Univ, Turkey

The 2005 Young Scientists Education Workshop organized under the auspices of the CRS Education Committee, and the second to be held at an annual meeting of the Controlled Release Society (CRS), was once again a resounding success. These workshops, designed to introduce Young Scientists (defined as anyone under the age of 40 or anyone who has entered the area of controlled release within the last 5 years) are the brainchild of Dr Michael Rathbone, Chair of the Education Committee.

The 2005 program was organized by Michael Rathbone, Farid Dorkoosh, Ali Siaboomi and Martyn Davies and attended by approximately 100 delegates. It provided an excellent opportunity for Young Scientists to listen to, and meet experts in, the field of controlled release.

In the "Let me introduce you to" Session, scientists heard about the life of Hans Junginger and his diverse and interesting career that has ended with him spending time in various countries and how his research interests allowed him to diversify into the cosmetics industry. Jorge Heller, in his unassuming way, told of his career in polymer science and how, after almost thirty years, he may have developed into a polymer chemist as a result of coming to "forks in the road" during his career and taking the right one (most often). Jennifer Dressman, the immediate past President of the CRS, discussed her career and provided young scientists with a role model, which exemplified the adage that hard work does pay off. During this session, an impromptu panel discussion with Hans Junginger, Jorge Heller, Ijeoma Uchegbu, Sevda Senel and Rod Walker prompted discussion about many aspects of careers in the area of controlled release. Two topics in particular were discussed: the difficult and challenging decision of selecting a career in academia versus industry and the issues and challenges facing women in science.

In the Polymer Session, newcomers to controlled release research gained an insight into polymers and their use in conventional sustained release systems (Ali Siahboomi), novel approaches to developing new polymers (Hamid Ghandehari), the use of bioerodible polymers (Edith Mathiowitz) and gene therapy (Ijeoma Uchegbu).

In the final session of the workshop a highly informative series of presentations were given by Patrea Pabst on intellectual property. The speaker spent time indicating costs, issues and challenges in acquiring and protecting patents. In addition current relevant examples of litigation with respect to patents in the pharmaceutical arena were presented and discussed. Of particular value was her suggestion that there may be simpler ways of protecting intellectual property other than spending large amounts of money on applying for a patent. Her take home message was that a patent is really only worth its weight if one is able to spend money defending it in court.

Colorcon and InterAg are thanked for sponsoring this years Young Scientists Education Workshop at the 2005 CRS Annual Symposium.

In addition to the Young Scientists Education Workshop, two "Get Up! Get Educated!" sessions formed part of the program for 2005. In the first of these two highly educational and informative sessions, Professor Vince Lee of the Food and Drug Administration took the audience through some of the biological barriers to delivery of proteins and peptides. In the second session Dr Steven Schwendeman, a previous Young Investigator awardee, gave an excellent overview of what a formulation scientist needs to consider should they choose to delve into protein and peptide delivery.

A reception for young scientists that enabled these individuals to meet socially with some of the leaders of the CRS was also organised, in addition to the formal program.

At the Awards Ceremony the CRS Education Committee announced the concept of the "Virtual Library." This initiative is designed to provide a web-based resource on all aspects of controlled release and has been driven forward by Farid Doorkish and Michael Rathbone. It is envisaged that by the start of 2006, the resource will be online and ready for use.

The CRS Education Committee has worked hard this year to establish several other initiatives. A major focus has been determination of the requirements of young controlled release scientists in industry and their needs are likely to be met at a workshop in Vienna next year. In addition several education articles have been published in the CRS Newsletter under the CReators banner and the first of a series of articles on Controlled Release Education Around the World was published in the latest edition of the CRS Newsletter.

For more information on the CRS Education Committee and its activities please contact Michael Rathbone at mjr@interag.co.nz. ■

To jab or not to jab

By David Brayden, University College Dublin, Ireland

The veterinary committee organized the Pearl's debate on vaccine delivery at CRS 2005 in Miami. The protagonists on the topic of "Non-injected vaccine delivery is not a high priority for vaccinology" were Dr. Terry Bowersock (Pfizer Animal Health) arguing for the motion and Dr. Gregory Glenn (Iomai Corporation) arguing against. In a well attended session, Terry Bowersock began by covering the great successes of injected vaccines over the past century in eliminating or reducing disease burden of whooping cough, measles and tetanus. The key to the success of these vaccinations was the discovery of way to attenuate the pathogenicity of wild-type agents, the success of producing novel recombinant antigens and the increased ability to mass vaccinate. He felt that many of these were under appreciated as societies tend not to notice when threats lessen. The idea of non-injected vaccines was laudable since the ability to induce mucosal immunity to pathogens invading through epithelial surfaces would be an important advance. However, recent data suggest that some new antigens administered with novel adjuvants/ immunopotentiators by injected routes can indeed induce both mucosal as well as systemic immunity, hence weakening the major discriminating argument for non-injected vaccination. In veterinary medicine, the higher priority for production animal vaccination was to reduce labour cost, have single dose administration and an immune response in the quickest time following vaccination. Therefore there was indeed some potential for needless-injectors to fulfill those criteria. On the other hand, Terry argued that syringe and needle systems for man were far safer than before since new technology had developed one-time usage systems with reduced capacity for needle-stick injury, while the opportunity of transferring diseased blood between patients could be eliminated. Another argument was that vaccines need to be cheap and there was little evidence that non-injected vaccination was any less costly since the necessary use of large doses was only partly offset by the savings in syringes, needles and trained personnel.

Greg Glenn focused on the advantages of transcutaneous immunization over needles. He argued that the current paediatic vaccine series involved up to 16 injections before the age of two and that parents were reluctant to bring their children back for boosters. In his opinion patches of antigens with adjuvants offered the potential to avoid needle stick injury, the ability to incorporate multiple antigens, to induce mucosal immunization and to be self-administered. In addition, skin immunization offered the chance eventually to address the fact that most vaccines require refrigeration, which is an issue for the hot countries of the developing world. Of all the non-injected routes it seems that skin immunization appears the most advanced, since oral immunization had largely disappointed and pulmonary delivery had safety issues. Importantly, he argued that the newer antigens required imaginative use of novel adjuvants and, to date, injected route approvals in the US were still limited to the adjuvant alum.

Contributions from the audience included remarks concerning the false dawns of single dose vaccination with microparticles. Despite the opportunity to test single injected biodegradable microparticles containing tetanus and diphtheria toxoids, intended trials in the developing world had not yet taken place despite the potential indicated by scientific studies. Another interesting comment was that many of the new vaccines being researched were mainly for diseases of the wealthy countries (e.g anthrax, West Nile) and that they could never be relevant to the developing world, irrespective of the delivery system used. Others questioned whether parenteral vaccination could ever really produce the level of mucosal immunity required to deal with newer type infections. Overall, while the motion was not put to a vote, there was general agreement that new adjuvants were required to help stimulate different types of immune response by both parenteral and non-injected routes and also that high priority should be given to funding new vaccines for the major world-wide diseases including HIV, malaria and TB vaccines. Finally, most contributors agreed that increasing the routes of immunization made sense and that the need for stimulating mucosal immunity was an important factor.

Mini-Symposium: *Innovations in Veterinary Drug Delivery*

Proposed Date:
Monday, July 24, 2006
2:00-4:00pm

Co Chairs:
- David Brayden, University College Dublin, Ireland
- Craig Bunt, University of Auckland, New Zealand

Speakers:

1. *Pharmacokinetic and pharmacodynamic responses to veterinary CR formulations in veterinary species: effects of dosing regimes*
   Pierre-Louis Toutain
   Ecole National Veterinaire de Toulouse,
   Laboratoire de Physiopathologie et Toxocologie
   Experimentales - INRA/ENVT
   23, Chemin de Capelles
   31076 Toulouse, Cedex
   Phone: +33 (5) 61 193915
   Fax: +33 (5) 61 1939 17
   E-mail: pl.toutain@envt.fr

2. *Potential drug interactions at the level of P-glycoprotein in canine mdr gene knock out models*
   Katrina Mealey
   Department of Veterinary Clinical Sciences,
   College of Veterinary Medicine, Washington State University,
   Pullman, WA 99164-6610, USA
   Phone: +1 509 335 2988
   E-mail: kmealey@vetmed.wsu.edu

3. *Innovative applications of chitosan in veterinary medicine*
   Sevda Senel
   Department of Pharmaceutical Technology
   Faculty of Pharmacy
   Hacettepe University
   Ankara, Turkey 06100
   Phone: +90 312 310 15 24
   Fax: +90 312 311 47 77
   E-mail: ssenel@hacettepe.edu.tr

4. *Ceftiofur Crystalline Free Acid: A Novel Sustained Release Parenteral Suspension for Livestock*
   Scott A Brown DVM, PhD, Diplomate, American College of Veterinary Clinical Pharmacologists (DACVCP)
   Director, Veterinary Medicine
   Pharmaceutical Research and Development
   Metabolism and Safety
   Pfizer Inc.
   7000 Portage Road RIC 190-045
   Kalamazoo, MI 49001-0199
   Tel 269-833-2412
   Fax 269 833-2695
   Email: scott.a.brown@pfizer.com

For more information contact co-chairs David Brayden David. Brayden@ucd.ie or Craig Bunt c.bunt@auckland.ac.nz

A Parameter Model for Filmcoating Processes

By Charles Frey, Coating Place, Inc., USA

INTRODUCTION

Filmcoating process parameters involve a balance of atomization, airflow, temperature, and spray rate. This article discusses drying capacity and actual process parameters from Wurster fluid bed and vented pan processes to impart a cursory filmcoating model.

EXPERIMENTAL METHODS

Wurster fluid bed coating work was performed on research and production coaters designed and manufactured by Coating Place, Inc. Pan coating work was performed on a Vector partially perforated 24" vented pan coater.

THEORETICAL DISCUSSION

Atomization

Over-atomization leads to spray drying and possible particle attrition, while under-atomization leads to over-wetting and granulation. Common droplet diameters for spray film-coating processes have been measured at 10 to 40 µma. Drying is a surface phenomenon; a theoretical conversion of water droplet diameter to surface parameters is shown in **Table I** and **Figure 1**. A given amount of water atomized to 10 µm diameter droplets compared to 20 µm has double the total surface area and half the number of molecular layers per droplet; thus, doubling the droplet diameter likely quadruples the drying time.

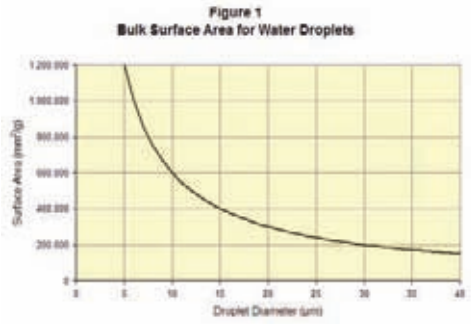
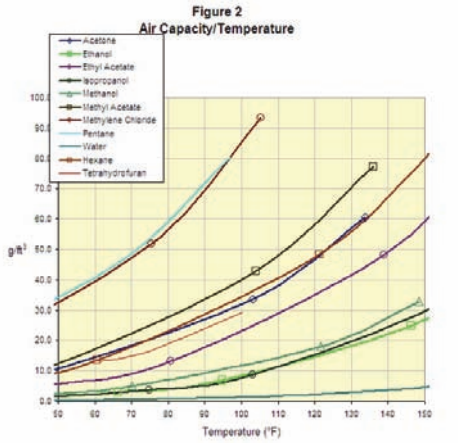


Table I
Theoretical Droplet Parameters for Water

Droplet Diameter (µm)	µg/Droplet	Droplets/ µg	µm²/ Droplet	mm²/g	Molecules/ Droplet	Molecular Layers/ Droplet
5	6.53E-05	15,325	78.54	1,203,611	2.18E+12	6,484
10	5.22E-04	1,916	314.2	601,805	1.74E+13	12,968
15	1.76E-03	568	706.9	401,204	5.89E+13	19,452
20	4.18E-03	239	1,257	300,903	1.40E+14	25,935
25	8.16E-03	123	1,963	240,722	2.73E+14	32,419
30	1.41E-02	71	2,827	200,602	4.71E+14	38,903
35	2.24E-02	45	3,848	171,944	7.48E+14	45,387
40	3.34E-02	30	5,027	150,451	1.12E+15	51,871

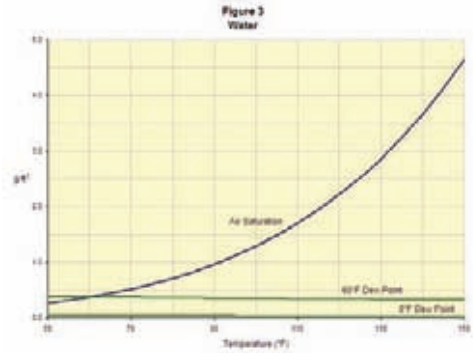
Solvent Volatility

Solvent volatility is related to vapor pressure and air capacity. Vapor pressure datab were converted to an air capacity basis and are shown in **Figure 2**. These data indicate the capacity of air to hold solvents at various temperatures. The curve for water is the dew point curve, indicating the quantity of water in saturated air versus temperature. The solvent curves are also dew point curves. The product of the value at a given temperature and process air (g/ft3 x ft3/min = g/min) indicates the solvent spray rate that would saturate the air without excess in a process. In actual practice, safety and other factors further limit capacity as discussed below.



Aqueous Solvent Systems

Water removal capacity is lowered to an extent dependent on the amount of water in the process air. **Figure 3** shows the dew point curve for water along with curves for 0°F and 60°F dew point process air. The actual capacity for removal of sprayed water is the difference between the saturation curve and the curve for the dew point of the process air.



Organic Solvent Systems

Organic solvent systems are limited by explosivity concerns. Organic solvents have lower and upper explosive limits (LEL and UEL). The potential for explosion exists at spray rates that bring the process air solvent content to a level between the UEL and LEL. Spray rate must remain below the lower explosive limit to remain safe during the process.

Solvent/Solid Interactions

Coating and core solids have a varying affinity for solvent molecules depending on chemical structure. These interactions slow the evaporation process. In addition, developing film-coat

barrier properties prevent escape of trapped solvent molecules. Also, particle agglomeration during the coating process entraps solvent molecules within agglomerated particles.
Retained solvent also plasticizes the film-coat. Plasticizing effects generally include a reduction in glass transition temperature (Tg). Above the Tg, the materials are typically soft and somewhat tacky. Both barrier properties and solvent retention concerns limit the application of polyvinylalcohol coating systems and polyvinylacetate systemsc.

