CONTROLLED RELEASE SOCIETY

Volume 24•Number 1•2007

NEWSLETTER

LONG BEACH

ARGENTINA

Check out the latest online issue of **Drug Delivery Technology** at

www.drugdeliverytech.com

Introducing

Drug Delivery Technology...online!

- No special software required
- Table of contents navigation
- Click through to advertisers' sites and content
- Print, send, and share articles with colleagues
- Interactive correspondence with editors and advertisers
- Content searchable by keywords
- Faster online distribution

CONTROLLED RELEASE SOCIETY
NEWSLETTER

Volume 24 • Number 1 • 2007

inthisissue

On the cover –

A glimpse of the recent 8th International Symposium and 3rd Technology Forum Held in Argentina and of the forthcoming 34th CRS Annual Meeting & Exposition in Long Beach, California.

Long Beach, CA, photos courtesy of the Long Beach Area Convention & Visitors Bureau.

Steven Giannos
Editor

Bozena Michniak-Kohn
Editor

Yvonne Perrie
Editor

Randall Mrsny
President

Craig Bunt
(no photo available)
Editorial Board

Jamileh Lakkis
Editorial Board

Rod Walker
Editorial Board

Controlled Release Society
3340 Pilot Knob Road
St. Paul, MN 55121
+1 (651)454-7250 telephone
+1 (651)454-0766 facsimile

Visit www.controlledreleasesociety.org or e-mail crs@scisoc.org on questions about membership, meetings, publications, and services.

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

FROM THE *Editors*

By Bozena B. Michniak-Kohn, Ph.D.
Rutgers-The State University of New Jersey
Ernest Mario School of Pharmacy, U.S.A.

Bozena B. Michniak-Kohn

Having read Yvonne Perrie's editorial in the last *Newsletter* (Volume 23, No. 3, 2006) I was reminded how the overabundance of conferences, as well as advances in technology, have affected our lives in science. As a young assistant professor, I remember I worried about finding funds for the conference I wanted to attend, and these days we worry which speaker invitation we should accept or decline. My thoughts for today move a little away from the overabundance of conferences to "death by e-mail". I remember that most people's reaction in science and in particular in academia was to embrace e-mail to a smaller or lesser extent (depending on how savvy one was with the computer). Today, in my opinion, we have become slaves of e-mail. Think of your average day and how much of it you spend on either answering or writing new messages. Even with spam filtering and e-mail organization schemes, we are still all overwhelmed and behind in our message centers. Blackberries allowed us to catch up a little, but with each technological advance, the number of messages incrementally increases—perhaps someone somewhere will publish the equation that predicts this relationship…

There are several approaches that may assist in making e-mail much more "friendly." Here are some thoughts:

Please try to keep messages brief and to the point. It is a disaster sometimes to see a screen full of a very well-written but extremely long e-mail that makes it's main point only after you've spent a couple of minutes scrolling down the screen…

Please try not reply "thanks" and hit the "Reply All" button.

Please try not to hold a "verbal" conversation through e-mail. This is something we easily fall prey to as we start a new topic that in the end requires that we send 5–10 e-mails and could have been so easily replaced by a single phone call. If we are not in the office, we all have a cell phone…

Please try to use a direct message header that allows easier screening of e-mails and that actually means something to the reader. How many people fall into the trap of heading a message with something so general that the reader scrolls down the messages list and leaves that one for later and finally for the "delete" basket? I still receive messages headed "Hallo" (and it's not from the Viagra folks) or from administrative assistants who are sending e-mails for their faculty with no reference in the header. I see it, do not recognize the name, and think this is another Rolex advertisement. Hence, the first temptation is to hit "Delete" and not read the message.

Please do not head a message with the "spam keywords". We have had so many problems at the medical school recently when for obvious reasons (since there is a cancer center there), people use e-mail headers such as "new publication for breast cancer proposal." These messages end up in the filtered trash…

However, when I need to reach our CRS Chapter members, I do feel blessed to be able to write one message and hit the send button once…no more long letters and stamp licking.

On another note, we have started a new year, and the abstract deadline is approaching for annual meeting submissions. I echo Yvonne's (and others) opinion about the excellence of CRS Annual Meetings. I attend many conferences during the year, usually because I want to hear good science; some I get invited to as a speaker, but each year I always look forward to the science that is presented at the CRS Annual Meeting. The conference has been able to maintain a broad scientific set of presentations, a balance between a good number of participants for networking purposes but not so many that you end up in topic "sections," excellent speakers old and new each year (rarely do we hear the same material every year), and superb venues (I unfortunately missed Vienna due to a conflict but regretted not being able to go). This year we are in Long Beach, California, and I am glad that Martyn Davies is still heading the Meetings Committee.

I am sure we will again have a wonderful meeting. I encourage you to submit your abstracts and send your students and colleagues. I look forward to seeing all of you in the summer!! ■

Randall Mrsny

From the President

CRS Elections Are Coming Up Make a Difference: Get Involved—Vote and Volunteer

By Randall Mrsny
Welsh School of Pharmacy, University of Wales, Wales, U.K.; and Trinity BioSystems, Inc., Menlo Park, CA, U.S.A.

Each year the CRS membership has the opportunity to elect its leaders for the future. This activity is probably the most important right an individual can have as a member of any group, representing not only a right but also an opportunity. Unlike some (okay, American) electoral processes in which the voting body can be stuck with a single leader for several years (even after losing the support of their electorate), the CRS uses a system in which a group of serially elected individuals provides the leadership that guides the society on a steady and appropriate course.

Under the current by-laws, the CRS membership elects a Vice President (VP) who serves a one-year term following instillation at the annual meeting. Acting as the head of the Awards Committee during that year, the VP becomes familiar with the various areas of the CRS that make up the diverse membership of the society. I see the CRS as a composite group of scientists, spanning biology to physics, with a common interest in controlled release technologies; others may have a different perspective. After one year, with the election of a new VP, the previous VP transitions to the office of President-Elect (PE). During this second year of service, the PE becomes more familiar with the functions of the president and focuses on tasks that serve to improve membership benefits. For example, the PE examines potential by-laws changes to ensure that the society is optimally serving its members. At the end of this second year, the PE transitions to the office of President.

The office of President is a job akin to herding kittens. The CRS leadership is full of brilliant minds that have many more ideas than can be realistically developed in a lifetime, let alone in a one-year period. It is up to the President to utilize established CRS committees and create new committees to address specific tasks to ensure a steady, proper course for the society. After surviving this year of organized chaos, the President becomes the Immediate Past President (IPP). The IPP functions as sort of a CRS sage; a person who has a current, working knowledge of the society who can be asked to help guide the society through tasks requested by the President. For example, one function of the IPP is to lead the Nominations Committee, ensuring that promising new leaders can be elected. It is important to realize that this CRS format of leadership allows governance by a series of serially elected individuals (VP to PE to President to IPP) that work together to ensure a logical, thoughtful direction for the good of the society and its members.

The above is a general description, from my perspective, of what a person might expect from and provide for the CRS after being elected as VP. The society also has the elected positions of Treasurer, Scientific Secretary, and two Members-at-Large that round out the CRS Board of Directors (BOD). Unlike the VP position, these positions remain constant over the term of the office, and each provides a critical role for the society. The Treasurer, obviously, ensures that the society remains solvent and examines financial implications of programs and events to be pursued by the CRS. I might add that the society is in excellent financial health at this time, largely due to the efforts of our Treasurer. The Scientific Secretary is responsible for all scientific content of our meetings and publications. With the CRS being a science-driven society, the Scientific Secretary has not only a very important position but also an awesome responsibility. Members-at-Large provide a member-biased perspective to BOD discussions and decisions. At present, our Members-at-Large are focusing on issues of globalization and member benefits.

I need to emphasize that the outline of roles for elected CRS officers detailed above represents only the highlights of these positions, from my perspective, of the society. The current BOD is undertaking the task of more exactly defining the roles for each of its members and preparing procedure manuals for each elected position. Such documents are critical for two reasons. The first reason is that individuals elected to these positions need to understand their specific roles to ensure that their efforts and responsibilities mesh optimally with those of other elected officers and that all the critical tasks of the society are handled properly. Also, by optimally matching the roles of these various offices, the CRS will function most efficiently. This, however, describes the tasks of the current leadership, and the intent of this letter is to drive home the importance of your involvement. Thus, my message, after this long-winded description of our leadership roles, is that you need to become involved in the CRS. We have a remarkable society that embodies the best scientific forum in the world for the biology, chemistry, and physics of controlled release materials for a tremendously diverse set of applications.

Your involvement in the CRS can come in many ways. The first and foremost is to VOTE in the upcoming elections. You will receive mailings, and you can go to the CRS website to get more information. As with most elections, everyone thinks their vote will not make a difference. This attitude, and the resulting poor voter turnout, is what will make your vote even more important to the ultimate outcome. Secondly, get involved in a CRS committee or activity. Many CRS committees were established to provide information and direction directly back to the BOD. Thus, your involvement on these committees would also have a direct and powerful effect on the society. There are also many activities (e.g., abstract review) that are critical for the society to maintain its high scientific standards. Saying that you, as an individual, can really make a difference is actually true in the case of the CRS.

I look forward to your voting in the upcoming election and hearing from each of you as to how you would like to become more involved with the CRS. It is a wonderful society made great by its members and their commitment to its success.

Randy Mrsny
President

CRS Staff Contacts

Annual Meeting and Exposition
Satellite Meetings and Workshops
General information and programming: Ronda Thompson
Abstract submissions/registration: Sue Casey
Exhibit sales and advertising: Debby Woodard
Sponsorships: Ronda Thompson

CRS Awards
General information: Linda Schmitt

Journal, Newsletters, and Books
Member journal subscriptions: Cheryl Sundquist
Newsletter materials: Jordana Anker
Advertising: Debby Woodard
Book publishing: Jody Grider

Membership
Member records/questions/renewals: Cheryl Sundquist
Joining CRS: Cheryl Sundquist
Local chapters: Ronda Thompson

Communication and Website
General information and submissions: Beth Elliott

Online Job Placement Service
Position postings: Iva Greenlee

Jordana Anker
Newsletter Technical Editor
janker@scisoc.org
Tel: +1.651.994.3866

Sue Casey
Meetings Coordinator
scasey@scisoc.org
Tel: +1.651.994.3846

Beth Elliott
Marketing and PR Coordinator
belliott@scisoc.org
Tel: +1.651.994.3847

Iva Greenlee
Placement Coordinator
igreenlee@scisoc.org
Tel: +1.651.994.3818

Jody Grider
Director of Operations
jgrider@scisoc.org
Tel: +1.651.994.3862

Linda Schmitt
Executive Assistant
lschmitt@scisoc.org
Tel: +1.651.994.3828

Cheryl Sundquist
Member Services Representative
csundquist@scisoc.org
Tel: +1.651.994.3801

Ronda Thompson
Education Manager
rthompson@scisoc.org
Tel: +1.651.994.3836

Debby Woodard
Business Development Manager
dwoodard@scisoc.org
Tel: +1.651.994.3817

Visit the CRS website at www.controlledreleasesociety.org for more information.

Controlled Release Society • 3340 Pilot Knob Road • St. Paul, MN 55121 U.S.A.
Tel: +1.651.454.7250 • Fax: +1.651.454.0766 • E-mail: crs@scisoc.org

34th CRS Annual Meeting & Exposition

Let's Go Back to the Beach!

Once again let's meet at the beach for the 34th CRS Annual Meeting & Exposition! Long Beach, California, is the place to hear the latest in scientific research and enjoy the sound of the surf July 7–11, 2007.

Scientific Secretary Martyn C. Davies and 2007 Program Chairs You Han Bae, Alexander Kabanov, Derek O'Hagan, Doug Dale, Chuck Frey, Craig Bunt, and Sevda Senel have an innovative and exciting program planned for you. You'll want to arrive early and stay until the exhibitors pack their bags, the final presentations are given, and the last posters are taken down.

Saturday, July 7, three CRS Educational Workshops will start this year's annual meeting and exposition off right. Make your selection soon as to which workshop you want to attend. The Micro- and Nanoencapsulation: Formulation, Applications, and Processes two-day workshop (July 7–8) chaired by Paul Richardson and J. Chris Soper offers attendees the opportunity to learn the basic concepts of various controlled release technologies, information on release mechanisms, and behaviors of key technologies in commercial use. A nanoencapsulation segment in the workshop will present overviews of nanocapsule and nanocrystal processes and their applications in pharmaceutical and polymer fields.

The Molecular Imaging and Drug Delivery workshop will be held on Saturday, July 7, and is chaired by Alexei Bogdanov and Zheng-Rong Lu. This workshop will address hot topics in molecular imaging and drug delivery. It will cover how molecular imaging could assist in drug development and translational research, non-invasive issues, such as evaluating therapeutic response with dynamic MRI, and visualization of *in vivo* drug delivery with polymers.

The Sustained Release Parenteral Products: *In Vitro* and *In Vivo* Considerations workshop chaired by Marilyn Martinez and Mike Rathbone will also be held on Saturday, July 7. The workshop will discuss the considerations and challenges associated with the development of discriminative and biologically relevant *in vitro* methods for assessing drug release for parenteral products, identify critical biopharmaceutical issues, such as the important physiological variables influencing drug release and the impact of altering injection volume and concentration, and address the possibility of establishing *in vitro* and *in vivo* correlations. Attendees will be provided an opportunity for an exchange from two perspectives—human and veterinary.

