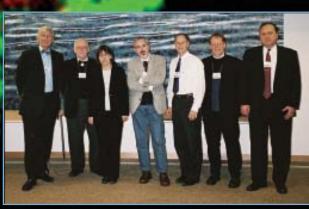
CONTROLLED RELEASE SOCIETY Volume 21-Number 2-2004



Hayat Onyuksel Wins Inventor Award



Measuring Flavour



United Kingdom and Ireland Chapter Meeting



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Ijeoma Uchegbu *Editor*



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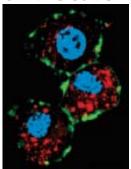
James Anderson President



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Hawaii CRS: Veterinary Controlled Release Programming.

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Fluorescently labeled cells provided by Dr. Dusica Maysinger and Dr. Radoslav Saviae, McGill University, Canada.

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

FROM THE Editors

Bozena Michniak, UMDNJ-New Jersey Medical School, U.S.A. and Ijeoma Uchegbu, University of Strathclyde, U.K.

It's again the time for travel plans to the annual meeting and what a destination for sharing our science and learning about the recent updates in the various aspects of controlled drug delivery! The island of Oahu with beautiful beaches, historic Pearl Harbor and Honolulu..... we hope you all submitted abstracts and agreed to be invited speakers at this superb venue.

The 2004 Program Committee has secured top quality international scientists and industrial experts for cutting-edge Plenary and Invited Speaker sessions. Examples include Plenary Sessions: Stem Cells (Jane Lebkowski, Geron Corporation, U.S.A.), Probiotic Therapy (George Macfarlane, University of Dundee, U.K.), DNA Medicines (Alain Rolland, Vical, Inc., U.S.A.) and World Epidemics and Novel Vaccines (Jeffrey Ulmer, Chiron Corporation, Italy). Invited Speaker sessions include: Veterinary session on "Appropriate Animal Models for Evaluation of Human and Veterinary Therapeutics" and Consumer and Diversified Products sessions on nanoparticles and nanotechnology, microencapsulation of cosmetic ingredients and microorganisms, controlled release techniques in agriculture, and controlled release also in flavors, food ingredients, and nutritional supplements. Bioactive Materials sessions include topics such as: vaccine development, triggered release, and receptor mediated targeting just to name a few.

We hope to see you all in sunny Hawaii this summer!!!

On another note, we have been working hard on the editorial team of the Newsletter, and we have been fortunate enough to appoint an Industrial Editor, Mr. Steve Giannos. We are truly an international Society with members scattered all over the world, and it is nice to see that our Newsletter team reflects our membership diversity too. Any comments should be addressed to us via the website, and we always appreciate any thoughts and ideas you may have. We sometimes have an overwhelming response to our Spotlight articles, and we hope that we can publish most of the articles even if they are resubmitted for later Newsletter issues. We hope that the authors note that we are restricted in space in the hard copy. Maybe it is time to have some Newsletter material on the Website. What do you think? Please email us your suggestions on this. What would you like to see on the Newsletter website? Interactive pieces, videos, more literature references, more articles? Keep the thoughts coming....

Editors Bozena Michniak & Ijeoma Uchegbu

Consumer & Diversified Products Special Feature Editor Jerome Barra

Industrial Editor Steven Giannos

Thanks to members of the Publications Newsletter Subcommittee for helping with this issue: Martyn Davies, Agis Kydonieus, Harlan Hall, and Mike Rathbone.

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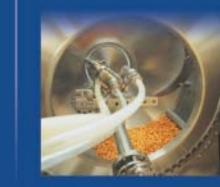
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by James M. Anderson Case Western Reserve University, U.S.A.



I had the opportunity to visit some of the members of the 2004 Program Committee while they were busy putting the final touches on this year's podium and poster sessions. You will be pleased with the job David Grainger, Lisbeth Illum, Kazunori Kataoka, Todd Becker, Anil Gaonkar, Terry Bowersock, David Brayden, and Martyn Davies have done for you.

The 2004 Annual Meeting & Exposition taking place June 12-16, in Honolulu, Hawaii, will showcase how international CRS truly is. Consider the fact that the prestigious Plenary speakers are from 3 different countries, the workshop presenters will be coming from 7 different parts of the world, the mini symposia speakers hail from 4 nations, the invited speakers represent 10 countries, and the submitted papers were received from 35 nations. The outstanding science being presented by such a global community is a good fit for this event in paradise.