PROCESS DATA

Data in **Table II** from a random selection of processes indicate the extent to which actual spray rates are below process air capacity. The "Spray % of Vehicle Removal Capacity" column represents spray rate as a percentage of solvent vehicle removal capacity. The "Individual Solvent Removal Capacity" column is the maximum rate that process air can remove pure solvent at the noted outlet temperature. The "Combined Removal Capacity" is a combined rate that has been weighted proportionally to each solvent as follows:

Combined Removal Capacity (g/ft3) = [(solvent 1 capacity) (weight fraction of vehicle) +
(solvent 2 capacity) (weight fraction of vehicle) …]

The product of the combined removal capacity (g/ft3) and the process air (ft3/min) provides the "Vehicle Spray Removal Capacity."

Note that organic solvent process spray rates are near 2 to 6% of the actual air capacity to remove them. This limit is likely due to either solvent affinity or the LEL.

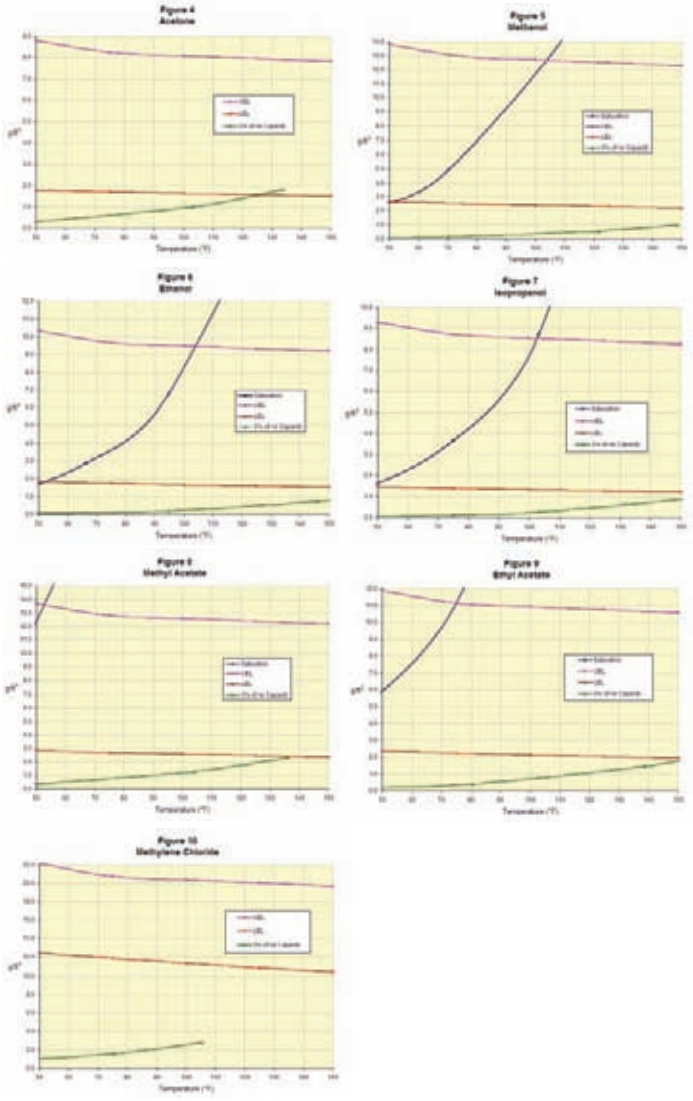
Water spray rates are typically at a higher percent of capacity than organic systems. Rates from near 10% to 100% of capacity are possible depending on core and coating material properties and the goal of the coating process.

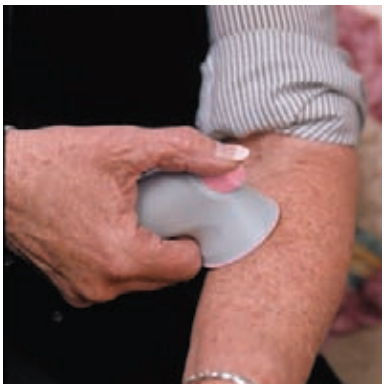
Figures 4 – 10 illustrate solvent removal concerns more fully with a comparison of solvent removal capacity (saturation, same as Figure 2), upper and lower explosive limits (UEL and LEL), and the 3% of capacity line. Per Table II data, the 3% line is an estimated target for organic solvents. Within the 50˚F to 150˚F temperature range shown, spray rates at 3% of removal capacity are safe for many solvents; however, it exceeds the LEL within this temperature range for acetone and methyl acetate. In the final assessment, spray must be safely below the LEL. Maximum safe rates are near 0.5 to 1.2 g/ft3 for common solvents.

Parameter Meter continued on page 26

Table II
Actual Application Data from Randomly Selected Filmcoating Processes

#	Coating Vehicle	Solution Solids	Process Air (ft3/min)	Outlet Temp. (˚F)	Individual Solvent Removal Capacities (g/ft3)	Combined Removal Capacity (g/ft3)	Removal Capacity (g/min) Vehicle Spray	Actual Solution Spray Rate (g/min)	Actual Vehicle Spray Rate (g/min)	Spray % of Vehicle Removal Capacity
1w	100%Water	30.00%	658	105	1.12Water	1.12	737	128	90	12.2%
2w	100%Water	8.00%	658	95	0.95Water	0.95	625	140	129	20.6%
3w	11%Water/7%Acetone/82%Ethanol	5.80%	1170	131	2.7Water/57.5Acetone/18.2Ethanol	11.05	12,929	780	735	5.7%
4w	11%Water/7%Acetone/82%Ethanol	5.80%	1400	131	2.7Water/57.5Acetone/18.2Ethanol	11.05	15,470	975	918	5.9%
5w	11%Water/7%Acetone/82%Ethanol	5.80%	1600	131	2.7Water/57.5Acetone/18.2Ethanol	11.05	17,680	1125	1060	6.0%
6p	95%Acetone/5%Ethanol	5.00%	300	86	25.0Acetone/4.6Ethanol	23.98	7,194	195	185	2.6%
7p	88%Acetone/12%Ethanol	5.00%	300	81	22.5Acetone/4.0Ethanol	20.28	6,084	290	276	4.5%
8p	6%Ethanol/94%MeCl2	4.50%	300	81	4.0Ethanol/56.5MeCl2	53.35	16,005	460	439	2.7%
9p	6%Ethanol/94%MeCl2	4.50%	300	81	4.0Ethanol/56.5MeCl2	53.35	16,005	510	487	3.0%
10p	95%Acetone/5%Ethanol	5.00%	300	84	24.5Acetone/4.6Ethanol	23.51	7,053	255	242	3.4%
11p	88%Acetone/12%Ethanol	5.00%	300	84	24.5Acetone/4.6Ethanol	22.11	6,633	325	309	4.7%
12p	6%Ethanol/94%MeCl2	4.50%	300	84	4.5Ethanol/62.0MeCl2	58.55	17,565	510	487	2.8%
13p	6%Ethanol/94%MeCl2	4.50%	300	82	4.1Ethanol/57.0MeCl2	53.83	16,149	410	392	2.4%
14p	95%Acetone/5%Ethanol	5.00%	300	82	23.0Acetone/4.2Ethanol	22.06	6,618	245	233	3.5%
15p	88%Acetone/12%Ethanol	5.00%	300	84	24.5Acetone/4.6Ethanol	22.11	6,633	290	276	4.2%
16w	80%Acetone/20%Methanol	11.00%	1200	100	32.0Acetone/11.8Methanol	27.96	33,552	1050	935	2.8%
17w	100%Water	9.10%	1650	95	0.95Water	0.95	1,568	300	273	17.4%
18w	100%Water	18.00%	1650	110	1.54Water	1.54	2,541	780	640	25.2%
19w	80%Acetone/20%Methanol	33.00%	556	90	27.0Acetone/9.3Methanol	23.46	13,044	450	302	2.3%
20w	5%Water/95%Acetone	10.00%	658	85	0.66Water/24.5Acetone	23.31	15,338	350	315	2.1%
21w	100%Water	25.00%	681	85	0.66Water	0.66	449	275	206	45.9%
22w	100%Methanol	35.00%	634	80	7.0Methanol	7.00	4,438	340	221	5.0%
23w	5.26%Acetone/94.74%Isopropanol	9.75%	703	120	47.0Acetone/15.3Isopropanol	16.97	11,930	450	406	3.4%
24w	100%Water	8.00%	497	120	2.06Water	2.06	1,024	80	74	7.2%
25w	100%Acetone	10.00%	497	85	24.5Acetone	24.50	12,177	250	225	1.8%
26w	100%Water	8.00%	452	115	1.78Water	1.78	805	180	166	20.6%
27w	100%Acetone	5.00%	497	85	24.5Acetone	24.50	12,177	250	238	2.0%





Look to Acrux.

Acrux is a dynamic Australian specialty pharmaceutical company developing and commercializing a range of patient-preferred healthcare products for global markets, using innovative technology to administer drugs through the skin.

Established in 1998 our core business is the development and commercialization of next-generation transdermal drug delivery technology originally discovered at Monash University.

Our product range includes treatments in the areas of women's health and central nervous system disorders.

Faster, Lower Cost, Less Risk

We use proven drugs in combination with our technology platform to develop multiple patented products simultaneously at low cost. Seventeen human clinical trials have been completed with seven different drugs. With fewer and shorter trials required because we use proven drugs, our products have less risk and an easier path to product approval compared with typical new drug development.

With a number of products in clinical trials and more in formulation development more opportunities exist to bring to market new and effective therapies.

More Than Just Skin Deep – Proprietary and Flexible Technology

The fast-drying, non-occlusive topical sprays or liquids provide an enhanced transdermal delivery platform with low or no skin irritation, superior cosmetic acceptability and simple, accurate and flexible dosing. The technology offers a delivery solution for drugs with low oral bioavailability and ideal for product lifecycle management. The technology has been peer-reviewed (e.g. J. Pharm. Sci. 1998 87(10) 1213;1219;1226) and is protected by 19 patent families (e.g. US Pat. No. 6,818,226).

Partnering For The Future

We have a track record of securing commercial partnerships for our products/technology with rights licensed for:

- Evamist™ (Estradiol MDTS®) and Testosterone MDTS® to **VIVUS, Inc** in USA
- Testosterone MDTS® and Fentanyl MDTS® to **CSL Limited** in AUS/NZ
- Veterinary healthcare products to **Eli Lilly**

Pipeline snapshot

- In Phase 3 trial with Evamist™ (Estradiol MDTS®) to treat symptoms of menopause
- Achieved positive results in large Phase 2b trial with Testosterone MDTS® to treat female hypoactive sexual desire disorder
- Successfully completed Phase 1 trial programme with Fentanyl MDTS® for severe pain
- Started Phase 2 and 3 programme with Testosterone MD-Lotion® to treat male androgen insufficiency
- Achieved positive results in Phase 1 trial for world's first contraceptive spray (Nestorone MDTS®) with Population Council

For more information about commercial opportunities with Acrux visit: www.acrux.com.au
or phone: +61 3 8379 0100 or email: igor.gonda@acrux.com.au

ACRUX
DRUG DELIVERY SOLUTIONS

Special Feature

The New Jersey Center for Biomaterials: Enabling the Future of Medical Devices with the Next Generation of Biomaterials

By Carole Kantor, New Jersey Center for Biomaterials, USA

The New Jersey Center for Biomaterials is one of the few leading academic programs that address the improvement of medical devices through interdisciplinary biomaterials science. The Center was founded in 1997, under the leadership of Joachim Kohn at Rutgers, the State University of New Jersey. Because the selection of biomaterials is fundamental to the design and development of all medical devices, Kohn has focused the Center's work on understanding how to control cellular interactions with artificial materials.

The Center is sponsored by Rutgers, the University of Medicine and Dentistry of New Jersey (UMDNJ), and New Jersey Institute of Technology. In addition to its academic members, the Center has 17 industrial members ranging from startups to global corporations. Through its research and academic programs the Center involves additional universities, federal laboratories, and research centers worldwide.

Research Programs
The Center's programs range from university-based science studies to focused collaborations with companies that are developing new therapies to direct licensing of university-owned technology. The principal academic project, called RESBIO, is funded by the NIH's National Institute for Biomedical Imaging and Bioengineering. RESBIO is a multi-investigator, multi-institutional effort that integrates technologies dealing with polymeric biomaterials. The goal is to accelerate the discovery of new biomaterials through coordination of research in combinatorial chemistry, materials science, bio-interfacial science, and computational modeling. These research concentrations converge toward developing methods and tools for predicting cell interactions with polymer materials, including in silico polymer libraries.

In addition to RESBIO, the Center facilitates a variety of collaborations led by faculty at New Jersey's research universities. Current investigations include studies of methods for delivering DNA, genes and drugs; of improving our understanding of the vasculature's response to prosthetic vessel grafts; and of creating scaffolds for the replacement and regeneration of bone, skin, and ligament, among other tissues.

The Center's newest program expands its academic-industrial network to include military organizations seeking early access to biomaterials-enabled medical products. In its first two years, the CeMBR program (Center for Military Biomaterials Research) is undertaking four projects: a) development of a robust spray wound dressing that can be delivered with a one hand; b) validation of a human skin equivalent for testing barrier creams against chemical warfare agents; c) development of a resorbable polyurethane/bone composite intramedullary rod for fracture fixation; and d) exploration of polymeric microspheres with targeting ligands for delivery of inhibitors against microbial and plant toxins. CeMBR's chief operating officer is Rutgers Associate Research Professor David Devore, a polymer chemist who most recently was a vice president of research for Ciba Specialty Chemicals.

Development Programs
One of medicine's success stories in the past decade has been the coronary stent, a device that has saved millions of patients from open-heart surgery but that also creates long-term problems such as restenosis. To improve upon the currently available stents, Kohn invented a revolutionary polymer that degrades over time, can deliver healing drugs to the artery, and is visible with X-rays, enabling safe and accurate placement.

Scientists at REVA Medical Inc. (San Diego, CA) and at Rutgers collaborated to select polymer compositions that would be ideally suited for use in REVA's unique stent design. With methods of combinatorial synthesis and computer modeling, Kohn's group fast-tracked the process and identified a promising polymer composition in less than a year. Based on both the rapid development from concept to prototype and the early success of pre-clinical studies, Boston Scientific Corporation (Natick, MA), the world's leading stent company, made a strategic alliance with and investment in REVA Medical Inc. Both REVA and Boston Scientific are member companies of the Center.

"We regard REVA's relationship with Boston Scientific as a pivotal chapter in our technology transfer initiative," said Kohn. "This technology transfer story is an example of how NIH-funded research can accelerate healthcare advances through application of basic sciences."

In addition to expertise in polymer design, another major asset of the Center is expertise in transdermal drug delivery, represented by Professor Bozena Michniak of the Ernest Mario School of Pharmacy at Rutgers, formerly of UMDNJ. Michniak has developed a collaboration with Center industrial member Apogee Technology, Inc. (Norwood, MA), a global provider of innovative silicon-based devices. Apogee will work with Michniak's Laboratory for Drug Delivery to study the compatibility of representative large molecule drugs with Apogee's proprietary, MEMS-based transdermal drug delivery device and patent-pending transdermal solution. Targets include treatments for diabetes, infectious disease, acute pain and chronic pain.