Young Scientists, watch for more details to come about the exciting new hands-on workshop being organized by the Consumer & Diversified Products Committee that will cover CR in personal care, food applications, and fragrances; fluid bed technology; IP search of CR technologies; flavor delivery systems; and encapsulation systems for industrial applications. There will even be a display booth to view C&DP products and experts available to ask all about them.

Highlights of Student Posters, Pearls of Wisdom, Releasing Technology Workshops, and Soapbox Sessions will be packed into Sunday, July 8. Visit www.controlledreleasesociety.org often for more details to come.

Steven Buchsbaum (Bill and Melinda Gates Foundation) is one of six Plenary Speakers for CRS in 2007. Joseph DeSimone (University of North Carolina) will present "Organic Delivery

Vehicles for Probing and Treating Biological Systems: Adapting Fabrication Processes from the Electronics Industry for Use in Nano-medicine." You'll want to hear about the "WHO Perspective on Vaccine Research and Development" presented by Marie-Paule Kieny (World Health Organization). Prof. Teruo Okano's (Tokyo Women's Medical College) topic of discussion is "Cell Sheet Tissue Engineering and Their Clinical Applications." Patrick Soon-Shiong (Abraxis Bio Science chair of the board and chief executive officer) will give a talk on "Receptor-Mediated Transcytosis: A Biologically Interactive Delivery Pathway—The First Clinical Application in Cancer Therapy." To complete this outstanding scientific display, be sure to hear David Tirrell (California Institute of Technology) present "Artificial Proteins and Artificial Amino Acids."

The 34th CRS Annual Meeting & Exposition offers you more than 30 invited speakers who will highlight their research in the hot topics of controlled release and delivery. The two-day Industrial Session, with more than a dozen presentations, will cover regulatory issues, preparing for liquidity events, packaging of drug-device combination products, project management, development of drug-device controlled release products, current uses and future trends in biodegradable polymers, an industrial perspective on quality by design, an FDA perspective on quality by design, oral controlled release product scale-up, nanotechnology, and much more.

A first for CRS will be the Juvenile Diabetes Research Foundation co-sponsored mini-symposium Recent Delivery in Diabetes. Delivery for Bioimaging, Gastroretention—Animal vs. Human, Liposomes: Alive & Kicking, and Stimuli Responsive Nanosystems round out the mini-symposia offerings in Long Beach. With such diverse topics, you'll definitely find what fits you and your areas of interest.

Of course, no CRS beach party would be complete without those distinguished party animals themselves—the Exhibitors! The Exhibit Hall at the Long Beach Convention Center will be packed with the companies and products you want to know more about. CRS Exhibitors will gladly discuss your needs and answer your questions. Take advantage of exhibit hours and activities in the Exhibit Hall. Bring your cash, checkbook, and credit cards. Be ready to deal—the Exhibitors will be.

When making your travel arrangements, you might want to fly directly into the Long Beach Airport (LGB). Alternative area airports include Los Angeles International (LAX) and Santa Ana/Orange County (SNA). These airports offer hundreds of flights into and out of the area and are only a quick 25 minutes from Long Beach.

Remember to visit www.controlledreleasesociety.org for up-to-the-minute details on these CRS offerings and more to come. Make your plans now to invade the beach and enjoy the science and breezy weather at CRS Long Beach, July 7–11, 2007. ■

Photos courtesy of the Long Beach Area Convention & Visitors Bureau.

WORKSHOPS

Attend an Educational Workshop to Make the Most of your Meeting Experience!

Select one of these three educational workshop offerings in Long Beach, California, July 7-8, 2007. Visit **www.controlledreleasesociety.org/meeting/program/EducationalWorkshops.cfm** for details.

Workshop 1: **Micro and Nanoencapsulation: Formulation, Applications, and Processes**

Generously Sponsored by Lipo Chemicals, Inc.

Chairs: J. Chris Soper, Givaudan Flavors, U.S.A., and Paul Richardson, Balchem Corporation, U.S.A.

This two-day workshop will provide an introduction to basic concepts of various controlled release technologies. It will offer information on release mechanisms and behaviors of key technologies in commercial use. A nanoencapsulation segment in the workshop will present overviews of nanocapsule and nanocrystal processes and their applications in pharmaceutical and polymer fields.

After attending this workshop, attendees should be able to examine a planned commercial product and determine initially the usefulness of encapsulation, the most likely encapsulation dosage form, the cost of encapsulation and the manufacturing method to put encapsulation into the product.

Workshop 2: **Molecular Imaging and Drug Delivery**

Chairs: Zheng-Rong Lu, University of Utah, U.S.A., and Alexei Bogdanov, University of Massachusetts, U.S.A.

This one-day workshop will address the hot topics in molecular imaging and drug delivery. You will learn how molecular imaging could assist in drug development and translational research. The workshops will also cover non-invasive issues such as evaluating therapeutic response with dynamic MRI and visualization of *in vivo* drug delivery with polymers. Presentations on targeted delivery will be given – from microbubbles to nanomaterials to enzyme-sensitive optical imaging agents. The workshop will provide information on gene expression imaging in assessing gene delivery and therapy.

Workshop 3: **Sustained Release Parenteral Products: *In Vitro* and *In Vivo* Considerations**

Generously Sponsored by InterAg

Chairs: Marilyn Martinez, FDA Center for Veterinary Medicine, U.S.A. and Michael Rathbone, InterAg, New Zealand

This one-day workshop will discuss the considerations and challenges associated with the development of discriminative and biologically relevant *in vitro* methods for assessing drug release for parenteral products, identify the critical biopharmaceutical issues such as the important physiological variables influencing drug release, the impact of altering injection volume and concentration, and address the possibility of establishing *in vitro* and *in vivo* correlations. Presentations will also provide an overview of experiences in correlating specific types of test procedures with category of parenteral controlled release product – implant, microspheres, and suspensions. These insights are intended to be used by both drug sponsors and by regulators for setting *in vitro* release test specifications that can insure product quality and performance and can be used in lieu of very long and expensive *in vivo* studies to support the chemistry and manufacturing changes likely to occur over the lifespan of a pharmaceutical product.

Human and veterinary medicine share similar challenges when trying to establish biologically relevant *in vitro* release methods and specifications for parenteral controlled release products. This workshop will provide an opportunity for an exchange from both experiences – human and veterinary – and of the corresponding challenges encountered in establishing discriminative and standardized *in vitro* methods, and the experiences with efforts to correlate the results of these *in vitro* tests with *in vivo* product performance.

By sharing the human and veterinary experiences and concerns, attendees will be provided with important insights into potential methods developing predictive *in vitro* test procedures and an overview of the diverse methodologies available for performing these tests.

Special Feature

Innovation in Drug Delivery

By Patrick Crowley
GlaxoSmithKline, Collegeville, PA
E-mail: Patrick.J.Crowley@gsk.com

Mergers, takeovers, and other enlargements in the R&D-based pharmaceutical industry have resulted in economies of scale, global reach, and critical mass to sustain discovery and development. It is sometimes alleged, however, that innovation has suffered because of such developments. Reasons advanced for such claims have been ascribed to greater bureaucracy, slow decision-making in large transnational organizations, and monolithic research programs, with "good science" losing out. The reduced numbers of novel medicines in recent times is cited as evidence to support the contention that big pharma is killing innovation.

Many reasons can be advanced to account for the reduced flow of new drugs, too many to consider in this brief polemic. Instead, I will focus on controlled release, pharmaceutical technologies, and similar facets of drug delivery in taking issue with the contention that there is a paucity of innovation in these areas because of the shortcomings of big pharma.

Measurements to quantitate innovation (or lack of) are not simple. Scientific publications can be one yardstick. However, "Big Pharma" does not necessarily publish work carried out in its laboratories. Activities are less transparent, so achievements are less obvious. However, publication is not necessarily a good indicator of the creative process. "Reduction to practice" is required to provide a truly useful application. This is an area in which big pharma is without peer. It can provide resources and expertise in safety evaluation, clinical studies, and regulatory acumen to ensure that the delivery system or technology–medication combination is safe and effective. It can provide the promotional skills to ensure that the advantages of the product are propounded and it is widely used. Hence, it is not unusual for smaller organizations with a good product or concept to partner with larger pharmaceutical organizations in mutually beneficial programs to progress from concept to a widely used technology or product.

Big pharma can bring the following resources and expertise to a partnership:

- Funding to sustain activities in the sponsored organization
- Testing capability for the "products" emanating from the collaboration
- Clinical, safety, and intellectual property expertise to navigate the development pipeline
- Registration, manufacturing, and marketing expertise

Commercial success can mean revenue from royalties for the smaller organization to fuel further innovative work. This happens in many industries, and the pharmaceutical industry is no exception. Pharma organizations seek novel ideas and concepts wherever they are to be found and have business development functions to identify and critique opportunities. Table 1 lists examples of successful collaborations.

Inter-company collaborations are usually well publicized in technical and (particularly) financial publications. Less well advertised are collaborations with academic institutes. Yet, here too large pharma organizations are willing to partner, sponsor, or otherwise fund programs deemed worthy of investment. Such munificence can vary depending on budgets and focus or the fate of a particular program in the sponsor organization (and such inconsistency can be frustrating to all who are closely involved), but it is safe to say that many doctoral programs are supported by pharmaceutical companies.

The pharmaceutical industry will consider opportunities, regardless of provenance. This may mean evaluating devices or technologies already available in other industries. Nano-particles, for instance, were pioneered in the photographic, electronic, and cosmetic industries. Only lately have they been applied to oral, parenteral, and possibly other modes of delivery. However, such applications require the development of processing and evaluative techniques that may differ from those used in earlier applications and demand no little innovative skill to turn concept into practice.

Innovative work associated with big pharma is not dominated by "outsourcing." In-house creativity is alive and well, even if less prominent, because of business, proprietary, and intellectual property considerations. The development of delivery devices is potentially one of the most exciting and promising trends in drug

Special Feature continued on page 10

Table 1. *Inter-organizational Collaborations*

Activity	Product/Technology	Collaboration
Drug delivery	Inhaled insulin	Nektar/Sanofi-Aventis/Pfizer
Safety evaluation	Sulphobutyl cyclodextrins	Pfizer/Cydex
CFC propellant replacement	Non-CFC alternatives	ICI and Several Pharma orgs

Special Feature continued from page 9

delivery. The "holy grail" of non-invasive delivery of insulin has now been found (with further improvements likely as new devices are progressively developed). Inhalation delivery has revolutionized asthma therapy, with incremental improvements to delivery systems continuously enhancing convenience and compliance. The device shown in Figure 1 is just one example of a system that does not require the cumbersome coupling of dosage form and delivery device that were a feature of earlier systems. Such devices are the product of innovative engineering and in-depth knowledge of the properties of the medication with respect to aerodynamics and other facets of accurate and targeted delivery.

Modifying the release of a drug from oral dosage forms has always been a popular way of improving the performance of a medication. Many great technologies and release-modifying agents have been developed to aid such delivery. However, a "one-size-fits-all" approach is never feasible, and at times pharma organizations must resort to creative approaches that match the capricious behaviors of a particular molecule.

A case in point concerns amoxicillin, a mature and effective broad-spectrum antibiotic. The continuing development of bacterial resistance, coupled with the failure to discover radically new and effective antibacterials, has caused novel approaches to be explored to render existing antibiotics more effective. In the case of amoxicillin, Woodnut and co-workers showed that provided serum levels exceeded the minimum inhibitory concentration for at least 35% of the dosage interval the compound remained effective against resistant *Streptomyces pneumoniae* (1). This was fine in concept. In practice, however, there were significant barriers to developing a dosage that met such delivery requirements *viz*

Figure 1. Inhalation product for asthma treatment.

- The very short half life of amoxicillin (ca. 1 hr) results in a short systemic residence time following oral dosage.
- Amoxicillin has relatively poor stability in acid, suggesting that gastro-retentive approaches to sustain delivery were unlikely to be effective.
- Its narrow "absorption window" militate s against prolonging absorption to prolong systemic levels (2). Absorption is less efficient in the jejunal and ileal regions of the small intestine, and "unabsorbed drug" could kill colonic symbiotic bacteria, causing gastrointestinal side effects consequent to overgrowth of resistant bacteria.

There was also a long history of unsuccessful attempts to formulate "sustained absorption" forms of amoxicillin (3).

Work in GlaxoSmithKline laboratories culminated in a novel sustained delivery approach to overcome barriers to delivery. Conventional release-retarding mechanisms were not employed (having been found wanting, largely due to the properties of the molecule that are listed above). Instead, it was shown that a combination of two forms of the drug, the traditional amphoteric (trihydrate) form and a sodium salt that interacted with citric acid on ingestion, provided plasma profiles that met the pharmacokinetic targets (Figure 2) and was effective against resistant organisms in Phase 3 clinical trials (4). To my knowledge this approach to sustaining release/absorption is without precedent, as no conventional release modifier or technology is employed.