There's always something new at a CRS Annual Meeting & Exposition, and this year is no exception. The Education Committee has initiated two new events for the Young Scientists of CRS. The Education Committee defines a young scientist as someone under the age of 40 or new to controlled release and delivery in the past 5 years. If you qualify, sign up now for the Young Scientist Education Workshop on Saturday and Sunday and the Get Up; Get Educated sessions on Monday and Tuesday. These events are free to attendees; however, space is limited. Reserve your seat today.

Back by popular demand are the Pearls of Wisdom sessions. These lively, informative debates will take place on Sunday and Monday afternoons. Prof. Ijeoma Uchegbu has once again selected controversial topics that will engage the audience in a lively discussion.

Exposition hours have been set, and new this year is the luncheon provided by our 2004 exhibitors. The complimentary luncheon on Wednesday, June 16 will take place in the Kamehameha Exhibit Hall. Take advantage of your opportunity to meet with exhibitors in a relaxing atmosphere to discuss their new, innovative technology.

I'm pleased to have so many of our exhibitors returning this year; and so far, there will be over a dozen new exhibitions on the floor. The 2004 sponsorship list continues to grow, and I am especially thankful to our major donors: ALZA, BASF, Banner Pharmacaps, Eurand, Guidant Corporation, and NOF Corporation. Be sure to spend time with the CRS exhibitors during the designated breaks. They'll appreciate your business, and we certainly appreciate theirs.

The 31st Annual Meeting and Exposition of the Controlled Release Society has something for everyone: 3 workshops on Saturday, Young Scientist workshop on Saturday and Sunday, Releasing Technology workshops and the Soapbox sessions on Sunday, Pearls of Wisdom sessions on Sunday and Monday, Young Scientist Get Up; Get Educated sessions on Monday and Tuesday, 6 world renowned Plenary speakers, 36 outstanding Invited Speakers, 5 mini symposia on hot topics, the Capsugel Special session on Tuesday, a Veterinary-Bioactive Materials joint session, 2 Consumer & Diversified Products and Bioactive Materials joint sessions, the Eurand Special session on Wednesday, 4 Consumer & Diversified Products sessions, 20 Bioactive Materials sessions, 2 poster sessions, and over 95 exhibitors. You can see there's going to be an enormous amount of science and groundbreaking research for you to experience.

Now how about some fun? The Opening Night Reception will be on Sunday evening; the Awards Ceremony will be on Monday morning; and the Grand Luau on Tuesday evening will feature island melodies, a scrumptious feast, and a spectacular Polynesian show. You'll want to witness the passing of the gavel to your incoming President, Jenny Dressman, at the Grand Luau.

Remember to visit the CRS website (http://

www.controlledrelease.org/) for the most current information on the 2004 program. From the website, you can renew your membership; register for the Annual Meeting, workshops, Young Scientist sessions, Releasing Technology workshops, and Grand Luau; reserve your sleeping rooms at the Hilton Hawaiian Village: link to a travel agent to make your flight reservations; and arrange for your children's care and entertainment, too. CRS is truly a full-service Society. With so much to look forward to, no wonder you'll forget to pack your tie!

CRS Updates

REGISTER NOW! Early registration ends May 16, 2004. Visit http://www.controlledrelease.org/meetings/hawaii/ index.cgi to join your friends and colleagues in gaining the best education in controlled release. Experience the essence of beauty and harmony on the Islands of Aloha. The 2004 Program Committee has prepared an extraordinary schedule! See you there!

From the Scientific Secretary

The CRS is truly a

global organisation.

One year we host a

meeting in Scotland,

hugely successful

the next on the

other side of the

world in Hawaii! It

by Martyn C. Davies University of Nottingham, United Kingdom



Lisbeth Illum, Martyn Davies, David Grainger

seems such geographical and cultural contrasts appeal to our membership as over 750 abstracts came flooding into the CRS offices for the 2004 meeting from all continents. The draw of a high quality scientific meeting on the doorstep of sun, sand, and surf was clearly irresistible for many!