In addition to its research projects and development collaborations with companies, a third important pathway the Center uses for advancing biomaterials into clinical use is direct licensing of university-owned technology to industry. Three companies hold licenses or options to license Rutgers patents from the Kohn laboratory.

***Special Feature** continued on page 32*

Scientifically Speaking

By Professor Gregory Gregoriadis, University of London and Lipoxen Technologies Ltd, United Kingdom

Polysialic Acids: A New Generation of Polymers for Peptide and Protein Delivery

Introduction

Advances in genomics and proteomics have revolutionized the use of therapeutic peptides and proteins. Beginning with insulin in the 1920s and with growth hormone and the interferons later on, the armamentarium of this class of drugs is continually supplemented with newer peptides and proteins of therapeutic potential, some of which are already applied clinically (Walsh, 2003). Unfortunately, the anticipated huge impact of peptide and proteins drugs in therapy is being compromised by a host of problems, mainly related to their interaction with the biological milieu following administration. For instance, such drugs can be unstable in the body as a result of peptidase action or rapidly removed from the circulation via the kidneys if of low molecular weight or through premature uptake by tissues such as the reticuloendothelial system. Moreover, peptides and proteins can be immunogenic or antigenic, rendering their chronic use untenable (Harris and Chess, 2003).

Application of peptide and protein drugs in therapy would be promoted considerably if ways could be found to improve their pharmacokinetics and pharmacodynamics while preserving their activity. Approaches to that end include modifications to the peptide backbone to render it less prone to degradation, addition of glycons onto the structure, or conjugation to polymers to augment residence in the circulating blood and, if needed, reduce immunogenicity, and incorporation into an array of nanoparticles such as liposomes. Of these approaches, the most successful so far has been conjugation to monomethoxy poly(ethyleneglycol) (mPEG) (Mehwar, 2000), commonly referred to as PEGylation. Known as "stealth" technology, PEGylation of peptides and proteins can substantially increase their circulatory half-life (and area under the curve), and also reduce immunogenicity. As a result, a number of PEGylated drugs have been licensed for clinical use. They include asparaginase (Oncospar™), interferons α-2a (Pegasys™) and α-2b (PEG-Intron™), tumour necrosis factor and granulocyte colony stimulating factor (Neulasta™), with several others in various stages of development. However, there are disadvantages as well: PEGylation can, depending on the chemistries and the PEG employed, inactivate much of the therapeutic, eg. interferon α-2a (Reddy et al, 2002) or growth hormone (Clark et al, 1996). More importantly, PEG is not biodegradable and although there is some evidence of enzyme-driven low rate oxidation to aldehydes and ketones, this is not a normal detoxification mechanism (Caliceti and Veronese, 2003). Indeed, it is very likely that PEGylated peptides that are able to escape kidney clearance will end up in tissues and accumulate intralysosomally to produce, on chronic use, a lysosomal storage "disease." Of similar concern is the finding that PEGylated proteins can generate an antibody response to PEG (considered a polyvalent hapten), an event that would influence the circulatory half-life of the conjugate (Caliceti and Veronese, 2003). Nonetheless, PEG immunogenicity has not as yet been reported for licensed PEGylated products, although these are administered in very small amounts. There are, however, other PEGylated peptides and proteins under development (eg. antibody fragments, insulin etc) which must be given chronically and in relatively large dosages, possibly large enough to eventually promote unacceptable lysosomal loading and/or immune responses to PEG.

Polysialic acids: Nature's ultimate stealth technology

An alternative way to render peptide and protein therapeutics "unnoticeable" in the body (without the disadvantages of PEG) is their modification with polysialic acid (PSA) (Fig 1), an α-(2→8) linked linear homopolymer of N-acetyl neuraminic acid (sialic acid). This non-toxic and biodegradable natural polymer is found in the body where it plays such diverse roles as modulating cell to cell inhibition thus facilitating neural tissue development or helping cancer cells to metastasise by reducing their adherence to tissues, in turn promoting migration. What is intriguing, however, is that certain bacteria have evolved to foil the body's defences by coating their walls with PSA so that host complement activation and phagocyte activity are reduced or abolished altogether. This unique ability of PSA to insulate microbes and cells alike from external insults was proposed in 1993 (Gregoriadis et al, 1993) as a means to protect therapeutic molecules from the biological milieu and improve their pharmacokinetics. Learning from bacteria, it was thought that by forming a "watery" cloud around the therapeutic by virtue of the extreme hydrophilicity of PSA, interaction with other molecules such as proteolytic enzymes, opsonins, neutralising antibodies or receptors on phagocytes would be interfered with, thus allowing the therapeutic to preserve the integrity of its structure and activity and prolong its presence in the body. The finding that injected PSA itself exhibits a long circulatory half-life that was directly related to its length (Gregoriadis et al, 1993), led us to suggest a dual role for the PSA in optimizing drug pharmacokinetics (Fig 2): In the case of relatively large proteins as well as drug delivery systems (eg. liposomes), a number of polymer chains of appropriate length attached randomly or strategically would ensure protection. In the case of small size therapeutics such as small peptides and conventional drugs on the other hand, these would

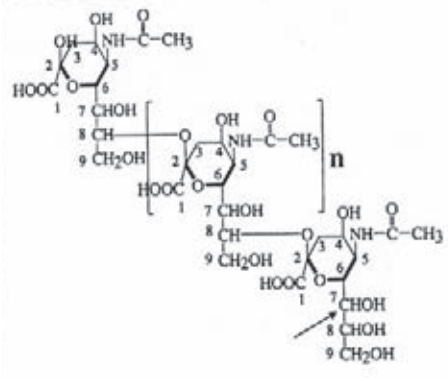


Figure 1

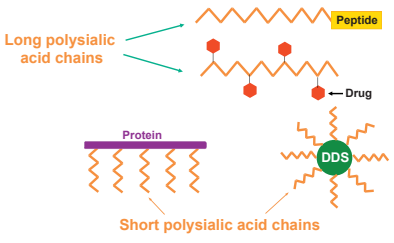


Figure 2

adopt the circulatory half-life of their PSA moiety. Moreover, the considerable increase in the size of the small therapeutic molecule as a result of its conjugation to PSA, together with the latter's highly ionic state, would contribute to reduced loss through the kidneys. Subsequent work (Fernandes and Gregoriadis, 1996, 1997, 2001; Gregoriadis et al, 2000; Jain et al, 2003; Gregoriadis, 2003; Jain et al, 2004) with a number of therapeutic peptides and proteins and also a small drug molecule confirmed some of the anticipated advantages of polysialylation, namely dramatic increases in the circulatory half-lives of injected therapeutics and curtailing of their immunogenicity and/or antigenicity.

Although several types of PSA exist (Mühlenholf et al, 1998), in terms of employing the polymer in the polysialylation of drugs, the α-(2→8) linked serogroup B capsular polysaccharide from Escherichia coli K1 (Fig 1) and its shorter derivatives (known as colominic acids) is the most appropriate. Being chemically and immunogically identical to PSA in the host organism, this bacterial PSA is, by virtue of structural mimicry, completely non-immunogenic even when conjugated to proteins. Furthermore, unlike other polymers (eg. dextran, mPEG), PSA is biodegradable (to sialic acid), an important advantage when used to improve the pharmacokinetics profiles of peptide and protein drugs administered chronically in relatively large doses.

Polysialylation of peptides and proteins

A variety of simple and gentle procedures have been developed for the conjugation of therapeutics to E.coli-derived α-(2→8)-linked PSA of the chosen chain length (usually 6KD to 60KD) with little or no loss of activity. Conjugation procedures involve modification of either of the terminal units of the (linear) polymer to activated structures that can interact with existing or introduced pendant groups in the therapeutic to generate conjugates with one or more PSA chains per molecule. Activation procedures include periodate oxidation of the non-reducing end of the PSA followed by interaction with the ε-aminogroups or the N-terminal of the protein and reductive amination (Fernandes and Gregoriadis, 1997; Jain et al, 1994). Other procedures (also the intellectual property of Lipoxen Technologies Ltd) using a variety of chemistries attach PSA strategically to regions of the protein away from its active site. Such procedures are conducive to high yield polysialylation within short time periods of incubation of the reactants. Additional techniques have been developed for the production of PSA with narrow polydispersity index (<1.05) and efficient isolation of conjugates from the reaction mixtures.

Polysialylation at Lipoxen (www.lipoxen.com) has been applied to a wide range of therapeutics, for instance, asparaginase, catalase, aprotinin, insulin, interferon α-2b, erythropoietin, granulocyte colony stimulating factor, antibody Fab, and Fc fragments and many others. Development of some of these proteins into products for clinical testing requires that a number of basic criteria deemed important in the application of such proteins in the treatment of disease are satisfied. These include the effect of polysialylation on the stability and function of therapeutics, their pharmacokinetics, and immunogenicity or antigenicity.

Stability and function of polysialylated therapeutics

Peptides and proteins are often vulnerable to proteolysis in the body, thus necessitating their administration in increased amounts. It appears that polysialylation protects against proteolysis. For instance, whereas asparaginase (used in the treatment of certain forms of leukaemia) exposed to blood serum at 37°C rapidly loses over 80% of its activity, this is fully retained with the polysialylated enzyme, even on prolonged (6 h) incubation (Fernandes and Gregoriadis, 1997). Polysialylation also preserves the function of therapeutics in terms of activity on their substrates or binding to relevant receptors. Thus, in the case of asparaginase identical kinetics (Km), values were observed before and after polysialylation (Fernandes and Gregoriadis, 1997). Similarly, there was quantitative preservation of interferon α-2b function (Fig 3), even though the "substrate" (receptor) is a much larger molecule than asparagine, confirming its unhindered access to the receptor binding site. Retention of activity on polysialylation also appears to occur in vivo as demonstrated in the case of asparaginase (Fernandes and Gregoriadis, 1997) and, more recently, for insulin (SuliXen™). Fig 4 shows that glucose levels declined similarly with both intact and polysialylated insulin.

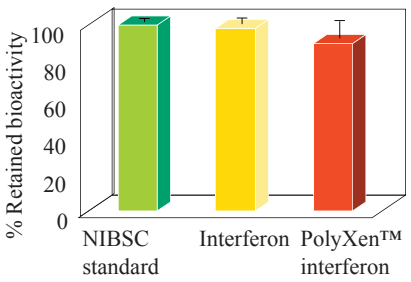


Figure 3

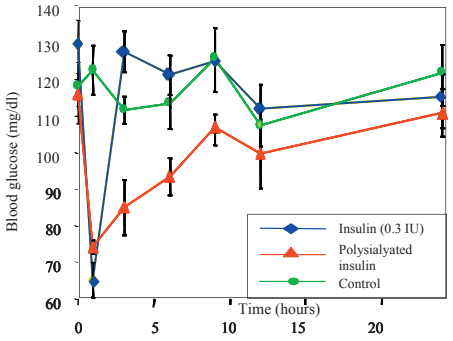


Figure 4

Polysialylated therapeutics exhibit prolonged pharmacological action

Wider adoption of polysialylation as a means to improve peptide and protein drug function depends crucially on the ability of the polymer to extend the presence of the active in the blood circulation. This should help to maintain therapeutic concentrations of the active for prolonged periods, in turn reducing dosages and frequency of injections. To that end, we tested four molecules of varying molecular weight, ie fluorescein (a model drug molecule) (Gregoriadis et al, 1993), insulin (Jain et al, 2003), a tumour specific antibody Fab fragment (Epenetos et al, 2002), and asparaginase (Fernandes and Gregoriadis, 1997). With all cases where plasma concentrations in injected animals were measured, circulatory half-life and area under the curve augmented considerably when the molecules were polysialylated.

***Scientifically Speaking** continued on page 16*

Scientifically Speaking *continued from page 15*

Importantly, in the case of the tumour specific Fab fragment, its prolonged circulation (Fig 5) was associated with increased localization in the relevant tumour (Epenetos et al, 2002). Thus, inspite of the presence of the PSA chains on the Fab, its antigen-recognising region was able to bind to the corresponding antigen on the cell surface. Lack of interference of PSA with the recognition of a large receptor molecule was also apparent, albeit indirectly, in the case of polysialylated insulin with its glucose lowering effect extending to 9 hours (Fig 4).

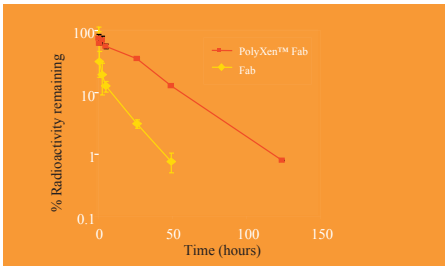


Figure 5

Immunogenicity and antigenicity of polysialylated therapeutics

Antibody formation against therapeutic peptides and proteins given chronically can neutralize their activity and potentially lead to anaphylactic reactions. Related examples of such antibody-mediated loss of activity include insulin, erythropoietin, and interleukin 2, even when made recombinantly using human genes (Caliceti and Veronese, 2003). It has been shown that polysialylation abrogates immunogenicity and/or antigenicity. In the case of asparaginase, for instance, the polysialylated enzyme still exhibits its greatly improved half-life (observed in naïve mice) in animals previously immunized with the enzyme. In contrast, the clearance of native asparaginase was accelerated (Fernandes and Gregoriadis, 2001), presumably because there were no PSA chains on its surface to prevent antibody complexing with the antigenic sites. Work with insulin on the other hand, revealed significant reduction of both immunogenicity and antigenicity (Jain et al, 2003). As indicated in Fig 6, PSA on the insulin molecule was able to prevent inactivation of the hormone by anti-insulin antibodies and allow it to reduce blood glucose.

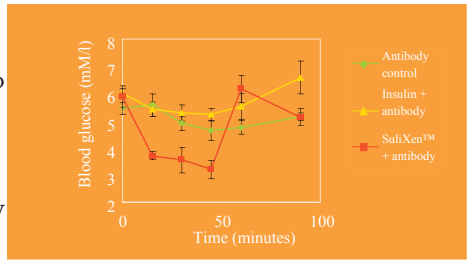


Figure 6

Conclusions

There is a huge variety of therapeutics either in clinical use or in the preclinical stage in need of improvement. Accumulating evidence indicates that many of the problems encountered in the direct use of peptide and protein therapeutics can be circumvented by polysialylation. However, the future of polysialylation in the development of new peptide and protein drug entities that will improve the quality of life in patients will depend on results obtained in the clinic. It is anticipated that PolyXen™ technology, presently applied to the development of a number of supergenerics such as erythropoietin, insulin, interferon α-2b and granulocyte colony stimulating factor will contribute significantly to the optimization of peptide and protein drugs.