Finally, many of the ideas for novel delivery of medication, or "better dosing regimens," emanate from clinical research programs in teaching hospitals or other institutes. Better knowledge on drug delivery "at the right time" (chronotherapy), pulsed delivery, even "delivery on demand," presents many opportunities for new concepts, technologies, and delivery systems. Much of this basic research is sponsored by R&D-based pharma organizations. In such a context pharmacogenetics and pharmacogenomics offer exciting possibilities for patient-specific dosage or other facets of personalized medicine. Most large pharma organizations now have in place or are building substantial "in-house" genomics-based programs. Findings from such research efforts will undoubtedly cascade to other disciplines and provide drug delivery opportunities for everybody. There have never been better opportunities for improved targeting of drugs. Such opportunities are available to everybody with the awareness to recognize them and the acumen to translate them into the design of better drug delivery systems.

Big Pharma is not killing innovation!

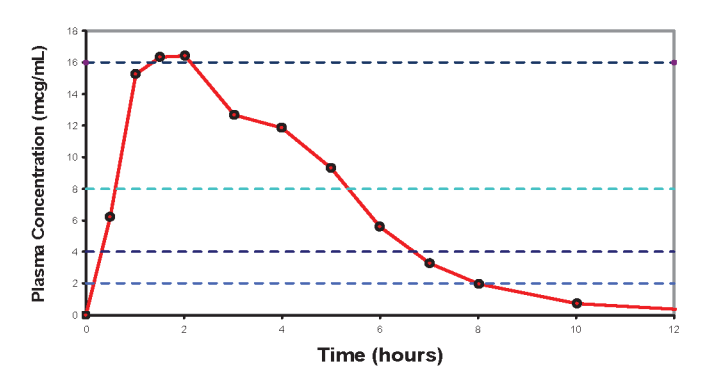

Figure 2. Amoxicillin plasma levels from Augmentin SR™ tablets.

References

1) Woodnut, G, Berry, V. Antimicrob. Agents Chemother. 43: 29-34 (1999).
2) Barr, WH, et al. Clin. Pharmacol. Ther. 56(3): 279-285 (1994).
3) Hilton, AK, Deasy, PB. Int. J. Pharm. 86: 79-88 (1992).
4) Kaye, CM, et al. Clin. Ther. 23: 578-584 (2001).

Note: This paper is a compilation of the ideas offered by the author when opposing the motion "The Death of Innovation; Are Big Pharma guilty?" at the CRS Meeting in Vienna, Austria, July 2006.

Scientifically Speaking

Right Delivery for Poorly BBB-Permeable CNS Drugs: Nose-to-Brain (Olfactory) Delivery of TS-002, Prostaglandin D_2 Analogue

By Kenji Yamada, Research Strategy Division
Taisho Pharmaceutical Co., Ltd., Japan

Introduction
It is well known that the olfactory region, located in the roof of the nasal cavity just under the cribriform plate, is a major site for the direct entry of viruses into cerebrospinal fluids (CSF) and/or brain (1,2). The euphoria in conscious subjects derived from sniffing cocaine occurs rapidly, within 3–5 min (3). Review articles have dealt with direct nose-to-brain delivery (Figure 1) of drugs and its possible transport pathways from nasal cavity to central nervous system (CNS) (4–6).

Direct nose-to-brain delivery could be an innovative and effective method for delivering CNS drugs to the CSF and/or brain by circumventing the blood–brain barrier (BBB), and the possibility has thus been raised regarding the development of novel drugs for CNS diseases such as Parkinson's, Alzheimer's, depression, acute pain, migraine, brain tumor, erectile dysfunction, nausea, and sleep disorder. However, it remains controversial as to whether a similar delivery could take place in humans (4,7–9). These controversial issues are mainly attributable to two factors. One is that it may be difficult to determine the contribution of direct nose-to-brain transport in total brain transport in the case of BBB-permeable drugs. The other is that most studies have been performed using rats with a large olfactory region (rats: about 50%; monkeys and humans: about 10%) (10), and thus, nose-to-brain delivery in rats may be overestimated. Therefore, for precisely predicting nose-to-brain delivery in humans, it is thought that a poorly BBB-permeable compound would be sensible as a drug model and that monkeys as an animal model would be suitable in terms of the similarity with humans of morphological features and the relative scale of the olfactory region.

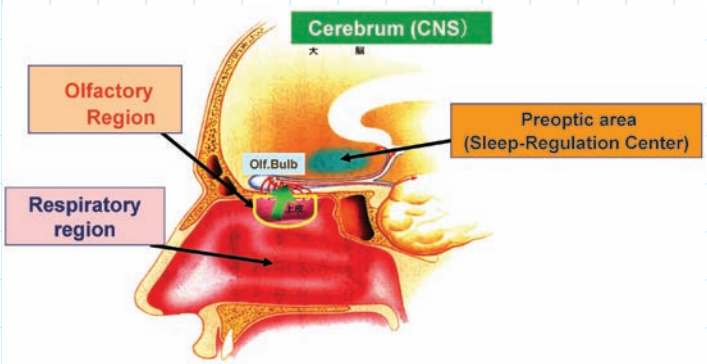

Figure 1. Nose-to-brain delivery.

Prostaglandin D_2 (PGD_2) is one of the endogenous sleep-regulating substances in the mammalian brain (including humans), and it induces natural sleep in monkeys. (11) TS-002 ($C_{20}H_{31}ClO_4S \cdot H_2O$, MW = 420.99), a PGD_2 analogue compound synthesized by Taisho Pharmaceutical Co., Ltd., is chemically stable, and its *in vitro* DP agonist activity (ED_{50} = 20*nM*) is about 10 times stronger than that of PGD_2. In *in vivo* monkey studies, we confirmed the appearance of a sleep electroencephalogram and the natural sleep-inducing effect following the intracerebral administration of TS-002. TS-002 was metabolically unstable and poorly BBB permeable, and thus, oral and intravenous delivery of TS-002 would be almost impossible. However, it was assumed that TS-002 would be a suitable compound for nose-to-brain delivery, so we challenged its possibility using cynomolgus monkeys (12).

Nose-to-Brain Delivery of TS-002
TS-002 (1%, w/w) was prepared as a dry powder coated on hydroxypropylcellulose (mucoadhesive carrier). Absolute bioavailability (BA) in monkeys following intranasal administration of TS-002 dry powder (0.1 mg/body, *N* = 5) was high (68.2%) compared with oral BA (0%). This high BA was caused by the prolongation of residence time on the nasal cavity and the avoidance of first-pass metabolism. Sleep-inducing effects (SIE) in monkeys following intranasal administration of TS-002 dry powder (0.05–0.4 mg/body, *N* = 4–8) were tested and compared with intracerebral (0.01 mg/body, *N* = 4) and intravenous (0.4 mg/body, *N* = 4) administration. SIE was evaluated as the accumulated time, monitored by a video camera for 0–3 hr after dosing, it took for a monkey to exhibit a monkey-specific sleeping posture (a motionless and crouching position). As shown in Figure 2, the SIE following intracerebral and intravenous administration suggested that TS-002 would have essentially very strong sleep-inducing activity and be poorly BBB permeable. The SIE following intranasal administration of dry powder showed dose dependency, and the SIE (2,529 sec) at 0.4 mg/body was two times stronger than that (1,221 sec) following intravenous administration. These data suggest that TS-002 nasally administered would be directly transported from the nasal cavity into the brain, and its SIE would mainly depend on direct nose-to-brain delivery.

To pharmacokinetically confirm the nose-to-brain transport of TS-002, brain distribution following intravenous and intranasal administration were investigated using rats. As shown in Figure 3, for intranasal administration, the brain concentrations of TS-

Scientifically Speaking continued on page 12

Scientifically Speaking continued from page 11

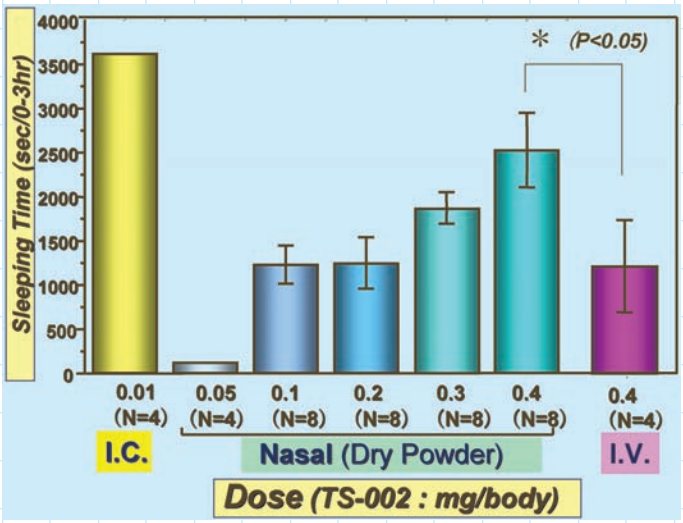

Figure 2. Sleep-inducing effects of TS-002 following intracerebral, intranasal, and intravenous administration to monkeys.

002 were obviously higher compared with intravenous administration. In particular, TS-002 concentration in the olfactory bulb at 10 min after dosing was 1.5 times higher than its blood concentration. These data support the theory that TS-002 was poorly BBB permeable and that TS-002 nasally administered was directly transported into the brain through the olfactory region.

Summary

Our findings demonstrate that TS-002 was directly transported from the nasal cavity (olfactory region) into the brain. Additionally, it was ascertained that poorly BBB-permeable compounds as a drug model and monkeys as an animal model would be appropriate for the precise prediction of nose-to-brain delivery in humans. TS-002 is potentially an ideal drug for treating insomnia and sleep disorders in terms of inducing a natural sleep without any side effects. This result would open up the possibility for developing new CNS drugs based on nose-to-brain (olfactory) delivery.

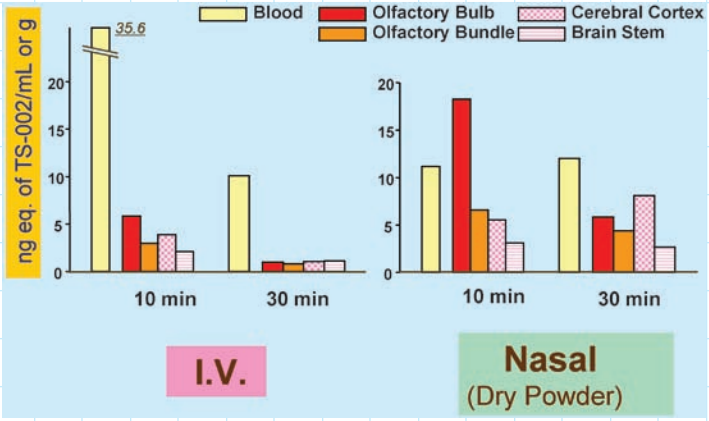

Figure 3. Blood and brain distribution of TS-002 following intravenous and intranasal administration to rats (3H-TS-002, 0.1 mg/kg).

References

1. Johnson, RT, Mims, CA. New Engl. J. Med. 278: 23-30, 84-92 (1968).
2. Barnet, EM, Perlman, S. Virology 194: 185-191 (1993).
3. Bromley, L, Hayward, A. Anaethesia 43: 356-358 (1988).
4. Mathison, S, Nagilla, R, Kompella, UB. J. Drug Target. 5: 415-441 (1998).
5. Illum, L. Eur. J. Pharm. Sci. 11: 1-18 (2000).
6. Sakane, T, Yamashita, S, Yata, N, Sezaki, H. S. T. P. Pharm. Sci. 7: 98-106 (1977).
7. Illum, L. J. Pharm. Pharmacol. 56: 3-17 (2004).
8. Born, J, Lange, T, Kern, W, McGregor, GP, Bickel, U, Fehm, HL. Nat. Neurosci. 5: 514-516 (2002).
9. Merkus, P, Guchelaar, H-J, Bosch, A, Merkus, FWHM. Neurology 60: 1669-1671 (2003).
10. Illum, L. J. Drug Target. 3: 427-442 (1996).
11. Onoe, H, Ueno, R, Fujita, I, Nishino, H, Oomura, Y, Hayaishi, O. Proc. Natl. Acad. Sci. 85: 4082-4086 (1988).
12. Yamada, K, Hasegawa, M, Kametani, S, Ito, S. J. Drug Target. (Submitted). ■

Scientifically Speaking

Designing Delivery Systems for Wildlife Applications—The Brushtail Possum

By Dr. Arlene McDowell, New Zealand's National School of Pharmacy
University of Otago, New Zealand
Dr. Bernie McLeod, AgResearch Invermay
Mosgiel, New Zealand
and Prof. Thomas Rades and Prof. Ian Tucker,
New Zealand's National School of Pharmacy, University of Otago, New Zealand

Controlled release delivery of biocontrol agents to manage wildlife is an emerging field of research that requires collaboration between wildlife managers, biologists, and formulation scientists. Delivery of bioactives to wildlife extends the challenges faced in veterinary applications of controlled release for a number of reasons, including not being able to administer the dosage form directly to the animal, the delivery system being exposed to prevailing climatic conditions in the field, and the need for target specificity because different animals could come into contact with the dosage form in the field.

In the case of the brushtail possum in New Zealand (Figure 1), new biocontrol methods are being developed for this pest species, and their success will rely on effective delivery systems that must be tailored for this particular situation.

Background

The current lethal methods used to reduce the number of brushtail possums in New Zealand (e.g., poisoning and trapping) are considered inhumane and are not sufficient to reduce the national population over the long term (1). Biocontrol agents that decrease fertility are being investigated, and it is likely that they will be protein or peptide molecules. The challenge is to deliver these biological control agents safely and specifically to a free-ranging, feral animal that has a widespread distribution across New Zealand, including remote and inaccessible areas. The oral route is the most prudent strategy, which necessitates particular formulation strategies due to the inherently low oral bioavailability of peptide and proteins. The techniques in the formulation and delivery of pharmaceutical compounds to humans and companion animals that have applications in wildlife management have been covered in a recent review (2).

*Figure 1. Mother brushtail possum with young (backrider). The brushtail possum (*Trichosurus vulpecula*) is a native Australian marsupial that was introduced deliberately into New Zealand in the 1850s. As they are a vector for bovine tuberculosis and they have an appetite for native plants (and birds), this species is now New Zealand's most significant ecological and economic pest occurring across more than 90% of the country.*

Any potential delivery system must be evaluated *in vivo* in the target species. Achieving appropriate pharmacological concentrations of the bioactive compound in the plasma is a critical part of achieving the desired response to a biological control agent (e.g., a reduction in fertility). To test the effectiveness of novel formulations, it is necessary to have a model protein that can be incorporated into delivery systems. Thus, a reliable and sensitive assay to measure the model protein *in vivo* in the target species is also essential.

Polymeric nanoparticles have the potential to be used to delivery the bioactives for a number of reasons, including the ability to effectively entrap and protect macromolecules from enzymatic degradation *in vivo*, the ability to cross the gut epithelia, and ease of production. In addition, when incorporated into an oral bait, they could avoid being crushed by the grinding teeth of this herbivorous animal. Our group has shown previously that poly(ethyl cyanoacrylate) nanoparticles can effectively deliver insulin to diabetic rats, resulting in a reduction in blood glucose levels (3). The direct application of such a delivery system to the brushtail possum is not straightforward, however.

Insulin and the Brushtail Possum

The development of oral formulation strategies using insulin as a model peptide for the brushtail possum is hindered because this species has not been as well studied as some other animals, and there are gaps in our knowledge of the brushtail possum gastrointestinal physiology. For example, the gastrointestinal

Scientifically Speaking continued on page 14

Scientifically Speaking continued from page 13

transit of particulates following oral administration has only recently been investigated (4). There is also a paucity of information on marsupial insulin, and insulin levels in plasma from the brushtail possum has not been reported. Consequently, it was necessary to investigate a method to measure the exogenous insulin from a delivery system in serum from the brushtail possum.

Animals were given a glucose challenge to stimulate the production of endogenous insulin. We found the response of brushtail possums to an oral glucose challenge was minimal, however, with a mean plasma insulin concentration 1 hr after dosing of only 3.4 µIU/mL (n = 3). This may indicate that the brushtail possum does not produce high levels of endogenous insulin. Alternatively, the antibodies in the RIA kit may not bind to native brushtail possum insulin. Using a radioimmunoassay for human insulin (Coat-A-Count®), we found low cross-reactivity (≈10%) for human insulin in possum serum. This low cross-reactivity may mean that the structure of brushtail possum insulin, at least in the antibody-binding region, is different from that of human insulin. We are currently investigating the sequence of possum insulin and its similarity to eutherian mammals.

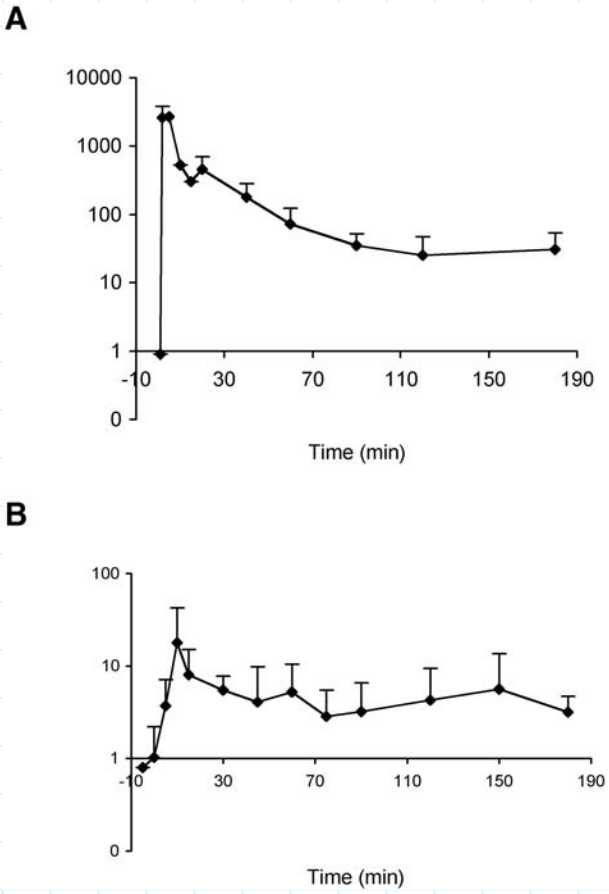

Figure 2. Semi-logarithmic plot of plasma profiles of insulin administered to brushtail possums (a) i.v. entrapped in poly(ethyl cyanoacrylate) (PECA) nanoparticles (1.0 IU/kg) (b) directly into the caecum as insulin-loaded PECA nanoparticles (10 IU/kg). Data points are mean ± SD (n = 3).

We have conducted *in vivo* experiments in which poly(ethyl cyanoacrylate) (PECA) nanoparticles, containing insulin as a model protein, were administered intravenously and directly into the caecum of the possum. The bioavailability of isolated insulin nanoparticles suspended in buffer and administered directly into the caecum was less than 1% (Figure 2). To obtain plasma concentrations of the bioactive that are sufficient to have the desired biological effect, the bioavailability will need to be enhanced significantly.

Summary

The low endogenous levels of insulin in the brushtail possum mean that it is not necessary to induce diabetes in this species to quantify the insulin released from test delivery systems. Consequently, this species may be a suitable non-diabetic animal model in which to test oral insulin formulations. The low bioavailability of insulin-loaded nanoparticles in the present study highlights the challenges of delivering macromolecules to this marsupial species and the importance of testing delivery systems *in vivo* in the target species.

References

1. Cowan, PE. Biological control of possums: Prospects for the future. In: Montague, T (ed), The Brushtail Possum: Biology, Impact and Management of an Introduced Marsupial, Maanaki Whenua Press, Lincoln, New Zealand, pp262-279 (2000).
2. McDowell, A, McLeod, BJ, Rades, T, Tucker, IG. Application of pharmaceutical drug delivery for biological control of the common brushtail possum in New Zealand: A review. Wildlife Res. (Accepted).
3. Watnasirichaikul, S, Rades, T, Tucker, IG, Davies, NM. *In-vitro* release and oral bioactivity of insulin in diabetic rats using nanocapsules dispersed in biocompatible microemulsion, J. Pharm. Pharmacol. 54: 473-480 (2002).
4. McDowell, A, Nicoll, JJ, McLeod, BJ, Tucker, IG, Davies, NM. Gastrointestinal transit in the common brushtail possum measured by gamma scintigraphy, Int. J Pharm. 302: 125-132 (2005). ■

CRS Committees—Your Connection to the Experts

Consumer & Diversified Products

A forum for applying controlled release technology to consumer and industrial products, including food ingredients, personal care, agriculture, and household products.

Contact: Teresa Virgallito at teresa.thomas@givaudan.com

Veterinary Committee

Join a team of experts in design, research, and development of controlled release dosage for animal applications.

Contact: Craig Bunt at craig.bunt@agresearch.co.nz or Sevda Senel at sevda@tr.net

Take Your Career to the Next Level

Connect with a CRS Committee

www.controlledreleasesociety.org

CRS Career Connections

Assisting Job Seekers and Employers Achieve Their Goals

Online Career Center—Opening Soon!

Job Seekers

- Post your resumé
- Search for open positions in YOUR field
- Connect with potential employers

Employers

- Post open positions
- Search and review resumés
- Connect with candidates

CRS Career Fair

Participate in the Career Fair at the CRS Annual Meeting & Exposition.

Details Coming Soon

July 7–11, 2007
Long Beach Convention Center
Long Beach, CA

Take Control of Your Future—Start Your Search Here

www.controlledreleasesociety.org

Retro Approaches for the Delivery of Active Ingredients in Foods

Job Ubbink
Nestlé Research Center, Vers-chez-les-Blanc
CH-1000 Lausanne 26, Switzerland
E-mail: johan.ubbink@rdls.nestle.com

Introduction

In recent years, the challenges for food technologists have rapidly increased as novel food products must satisfy an increasing number of, often conflicting, demands. Apart from traditional factors principally related to food safety, stability, the efficiency of the production process, and basic sensory impact, food technologists today often must satisfy a wide range of demands relating to advanced nutritional properties, consumer appeal, and convenience.

From the food engineer's perspective, the translation of such a complex variety of demands into innovative food concepts and manageable food manufacturing processes is far from trivial as it requires insights and understanding extending far beyond the traditional field of food science and technology (Figure 1). While nutritional advances are still based on scientific or medical data and, thus, may be included in rational strategies for the development of novel food products, it is even more difficult to harness the potential from consumer insights, sensory evaluations, or innovative ideas into feasible strategies for product development.

As many of the new advances in food development are related to the incorporation of (bio)active ingredients in food, a main focus for food technologists is the creation of novel functionalities for these active ingredients in complex food systems (Table 1). A central approach is to exploit the physical properties of food ingredients to create novel structures with applications in the formation of texture or for the stabilization and controlled release of bioactive ingredients and flavors (1). Because of the complexity of modern food systems, interdisciplinary scientific approaches are needed to enable such developments.

Whereas for simple food systems under controlled conditions of temperature and water activity (e.g., instant beverages, chewing gum, and dehydrated or frozen foods) trial-and-error approaches for the incorporation of active ingredients have often proved successful, for more complex food products, such as chilled meals and ready-to-drink and shelf-stable beverages, they have generally failed to provide efficient solutions (2,3). This is primarily the case because trial-and-error approaches are not efficient in finding a rational compromise between the large number of physical, chemical, and biological factors influencing the performance of the food system (Table 1).

Recently, a conceptually new approach was introduced in which the target application is analyzed based on physical principles, including materials science, physical chemistry, and biophysics, to develop a range of solution strategies from which the most promising may be selected for final application (4). As this approach is based on systematic scientific analysis, it provides an incentive for further scientific advances in the food and nutrition fields.

Retro Approaches in the Design of Novel Food Products

In a retro design approach to the delivery of active ingredients, the food application is placed at the start, and from there, one systematically works back to find a feasible technology to introduce the active ingredient into the food product. The principle of retro design, as developed in organic synthesis, allows the systematic evaluation of all steps and routes starting from the final product to the raw materials (5) and facilitates the choice of the favored synthesis route. In addition, the approach has proved useful because it allows the developer to define chemical transformations that do not yet exist but the development of which may then be attempted (5).

In the food processing field, a similar retro approach is very useful for two reasons. First, there is the increased tendency in

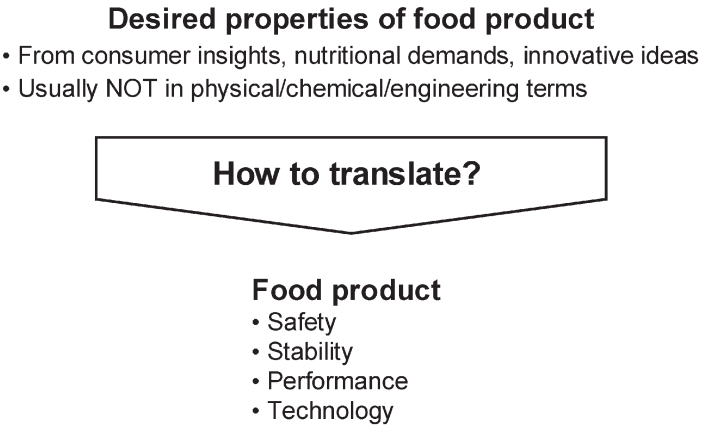

Figure 1. Product development in the food field is increasingly based on defined product properties. The major issue for the food developer is how to translate these properties, which are generally not stated in physical and chemical terms, into a feasible technological strategy.