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Figure Legends

Fig 1
Structure of polysialic acid (colominic acid) N-acetylneuraminic acid units are linked via α-(2->8) glycosidic linkages. The arrow indicates the carbon atom (C7) at the non-reducing end of the sugar where periodate oxidation introduces an aldehyde group

Fig 2
Schematic representation of polysialylated constructs

Fig 3
Receptor (Daudi cells) binding ability of polysialylated interferon α-2b

Fig 4
Hypoglycaemic action of intact and polysialylated insulin in subcutaneously injected mice. Animals were injected with 0.3 international units of intact or polysialylated insulin. Control animals received saline.

Fig 5
The effect of polysialylation on the circulatory half-life of an antibody Fab fragment injected intravenously into mice

Fig 6
Hypoglycaemic action of intact and polysialylated insulin in subcutaneously injected mice following incubation with anti-insulin antibody. Note retention of activity for the polysialylated hormone. Antibody control denotes animals injected with antibody only. ■

ICI is one of the world's major specialty chemicals and paints businesses with products and ingredients developed for a wide range of markets.

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IntheNews

compiled by Steven Giannos
Industrial Editor, USA

Estradiol-Releasing Vaginal Ring And Tablets Equally Effective, Safe
Women's Health Weekly via NewsEdge Corporation:
July 14, 2005 - (NewsRx.com) -- Low-dose estradiol administered either by a vaginal ring or by tablets shows equal endometrial safety and efficacy, a study from Australia shows.

E. Weisberg and colleagues at the Sydney Center for Reproductive Health Research conducted a prospective, randomized study to "compare the safety of a continuous low-dose estradiol-releasing vaginal ring (ESTring) to that of a vaginal estradiol tablet (Vagifem) on the endometrium and the relief of subjective symptoms and signs of urogenital estrogen deficiency. Quality of life and acceptability of treatment delivery were also assessed."

According to their report, 185 "women were assigned in a 2:1 ratio to ESTring and Vagifem and followed for 12 months. The primary endpoint was endometrial safety, based on the results of ultrasound measurement of endometrial thickness and a progestogen challenge test at baseline and week 48. Efficacy was determined by subjective assessment of urogenital estrogen deficiency symptoms at baseline and weeks 3, 12, 24, 36, and 48 and assessment of signs of vaginal epithelial atrophy by the clinician at baseline, 12 and 48 weeks.

Weisberg and team reported, "There was no statistical difference between the groups in the alleviation of symptoms and signs of urogenital estrogen deficiency. Maturation indices increased in both groups, from generally atrophic at baseline to proliferative or highly proliferative at 48 weeks.

The researchers said, "General health status in both groups was unchanged but the urogenital component of health burden was significantly improved in both groups. Bladder diary variables showed no differences between treatment groups." They concluded, "Equivalent endometrial safety and efficacy in the relief of the symptoms and signs of urogenital estrogen deficiency were demonstrated for the 12 months' use of a low-dose estradiol-releasing vaginal ring and a vaginal estradiol tablet."

Weisberg and coauthors published their study in Climacteric (Endometrial and vaginal effects of low-dose estradiol delivered by vaginal ring or vaginal tablet. Climacteric, 2005;8(1):83-92). For additional information, contact E. Weisberg, Sydney Center Reproductive Health Research, Research Division FPA Health, 328-336 Liverpool Rd., Ashfield, NSW 2131, Australia.

Merrion Pharmaceuticals, Inc. Is Issued US Drug Delivery System Patent
Business Wire via NewsEdge Corporation:
WILMINGTON, N.C.& DUBLIN, Ireland--(BUSINESS WIRE)--July 13, 2005--Merrion Pharmaceuticals, Inc., a specialty pharmaceutical company with novel approaches to oral drug delivery, is pleased to announce the issuance of United States Patent No. 6,780,846, "Membrane translocating peptide drug delivery system." This patent covers new peptide compounds which can be physically or chemically complexed with an active substance, either a drug or a biological, in order to improve delivery across biological membranes.

The ability of these drug-peptide complexes to cross biological membranes such as the epithelium of the gastrointestinal tract is enhanced considerably over the ability of the active substance alone. Using such complexes to improve the delivery of a drug to a specific target tissue both enhances the efficacy and reduces the side effects of the drug. Finally, this delivery technology can also be used to enable the oral administration of compounds that are normally administered only as injectables. Merrion (www.merrionpharma.com) is focused on novel oral drug delivery solutions to improve product performance and patient compliance.

Methods Of Drug Delivery Using Sulphated Chitinous Polymers
Release Date: 7/8/2005
European Patents via NewsEdge Corporation:
Pub. Number EP1546216 Appl. Data EP03793024 20030807 Applicant Chitogenics, Inc. Universiteit Leiden Inventor(s) KYDONIEUS, Agis ELSON, Clive THANOU, Maya Title METHODS OF DRUG DELIVERY USING SULPHATED CHITINOUS POLYMERS. Abstract: The present invention provides methods and compositions for delivering a therapeutic agent across a membrane that has limited permeability for the therapeutic agent. The method includes delivering the therapeutic agent to the membrane in a composition, which includes a sulphated chitinous polymer as a primary carrier.

Ktenate Nanoparticles Used To Deliver Drugs To Parasites And Tumors
Immunotherapy Weekly via NewsEdge Corporation:
July 6, 2005 - (NewsRx.com) -- According to a study published in the Journal of Drug Delivery Science and Technology from Germany, specific delivery of substances to distinct target cells may lead to new perspectives in diagnosis and therapy. The drug delivery system has been developed based on nanoparticles made of polyvinyl alcohol grafted with polylactide side chains terminating in amino groups.

"These particles, termed 'bdellosomes,' were loaded with substances of pharmacological interest, coated with polyethyleneglycol-3400 to evade immune reactions, and linked to target-specific ligands, such as transferrin or anti-transferrin receptor-antibody fragments. In vivo distribution studied showed a prolonged circulation time of the PEGylated (polyethylene glycol-linked) particles compared to non-PEGylated controls. The nanoparticles were capable of specifically and efficiently delivering their content both to neoplastic cells and to eukaryotic parasites," said researchers.

"Tests with daunomycin were performed on Trypanosoma brucei brucei and Jurkat (human T-lymphoma cells) as model targets. When the particles were linked to transferrin or the transferrin receptor-antibody fragments, a significant cytotoxic effect of the daunomycin loaded particles could be observed, which was absent when the particles were not linked to the cell specific ligand," reported R.M. Flaig and coworkers at the University of Heidelberg.

"Thus, bdellosomes present a novel drug delivery systems with the potential of drug targeting," the authors concluded.

Flaig and colleagues published their study in the Journal of Drug Delivery Science and Technology (Ktenate nanoparticles

(Bdellosomes): a novel strategy for delivering drugs to parasites or tumors. J DRUG DELIV SCI TECHNOL, 2005;15(1):59-63). For more information, contact G. Fricker, University of Heidelberg, Institute Pharmacy & Molecular Biotechnology, D-69120 Heidelberg, Germany.

FzioMed Reports Promising Results Of Novel Bone Growth Factor In Preclinical Studies And Demonstrates Oxiplex Gel As Effective Drug Delivery Platform
Business Wire via NewsEdge Corporation: SAN LUIS OBISPO, Calif.--(BUSINESS WIRE)--July 6, 2005--FzioMed, Inc. announced today the presentation of preclinical studies demonstrating Oxiplex Gel as an injectable drug delivery system for a novel, synthetic peptide bone growth factor. The poster presentation is being made at the 12th International Meeting on Advanced Spine Techniques (IMAST) held in Banff, Alberta, Canada from July 7 through July 9, 2005.

Oxiplex is a synthetic, bioabsorbable, injectable gel formulated by FzioMed for the percutaneous delivery of therapeutics. FzioMed is developing Oxiplex gels for use in a variety of surgical applications, including the prevention of post-surgical adhesions in spine, gynecologic and general surgeries.

The first study tested Oxiplex for its utility as a drug delivery system. The results demonstrated that Oxiplex loaded with the antibiotic ampicillin was easily injected into a site and did not impact the activity or diffusion of the ampicillin.

The second study evaluated Oxiplex as a vehicle for the delivery of a novel peptide bone growth factor being developed by FzioMed. The study compared healing in a bone defect filled with Oxiplex containing the growth factor to controls where the defect was filled with either Oxiplex alone or left unfilled. The results showed that Oxiplex alone had a positive stimulatory effect on bone healing. However, when Oxiplex was combined with the bone growth factor, there was an additional acceleration of bone healing.

"The promising results of this new bone growth peptide will support our expansion in orthopedic surgery," said Richard Berg, PhD, Vice President of Research and Development at FzioMed. "We continue to build compelling evidence for the use of FzioMed's Oxiplex technology as a drug vehicle with broad application."

FzioMed(R) and Oxiplex(R) are registered trademarks of FzioMed, Inc.
CONTACT: FzioMed, Inc. Richard Berg, PhD, VP of Research and Development 805-546-0610, ext. 125 (www.fziomed.com)

Nanoparticles Carry Cancer-Killing Drugs Into Tumor Cells
Cancer Weekly via NewsEdge Corporation:
July 5, 2005 - (NewsRx.com) -- University of Michigan scientists have created the nanotechnology equivalent of a Trojan horse to smuggle a powerful chemotherapeutic drug inside tumor cells - increasing the drug's cancer-killing activity and reducing its toxic side effects.

"This is the first study to demonstrate a nanoparticle-targeted drug actually leaving the bloodstream, being concentrated in cancer cells, and having a biological effect on the animal's tumor," said James R. Baker Jr., MD, the Ruth Dow Doan Professor of Biologic Nanotechnology at the University

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of Michigan, who directed the study. Results of the study were published in Cancer Research.

The drug delivery vehicle is a manmade polymer molecule called a dendrimer. Dendrimers have a tree-like structure with many branches where scientists can attach a variety of molecules, including drugs. U-M scientists attached methotrexate, a powerful anticancer drug, to branches of the dendrimer. On other branches, they attached fluorescent imaging agents and their secret ingredient - a vitamin called folic acid.

Folic acid, or folate, is an important vitamin required for the healthy functioning of all cells. But cancer cells, in particular, seem to need more than average amounts. To soak up as much folate as possible, some cancer cells display more docking sites called folate receptors on their cell membranes. By taking advantage of a cancer cell's appetite for folate, U-M scientists are able to prevent the cells from developing resistance to chemotherapeutic drugs.

"It's like a Trojan horse," Baker explains. "Folate molecules on the nanoparticle bind to receptors on tumor cell membranes and the cell immediately internalizes it, because it thinks it's getting the vitamin it needs. But while it's bringing folate across the cell membrane, the cell also draws in the methotrexate that will poison it."

The research was funded by the National Cancer Institute. The University of Michigan has filed a patent application on targeted nanoparticle technology. A licensing agreement is currently being negotiated with Avidimer Therapeutics, a biopharmaceutical company in Ann Arbor, Michigan. Baker holds a significant financial interest in the company (Cancer Research, 2005:65(12)).

Utility of High-Resolution Magic-Angle Spinning NMR Evaluated for Drug Delivery Analysis

Drug Week via NewsEdge Corporation: June 24, 2005 - (NewsRx.com) - In a study from the United States, the utility of HR-MAS NMR "for studying drug delivery in whole tissues was explored by dosing female Sprague-Dawley rats with topical or injectable benzoic acid (BA)."

"In principle, HR-MAS NMR permits the detection of both intra-and extracellular compounds," explained L.H. Lucas and colleagues at the University of California-Riverside. "This is an advantage over the previous detection of topically applied BA using microdialysis coupled to HPLC/UV, as microdialysis samples only the extracellular space."

"Skin and muscle samples were analyzed by 1H HR-MAS NMR, and BA levels were determined using an external standard solution added to the sample rotor," the scientists said. "One to two percent of the BA topical dose was detected in the muscle, showing that BA penetrated through the dermal and subcutaneous layers."

"Since BA was not detected in the muscle in the microdialysis studies, the NMR spectra revealed the intracellular localization of BA," according to the report. "The amount of BA detected in muscle after subcutaneous injection correlated with the distance from the dosing site."

"Overall, the results suggest that HR-MAS NMR can distinguish differences in the local concentration of BA varying with tissue type, dosage method, and tissue proximity to the dosing site," the researchers concluded. "The results illustrate the potential of this technique for quantitative analysis of drug delivery and distribution and the challenges to be addressed as the method is refined."

Lucas and coauthors published their study in Analytical Chemistry (Concentration profiling in rat tissue by high-resolution magic-angle spinning NMR spectroscopy: Investigation of a model drug. Anal Chem, 2005;77(9):2978-2984). For additional information, contact C.K. Larive, University of California-Riverside, Dept. of Chemistry, Riverside, CA 92521, USA.

Intec Pharma Breakthrough In Gastric Retention: Accordion Pill Doubles Drug Absorption

PR Newswire via NewsEdge Corporation: MIAMI, Florida, June 21 /PRNewswire/ -- Intec Pharma Ltd. (Israel) announced today the successful results of a clinical trial using a drug marker on healthy volunteers at the Sheba Medical Center in Israel. The results validate the company's proprietary Accordion Pill, a novel gastroretentive platform that targets drugs that must be absorbed by the body in what is known as the Narrow Absorption Window, the intestine segment below the stomach.

The study used Riboflavin (vitamin B2) as a model active ingredient to demonstrate the unique capability of the Accordion Pill formulation to prolong absorption of pharmaceuticals into the blood. The prolonged absorption enables greater bioavailability while reducing dosage and side effects. Many important pharmaceutical compounds are limited in their therapeutic action because insufficient amounts are absorbed into the body through this area,

"The study results confirm Accordion Pill as the first gastroretentive formulation to maintain controlled release and absorption of a drug for more than 6 hours following a low-calorie meal," said Efi Cohen-Arazi, CEO of Intec Pharma. "This is a major milestone, positioning Intec Pharma as a leader in the gastric retention field with a platform technology that can improve the bioavailability of drugs in an estimated $50 billion market," he added.

The study results were presented by Prof. Amnon Hoffman of the Hebrew University at the 32nd annual meeting of the Controlled Release Society in Miami, Florida. Prof. Hoffman together with Prof. Michael Friedman is co-developer of the Accordion Pill and a member of the Intec Pharma Scientific Advisory Board. For more information visit www.intecpharma.com or contact Etti Lavian +972-2-586-4657 ext. 101 etti@intecpharma.com Intec Pharma Ltd. 10 Hartom St Jerusalem 91450, Israel

Spherics Presents Proof-Of-Concept Studies Demonstrating Advantages Of Oral Delivery Platform Technologies; Human And Preclinical Studies

Business Wire via NewsEdge Corporation: BIOWIRE2K LINCOLN, R.I.--(BUSINESS WIRE)--June 21, 2005--Spherics, Inc., announced today the results of proof-of-concept studies with three marketed compounds demonstrating the potential of the company's polymer-based oral delivery platform and Phase Inversion Nanotechnology to improve the drugs' oral bioavailability. The four studies, which involved human and preclinical studies with itraconazole and preclinical studies with acyclovir and paclitaxel, were presented at the 2005 annual meeting of the Controlled Release Society, in Miami, Florida.