Table 1. *Selected examples of delivery of functionality in foods using (bio)active ingredients.*

Desired Functionality	Active Ingredient	Technology	Remarks/Issues
Texture	Hydrocolloids (viscosity)	Fermentation	Requires specific precursors in food matrix
		Direct addition	Labeling
	Gas (aeration)	Fermentation (yeasts)	Difficult to trigger at appropriate moment; slow process
		Encapsulation of gas	High sensitivity for water and elevated temperatures
		Chemical agent	Off-taste, labeling
Digestive health	Fibers	Various	Important, but limited, functionality
	Probiotic microorganisms	Encapsulation technology using bioprotectants	High losses of viability in food matrix
Nutrient absorption	Various	Complex fluids encapsulation	Complex fluid system is highly sensitive to phase transitions
		Micronization	Physical transformation of ingredient
		Use of extracts	Often complex mixtures
Taste and aroma	Flavors	Various (e.g., spray drying, extrusion, in situ generation, coacervation)	Chemical interactions, undesired complexation, undesired release

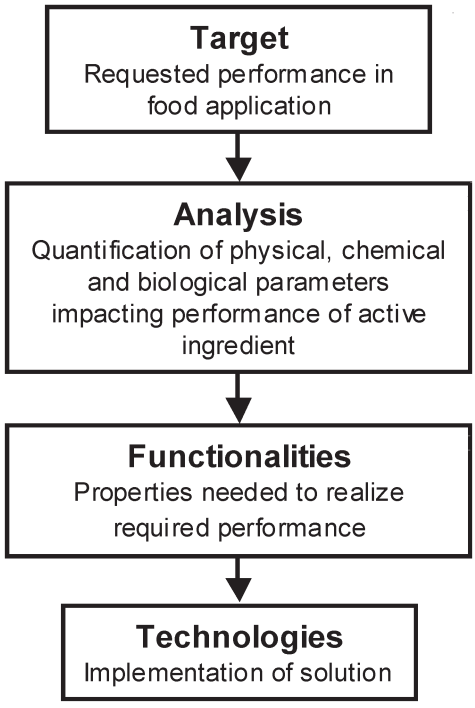

Figure 2. Retro design approach for the delivery of active ingredients in foods.

the food industry to start food development by defining the properties of the final product. This is in contrast to the traditional approach, which focuses on the raw materials and basic conversion steps. Second, a retro approach toward food development has the major advantage that it encompasses a systematic analysis of the various physical, chemical, and biological factors influencing the performance of the food product. In this way, it orients the food engineer toward using relevant scientific information in addressing the food development issue at hand, rather than focusing on raw materials and unit operations.

If the retro design approach is applied for the delivery of active ingredients in foods, one starts by defining precisely the functionality and performance of the active ingredient desired in the final application (Figure 2). This target sets the required functionality and performance of the active ingredient.

Subsequently, the physical, chemical, and biological properties of the active ingredient and the conditions prevailing in the food matrix are analyzed. In this phase, quantitative scientific knowledge of both the food system and the active ingredients is essential, as well as an understanding of the organoleptic or physiological role of the active ingredient. Based on this knowledge, the functionality needed to resolve any cause of

C&DP continued on page 18

C&DP continued from page 17

incompatibility of active ingredient and food matrix is defined. Its definition is solely based on the analysis of the interaction of the active ingredient and food matrix and the desired functionality of the active ingredient; it does not yet relate to a specific technology.

Only in the last stage is a technology selected to implement a solution to the problem at hand. Such a technological solution may be the use of a delivery system or may imply a reformulation of the food product. The major advantage of introducing concept functionality is that it postpones the selection of a technology to a later stage, allowing the optimal matching of the different factors influencing the stability of the active ingredient. It thereby enables a clear definition of the requirements a novel technology should fulfill in satisfying the specific application.

Molecular and Supramolecular Physics of Foods

Because the adoption of a retro approach in the development of novel food products requires increased insights into the properties of food systems, it provides an impetus for the molecular science of foods, in particular the physics of foods, food materials science, and the biophysics of active ingredients. Physically inspired approaches to the design of modern foods are increasingly being adopted (6), but further investigations are warranted, in particular those focusing on the molecular and supramolecular levels. For instance, we have been addressing the molecular physics of carbohydrates in low-moisture matrices, with an emphasis on the relationship between molecular packing, hydrogen bonding, and the properties of carbohydrates as barrier materials (7,8) and bioprotectants (9).

Apart from carbohydrate matrices, other classes of materials deserve extended attention as well, such as lipids and proteins and, in particular, supramolecular complexes of food materials (6). The mechanisms ruling the formation of such complex are only partially understood but are of importance, as the supramolecular organization of foods is expected to strongly impact ingredient bioavailability and digestion.

Perspectives

With the rapidly increasing emphasis on the nutritional quality and balance of foods, which is driven by both advances in nutritional sciences and by the developing obesity crisis in the Western world, food technologists are pressed to find ways to develop more balanced and healthier foods without compromising taste, texture, and consumer appeal. Since functional foods must be structured in such a way as to accomplish a specific function while preserving good taste and perception properties, food design must be tackled from multiple perspectives, taking into account material properties, physical aspects, sensory quality, and nutritional issues. This will increasingly warrant a systematic, scientifically driven approach to food technology, based on advances in the nutrition and medical fields, and in open interaction with consumers and society as a whole.

References

1. Risch, SJ, Reineccius, GA. Encapsulation and controlled release of food ingredients, ACS Symp. Ser. 590 (1995).
2. Gouin, S. Microencapsulation: Industrial appraisal of existing technologies and trends, Trends Food Sci. Technol. 15: 330-347 (2004).
3. Ubbink, J, Schoonman, A. Flavor delivery systems, In, Kirk-Othmer Encyclopedia of Chemical Technology, Wiley, New York (2003).
4. Ubbink, J, Krueger, J. Physical approaches for the delivery of active ingredients in foods, Trends Food Sci. Technol. 17: 244-254 (2006).
5. Corey, EJ, Cheng, XM. The Logic of Chemical Synthesis, Wiley, New York (1989).
6. Mezzenga, R, Schurtenberger, P, Burbidge, A, Michel, M. Understanding foods as soft materials, Nat. Mater. 4: 729-740 (2005).
7. Kilburn, D, Claude, J, Mezzenga, R, Dlubek, G, Alam, A, Ubbink, J. Water in glassy carbohydrates: Opening it up at the nanolevel, J. Phys. Chem. B 108: 12436-12441 (2004).
8. Kilburn, D, Claude, J, Schweizer, T, Alam, A, Ubbink, J. Carbohydrate polymers in amorphous states: An integrated thermodynamic and nanostructural investigation, Biomacromolecules 6: 864-879 (2005).
9. Kilburn, D, Townrow, S, Meunier, V, Richardson, R, Alam, A, Ubbink, J. Organization and mobility of water in amorphous and crystalline trehalose, Nat. Mater. 6 (August 2006). ■

Chapter News

Report on the 8th International Symposium and 3rd Technology Forum Held in Argentina

The CRS-Filial Argentina successfully organized the 8th International Symposium, "Avances Tecnológicos en Liberación Controlada de Fármacos," and 3rd Technology Forum, "Sistemas de Liberación Controlada." The meeting took place October 5–6, 2006, in the beautiful and peaceful city of Villa Giardino, Córdoba, Argentina, located 1,000 km from Buenos Aires. Following the CRS style, the meeting was held in a natural environment, away from day-to-day problems, as this is a propitious way to create a friendly atmosphere and professional interaction between the attendees and closer interaction with the lecturers. The conferences took place during the morning and late in the afternoon, allowing people to enjoy the beautiful weather in the afternoon and the hospitality of Villa Giardino.

Invited speakers for the 8th International Symposium included Prof. Dr. Ruggero Bettini (associate professor, School of Pharmacy, University of Parma, Italy), Prof. Dr. Patrizia Chetoni (Department of Pharmaceutical Sciences, University of Pisa, Italy), and Prof. Dr. María José Blanco Prieto (Dto. Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Navarra, España).

Dr. Ruggero Bettini presents his lecture on "Modern Drug Delivery Requirements."

One of our goals was to encourage people from different places throughout Argentina to learn, teach, and perform research in the field of controlled release. With this in mind, the province of Córdoba was chosen. The province contains one of our most important and oldest universities, the Universidad Nacional de Córdoba, as well as others with sound experience in chemistry, engineering, and pharmacy who are part of the active research teams in the pharmaceutical technology area in Argentina. The symposium was filled with opportunities to collaborate and explore new ideas with a global community of professionals focused on controlled release.

Dr. Ruggero Bettini, Dr. María José Blanco Prieto, Dr. Betina Martínez, and Dr. Blanco's husband enjoy dinner.

The symposium was very successful, with 67 attendees participating in the meetings: 35 of them from academia and 32 from industry (13 post-graduate students). People from abroad attended the meeting as well, coming from Uruguay, Chile, Spain, Colombia, and Brazil. Seven universities also were represented: Buenos Aires, Rosario, Córdoba, San Luis, Quilmes, and La Plata (all from Argentina) and the University of Sorocaba (from Brazil).

During the meeting a poll was performed. We obtained excellent results; for example, 100% of those polled answered that the topics discussed were satisfactory and according to their expectations. We also received feedback on which topics are of interest to attendees, which will help us in choosing the topics and lecturers for next year.

Participants and lecturers enjoy a sunny day by the pool.

Chapter News continued on page 20

Chapter News continued from page 19

The 3rd Technology Forum took place simultaneously with the symposium. It was organized to encourage researchers to share their experiences in different areas and to deliver knowledge by advancing science and technology in the field of controlled release. The quantity of abstracts exceeded our expectations—more than 25 abstracts from different universities in Argentina and Brazil were received, and although we had a very tight agenda, the attendees had the opportunity to discuss cutting-edge research on several topics, such as microencapsulation, bioadhesive systems, nanotechnology, etc.

A social event was held the night before the symposium. A tango show was the perfect excuse to meet the lecturers in a relaxed atmosphere and talk about their professional experience.

Executive Committee of the CRS-Filial Argentina
The designation of new committee members took place during the Executive Committee Meeting held after the symposium and was properly communicated during the meeting. The current members of the Executive Committee of the CRS Filial Argentina are

President: Dr. Joaquina Faour
Vice-President: Dr. María Luz Cassará
Scientific Secretary: Prof. Dr. Marcelo Nacucchio
Secretary: Dr. Betina Martínez
Treasurer: Dr. Rodolfo RubioGarcía
Board of Advisors: Dr. Silvia Giarcovich
Dr. Cosme de los Santos Carballido
Dr. Rubén Manzo
Dr. Gabriel Porto
Dr. Darío Carrara
Dr. María Emilia Szeliga
Dr. María Celina Lamas
Dr. Adriana Quiroga
Dr. Alejandro Sosnik ■

What's on Board

CRS Placement Service

The Controlled Release Society (CRS) and the American Association of Pharmaceutical Scientists (AAPS) have entered into an agreement to establish, develop, and operate a career services program. This new member service will debut at the CRS Annual Meeting in Long Beach, California, this July. In addition to the career fair offered at the annual meeting, a job board will be available year-round via the CRS website. This new service is being designed to facilitate career development and advancement in and surrounding the field of controlled delivery of bioactive substances through the posting of candidates' résumés, as well as employment openings.

CRS Branding

As CRS begins to expand its product offerings to include satellite meetings and books, the Board has identified the need for a comprehensive branding program that will reinforce the CRS brand across all aspects and activities of the organization. Their first step is to consider a new logo. The objective is to create a simpler, more contemporary logo that focuses on the acronym CRS that will help represent the organization from the broadest perspective. While our members, actions, and results will shape the image and personality of CRS, the visual identity will reinforce the unity of our organization and enable us to project a consistent image among other professionals and potential members worldwide.

Future Meeting Sites

The Controlled Release Society Board of Directors has been investigating future meeting sites. Planned are

July 7–11, 2007, Long Beach, California
July 12–16, 2008, New York City, New York
July 18–22, 2009, Milan, Italy
July 10–14, 2010, Portland, Oregon
July 30–August 3, 2011, Gaylord National, Maryland. ■

Veterinary Group Activities

By Sevda Senel, Hacettepe University, Ankara, Turkey

Among the activities of the CRS Veterinary Committee since July 2006, we can first mention the successful 2nd Joint AAPS/AAVPT/CRS Workshop on Collaboration in the Research and Development of Veterinary Pharmaceuticals, which was held October 27–29, 2006, at the Henry B. Gonzalez Convention Center, Antonio, Texas. The meeting included contributions from a range of distinctive speakers from industry, academia, and the FDA. On the first day "Challenges in Dosing Animals" were discussed for companion and food animals. Carol Davis (Davis Consulting & Training) moderated the first day and introduced Mark Papich (North Carolina State University) and Ronette Gehring (Kansas State University), who discussed dosing companion animals and food animals, respectively. Moving on to clinical development and regulations, Simon Blanchflower (Pfizer Animal Health) discussed pre-clinical aspects, while Laura Hungerford (University of Maryland) focused on regulatory issues in veterinary medicines. Considering aspects of drug absorption, Jim Riviere (North Carolina State University) discussed the species differences that influence drug absorption, and Kazuko Sagawa (Pfizer Global R&D) compared the GI physiology among various species. David Brayden (University College Dublin) further discussed absorption at the cellular level, in particular p-glycoprotein transport, and the pharmacogenomics in animals and effect of drug metabolism were outlined by Alastair Cribb (University of Calgary). The session was completed by Marilyn Martinez, who presented a case study on the impact of formulation on drug absorption in ruminants.

On the second day the challenges in developing new veterinary drug delivery systems were discussed from different aspects. Raafat Fahmy (U.S. Food and Drug Administration) opened the session by looking at drug properties and formulation suitability in veterinary oral solid dosage forms. Following this Sunil Narishetty (Pfizer) looked at novel aspects of vet drug formulation, and Julie Lorenz (Kellogg Company) presented issues in developing palatable formulations for small animals. GI transit times in animals was discussed by Steven Sutton (Pfizer Global R&D), and Raafat Fahmy presented information on *in vitro* drug release in veterinary oral dosage forms. Looking at possible delivery platforms for vet medication, Jorge Heller (Advanced Polymer systems) presented studies on thermogels, and Mike Rathbone discussed InterAg's research into developing intravaginal implants. Closing the session, Todd Foster (Pfizer) looked at oil suspension systems for controlled release. The final day of the meeting focused on in *vitro/in vivo* studies (Marilyn Martinez) and correlation of BCS class drugs with their bioavailability in dogs (Mark Papich).