"Each of these drugs has distinct and challenging bioavailability issues that limit effectiveness, increase potential for adverse effects, or in the case of paclitaxel, preclude use as an oral agent," said Avinash Nangia, Ph.D., Vice President of Research and Development at Spherics and one of the

study's authors. "In these studies, we have shown we can significantly enhance the oral bioavailability profiles of these drugs, providing strong proof-of-concept for our oral drug delivery technology platform."

Spherics has developed advanced drug delivery systems with a focus on oral delivery. The company's technologies are designed to increase drug residence time at target sites within the gastrointestinal tract, thereby improving bioavailability. The platform includes bioadhesive polymer-based delivery systems. The company's Phase Inversion Nanotechnology ("PIN") process generates nano-size drug particles for systemic absorption of drugs with low solubility and poor permeability. Spherics is using the platform to establish a proprietary pipeline of products and the company expects to collaborate with partners in life-cycle management. Spherics' pipeline is focused principally on drugs to treat central nervous system disorders, gastrointestinal diseases, and cancer. For more information, visit www.spherics.com.

Cephalon And Alkermes Announce Agreement For The Commercialization Of Vivitrex For The Treatment Of Alcohol Dependence; Companies To Share Profits From Future Sales Of Vivitrex Equally
Business Wire via NewsEdge Corporation:
FRAZER, Pa. & CAMBRIDGE, Mass.--(BUSINESS WIRE)--June 24, 2005 - Cephalon, Inc. (Nasdaq: CEPH) and Alkermes, Inc. (Nasdaq: ALKS) announced today that they have entered into an agreement to develop and commercialize Vivitrex(R) (naltrexone long-acting injection) in the United States. Vivitrex is an investigational drug in development by Alkermes for the treatment of alcohol dependence. Alkermes submitted a New Drug Application (NDA) for Vivitrex to the U.S. Food and Drug Administration (FDA) on March 31, 2005, which has been granted priority review.

Cephalon and Alkermes will form a joint commercialization team and will share responsibility for developing the commercial strategy for Vivitrex. Cephalon will have primary responsibility for the marketing and sale of Vivitrex, and Alkermes will augment this effort with a team of treatment system specialists. Alkermes also will be responsible for obtaining marketing approval for Vivitrex for the treatment of alcohol dependence and for manufacturing the product.

PEG/PLA Semi-Interpenetrating Network Controls Delivery Of Protein Drugs
Angiogenesis Weekly via NewsEdge Corporation:
June 17 2005 - (NewsRx.com) -- A PEG and PLA semi-interpenetrating network controls the delivery of protein drugs.

According to a study from the United States, "We have prepared a semi-interpenetrating network (lPN) of poly(ethylene glycol) dimethacrylate (PEGDMA) with entrapped poly(D,L-lactide) (PLA) using photochemical techniques. These lPNs were developed for the controlled delivery of protein drugs such as growth factors."

"The PEG component draws water into the network, forming a hydrogel within the PLA matrix, controlling and facilitating release of the protein drug, while the PLA component both strengthens the PEG hydrogel and enhances the degradation and elimination of the network after the protein drug is released.

"The rate and extent of swelling and the resultant protein release kinetics could be controlled by varying the PEG/PLA ratio and total PLA content," wrote C.D. Brown and colleagues at the University of Washington in Seattle.

"These lPNs were prepared using a biocompatible benzyl benzoate/benzyl alcohol solvent system that yields a uniform, fine dispersion of the protein throughout the PEG/PLA lPN matrix. lPNs composed of high molecular mass PLA and lower PEG/PLA ratios exhibited lower equilibrium swelling ratios.

"The release of bovine serum albumin (BSA), a model protein, from these IPNs was characterized by a large initial burst," reported the authors, "regardless of the PEG/PLA ratio, due to the entrapment of residual solvent within the network."

Brown continued, "Microparticles of the PEG/PLA IPNs were also prepared using a modified Prolease strategy. Residual solvent removal was significantly enhanced using this process. The microparticles also exhibited a significant reduction in the initial burst release of protein."

"Mixtures of different compositions of PEG/PLA microparticles should be useful for the delivery of a variety of protein drugs with different release kinetics from any tissue-engineering matrix," concluded scientists.

Brown and colleagues published the

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results of their research in the Journal of Biomaterials Science - Polymer Edition (Semi-interpenetrating network of poly(Ethylene glycol) and poly(D,L-lactide) for the controlled delivery of protein drugs. J Biomater Sci-polym Ed, 2005;16(2):189-201). For additional information, contact A.S. Hoffman, University Washington, Department Bioengineering, Box 352255, Seattle, WA 98195, USA.

Clinical Progress With Mannkind's Inhaled Insulin

in-PharmaTechnologist.com

June 13, 2005 - An inhaled formulation of insulin developed by MannKind has been shown to mimic the normal insulin response after a meal and reduce glucose levels sooner than conventional insulin injections. In individuals without diabetes, there is a normally occurring rapid and intense first phase insulin secretion in response to a meal. This spike is lost in patients with diabetes, who consequently experience higher and protracted blood glucose increases after a meal. Long-term uncontrolled elevations of blood glucose have been shown to cause irreversible damage.

Mannkind's study, reported at the ongoing American Diabetes Association annual meeting in San Diego, found that mimicking the first phase insulin release by giving a dose of its inhaled insulin preparation - TI - allowed glucose elimination to reach maximum levels much faster than with regular subcutaneous insulin.

Glucose elimination occurred in just 45 minutes with TI, compared to 240 minutes with subcutaneous insulin. It is important for patients with diabetes to have tight glucose control prior to, during and following a meal to avoid serious complications of diabetes like blindness and irreversible damage to the kidneys and nerves.

Meanwhile, a second study reported at the ADA found that this rapid onset of glucose control was not associated with any increase in hypoglycemia, a serious complication that can follow insulin therapy.

Hypoglycaemia is a life-threatening situation where blood glucose falls below normal levels. It is a current therapeutic goal to bring blood glucose back to normal levels within 2-3 hours after a meal. However, conventional subcutaneous insulin doses that are sufficient to achieve this goal often extend their effect on glucose beyond the time when normal levels have been reached, potentially inducing hypoglycaemia late after a meal. The risk of hypoglycemia is an obstacle both for achieving good glucose control and reducing complications associated with diabetes.

In the ADA study, TI was found to exert about 74 percent of its glucose-lowering activity within the first three hours following administration. In contrast, regular subcutaneous insulin only exerted approximately 30 per cent of its activity within the same time period.

As a result, "TI appears to have the ability to achieve glucose-lowering activity earlier than subcutaneous insulin without increasing the risk of late postprandial hypoglycaemia commonly associated with regular subcutaneous insulin," said Mannkind.

TI is based on Mannkind's Technosphere drug delivery technology, which involves the inhalation of very small particles of the insulin formulation, using a proprietary inhaler device that causes deposition of the active drug deep in the lungs.

A raft of companies are trying to bring non-injectable formulations of insulin to the multibillion dollar insulin market, with the first commercial launch of a product, Generex Biotechnology's Oral-Lyn, taking place in Ecuador in May. This formulation is delivered via an inhaler-type device but is actually absorbed into the bloodstream through the buccal mucosa, with no lung deposition.

Meanwhile, Pfizer and Sanofi-Aventis filed for approval of their inhaled insulin product Exubera in the US in April, after delays caused by regulatory requests for data to support the safety of delivery the peptide into the lungs. Last September, the companies presented data suggesting that diabetics taking the drug exhibited no decline in lung function after two years. Other inhaled insulins are in Phase III clinical development from Eli Lilly/ Alkermes and Novo Nordisk/Aradigm.

Multilayer Drug-eluting Coating For Cardiovascular Stents Effective In Trials

Drug Week via NewsEdge Corporation: MAY 27, 2005 - (NewsRx.com) -- MIV Therapeutics, Inc., (MIVT) announced that it received encouraging reports from independent researchers evaluating the company's novel multiplatform/multidrug delivery solution in short-term animal studies.

The independent porcine studies evaluated MIVT's proprietary hydroxyapatite (HAp)-based coatings designed for drug-eluting cardiovascular stents and other implantable medical devices. The studies were conducted at Cardiovascular Interventions Core of the Methodist Hospital Research Institute.

Researchers from these institutions have supplied a final report that summarized the outcome of preliminary short-term animal study of MIVT proprietary drug eluting formulas. The studies were conducted on stents coated with a combination of HAp and Paclitaxel-eluting nonpolymeric composite coating.

"In summary, stents coated with hydroxyapatite and Paclitaxel have shown uncompromised biocompatibility and safety at 19 days," said Dr. Greg L. Kaluza, scientific director of the cardiovascular intervention core at the Methodist Hospital Research Institute, who directed the study.

Drug-eluting stents deliver medicines at the point of implantation to reduce unwanted side effects such as excessive neointima and restenosis. In addition to its drug-eluting features, MIVT's HAp technology provides an exceptional degree of biocompatibility, or biological acceptance, compared to traditional bare metal stents. The Methodist study was performed on stainless steel stents coated with a multilayer drug-eluting coating that included MIVT's proprietary D4080 Hydroxyapatite "passive" ultra-thin coating, with a second coating layer of a proprietary drug-eluting composite which, for engineering reasons, was encapsulated in thin shell of biodegradable polymer.

Star Amphiphilic Block Copolymer Developed As Drug Carrier

Drug Week via NewsEdge Corporation: MAY 27, 2005 - (NewsRx.com) -- A novel star amphiphilic block copolymer has been developed and evaluated for use in a drug delivery system.

"The core of the star polymer is polyamidoamine (PAMAM) dendrimer, the inner block in the arm is lipophilic poly(epsilon-caprolactone) (PCL), and the outer block in the arm is hydrophilic poly(ethylene glycol) (PEG)," scientists in Massachusetts explained. "The star-PCL polymer was synthesized first by ring-opening polymerization of epsilon-caprolactone with a PAMAM-OH dendrimer as initiator."

"The PEG polymer was then attached to the PCL terminus by an ester-forming reaction," added F. Wang and coauthors working at EIC Laboratories in Norwood. "Characterization with SEC, 1H NMR, FTIR, TGA, and DSC confirmed the star structure of the polymers."

"The micelle formation of the star copolymer (star-PCL-PEG) was studied by fluorescence spectroscopy," according to the report. "Hydrophobic dyes and drugs can be encapsulated in the micelles."

"A loading capacity of up to 22% (w/w) was achieved with etoposide, a hydrophobic anticancer drug," published data showed. "A cytotoxicity assay demonstrated that the star-PCL-PEG copolymer is nontoxic in cell culture and that this type of block copolymer can be used as a drug delivery carrier," the researchers concluded.

Wang and colleagues published their study in Bioconjugate Chemistry (Synthesis and evaluation of a star amphiphilic block copolymer from poly(epsilon-caprolactone) and poly(ethylene glycol) as a potential drug delivery carrier. Bioconjugate Chemistry, 2005;16(2):397-405). For additional information, contact F. Wang, EIC Laboratories, Inc., 111 Downey St., Norwood, MA 02062, USA.

Intravenous Gene Therapy Delivery Outpaces Intra-peritoneal Transfer In Mice
Gene Therapy Weekly via NewsEdge Corporation:
MAY 26, 2005 - (NewsRx.com) --
According to recent research published in the World Journal of Surgery, "suicide gene therapy has been shown to be an effective means of destroying pancreatic cancer cells. Liposomes have been described as having better efficacy in gene delivery, and an advantage of using liposomes as gene carriers is that they can be used repeatedly in vivo."

"The objective of this study is to compare the effect of gene delivery routes and to determine whether systemic delivery of the rat insulin promoter (RIP) directed suicide gene construct would permit cell-specific gene delivery in vivo," wrote X.P. Wang and colleagues, Baylor College of Medicine, Michael E. DeBakey Department of Surgery.

"Severe combined immunodeficient (SCID) mice were injected with liposome-RIP-TK (thymidine kinase) complex by either the intraperitoneal or the intravenous route. Twenty-four hours post gene delivery mice received ganciclovir (GCV) treatment twice daily for 14 days.

"HSE staining indicated that both intravenous and intraperitoneal liposome-RIP-TK gene expression had no effect in normal endocrine islet cells. Both gene-delivery routes in mice resulted in normal glycemia and serum insulin levels. The endocrine islets were intact, with a normal distribution pattern of insulin-producing beta cells and glucagon-secreting alpha cells," scientists indicated. "However, serum chemistry analysis revealed significantly elevated levels of liver enzymes; suggesting that possible liver damage had occurred with the intraperitoneal gene delivery of liposome-pRIP-TK. Intravenous liposome-mediated gene delivery had no effect on liver enzyme levels."

Wang and colleagues published their study in World Journal of Surgery (Intravenous delivery of liposome-mediated nonviral DNA is less toxic than intraperitoneal delivery in mice. World J Surgery, 2005;29(3):339-343). For additional information, contact X.P. Wang, Baylor College Med, Michael E. DeBakey Department Surgery, 6550 Fannin , Suite 1661, Houston, TX 77030, USA.

Added Polymers Stabilize Microcapsules Used For Cell-based Therapies
Gene Therapy Weekly via NewsEdge Corporation :
MAY 26, 2005 - (NewsRx.com) -
- "Implantation of microencapsulated recombinant cells is an alternative approach to gene therapy. These genetically engineered cells enclosed in microcapsules to deliver therapeutic recombinant products have been effective in treating several murine models of human diseases. However, the most commonly used microcapsules fabricated from alginate ionically cross-linked with calcium suffer from loss of long-term mechanical stability," researchers in Canada report.

"We now report on a method to improve their stability by introducing additional polymers to provide covalent linkages via photopolymerization. Vinyl monomers and a photoinitiator were allowed to diffuse into the initially formed calcium-alginate microcapsules. In situ photopolymerization in the presence of sodium acrylate and N-vinylpyrrolidone substantially enhanced their mechanical strength," wrote M.S. Wang and colleagues, McMaster University, Health Sciences Center.

"After 4 months of storage in saline, >70% of these capsules remained intact in the osmotic pressure test, while the unmodified alginate microcapsales totally disintegrated. Tests of their permeability to polyethylene glycol of different molecular weight and their ability to support cell survival showed that these properties remained unaffected by the photopolymerization."

"Hence, these microcapsules modified by adding a network of vinyl polymers are promising candidates to use for long-term delivery of recombinant gene products in this cell-based method of gene therapy," researchers concluded.

Wang and colleagues published their study in the Journal of Biomaterials Science - Polymer Edition (A novel method to enhance the stability of alginate-poly-L-lysine-alginate microcapsules. J Biomater Sci-polym Ed, 2005;16(1):91-113). For additional information, contact P.L. Chang, McMaster University, Hlth Science Center, Department Pediatrics, Room 3N18, 1200 Main St. W, Hamilton, ON L8E 4J9, Canada.

Nasal Vaccine Delivery Tech Clears Milestone
in-PharmaTechnologist.com
May 25, 2005 - A delivery technology that could allow vaccines to be administered intranasally and does not require refrigeration has passed its first clinical hurdle. DelSite Biotechnologies said results from the Phase I clinical trial showed that its GelVac powder delivery system was safe and well tolerated and that doses were consistently and reproducibly dispersed into the nasal cavity.

If the concept proves successful in further trials, it could lead to the development of dry powder vaccines that do not require refrigeration making it easier to supply immunizations to remote areas of the world, and do not need preservatives such as mercury additives that have been linked to side effects. Moreover, doing away with the need for injections should boost the safety of vaccination programs by cutting out the risk of blood-borne disease transmission and needlestick injuries.

The clinical trial looked at the safety, nasal deposition, nasal retention time and the performance of the single dose delivery device using radio-labeled test materials.

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It involved 15 healthy adult volunteers and compared two selected particle sizes of GelVac powder and a control powder.

The GelVac system is based on a polymer, called GelSite, that is water-based and is capable of in situ gelation – ie it changes from a liquid or a powder to a gel upon contact with body fluids. It is a member of a family of plant polysaccharides that has been classified by the US Food and Drug Administration (FDA) as Generally Recognized As Safe (GRAS).

GelSite's mucoadhesive properties are used to entrap the vaccine antigen in the nose, providing a mechanism for prolonged exposure of the antigen to local immune tissues and, potentially, enhancing the protective immune response. DelSite, a subsidiary of Carrington Laboratories, said this nasal delivery platform may also be suitable for delivering live attenuated viruses.

Buccal Tablet Could Reduce Systemic Antifungal Use
in-PharmaTechnologist.com
May 24, 2005 - An antifungal product in development at France's BioAlliance Pharma has been shown to treat a yeast infection in the mouth with similar efficacy but 10 times less drug than its nearest competitor.

A Phase III trial of the buccal tablet, called Lauriad (miconazole), showed that the product was at least as effective as an oral gel formulation of the antifungal in the treatment of oropharyngeal candidiasis, also known as thrush.

Lauriad was also administered with a more convenient schedule than the miconazole oral gel comparator - once-daily rather than four times a day - suggesting that it could improve compliance with therapy This is significant, because while current treatment guidelines recommend the use of topical or localised therapies such as gel, lozenges and mouthwashes for oropharyngeal candidiasis, they have been generally unsuccessful in treating this infection.

Patients have resisted the multiple daily applications and unpleasant taste, while transient drug concentrations in the oral cavity have limited efficacy. And this has resulted in the preferential use of systemic antifungal agents, which carry a greater risk of side effects and the generation of resistant fungal strains.

Lauriad is placed beneath the upper lip and adheres to the mouth lining while it releases the antifungal agent. It is made up of a natural polymer that gradually absorbs water, triggering sustained release of miconazole as the tablet erodes. Once the tablet is in place, patients can eat, drink and carry on normal daily activities while the tablet dissolves.

BioAlliance is also developing its buccal tablet technology to deliver drugs for other applications, including acyclovir for oral herpes and the opioid analgesic fentanyl for severe pain.

Single Injection Rivals Implant For Drug Delivery
in-PharmaTechnologist.com
May 19, 2005 - A single injection could replace implants for some drugs that require continuous administration, according to preliminary experiments with a novel drug delivery technology. The delivery vehicle, called BioSilicon and developed by nanotechnology company pSivida, BioSilicon's porous nanostructure effectively stores an active compound in tiny pockets that release minute amounts of drug as the silicon dissolves.

The study, performed by pSivida in collaboration with Australian company EpiTan, compared four BioSilicon formulations containing the tanning agent Melanotan (alpha-melanocyte stimulating hormone) to EpiTan's implantable formulation, currently in clinical development.

Melanotan is designed to promote the formation of the skin pigment melanin in the skin without exposure to ultraviolet light and thereby protect fair-skinned people in sunny climates from developing skin cancer. Previously the drug has been delivered as a daily injection that required significantly higher quantities. As with any pharmacological agent, it is preferable to limit the amount delivered to reduce the risk of side effects Data obtained from the in vivo study conducted at the Institute of Medical and Veterinary Science in Adelaide, South Australia, indicated that a single injection of BioSilicon loaded with Melanotan released the active drug over a sustained, 14-day period.

In February, EpiTan announced that it had filed a patent application for discoveries surrounding the increased efficacy (i.e. increase in melanin) of Melanotan when given at significantly lower dose levels in a sustained manner. This patent covers the collaboration work by EpiTan and pSivida. The next stage of development will progress towards a commercially viable version of this

formulation. Meanwhile, the implantable version of Melanotan is scheduled to be available in 2007, after the successful completion of clinical trial programs and registration with the relevant regulatory authorities around the world.

BioSilicon has also shown promise in a proof-of-principle study looking at its ability to deliver localized radiotherapy to tumors in the form of implantable beads, a procedure known as brachytherapy.

Linker Peptide Joins Drugs To Devices
in-PharmaTechnologist.com
May 18, 2005 - Engineers in the US have found a way to modify a plastic so that it can anchor molecules that promote nerve regeneration, blood vessel growth or other biological processes. The team, from the University of Texas at Austin, has accomplished the feat by identifying a peptide that attaches to polypyrrole, a synthetic polymer that has promise as a new biomaterial for medical devices.

The researchers screened a billion candidates to find the molecule-binding peptide, called T59, and also developed a modification of it that can be used to bind cells.

Christine Schmidt, who led the research team, said: "It will be very useful from a biomedical standpoint to be able to link factors to polypyrrole in the future that stimulate nerve growth or serve other functions." The work is published online in the journal Nature Materials.

Polypyrrole is of interest for tissue engineering and other purposes because it is a non-toxic plastic that conducts electricity. Researchers in Schmidt's laboratory have been investigating the material's ability to help severed nerve branches (neurites) regenerate.

If the severed neurites are wrapped in the polymer, the application of an electric field has been shown to enhance neurite repair. Now, the ability to attach proteins to polypyrrole means that growth-enhancing factors could also be linked to this plastic wrapping, further stimulating neurite regeneration. In time, the hope is that the technique could be scaled up to allow the repair of bigger nerves.

Schmidt's laboratory intends to study T59 as a linker to other molecules in the future, possibly including vascular endothelial growth factor, which stimulates the growth of new blood vessels, in the hope of developing materials that could be used to treat cardiovascular diseases. In addition, they will use the bacteriophage analysis approach, called high-throughput combinatorial screening, to look for peptide linkers for other plastics such as polyglycolic acid under study for tissue-repair or tissue-engineering purposes.

Protein Carrier Makes Oral Drugs Out Of Injectables
in-PharmaTechnologist.com
May 11, 2005 - Researchers in the US have developed a way to make large, protein-based drugs suitable for oral rather than injectable delivery by fusing them with a carrier molecule. The scientists, from the University of Southern California School of Pharmacy, have found that joining proteins such as granulocyte colony-stimulating factor (G-CSF) to transferrin, a plasma protein, allows the drug to survive the journey through the gastrointestinal (GI) tract and cross over into the bloodstream.

Dr Wei-Chiang Shen, professor and acting chair of the university's department of pharmaceutical sciences, along with colleagues David Ann and Yun Bai, reported in the 17 May issue of the Proceedings of the National Academy of Sciences the process by which transferrin was fused with G-CSF and initial studies of the resulting molecule in mice.

Pharmaceutical scientists have looked at other ways to deliver protein-based drugs such as via needle-free injections or through inhalation, but these delivery methods have posed their own problems. For example, Pfizer and Sanofi-Aventis have faced a long regulatory path to approval for an inhaled formulation of insulin because of concerns that long-term treatment with their drug, called Exubera, could adversely affect lung function.

The team's first breakthrough came when they discovered that transferrin can bind to receptors on the intestinal epithelial cells and be transported across the GI tract to the bloodstream. The next step, Shen explained, was isolating the genetic code for G-CSF, a protein factor that stimulates white blood cell production in the body. G-CSF is used to make Amgen's Neupogen (filgrastim) and Neulasta (pegfilgrastim) - injectable drugs that are used to keep cancer patients' white blood cell count at normal levels during chemotherapy.

"Through recombinant DNA technology, we combined the genetic codes for both human transferrin and G-CSF to create a new recombinant DNA, which, when expressed in a cell, will produce a protein with half transferrin and half G-CSF," said Shen.

The researchers administered the resulting recombinant fusion protein orally to mice, and found that it increased the white blood cell count for three days, three times the duration of action seen with Neupogen. Importantly, "this technique can be used to create orally-administered versions of other currently injectable protein drugs such as insulin, growth hormone, and erythropoietin, a medication to increase red blood cell counts," said Shen. USC holds the patent to the new recombinant fusion protein technology, and the research was supported by grants from the National Institutes of Health.

Antares Unveils Oral fast Melt Drug
in-PharmaTechnologist.com
April 28, 2005 - Antares Pharma has announced that it has completed formulation and preclinical activities for its first fast melt oral tablet incorporating a nonsteroidal anti-inflammatory drug (NSAID) using its Easy Tec fast melt technology. Antares' Easy Tec technology can reduce the manufacturing and packaging costs. The formulation contains excipients already used in marketed products and all are GRAS. As a result no additional toxicity studies are required to support the use of the excipients in a formulation.

The product, currently named AP-159, is a fast melt based formulation that the company intends to develop in two different dosage strengths similar to conventional tablets in the marketplace. Given once daily, the product is indicated for relief of the signs and symptoms of osteoarthritis. AP-159 is a small tablet that disintegrates in the mouth in less than 15 seconds without requiring water. After the quick disintegration, no aftertaste or residue remains.

The product has been developed for the treatment of osteoarthritis and the company anticipates that its scale-up will be initiated with a US manufacturer in the coming months followed by the relevant bioequivalence studies planned by the fourth quarter of 2005. The company said it intends to file an ANDA early in 2006. The fast-melt market is one of the fastest growing sectors

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In the News *continued from page 25*

of the drug delivery market with industry experts projecting a 20 percent annual growth rate for the next several years.

Journal of Controlled Release Highlights
by Morgan Leaming and Kinam Park, Purdue University, USA
Wouldn't it be great if you could hack into your fellow scientist's computer to see what new research he is reading about? You could avoid those embarrassing moments at conferences when everyone is talking about the new article published in the Journal of Controlled Release — the one you forgot to read. To help you identify the downloaded articles that are captivating your colleagues' attention, ScienceDirect releases the Top25 Hottest Articles from the Journal of Controlled Release. While there is no particular publication date associated with the articles, the list is created from download data compiled quarterly.

In the rankings for January, February and March 2005, fifteen out of twenty-five articles each contained one of the following keywords: chitosan, drug delivery, and nanoparticle. The majority of the downloaded articles containing these keywords were found in issues of the journal published in 2004 and 2005. These keywords may be general, but the fact that fifteen of the twenty-five articles use the words to classify their content says a lot about what the controlled release community is reading. Although "drug delivery" is an obvious keyword for the articles published in the journal, "nanoparticle" clearly indicates the current trend in nanoparticulate drug delivery systems. "Chitosan" continues to be the hot topic in controlled drug delivery.

While these fifteen articles share a common theme, the two most downloaded articles each address a topic of their own. The review, Microencapsulation by solvent extraction/evaporation: reviewing the state of the art of microsphere preparation process technology, Journal of Controlled Release, Volume 102, Issue 2, Pages 313-332, secured the top spot on this quarter's list. This review comments upon the most updated microencapsulation technologies based on the traditional solvent extraction/evaporation.

Coming in at number two is, Cationic TAT peptide transduction domain enters cells by macropinocytosis, Journal of Controlled Release, Volume 102, Issue 1, Pages 247-253. This article addresses novel biologically active transducible anticancer PTD peptide therapeutics. This article represents those dealing with cellular uptake of drug delivery vehicles, which is one of the critical steps in the successful drug delivery.

The listing of the Top25 Hottest Articles is just one of the services Elsevier and the Journal of Controlled Release provide to its readers. We are continually thinking of new ways to improve the journal and provide the community with a first-rate vehicle to publish novel research. As scientists in the area of drug delivery, we welcome you to actively participate in the future development of the journal. Any comments and suggestions that you have will always be appreciated. ■

Parameter Meter *continued from page 11*

PARAMETER MODEL

Combining information discussed above, a model can be derived:

1) Establish temperature restrictions from melt point, Tg, affinity of solvents for the core and film-coat, plasticizing effects, degradation temperature, and other pertinent information. Maintain inlet temperature below the temperature limit.

2) Establish process air. Equipment design and data from similar-sized materials or properties can be used in this assessment.

3) Use Figures 2 - 10 to establish spray rate. A spray rate for organic solvent-based solutions can be estimated using the following equation:
Solution Spray Rate (g/min) = [(A1) (B1) + (A2) (B2) + ….] x C / D
where
A1 = g/ft3 at 3% of capacity for solvent 1 at process outlet temperature (from appropriate graph)
B1 = % of solvent 1 in the solvent vehicle
A2 = g/ft3 at 3% of capacity for solvent 2 at process outlet temperature (from appropriate graph)
B2 = % of solvent 2 in the solvent vehicle
C = Process airflow (ft3/min)
D = % Total solvent in coating solution

   If solvent affinity for coating or core material is high, use 2/3 of the calculated value. If affinity is low, double the calculated value. Water systems can be run at between 10 and 100% or more of the saturation and process air dew point line difference depending on affinity factors and goals of the process.

4) Verify spray rate is safely below the LEL.

5) High process temperatures and high atomizing air conditions could cause spray drying, nozzle capping, and/or particle attrition. Compensate with temperature and solution adjustments.

REFERENCES

a. Unpublished data for product and research spray nozzles at Coating Place, Inc., Verona, Wisconsin.

b. Data derived from Handbook of Chemistry and Physics; R. C. Weast, Editor; 67th Edition (1986).

c. Charles R. Frey, Rachael A. Hopp, and Tom Breunig; "Residual Solvent in Polyvinylacetate Filmcoats Applied with the Wurster Fluid Bed Coating Process"; poster at the 2004 Annual CRS Meeting.

ACKNOWLEDGEMENTS

The author acknowledges the helpful advice and insight of Mr. Harlan Hall, Coating Place, Inc.