After such a successful meeting, the Veterinary Committee is now aiming to increase the number of participants, both scientifically and socially, which would enhance and enlarge the activities of this committee. We should emphasize the precious contributions of the animal health divisions of the pharmaceutical companies who are leading in this field to the CRS Veterinary Committee (both financially and personally). Nevertheless, the Veterinary Committee needs more volunteers to work with it and who can provide new ideas and new approaches to improve and maintain controlled release veterinary drug delivery and share the information across human and veterinary applications.

At the coming meeting in Long Beach, a mini-symposium on "Gastroretention—Animal vs. Human" (generously sponsored by Novartis Animal Health US, Inc.) will be held by veterinary program chairs Craig Bunt and Sevda Senel. Speakers include

- **Keith Ellis** (Consultant, New Zealand), "Large Animal Gastro-retention"
- **Marilyn Martinez** (Food and Drug Administration, Center for Veterinary Medicine, U.S.A.) "Factors Influencing the Gastric Transit of Solid Materials in Dogs"
- **Kazuko Sagawa** (Pfizer Global Research and Development, U.S.A.), "Human Versus Veterinary Species Comparison in GI Physiology"
- **Clive Wilson** (University of Strathclyde, Scotland), "Accidental Gastro-retention in Man"

In addition, there will be a Veterinary Oral Session titled "Emerging Role of Alternative Delivery in Veterinary Medicine" (generously sponsored by Novartis Animal Health US, Inc.), with invited speaker Katrina Mealey (Washington State University, U.S.A.). Her presentation will be on "Pharmacogenetics in Veterinary Medicine." Oral presentations will be selected from the submitted abstracts. This session will reflect the increased interest in veterinary controlled drug delivery systems in the recent years.

There also will be a Vet Get Together (generously sponsored by Pfizer Animal Health) organised during the meeting. We invite you all to join in the fun with the CRS veterinary members to listen to guest speaker Ramesh Panchagnula (Pfizer) at the Vet Get Together. The lively presentation and discussion that follows is an important networking opportunity for all those in the veterinary field. You do not necessarily have to be involved in veterinary research, but might want to be after this session!!!!

See you all at the veterinary sessions in Long Beach, and please try not to miss the Veterinary Committee meeting—the date will be announced in the program book. ■

LONG BEACH

CALIFORNIA

34th Annual Meeting & Exposition of the Controlled Release Society

July 7–11, 2007
Long Beach Convention Center
Long Beach, California U.S.A.

✦✦✦

Plenary Speakers

- Steven Buchsbaum
  Bill and Melinda Gates Foundation, U.S.A.
- Joseph M. DeSimone
  University of North Carolina, U.S.A.
- Marie-Paule Kieny
  World Health Organization, Switzerland
- Teruo Okano
  Tokyo Women's Medical College, Japan
- Patrick Soon-Shiong
  Abraxis BioScience, Inc., U.S.A.
- David A. Tirrell
  California Institute of Technology, U.S.A.

Mini-symposia Topics

- Liposomes: Alive & Kicking
- Recent Delivery in Diabetes
  Co-sponsored by the Juvenile Diabetes Research Foundation
- Stimuli Responsive Nanosystems
- Gastroretention—Animal vs. Human

✦✦✦

Registration Opens in April 2007

Interested in Exhibiting?
Visit the website for more information.

www.controlledreleasesociety.org

InTheNews

Compiled by Steven Giannos
Industrial Editor

Penwest Begins Next Study in Development of Nalbuphine ER

PRNewswire-FirstCall: Jan. 19, 2007, DANBURY, Conn. – Penwest Pharmaceuticals Co. (Nasdaq: PPCO) has announced that it has begun a Phase I safety study on a nalbuphine hydrochloride extended release tablet formulation (Nalbuphine ER) that the company is developing for the treatment of pain. Nalbuphine ER is a controlled release formulation of nalbuphine hydrochloride that Penwest is developing using its TIMERx® drug delivery technology. It is designed to be taken as a twice-daily tablet.

The primary objective of the Phase I safety study is to evaluate the safety and tolerability of the drug in healthy subjects at escalating dosage levels during multiple-dose steady-state administration. The secondary objective is to evaluate the pharmacokinetics of nalbuphine during steady-state administration and the effect of different nalbuphine ER dosage levels on typical opioid-related side effects.

Acusphere Receives U.S. Patent for Drug Delivery Technology

Business Wire via NewsEdge Corporation: Jan. 16, 2007, WATERTOWN, Mass. – Acusphere, Inc. has announced the issuance of U.S. Patent No. 7,160,557 B2, "Matrices Formed of Polymer and Hydrophobic Compounds for Use in Drug Delivery." The patent covers the sustained drug release features of Acusphere's porous microparticle formulations using a biodegradable shell material. These porous microparticle formulations have tightly controlled size distributions and can allow drugs to be released over periods of time ranging from days to weeks by intravenous, inhalation, subcutaneous, or oral routes of administration. The technology is applicable to both water-soluble and water-insoluble drugs.

"Controlled-release of drug delivery represents an intriguing potential application for our technology and this new patent expands Acusphere's intellectual property protection in this important area," commented Sherri C. Oberg, president and CEO of Acusphere. "There are many drugs currently on the market and many more in development that do not have ideal delivery characteristics and could potentially benefit from controlled release reformulation. We are actively investigating ways to couple our technology with such drugs as we look to expand our product pipeline."

Nanotech-Based Drug Delivery System from Dabur

India Business Insight via NewsEdge Corporation: Jan. 8, 2007 – Dabur Pharma Ltd. has launched a nanotechnology-based drug delivery system, Nanoxel, for the anti-cancer drug, Paclitaxel. The new system is water soluble and is expected to have lesser side effects. The company has priced Nanoxel at Rs16,000 for a single chemotherapy cycle. The company has received approval from the U.S. Food and Drug Authority (FDA) for generic Paclitaxel. Dabur is planning to file for European and U.S. approvals for Nanoxel.

Apogee Completes Medical Laboratory To Develop Advanced Drug Delivery Systems

MARKET WIRE: Jan. 3, 2007, NORWOOD, Mass. – Apogee Technology, Inc. (AMEX: ATA), an emerging micro-systems and nanotechnology company that designs, develops, and commercializes medical devices and sensor products, has announced that it has completed the installation of a dedicated laboratory facility at its headquarters to support the research and development efforts associated with its Medical Products Group. This new capability and planned expansion in staff will be used to further develop Apogee's PyraDerm™ drug delivery system and enhance its pursuit of polymer drug formulations that can be applied to its transdermal delivery systems.

"Our Medical Products Group is focused on the development of advanced transdermal and intradermal delivery systems. In the regulated area, we are developing PyraDerm™, a proprietary micro-needle based device that is being developed to provide delivery of drugs and vaccines through the skin, thereby avoiding injection pain and, in certain cases, the shortcomings of conventional drug delivery. In the non-regulated area, we are developing other transdermal products for the delivery of cosmeceutical and nutraceutical active ingredients."

Approvable Letter from U.S. FDA for Pennsaid

Jan. 2, 2007 – Nuvo Research Inc. (TSX: NRI) has announced that it has received an approvable letter from the U.S. Food and Drug Administration (FDA) for Pennsaid® (1.5%, w/w, diclofenac sodium solution), a topical non-steroidal anti-inflammatory (NSAID) developed by Nuvo for use as a treatment of osteoarthritis (OA) of the knee. Pennsaid® is based on Nuvo's skin-penetrating technology that allows diclofenac to be delivered directly to the knee via topical application to the surface of the skin, thus minimizing systemic side effects often associated with oral therapies.

Cydex Announces Captisol Technology Used in Recently Launched Injection Formulation of Antipsychotic Medication ABILIFY® (Aripiprazole)

Dec. 14, 2006, LENEXA, Kans. – CyDex, Inc., a specialty pharmaceutical company developing improved products through innovative drug delivery, has announced that ABILIFY® Injection, a new intramuscular form of the antipsychotic medication ABILIFY® (aripiprazole) from Bristol-Myers Squibb Company and Otsuka Pharmaceutical Co., Ltd., contains CyDex's Captisol® technology.

ABILIFY® Injection is the third drug formulation commercially available in the

In the News continued on page 24

In the News continued from page 23

United States utilizing CyDex's Captisol®-enabling technology. The U.S. Food and Drug Administration (FDA) approved ABILIFY® Injection on September 20, 2006. CyDex's patented Captisol® technology improves water solubility, bioavailability, and complexation characteristics of insoluble and/or unstable drugs. In addition to injectable products, the CyDex pipeline of licensed and proprietary Captisol®-enabled formulations targets a range of market segments, including oral solutions and capsules, ophthalmic solutions, oral solids, and inhalation.

"Bristol-Myers Squibb's and Otsuka's launch of ABILIFY® Injection further demonstrates the value of Captisol® in supporting line extension strategies for successful pharmaceuticals," said CyDex Chief Executive Officer John M. Seibert. "An expanding roster of CyDex pharmaceutical industry partners recognize that Captisol® offers tremendous solubility advantages, and we look forward to future product launches by these partners in the years ahead."

Roche Invests in New "Molecular Machete" Drug Delivery Enhancer

In-PharmaTechnologist.com: Dec. 13, 2006 – Roche has invested $20 million in a new technology that has the potential to dramatically enhance the delivery of subcutaneous drugs by acting like a "molecular machete."

The novel technology was developed by Halozyme Therapeutics and is based on recombinant human hyaluronidase (rHuPH20). Called Enhanze, the enzyme technology temporarily clears space in the matrix of tissues such as skin, allowing rHuPH20 to improve drug delivery by enhancing the entry of therapeutic molecules delivered through the skin by subcutaneous (SC), intramuscular (IM), or intravenous (IV) methods.

The proprietary enzyme works by breaking down hyaluronic acid (HA), the gelatinous component of skin and tissue that traps a lot of the drug when it is delivered subcutaneously and prevents it from being absorbed. In this way, when it is combined with an injectable drug it acts like a "molecular machete," facilitating increased bioavailability (better absorption) of the drug.

Enhanze can deliver up to 100% of the subcutaneously delivered drugs into the bloodstream—something that has been demonstrated in preclinical studies. What is more, the enzyme only temporarily opens up the flow channels under the skin, with the effects lasting only 24 hr. After this time, the HA begins to grow back.

Inovio Biomedical and Tripep Advance Pre-clinical Development of DNA Vaccine for Hepatitis C

Business Wire: Oct. 24, 2006, SAN DIEGO, Calif. – Inovio Biomedical Corporation (AMEX: INO), a leader in enabling the development of DNA vaccines using electroporation-based DNA delivery, has announced that its partner, Tripep AB of Sweden, recently demonstrated that Tripep's proprietary DNA vaccine, ChronVac-C®, administered using Inovio's MedPulser® DNA drug delivery system activated a T-cell response in mice that appears capable of clearing liver cells expressing hepatitis C virus protein in a murine model of hepatitis C. In the current study, a comparison with the gene gun delivery method also indicated that the MedPulser® gene delivery system performed as well as or better than the gene gun in inducing immune responses capable of clearing liver cells expressing hepatitis C virus proteins. These data complement the results of previous studies, demonstrating that electroporation using the MedPulser® gene delivery system was as good as or better than the gene gun in inducing humoral immune responses in mice.

These data were obtained in support of a planned application for a clinical trial designed to test the therapeutic use of the combination of the ChronVac-C® DNA vaccine and Inovio's MedPulser® gene delivery system in chronic hepatitis C infections. Tripep intends to conduct this Phase I clinical study with healthy volunteers in Sweden in the first half of 2007.

Results of Phase 1 Clinical Trial Show Excellent Safety Profile for IDDS

PRNewswire: Oct. 24, 2006, SEATTLE, Wash. – Dharma Therapeutics, Inc., a transdermal drug delivery company and wholly owned subsidiary of Transcutaneous Technologies Inc. (TTI), Tokyo, Japan, has announced the successful completion of its first human Phase 1 clinical trial using an active transdermal delivery technology known as iontophoresis, which administers lidocaine and epinephrine through the skin via a mild electrical current.

The trial evaluated the safety of the iontophoretic drug delivery system, dermal patch, and direct current power source with lidocaine and epinephrine (IDDS) at three dosage levels (as determined by the designed time of administration) to induce dermal anesthesia during a vascular access procedure (I.V. catheter insertion/venipuncture) in adult volunteers. A subset of the study was included to determine if lidocaine levels in plasma were detectable by standard clinical laboratory methods, as well as the duration of anesthesia.

In this clinical study 60 subjects evaluated the level of pain they experienced during venipuncture by rating their pain from 0 (no pain) to 10 (maximum pain imaginable). The results of the trial and evidence show that administration of lidocaine and epinephrine was effective in reducing pain associated with a vascular access procedure for all dosing groups. Pain was eliminated using the IDDS, and 80% of the subjects in the higher dosing groups would use the system again.

Connetics Corporation and Stiefel Laboratories, Inc. Sign Definitive Merger Agreement

Business Wire: Oct. 23, 2006, PALO ALTO, Calif. – Connetics Corporation (NASDAQ: CNCT), a specialty pharmaceutical company that develops and commercializes dermatology products, has announced that it has signed a definitive merger agreement with Stiefel Laboratories, Inc., a privately held company based in Coral Gables, Fla. Upon the closing of the transaction, holders of Connetics' common stock will receive $17.50 per share in cash, representing a

62% premium to Connetics' average closing price for the previous four weeks. The aggregate value to be received by Connetics' stockholders is approximately $640 million.