Contact Charles Frey at cfrey@encap.com for more information. ■

Journal of Controlled Release Highlights

By Morgan Leaming and Kinam Park, Purdue University, USA

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Patent Watch
TRANSDERMAL UPDATE

By Priya Batheja, and Bozena Michniak, Rutgers University, USA
Agis Kydonieus, Samos Pharma, USA

Our patent search spanning the last six months of 2004 revealed 192 patents and patent applications. From these, 21 were US issued patents, 29 EP issued patents, 7 World issued patents, 82 US patent applications, 17 EP patent applications and 36 World patent applications.

In this Update we have reviewed only the US-issued patents and US patent applications. Sixty two of these patents pertained to methods, devices, drugs used and components of transdermal systems. Forty-one pertained mainly to permeation enhancement from which 25 involved chemical enhancers and sixteen electrophysical enhancers including iontophoresis, electroporation, ultrasound and stratum corneum ablation. Some of the more pertinent patents are summarized below.

Several activities of commercial interest were announced during the second half of 2004. In September, Schwarz Pharma announced that it had filed with both the FDA and EMEA (European Medicines Agency) applications for marketing approval of its once per day transdermal patch of rotigotine, to treat patients in early stages of Parkinson's disease. Rotigotine, a novel dopamine receptor agonist was tested in more than 1500 patients in 15 clinical trials. In October, Schwarz Pharma also announced that the results of clinical trials in the USA and Europe of the rotigotine patch as adjunctive therapy in patients with advanced stage Parkinson's disease showed statistical significance, meeting both primary endpoints.

A lot of activity took place in the extended chronic pain relief, using opioid patches. Firstly, the US District Court ruled against Mylan, however later in the year Mylan's generic version of the fentanyl patch was approved for marketing. Other fentanyl patches were also approved for marketing and there are more than half a dozen companies awaiting approval of their generic versions.

In July 2004 Alza announced that it had received an approvable letter from the FDA for its iontophoretic fentanyl-containing patch. The presumed advantages of this patch as compared to the passive delivery patches are rapid analgesic action and delivery on demand.

Finally, Durect announced that they are in Phase II clinical trials with a sufentanil patch. Sufentanil belongs to the same family of opioids as fentanyl, but it is approximately ten times more potent. Durect expects that its patch will have a 7-day duration of action as compared to the 3 day duration of the fentanyl patches. The fentanyl patch business was over 2 billion dollars in the 2004 calendar year.

In the hormone area, P&G announced in September that the FDA had granted priority review for its female testosterone patch for the treatment of Hypoactive Sexual Desire Disorder. The product, however was not recommended for approval by FDA's expert panel. Antares and its marketing partner Biosante announced that phase II studies with their testosterone transdermal gel significantly increased satisfying sexual activity in women suffering from female sexual dysfunction. They also reported that they were on track to enroll all subjects by year end 2004 and complete the study by the first quarter of 2005. Sontra Medical reported that their SonoPrep device and procedure tray for use with topical lidocaine to achieve rapid skin anesthesia (within 5 minutes) was approved by the FDA in August and the product was introduced into the market place in September 2004.

In December, Bristol Myers reported that it had entered into an agreement with Somerset Pharmaceuticals to market Ensam™ a transdermal patch to treat depression. Somerset had received an approvable letter from the FDA in February of 2004.

ELECTROPHYSICAL ENHANCERS

Method and Apparatus for the Enhancement of Transdermal Transport (Sontra Medical) US 2004/0236268 A1 and US 2004/0171980 A1

The invention pertains to the enhancement of transdermal permeation by using low frequency ultrasound. The method comprises the creation of a volume of fluid adjacent to the skin and containing the substance to be transported, determining an electrical parameter of the solution, applying the low frequency ultrasound, monitoring the changes in the electrical parameter of the solution and controlling the low frequency ultrasound based on the changes in the electrical parameter of the fluid. The substance can be a drug, a vaccine, or a component of interstitial fluid.

Handheld Apparatus and Method for Transdermal Drug Delivery and Analyte Extraction (Avrahami) US 2004/0230227 A1 and US 2004/0158240 A1

A handheld device is described which includes a plurality of electrodes, which are adapted to be placed in contact with the skin and then moved across the skin. A power source applies current between the electodes at the same time as the electrodes are moved through the skin, so as to create narrow channels through the stratum corneum, but not affect the epidermis below the stratum corneum. The ablated skin allows the transport of large molecules, which would not otherwise permeate the skin. The 0158240 application pertains to the ablation of the stratum corneum by applying electrical energy between two electrodes as to cause ablation in an area intermediate to the respective points.

Transdermal Delivery System for Dried Particulate or Lyophilized Medications (Stern) US 2004/0137044 A1

The invention pertains to the delivery of peptides and proteins in a dry form, which has the advantage of keeping them stable. The system comprises an apparatus that generates hydrophilic micro-channels and a patch comprising the therapeutic active agent. The micro-channels can be generated by any method

known in the patent literature and the patch is preferably produced by printing the protein onto a polymer film. Human Growth Hormone and Insulin were proteins of interest and were delivered at 30 to 100% bioavailability.

Method for Skin Absorption Enhancement and Transdermal Drug Delivery (Mattioli Engineering) US 2004/0220622 A1

A treatment method is provided for the enhanced permeation of a substance through the skin, which includes applying the substance onto the skin by way of a probe head.The probe is able to simultaneously provide bursts of electrical pulses to the skin, as well as vibrations to the skin surface. The vibrations are applied to the skin surface at the same frequency rate as the burst rate of electrical pulses. When dermabrasion treatment is initially provided to the skin, vibrations can be applied at 10 to 200 Hz and bursts of electrical pulses at frequencies between 50 and 15000 Hz.

Electrophoretic Device for in vivo Delivery of Therapeutics (Hisamitsu) US 6775569

An electroporation device is described comprising two contact electrodes attached to a permeable membrane. Such a membrane is useful for electroporetic delivery of drugs, when specific pulses, at specified intervals are applied. The membrane can be assembled in such a way so that an iontophoretic electrode is incorporated in the same device. The device can then be utilized for electrophoretic and iontophoretic drug delivery at the same time.

Effect of Electric Field and Ultrasound for Transdermal Drug Delivery (MIT) US 2004/0210184 A1

A method of enhancing transdermal transport is described, comprising the administration to the skin of low frequency ultrasound to cause cavitation of the skin lipids and increase permeation, without increasing the temperature of the skin appreciably. Prior to, or at he same time an electric field can be applied, such as iontophoresis or electroporation, to further increase the transdermal enhancement. The ultrasound is administered at frequencies of less than 1 MHz and intensities of less than 2.5 W/cm2.

Solid Solution Perforator for Transdermal Delivery (Kwon) US 2004/0199103 A1

A solid drug perforator (SDP) system is claimed which includes biodegradable or soluble perforators which rapidly degrade upon penetration through the skin to release their drug contents. Additional drug maybe released through the perforations formed by the perforating needles or blades by a patch reservoir attached to the SDP. Formulations and fabrication procedures are also described. Suitable matrix materials for the SDP include polyvinyl pyrrolidone, polyvinyl alcohol, polyethylene glycol, polysaccharides, cellulosics, carbohydrate derivatives and many other biopolymers.

Skin Treatment Method for Sustained Transdermal Delivery (J&J) US 2004/0181203 A1

An expandable skin stretching device is claimed to keep open the stratum corneum micropathways formed by microneedle or microablation devices, which close even within a few hours of formation. The stretching device expands and stretches the skin between the opposite ends, with the skin placed under tension of about 0.01 and 10 megapascals. Alternative embodiments of skin stretching devices use suction or normal force to stretch the skin.

Photokinetic Delivery of Biologically Active Substances Using Pulsed Incoherent Light (Kraft) US 2004/0131687 A1

The invention provides formulations and methods for the enhanced transdermal and transmucosal delivery of biologically active substances using pulsed incoherent light. Incoherent light refers to electromagnetic waves that are unorganized and propagate with different phases, such as the light emitted by light emitting diodes (LED). Formulations comprise gelling agents, solvents and photocatalytic agents in addition to the biologically active agent. Photocatalytic agents include titanium dioxide and zinc oxides. Methods of photokinetic (change in rate of motion in response to light) delivery comprise the application of the formulation to the skin and illuminating the formulation with pulsed incoherent light having a selected wavelength, pulse rate, duty cycle and intensity. These incoherent light parameters allow for the modulation of drug permeability through skin. Actives tested included, insulin, enkephalin, estradiol, lidocaine, testosterone and amphoteresin B among others.

ENHANCERS

Dual enhancer composition for topical and transdermal drug delivery (Dermatrends, Inc.) US 6835392

The invention describes a combination enhancer for transdermal or topical administration that can increase the permeability of an agent through skin or mucosal tissue and is equally effective with hydrophilic and lipophilic drugs. The enhancer combination consists of both a hydrophilic component and a lipophilic component, where the hydrophilic component is a hydroxide-releasing agent in combination with a lipophilic co-enhancer such as a fatty alcohol, a fatty ether, or a fatty acid ester. The amount of hydroxide-releasing agent is the total of the amount required to neutralize any acidic species in the composition plus an amount equal to approximately 0.5 wt % to 4 wt % of the composition. Also described is a drug delivery system that consists of a reservoir containing the drug and the enhancer composition with a backing layer and a method for increasing the rate at which an active agent permeates through the body surface. The method involves administering the agent with permeation enhancer composition where the amount of the enhancer composition is that which provides a pH at the body surface in the range of about 8.0 to 13.

Cubic liquid crystalline compositions and methods for their preparation (Children's Hospital Research Foundation,Cincinnati, OH) US6773627

The invention pertains to cubic liquid crystalline gel precursors, bulk cubic liquid crystalline gels, and dispersions of cubic liquid crystalline gel particles which can be used as skin penetration enhancers and describes methods for their preparation. The cubic liquid crystalline phase gels are prepared in the presence of a hydrotrope that do not detrimentally affect the cubic liquid crystalline structure of the gels and particles. The gel precursor comprises of a hydrotrope and an amphiphile that can form

Patent Watch *continued on page 30*

Patent Watch *continued from page 29*

cubic liquid crystalline phase structures. The bulk cubic liquid crystalline gel requires a solvent in addition to the hydrotope and the amphiphile. The dispersed cubic liquid crystalline gel particles contain a stabilizer in addition to the hydrotope, amphiphile and the solvent. The invention also describes methods for preparing all the compositions of this invention that do not require the difficult process of fragmentation.

Mixture for transdermal delivery of low and high molecular weight compounds, (Oryxe) US6759056
A novel transdermal delivery system that can deliver high molecular weight pharmaceuticals and cosmetic agents to skin cells has been described. . The formulation consists of a delivery agent, a penetration enhancer and an aqueous adjuvant, and enables the delivery of a number of agents that have molecular weights ranging from less than 100 daltons to greater than 500,000 daltons. The delivery system can be used for cosmetic purposes for delivering collagen preparations or for pharmaceutical applications including delivery of non-steroidal anti-inflammatory drug (NSAID), a capsaicin or Boswellin. Methods of making and using the transdermal delivery devices of the invention for the treatment and prevention of human disease and cosmetic condition are also provided.

Alcohol-free transdermal analgesic composition and processes for manufacture and use thereof (Fishman, Robert) US2004/0202722 AI
This invention pertains to an analgesic composition in combination with an alcohol-free dermal delivery system for transdermal application. The drug delivery system consists of an aqueous base vehicle that includes American Emu oil, Isopropyl Palmitate (PROTACHEM IPP), PEG-8 (a polyethylene glycol available under the tradename PROTACHEM 400), methylsulfonylmethane (MSM) and SEPIGEL 305 (a combination including polyacrylamide/C.sub.13-C.sub.14 Iso-paraffin and LAURETH 7, to which an analgesic is added. The system is alcohol free and therefore can demonstrate better shelf-life. It provides enhanced penetration via the dermal layers, thus providing a safe and effective system for delivering an analgesic composition to provide systemic relief from the discomfort of pain and/or inflammation.

Compositions for rapid and non-irritating transdermal delivery of pharmaceutically active agents and methods for formulating such compositions and delivery thereof (Transdermal Technologies, Inc.) US6787152
The invention pertains to a formulation for transdermal delivery that addresses the design of the skin as a biologically responsive physical, chemical and bioelectrical barrier acting against the diffusion and absorption of the active agent and the solvents. The TDS is composed of an active agent and a selection of solvents, solvent modifiers, solute modifiers and skin stabilizers, which form a true solution with the agent, and thus help it to rapidly cross the skin barrier. The modifying components also form non-permanent complexes that facilitate movement of the components through the skin into the circulation. All the complexers and modifiers separate from the active agents at the site of action and the agents is set free to act on the receptors. The modifiers and the solvents also render the agent more "slippery" thus facilitating its movement across the skin. The TDS improves delivery of active agents having a molecular weight greater than 340 Daltons.

METHODS AND DEVICES

System and method for optimizing tissue barrier transfer of compounds (Transform Pharmaceuticals, Inc.) US6758099
High-throughput systems and methods to prepare a large number of component combinations, at different concentrations and identities, at the same time are described in the invention. High-throughput methods have also been stated to test tissue barrier transfer of components in the combinations of the components. In addition the methods allow determination of the effects due to the additional components in a formulation, such as excipients and additives on the transfer of the active components across a tissue. ..

Dual adhesive transdermal drug delivery system (Samyang Corporation,Seoul, KR) US 6791003
The invention pertains to a drug-containing laminated transdermal delivery system which can cause rapid release of the drug early on leading to early attainment of therapeutic levels followed by maintenance of the plasma levels of a drug leading to persistent long-term therapeutic effect. The present invention comprises at least two adjacent drug containing pressure-sensitive adhesive (PSA) layers that have different solubilities for the drug. One side of each layer is laminated to an impermeable backing support and the opposite side can adhere to the skin of a patient. The solubility of the drug in the adhesive layer and the ratio of the surface areas of the adhesive layer affect the rate of delivery of drug. The invention can be used for the transdermal delivery of highly potent and rapidly metabolized drugs that have narrrow therapeutic indexes.

Methods of making such a transdermal drug delivered device have also been described.

Covalent and non-covalent crosslinking of hydrophilic polymers and adhesive compositions prepared therewith (Feldstein, Mikhail, M et al.) US2004/0242770 AI
A water-insoluble, hydrophilic adhesive polymer is described wherein the polymer is prepared by polymerization of a composition consisting of a hydrophilic monomer and a dual-function monomer that undergoes polymerization with the hydrophilic monomer, and thus provides crosslinks in the polymer product. Other water-insoluble crosslink-free hydrophilic adhesive polymer blends are also described. The different polymers can find applications in various hydrogel and bioadhesive systems, which can be used as drug delivery systems for topical, transdermal and iontophoretic use. Some examples are wound healing products, dressings, tooth whitening strips, masks and patches.

Transdermal device having a phase change material (Van Duren, Albert, Philip MN, US) US2004/0191301 AI
The invention consists of a transdermal device that contains a phase change material and another material. The phase change

material denotes a substance that changes state in response to heat, thereby undergoing transitions from the solid to liquid form. The device may contain a drug that is either mixed with or placed near the solid phase change material, which on application of heat changes to the liquid state thereby releasing the drug. One described system contains a transdermal patch that is comprised of a backing layer, a reservoir containing a drug and a phase change material in the particulate form, where the drug and the particles are mixed so that the particles are dispersed throughout the drug. These types of systems can be used for treatment of breakthrough pain by enhancing the rate of delivery of a drug in response to an increase in heat.

Crystallization inhibition of drugs in transdermal drug delivery systems and methods of use (Noven Pharmaceuticals, Inc.) US 2004/0142023 AI

Rosin esters have been used in the invention to suppress or prevent crystal formation of active agents in transdermal systems. The system consists of the rosin esters with the active agents incorporated in a pressure-sensitive adhesive carrier composition that can deliver a therapeutically effective amount while retaining good physical adhesive properties. The delivery system can achieves a zero-order kinetic rate of drug delivery for over a period of time in excess of 24 hours and at least 72 hours.

Transdermal drug delivery device with multilayer backing (3M Innovative Properties Company) US 2004/0219198 A1

The invention is directed toward a transdermal device comprising a backing material that has low moisture transmission, moderate to high oxygen transmission, good resistance to component diffusion, and good flexibility. The device consists of a reservoir containing the active agent and a multilayer polymeric film backing. The multilayer polymeric film backing comprises an outer shell layer, an inner shell layer, and an inner core that is comprised of 11 or more alternating layers of a thermoplastic elastomer and an olefinic polymer, with weight ratios below about 85:15 and above about 5:95. The inner shell layer is placed between the outer shell layer and the reservoir and is adjacent to the reservoir. A polymer from the group consisting of a homopolymer of polypropylene, a copolymer of polypropylene, a homopolymer of poly-4-methyl-1-pentene, a copolymer of poly-4-methyl-1-pentene, or blends, are used in al least one of the shell layers. Another aspect of the invention describes a transdermal drug delivery device comprising a reservoir and a multilayer polymeric film backing wherein the oxygen transmission rate of the multilayer polymeric film backing is between about 400 and about 4000 cm.sup.3/m.sup.2/day. ■

2006 Meeting

Vienna Waits for You

Vienna, Austria, is where you want to be July 22-26, 2006. Vienna is an experience for all your senses and the host of the 33rd Annual Meeting and Exposition of the Controlled Release Society. A European Union capital city, Vienna offers visitors both historic and modern sites, sounds, and tastes. An extensive public transportation system will get you to where your senses take you.

For your viewing enjoyment, there are a multitude of museums with collections ranging from art to natural science, modern to historic. Learn about your host city by visiting the Wien Museum Karlsplatz that documents the 2,000-year history of Vienna or the Museum of Natural History which offers a rooftop tour with a unique view across Vienna's historical old city. There are museums that occupy the former residences of the imperial family, such as the Austrian Gallery Belvedere which houses Austrian and international art of the 19th and 20th centuries, the Albertina which houses the world's largest collection of graphic art, and the MuseumsQuartier. The MuseumsQuartier is the former imperial stables that have been transformed to one of the ten largest cultural complexes in the world. It is a spectacular combination of old and new, a collection of museums around an enormous courtyard. And speaking of stables, don't miss the world reknown Lipizzaner stallions at the Spanish Riding School.

Vienna is known as the world's music capital. From the masters of classical, to the groove of jazz, to marching bands in outdoor courtyards, your ears will enjoy the experience. The sounds of Johann Strauss, Mozart, and Beethoven can be heard at a number of venues, inside and out. In addition, 2006 is the 250th anniversary of Wolfgang Amadeus Mozart's birth. Be prepared to celebrate the life of this best-known musical genius. Attend one of the many concerts, films, ballet or opera performances scheduled. From daytime into night, the night club scene never sleeps. The DJs and live acts of Vienna's nightlife can satisfy your thirst for world-class jazz to the latest music trends on the club turntable.

Savor what Vienna has to offer! Traditional to contemporary cuisine at sausage stands, cafés, bistros and gourmet restaurants; from sweet delicacies, to savory snacks, to hearty meals, you will experience a diverse palate. And there is not only food, but drink too. From tea and coffeehouses, to local brew pubs, and wine taverns, your beverage of choice will complete your culinary experience. And for those items that you can't consume, there is shopping. Your fashion sense will be exhilarated by over 20,000 stores, ranging from exclusive fashion and jewelry to typical Viennese products to flea market finds.

Experience the science, technology and the art of living that Vienna and the Controlled Release Society can provide July 22-26, 2006. Visit www.vienna.info to plan a trip that will invigorate all of your senses. ■

To Jab or Not to Jab continued from page 9

Vet Get-Together
At CRS Miami, the traditional vet get-together was sponsored by Bayer (Germany) and it proved a great success. Avinash Thombre of Pfizer (Groton) gave a light hearted comparison of gastro-retentive systems between humans and production animals. Many of his stark photographs of the insides of rumen nearly led to regurgitation of canapés and beer amongst the attentive attendees. He also showed some nice gamma scintigraphy of a human stomach in which a gastro-retentive device was being tracked. It seems that we are all recognized by our pylori, as the actual volunteer sitting in the second row of the audience immediately owned up with a degree of surprise and not a little pride. One of the main points of the presentation was to accentuate the device-led innovation amongst veterinary controlled release researchers working on intra-ruminal delivery of anti-parasitic agents, while highlighting the comparative physiological differences between ruminants and non-ruminants. The session was attended by at least 70 people and the topic clearly appealed to vets and non-vets alike.

Vet Podium Session
The vet podium session was led by two invited speakers, Dr. Ron Baynes of North Caroline State University Veterinary School and Greg Glenn (see above). Ron Baynes described various formulations including spot-ons, pour-ons and sprays to put veterinary controlled release skin delivery in context. Following a discussion of skin differences between species, he then described the use of fentanyl-loaded patches in different species for post-operative pain relief. He did not believe that patches would be applicable for many species for many drugs since the issues of fur and animal restraint were difficult. He highlighted the Franz cell apparatus used to measure drug delivery across the isolated skin from animals in vitro. Finally, he offered convincing data to the effect that veterinary use of pluronic leicithin gels for delivery had not led to demonstrable blood levels in contrast to the use of patches. Greg Glenn updated the conference in human skin immunization patches incorporating the adjuvant, heat labile enterotoxin (LT) from E. coli. His focus was on antigen delivery to the Langerhans dendritic cells of the epidermis using transcutaneous immunization and he showed data to indicate that LT enabled delivery and subsequent draining into lymph nodes. Human trial data presented was for LT itself as part of an E. coli vaccine. He also showed that intradermal delivery of flu vaccine only needed 20% of the injected dose to induce an effective immune response and that an LT patch acted as a general immunostimulant in combination with a parenterally administered vaccine for human subjects with underactive immune systems (e.g. the elderly). ■

Special Feature continued from page 13

* **TyRx Pharma Inc.** (Monmouth Junction, NJ), holds licenses to a suite of Rutgers' patents that define a class of tyrosine-derived biomaterials called polyarylates. TyRx focuses on developing a family of proprietary bioresorbable drug-eluting polymers for use in combination medical devices and specialty pharmaceuticals.
* **Osteotech, Inc.** (NASDAQ:OSTE, Eatontown, NJ), a leading provider of processed bone products, has obtained an exclusive license to Rutgers' patent rights in musculoskeletal uses of a combination bone/polycarbonate product, capable of being machined, molded, or otherwise formed into musculoskeletal products for use in orthopedic, cranio-maxillofacial, or periodontal applications.
* **SurModics, Inc.** (NASDAQ:SRDX, Eden Prairie, MN), a leading provider of surface modification and drug delivery technologies to the healthcare industry, has obtained an option to acquire an exclusive license from Rutgers to two classes of biodegradable polymers for use in site-specific delivery of drugs to the eye.

Summary
With its diversity of faculty and research partners, the New Jersey Center for Biomaterials conducts a vibrant program of biomaterials discovery, development and early stage commercialization. All the Center's programs are aligned toward its overarching goal of improving health care and the quality of life by developing advanced biomedical products for tissue repair and replacement and the delivery of drugs.

For further information visit http://www.njbiomaterials.org.

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** R.I. Sharma, J. Kohn, and P. V. Moghe, "Poly(ethylene glycol) Enhances Cell Motility on Protein-based PEG-polycarbonate Substrates: A Mechanism for Cell-Guided Ligand Remodeling." J. Biomed. Mater. Res. 2004, (69A), 114-23.*

**V.M. Meidan, B.B. Michniak, "Emerging Technologies in Transdermal Therapeutics." Amer. J. Ther. 2004, 11 (4), 312-6.* ■

Soapbox Session continued from page 7

Below is a recap of the Miami Soapbox Sessions:

Session 1
- **Novel Applications in Hot Melt Extrusion Using Polymeric Excipients**
  Tina Dasbach, The Dow Chemical Company
- **PEG-linkers for Biopharmaceuticals: The Next Generation**
  Hong Zhao, Enzon Pharmaceuticals, Inc.
- **New Drug Delivery Systems Platform Technology**
  Massimo Pedrani, Farmatron, Ltd.
- **Advancing the State of Active Transdermal Delivery**
  James Garrison, Vyteris
- **An Overview: Microstructured Transdermal System and Dry Powdered Inhalation Drug Delivery Technologies**
  Steve Wick, 3M Drug Delivery Systems
  - **New Method for Manufacturing and Coating Small Granules**
    John Bender, Fluid Air, Inc.
- **Innovative Microneedle Technology for Transdermal Application**
  Yashi Osaka, Texmac, Inc.

Session 2
- **OraVescent® Transmucosal Technology**
  Raj Khankari, CIMA LABS, Inc.
- **Discovering the Knowledge Buried in Your Data**
  Elizabeth Colbourn, Intelligensys Ltd
- **Simple Solutions to Complex Problems**
  Paul Titley, Encap Drug Delivery
- **Chrono-pharmacology: Applying Drug Delivery Technologies to Meet the Challenges of Long-term and Chronic Diseases**
  Guy DiPierro, ChronoDose
- **Clinical Research Testing For Your Transdermal Drug Delivery Product**
  Bryan Reynolds, Hill Top Research
- **Advances in Microdelivery Systems for Transdermal and Transmucosal Drug Applications**
  Gary Cleary, Corium International, Ltd.
- **Ceramic Particles for Controlled Release**
  Christophe Barbe, ANSTO
- **Dimethyl Sulfoxide USP, High Purity and Versatility for Drug Delivery**
  Artie McKim, Gaylord Chemical Corporation

Session 3
- **Solvent-free Processing of Biopharmaceuticals for Controlled Release Applications**
  Owen Davies, Critical Pharmaceuticals
- **Innovative Nano Delivery Systems**
  Isabelle Trempe, Labopharm
- **Practical Chemical Imaging Solutions for Drug Delivery**
  David Tuschel, ChemImage Corporation
- **M/DVT-22 Laboratory Unit**
  William Barker, Littleford Day, Inc.
- **Pulmonary Use of Captisol**
  Tom Krol, CyDex
- **Supercritical Fluid Technology in Pharmaceutical Technology and Drug Delivery**
  Hubert Pellikaan, FeyeCon D&I
- **Softgel-Based Drug Delivery - Tools for the Future**
  Xiaodi Guo/Edgar Jaynes, Banner

Session 4
- **Use of Constant Surface Geometry in Oral Drug Delivery**
  Bertrand Bolduc, Mistral Pharma
- **Novel Oral Drug Delivery Systems**
  Rich Ryzenga, UPM, Inc.
- **Intec Pharma's Unique Gastric Retention Drug Delivery Platform**
  Stanley Fass, Intec Pharma Ltd.
- **ClaroSip DST - A Novel Dosage Form for Sipping of Antibiotics in a Drinking Straw System**
  Iris Ziegler, Gruenenthal GmbH
- **Encapsulation as a Powerful Tool**
  David Mines, Inotech Biosystems International
- **OctoPlus: New Formulations and Technologies for New Drugs**
  Henrik Luessen, OctoPlus

Session 5
- **Your Proven Partner in Contract Manufacturing**
  Don Finley, Sigma-Aldrich
- **Application of Fast Melting Tablets**
  Yourong Fu, Akina, Inc.
- **Conducting Phase I Clinical Trials in Canada**
  Tamar Aghamanoukian, Biovail Contract Research
- **Iontophoretic Drug Delivery Systems**
  Margaret Szlek, IOMED
- **IVIVC and Its Role in Controlled Release Drug Delivery**
  Stuart Madden, GloboMax
- **Microsphere Technology for Drug Delivery**
  Terrence Scott, Epic Therapeutics
- **Multi-Compartment Drug Delivery System for Incompatible Combination Drugs with Multiple Release Profiles**
  Fred Miller, INNERCAP Technologies, Inc.
- **MediChew® A New Patient-friendly Way of Oral Delivery**
  Merle Conradi-Larsen, Fertin Pharma

The Soapbox Session is a valuable part of the annual CRS conference. It gives the attendee the wonderful opportunity to not only learn a great deal about the newest companies and technologies but also to meet the presenters at the 20-minute breaks in between sessions.

So if you missed this year's Soapbox Session: Emerging Drug Delivery and Biotech Companies in Miami, please make plans to attend next year's Annual Meeting in Vienna. It's an excellent source for both scientist and entrepreneur. ■

NEWSLETTER
CONTROLLED RELEASE SOCIETY
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Calendar of events

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

AIChE Annual Meeting & Exposition
October 30 - November 4, 2005
Cincinnati Convention Center
Cincinnati, Ohio, USA
http://www.aiche.org/annual/

American Association of Pharmaceutical Scientists Annual Meeting & Exposition
November 6 - 10, 2005
Gaylord Opryland Resort & Convention Center
Nashville, Tennessee, USA

Materials Research Society
November 28 - December 2, 2005
Hynes Convention Center and Sheraton Boston Hotel
Boston, Massachusetts, USA
www.mrs.org/meetings/fall2005/

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
ph: 617-253-3413

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

33rd Annual Meeting of the Controlled Release Society
July 22-26, 2006
Austria Center
Vienna, Austria
planner@controlledrelease.org
www.controlledrelease.org
ph: 763-512-0909

34th Annual Meeting of the Controlled Release Society
July 7-12, 2007
Long Beach Convention Center
Long Beach, CA, USA
planner@controlledrelease.org
www.controlledrelease.org
ph: 763-512-0909

35th Annual Meeting of the Controlled Release Society
July 12-16, 2008
Hilton New York
New York City, NY, USA
planner@controlledrelease.org
www.controlledrelease.org
ph: 763-512-0909