The parties anticipate closing the transaction in late 2006 or early 2007. The closing is subject to approval by holders of a majority of Connetics' outstanding common stock, antitrust clearance, and other customary closing conditions. Goldman, Sachs & Co. acted as financial advisor to Connetics in connection with the transaction. The transaction was unanimously approved by Connetics' Board of Directors.

LifeCycle Signs Three Deals for New Drug Delivery System

In-PharmaTechnologist.com: Oct. 17, 2006 – LifeCycle has signed three collaboration agreements with big pharma companies for the development of new anti-cholesterol products using its novel drug delivery technologies.

First, the Danish biotechnology firm has entered into an exclusive deal with German generics company Sandoz for the development of an undisclosed fenofibrate product—fenofibrate is used to reduce the amount of cholesterol and fatty substances in the blood. LifeCycle has also teamed up with Merck Generics, a subsidiary of chemical giant Merck KgaA, through a similar deal for the development of another undisclosed fenofibrate product developed by LyfeCycle, but this time targeting the European markets.

Fenofibrate has proven to be effective at lowering triglyceride (TG) concentrations and increasing high-density lipoprotein (HDL), also known as good cholesterol. The main drawback for oral absorption of drugs with low water solubility is the transfer of drug substance particles into soluble molecules that can penetrate the gastrointestinal tract and enter the bloodstream. These new fenofibrate products will be created with LifeCycle's Meltdose technology, a drug-delivery system that improves the bioavailability of compounds with low water solubility, according to the firm. LifeCycle said its Meltdose technology allows these solubilized individual molecules to be formulated into tablets and, therefore, eliminates the primary limitation of oral absorption of drugs.

Meanwhile, LifeCycle has also announced a third agreement, with Lundbeck—the company from which LifeCycle was spun out in June 2002. Under the terms of the deal, Lundbeck has been granted rights to LifeCycle Pharma's MeltDose technology in connection with Lundbeck's further development of two internal preclinical central nervous system (CNS)-related projects.

Capsulution and Ebara Team Up on New Drug Delivery System

In-PharmaTechnologist.com: Oct. 9, 2006 – Japanese firm Ebara and Berlin-based Capsulution NanoScience are working together to develop a new time-controlled release technology for pharmaceuticals. To achieve this, the two companies will improve the delivery properties of selected concrete active agents using Capsulution's new LBL technology.

The LBL (layer-by-layer) technology is a high-tech tool for making unique multifunctional nano- and micro-sized capsules that are invisible to the human eye. Capsulution said that these nano-sized capsules can be made to function in a manner suited to the intended application and can be given biochemical, electrical, optical, and magnetic properties. In addition, the firm expects that the use of their nanocapsules will show a better performance in evaluating the bioavailability for poorly water-soluble pharmaceuticals.

Therefore, the technology can be used to develop tailor-made drug delivery systems, resulting in the development of more effective and convenient therapies for the patient. The firm claims that this process simplifies the delivery of medications, reduces side effects, and increases therapeutic success. Additional research is aiming for a new effectiveness of the Capsulution nanocapsules that could potentially replace the common progress of multiple medication treatments, especially for modern cancer therapy methods.

Claris Acquiring New Technology To Fuel Its Future

India Business Insight via NewsEdge Corporation: Oct. 7, 2006: Claris Lifesciences, which is engaged in the business of injectable drugs administered through the intravenous route, is acquiring new technologies to increase its future growth. These include needle-free injections and transdermal patches. The new drug delivery systems are designed to provide patients with a painless, convenient, and accurate method of drug delivery.

Nanotechnology Research Gets Right Under Your Skin

The Nation (Thailand) via NewsEdge Corporation: Oct. 3, 2006 – The cosmetics industry will soon reap benefits from nanotechnology thanks to the development of the so-called nanocapsule, a kind of drug delivery system that allows active ingredients to be better absorbed, deep down under the skin.

The capsule is now being developed at the Centre of Chitin-Chitosan Biomaterials, Chulalongkorn University, with the aim of improving the delivery system for active ingredients, especially for the cosmetics industry. Started a year ago, the project is designed to develop nanocapsules from biomaterials that contain turmeric oil. As the oil comes with antibacterial properties, it can be used for acne treatment.

Researcher Pranee Lertsutthiwong said she was studying two kinds of materials—alginate, a kind of polymer derived from brown seaweed, and chitosan, a by-product extracted from seashell waste—to develop the new nanocapsule. "Since the capsule will be used on human skin, the materials we use will have to be bio-degradable, dissolving naturally and not leaving any trace on the skin," she said. She has started to look into the details of the properties of the two materials and plans to develop nanocapsules in three ways. The first is to use only alginate as a key material for the development, while the second is to use pure chitosan. The third is to use a combination of the two.

Pranee said she plans to study each material used to make nanocapsules that

In the News continued on page 26

In the News continued from page 25

contain turmeric oil, as well as their efficiency. She has started the process of developing nanocapsules from alginate. She said preparation, development processes, and packaging techniques were required to create nanocapsules from the polymer. "Apart from selecting proper materials, we have to develop our own technique to produce the nanocapsule and pack the active ingredients into the capsule. This is an important step in our research," she added.

So far, she has succeeded in developing nanocapsules from alginate between 50 and 100 nm in size. Next, she will test its efficiency after it is used. "We have to look at the nanocapsule material, in particular how long it can hold the active ingredient, as well as the time it takes to release the ingredient itself. This is important information and will help us choose the proper material and correct doses," she said.

After testing the alginate-based nanocapsule, Pranee will develop the capsule from chitosan and then from a combination of both alginate and chitosan. For research on the last combination, she will make a multi-layer capsule by coating alginate as one layer and chitosan as the other. Pranee said she would study the results from each method to determine the best method for further development.

Supported by the Thailand Research Fund, the project is expected to be complete next year with a prototype nanocapsule containing turmeric oil. The prototype is hoped to be a foundation for further development of new cosmetic products, including washing foam, moisturizing cream, and other skincare products.

Nanoparticle Drug Delivery Could Replace Eye Drops

In-PharmaTechnologist.com: Oct. 3, 2006 – Researchers have discovered a new method for delivering drugs to the eye using biodegradable polymer nanoparticles that promise controlled release and better bioavailability than eye drops.

A team of scientists at the University of Portsmouth, led by biomaterials and drug delivery expert John Tsibouklis, has found that biodegradable polymers can be combined with drugs in such a way that the medicine is released into the eye in a very precise and controlled manner. Although easy to use, eye drops have many disadvantages, two main ones being the need to administer drops regularly and too little of the drug getting to areas of the eye most in need.

The common alternative to eye drops, ophthalmic inserts, achieve sustained drug delivery but suffer from limitations—they are difficult to insert, easy to misapply, and expensive to manufacture. Very few new ophthalmic drug delivery systems have been commercialized so far, but current research on polymeric systems holds considerable promise, the researchers claim.

Certain polymers are already used as carriers or sustained release vehicles, while smart hydrogels, which react to disease-specific environmental triggers or chemical signals to effect drug release, are emerging as components of a new generation of therapeutics. Thus, the formulation of biodegradable polymers as colloidal systems holds significant promise for ophthalmic drug delivery, since it is suitable for poorly water-soluble drugs and would allow drop-wise administration while maintaining drug activity at the site of action. "The drug's release can be timed so it is constant, cyclic or triggered by an environmental or chemical signal, and the drug delivering polymer can be broken down naturally by the body when it is no longer needed," Tsibouklis said.

Furthermore, surface-modified nanoparticulate carriers may be used to accommodate a wide variety of actives. Nonetheless, major developmental issues must be resolved, including formulation stability, particle size uniformity, control of drug release rate, and large-scale manufacture of sterile preparations. At present, copolymer vesicles and tubules and thermoresponsive polymeric micelles have been investigated as intelligent targeted carrier systems, while the versatility of polymers is turned to account in the design of new prodrugs.

These approaches await validation in drug release ophthalmic applications, and most probably a combination of technologies holds the key to success, the researchers believe. Indeed, Tsibouklis claims progress in the characterization of ocular enzyme systems and cellular transporters is likely to make transporter/receptor mediated ophthalmic drug delivery a viable approach.

Since drugs can be covalently coupled to the side chain of amino acids, making them recognizable by specific transporters, the broad substrate specificity and concentrative ability of amino acid transporters expressed in the eye may prove effective delivery systems for a wide variety of actives.

FDA Approves Connetics' Verdeso Foam for the Treatment of Mild-to-Moderate Atopic Dermatitis

Business Wire: Sep. 19, 2006, PALO ALTO, Calif. – Connetics Corporation (Nasdaq: CNCT), a specialty pharmaceutical company that develops and commercializes dermatology products, has announced that the U.S. Food and Drug Administration (FDA) has approved Verdeso™ (desonide) foam (0.05%) for the treatment of mild-to-moderate atopic dermatitis. Verdeso™, previously referred to as Desilux™, is a low-potency topical steroid and is the first approved product formulated in Connetics' proprietary VersaFoam®-EF emulsion formulation foam vehicle. Connetics expects to begin marketing Verdeso™ to physicians in the fourth quarter of 2006 in 50- and 100-g trade unit sizes.

Mucoadhesive Nanoparticulate Drug Delivery System Has Been Developed

NewsRx.com: Sep. 10, 2006 – Scientists have developed a mucoadhesive nanoparticulate drug delivery system. "It was the aim of this study to develop a mucoadhesive nanoparticulate delivery system. Nanoparticles were generated by in situ gellation of the thiomer chitosan-4-thiobutylamidine (chitosan-TBA) with tripolyphosphate (TPP) followed by stabilization via the formation of inter- and intrachain disulfide bonds by oxidation with H_2O_2 in various concentrations. Afterwards TPP was removed by exhaustive dialysis at pH 1–2," stated investigators.

"Incorporation of the model compound fluorescein diacetate (FDA) was achieved by incubation of this fluorescence marker, dissolved in acetonitrile, with aqueous particle suspensions for one hour at room temperature," said Andreas Bernkop-Schnurch and colleagues at Leopold-Franzens-University Innsbruck and Thiomatrix GmbH.

Bernkop-Schnurch and coauthors published their study in the *International Journal of Pharmaceutics* (Thiomers: Preparation and in vitro evaluation of a mucoadhesive nanoparticulate drug delivery system. Int J Pharm, 2006;317(1):76-81).

Transave's SLIT Amikacin Granted Orphan Drug Status by European Commission

NewsRx.com: Sep. 8, 2006 – Transave, Inc., a biopharmaceutical company focused on the development of inhaled, liposomal formulation of drugs for treating lung diseases, has announced that the European Agency for the Evaluation of Medicinal Products (EMEA) has granted SLIT Amikacin orphan drug status for the treatment of *Pseudomonas aeruginosa* (*Pa*) lung infections in cystic fibrosis (CF).

Cystic fibrosis is a life-threatening, genetic disease affecting approximately 40,000 people in Europe. Approximately 80% of CF patients are chronically infected with *Pa,* and the infection is associated with a more rapid decline of lung function. More information regarding CF is available through the European Cystic Fibrosis Society and the North America Cystic Fibrosis Foundation websites.

Studies from Canada, the United States and the United Kingdom Advance Knowledge in Drug Delivery Research

Drug Week via NewsEdge Corporation: Sep. 8, 2006 – Drug delivery research advances have been reported from Canada, the United States, and the United Kingdom.

Study 1: Novel poly(ethylene glycol)-lipid conjugates are more stable in liposomal formulation and less toxic upon systemic administration. Scientists writing in the J*ournal of Controlled Release* report, "Liposomal formulations have been used to encapsulate and deliver a wide variety of therapeutic and diagnostic agents. Their circulation can be prolonged by the addition of neutral, hydrophilic polymers such as poly(ethylene glycol) (PEG) to the outer surface. An extended circulation lifetime allows them to take advantage of the enhanced permeability and retention effect (EPR), resulting in increased delivery to target sites. Incorporation of PEG also prevents aggregation and aids in the formation of uniform, small monodisperse particles. This is often accomplished with the use of PEG-lipid conjugates, PEG molecules with a hydrophobic domain to anchor them into the liposomal bilayer upon formulation."

J. Heyes and colleagues (Protiva Biotherapeutics) wrote, "Here we present data showing that some commonly used PEG-lipids are chemically unstable due to the presence of carboxylic ester bonds. This instability limits their utility in aqueous environments common to many liposomal preparations. To address this problem, we designed and synthesized three alternative PEG-lipids. Using SPLP (PEG-stabilized liposomal vesicles encapsulating plasmid DNA) as a model system, we investigated the properties of the novel PEG-lipids. An accelerated stability study was conducted at 37°C for 42 days to confirm chemical stability and an in vivo model was used to assess the pharmacokinetics, toxicity and activity of the SPLP." The researchers concluded, "We show that the novel PEG-lipids are more stable in liposomal formulation, less toxic upon systemic administration, and accordingly, are suitable replacements for the PEG-lipids described previously."

Heyes and colleagues published their study in the *Journal of Controlled Release* (Synthesis and characterization of novel poly(ethylene glycol)-lipid conjugates suitable for use in drug delivery. J Control Release, 2006;112(2):280-290). Additional information can be obtained by contacting J. Heyes, Protiva Biotherapeutics, 100-3480 Gilmore Way, Burnaby, BC V5G 4Y1, Canada.

Study 2: pH triggers the release of protective poly(ethylene glycol)-b-polycation copolymers from liposomes. According to a study from the United States, "Triggered release of adsorbed polymers from liposomes enables protection against immune recognition during circulation and subsequent intracellular delivery of DNA. Polycationic blocks, poly[2-(dimethylamino) ethyl methacrylate] (DMAEMA) (0.8, 3.1 4.9, or 9.8 kg/mol) or polylysine (K) (3 kg/mol), act as anchors for poly(ethylene glycol) (PEG) (2 or 5 kg/mol) protective blocks. In addition, a copolymer with 15 strictly alternating blocks of PEG (2 kg/mol) and cationic amine sites was evaluated as a protective coating."

"Incorporation of 1,2-dioleoyl-3-dimethylainmonium-propane, a titratable lipid with a pKa of approximately 6.7, allows the liposome's net charge to increase as the pH shifts from 7.4 in the bloodstream to 5.5 in the endosome," said Debra T. Auguste at Princeton University and collaborators in the United States. "The increased net liposome cationicity results in decreased cationic polymer adsorption. The EMPEG113-DMAEMA31 and EMPEG113-DMAEMA62 association constants decrease from 3.1 and 6.2 $(mg/m^2)/(mg/mL)$ at pH 7.4 to 1.7 and 3.2 $(mg/m^2)/(mg/mL)$ at pH 5.5, respectively. However, EMPEG45-DMAEMA5, EMPEG45-DMAEMA20, and EMPEG45-N-DP15 did not show a strong response to changes in pH." The researchers concluded, "Cationic polymer adsorption exceeds calculated values for liposome neutralization, resulting in adsorption profiles in the brush regime."

Auguste and her coauthors published their study in *Biomaterials* (pH triggered release of protective poly(ethylene glycol)-b-polycation copolymers from liposomes. Biomaterials, 2006;27(12):2599-2608). For more information, contact Robert K. Prud'homme, Department of Chemical Engineering, Princeton University, Engineering Quadrangle, Princeton, NJ 08544, U.S.A. E-mail: prudhomm@princeton.edu.

Study 3: Modulation of the pH-responsive properties of poly(L-lysine isophthalamide) grafted with a poly(ethylene glycol) analogue investigated for potential drug delivery options. "A pH responsive pseudopeptide, poly(L-lysine isophthalamide), has been modified with a

In the News continued on page 28

In the News continued from page 27

hydrophilic poly(ethylene glycol) analogue, Jeffamine M-1000, and the effect of grafting ratio on the pH responsive behavior of the grafted polymers in aqueous solution investigated using fluorescence and 1HNMR spectroscopy," scientists in England report.

"It was demonstrated that at below 35.1 wt% grafting, the modified polymers retained the pH-driven conformational transition of the parent polymer from an expanded structure at high degrees of ionisation to a compact hydrophobically stabilized structure at low degrees of ionisation. The onset of pH response and the pH range over which the conformational transition occurred varied significantly with degree of grafting. At Jeffamine M-1000 ratios in excess of 48.0 wt%, the graft polymer existed in a micellular form over the whole pH studied," wrote Z. L. Yue and colleagues (University of Cambridge). "Potential applications in drug delivery of both the linear and micellular forms are discussed," finished the investigators.

Yue and colleagues published their study in *Biomaterials* (Modulation of the pH-responsive properties of poly(L-lysine isophthalamide) grafted with a poly(ethylene glycol) analogue. Biomaterials, 2006;26(32):6357-6366). For additional information, contact N. K. H. Slater, University of Cambridge, Department of Chemical Engineering, Pembroke St., Cambridge CB2 3RA, U.K.

AerovectRx Corp. Announces Initial Funding To Commercialize New Inhaled Drug Delivery Technology; Technology Developed at U.S. CDC Targets $12 Billion Market

Business Wire: Sep. 8, 2006, ATLANTA, Ga. – AerovectRx Corporation, developer of new pain-free, inhaled drug delivery technology, announced that it received its first round of venture funding. The financing was led by Georgia Venture Partners, Inc. of Atlanta, Emergent Growth Fund, LLC, of Gainesville, Fla, and the Advanced Technology Development Center Seed Fund of Atlanta.

The financing enables AerovectRx to accelerate the commercialization of its proprietary inhaled drug delivery platform technology. The technology was licensed from the U.S. Centers for Disease Control and Prevention (CDC), where it was developed with support from the U.S. government and the Bill and Melinda Gates Foundation. The technology delivers novel therapies and vaccines in an easy to breathe microscopic mist. It utilizes a vibrating mesh nebulizer with a disposable mesh and medication cartridge, and it is the first such technology to receive clearance to market (510k) from the U.S. Food and Drug Administration (FDA).

AerovectRx Corporation is an early-stage aerosol therapeutic company providing versatile drug delivery solutions and effective, efficient, and dosage-controlled therapeutics utilizing the lung as the gateway for better health. Products under development by AerovectRx are designed to deliver a wide variety of therapies through multiple-use mass immunization, as well as personal-use nebulizers. Potential targeted therapeutic candidates for the AerovectRx technology include treatments for asthma, cystic fibrosis, pulmonary hypertension, chronic obstructive pulmonary disease (COPD), diabetes, pain management, and delivery of vaccines and anti-viral drugs. For more information, visit www.aerovectrx.com.

Transdermal Delivery of Caffeine, Theobromine, Theophylline, and Catechin Is Studied

Drug Week via NewsEdge Corporation: Aug. 9, 2006 – The simultaneous transdermal delivery of the major active stimulant compounds of guarana is established. "Extracts of guarana (*Paullinia cupana*) feature as putatively stimulating ingredients in a number of foods, drinks and dietary/herbal supplements. The objective of this work was to investigate in vitro the transdermal delivery of the major pharmacologically active compounds contained in guarana extract," researchers in Wales report.

"Saturated solutions of guarana were prepared in polyethylene glycol 400 (PEG400), propylene glycol (PG) and H_2O at 32°C. Guarana extract was also formulated in Duro-tak 2287 transdermal adhesive in a range of concentrations and the diffusional release was determined in addition to adhesive properties. Transdermal delivery across full thickness pig ear skin was investigated in vitro using Franz-type diffusion cells, with reverse-phase HPLC being used for the quantification of the permeation of theobromine (TB), theophylline (TP), (+)-catechin (C) and caffeine (CF)," wrote C. M. Heard and colleagues (University of Cardiff).

They continued, "Based upon a combination of release and adhesive property data a patch containing 5.55 mg guarana extract cm^{-2} was deemed optimal. The general trend for the delivery of the 4 analytes was: water >5.55 mg cm^{-2} patch approximate to PG >PEG400. For CF the greatest steady state flux was obtained from the water vehicle: 19 mcg cm^{-2} h^{-1}, with similar to 420 mcg cm^{-2} permeating after 24 h."

"This was some 6x times more than from the drug-in-adhesive patch and 10x greater than PG, a well-known penetration enhancer, and 50x that of the 'regular' excipient PEG400. A water vehicle also provided the greatest delivery of TB (0.45 mcg cm^{-2} h^{-1}), TP (0.022 mcg cm^{-2} h^{-1}), and C (0.10 mcg cm^{-2} h^{-1}). An inverse relationship was noted between lipophilicity and k(p) in each vehicle."

The researchers concluded, "The simultaneous transdermal delivery of the major actives of guarana was established, with permeation rates being highly concentration and vehicle dependent." Heard and colleagues published their study in the *International Journal of Pharmaceutics* (In vitro transdermal delivery of caffeine, theobromine, theophylline and catechin from extract of Guarana, *Paullinia cupana*. Int J Pharm, 2006;317(1):26-31). ■

Journal of Controlled Release Highlights

By Morgan Leaming and Kinam Park

According to the latest listing of the Top 25 Downloaded Articles for *Journal of Controlled Release* (JCR), many of the topics remain consistent with previous downloaded data. Review Articles and those researching applications of nano/micro-particles continue to capture the attention of our readers. Some of the work that has fascinated the readership of JCR from July to September 2006 is listed below.

Review Articles

Review Articles hold their place in the top 25 list by providing an overview of the research being conducted in specific areas, including chitosan nanoparticles, bioadhesives, cationic polymers, and microbubbles for gene delivery, calcium phosphate, and microencapsulation. Two of the reviews are listed below.

Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. Volume 113, Issue 3. Pages 189-207. Ratnam, D.V., Ankola, D.D., Bhardwaj, V., Sahana, D.K., Kumar, M.N.V.R. This review comments on the research, indicating that antioxidants are emerging as prophylactic and therapeutic agents.

Polyionic hydrocolloids for the intestinal delivery of protein drugs: Alginate and chitosan. Volume 114, Issue 1. Pages 1-14. George, M., Abraham, T.E. This paper reviews the technology used to deliver drugs via the oral route.

Nano/Micro-particles

Review and research articles on nano/micro-particles continue to dominate the drug delivery field. This enhanced interest is partly due to recent advances in nanotechnology. Interest in biodegradable nanoparticles, polymer micelles, liposomes, and microencapsulation technology is expected to continue to grow in the coming months and years. Oral delivery of protein drugs using nanoparticles would be one of the ultimate challenges in drug delivery. Two articles in this area made the list.

Biodegradable nanoparticles loaded with insulin-phospholipid complex for oral delivery: Preparation, *in vitro* characterization and *in vivo* evaluation. Volume 114, Issue 2. Pages 242-250. Cui, F., Shi, K., Zhang, L., Tao, A., Kawashima, Y. This article describes preparation of biodegradable nanoparticles loaded with insulin-phospholipid complex by a novel reverse micelle-solvent evaporation method. Soybean phosphatidylcholine (SPC) was employed to improve the liposolubility of insulin, and biodegradable polymers were used as carrier materials to control insulin release.

Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability. Volume 114, Issue 1. Pages 53-59. Luo, Y., Chen, D., Ren, L., Zhao, X., Qin, J. The authors adopted an ultrasonic-solvent emulsification technique to prepare vinpocetine loaded glyceryl monostearate (GMS) nanodispersion with narrow size distribution. ■

Welcome New Members

Paulo Almeida
Anton Amann
Mehdi Ansari Dogaheh
Muhip Asutay
Helen Baldascini
Brian C. Baxter
Richard A. Baylor
Sonia Bedi
Nader S. Berchane
Sanjay S. Bhanushali
Christoph Bluemer
Mario Brands
Gary Burnett
Maria Luiza Caramori
Mathew Cherian
Henry R. Costantino
Jane Cowley
Dariush Davalian
Ken I. Downie
Julie Ducreux
Tetsuya Endo
Francoise Falson
Ingrid Fischbach
Ralf U. Frese
Toby Freyman
Yasuhiro Fukuda
Cavallaro Gennara
Peter S. Given
Robert J. Gyurik
Josh A. Hagen
Barry V. Hamory
Telli Hekmatara
Yuan Hung Hsu
Sang Deog Kang
Nandini Kashyap
Je Hak Kim
Seon Ja Kim
Soonyun Kim
Ralf Klabunde
Katerina Kotti
Shawn A. Kucera
Todd A. Kullmann
Young Jik Kwon
Thao Le
Eunhye Lee
Ji-Young Lee
Young Seek Lee
Wenzhong Li
H. Peter Matthiessen
Lawrence Mayer
Bernard McDonald
Hendrik Metz
Wen Minkoff
Shosaku Murayama
Robert J. Murray
Julia Myschik
Rosado Neyda
Ramesh Panchagnula
Ji Sun Park
Suck Yong Park
Mittapalli Pavan Kumar
Adel Penhasi
Zeibun Ramtoola
Annemie Rehor
Carsten Rudolph
Matthias Saba-Lepek
Fergal Seeballuck
Wolfgang Seitz
Mikhail Shtilman
Serhan Simsek
Sandra Struebing
Peter L. Turecek
Vobalaboina Venkateswarlu
Atsushi Yamashita
Jo Young-G
Lin Zhu

NEWSLETTER
CONTROLLED RELEASE SOCIETY
3340 Pilot Knob Road
St. Paul, MN 55121 USA

calendar of events

who…what…where…when

Pharmaceutical Sciences World Congress

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

CIPTC 2007 – Oral Controlled Release Development and Technology

May 10-14, 2007
Shanghai Everbright Convention & Exhibition International Hotel
Shanghai, China
www.ciptc.org

AAPS National Biotechnology Conference

June 24-27, 2007
San Diego Convention Center
San Diego, California, USA
www.aapspharmaceutica.com/nationalbiotech

34th Annual Meeting of the Controlled Release Society

July 7-11, 2007
Long Beach Convention Center
Long Beach, California, USA
www.controlledreleasesociety.org
ph: 651-454-7250

36th Annual Meeting of the American College of Clinical Pharmacology

September 9-11, 2007
The Palace Hotel
San Francisco, California, USA
www.ACCP1.org

AAPS Annual Meeting & Exposition

November 11-15, 2007
San Diego Convention Center
San Diego, California, USA
www.aapspharmaceutica.com/meetings/index.asp

35th Annual Meeting of the Controlled Release Society

July 12-16, 2008
Hilton New York
New York City, New York, USA
www.controlledreleasesociety.org
ph: 651-454-7250