Wistfully thinking of the palm trees and sand between my toes, I headed off to Washington, D.C., to meet with Lisbeth Illum and David Grainger (two of the Programme Chairs for the Bioactive Sessions), Todd Becker (Lead Programme Chair for the C&DP Sessions), and Ronda Thompson and Karen Kazmierczak (from CRS Headquarters) to put the finishing touches to the scientific programme for the 2004 meeting. All the Programme Chairs who were in D.C., and the Programme Chairs who did their planning online - Kazunori Kataoka (Bioactive), David Brayden and Terry Bowersock (Veterinary)

and Anil Gaonkar (C&DP) have done so much this year to create a format and content which is innovative and also played a key role in reviewing abstracts. In this respect, the Board of Scientific Advisors have also played a key and impressive role in a new reviewing system designed to lighten the load of reviewing and also meet the tight deadlines required.

All abstracts were reviewed that



Kazunori Kataoka





Terry Bowersock

Todd Becker

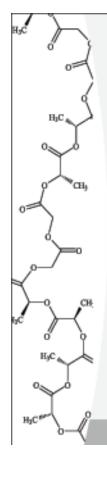




Anil Gaonkai

weekend, and the difficult process of selection of papers for contributed oral presentations provoked much lively discussion and argument from all present. This is always an arduous process as there are always so many good papers at the CRS meeting. The individual sessions were streamed in the conference schematic to try to ensure minimum of overlap between sessions and that there was,

wherever possible, a varied and exciting programme throughout the meeting.



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This year's plenary sessions look the strongest to date and range from basic science through to clinical perspective. Five mini symposia, a full exhibition, soapbox sessions, excellent workshops and an encore of the popular Pearls of Wisdom sessions, again organised by Ijeoma Uchebu, will ensure there is something for everyone to enjoy. This year builds on last year's Education Programme with the role out of an "all new" Young Scientists Workshop the weekend before the meeting and Get-up and Get Educated sessions on Monday and Tuesday mornings, all ably developed and coordinated by Mike Rathbone and his Education committee.

The task done and dusted, we sat back and toasted to the success of the summer 2004 meeting (See Lisbeth, Dave, and I laughing at the thought of the President in Hawaiian shirt and shorts). I, for one, am looking forward to a great meeting and experiencing the sights and sounds of the exotic Hawaiian Islands.

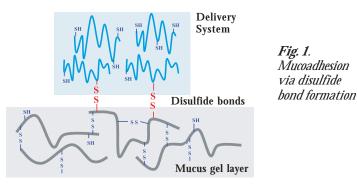
Scientifically Speaking

Thiomers: A New Generation of Polymeric Excipients

by Andreas Bernkop-Schnürch Institute of Pharmacy, Austria

The Thiomer Technology

The mucoadhesive properties of well-established polymeric excipients such as poly(acrylates) or chitosan can be strongly enhanced by the immobilization of thiol groups on these polymers. Thiolated polymers designated thiomers are capable of forming disulfide bonds with cysteine-rich subdomains of mucus glycoproteins covering mucosal membranes (1). The mechanism is illustrated in Fig. 1. Consequently, the bridging structure most



commonly used in biological systems is utilized to bind drug delivery systems on mucosal membranes such as the gastrointestinal, nasal, buccal, vaginal or ocular mucosa. By immobilization of thiol groups the mucoadhesive properties of poly(acrylic acid) and chitosan, for instance, were 100-fold and 250-fold improved (2,3). Accordingly, drug delivery systems comprising a thiomer remain for a comparatively longer period of time on the mucosa. By this prolonged and intimate contact of the delivery system with the absorption membrane a steeper concentration gradient of the drug to the absorption membrane representing the driving force for passive drug uptake—can be achieved. Consequently, a relative higher bioavailability for poorly absorbed drugs can be achieved. In the case of oral peptide delivery the bioavailability is additionally improved as enzymatic degradation of the drug on the way between the delivery system and the absorption membrane can be excluded by the intimate contact of the mucoadhesive polymeric drug carrier matrix with the gastrointestinal mucosa. Furthermore, due to a prolonged residence time of the delivery system on mucosal membranes a comparatively longer lasting therapeutic effect can be provided after single dosing (4). In addition, thiomers were shown to exhibit also strong cohesive, permeation enhancing (5) and enzyme inhibitory properties (6).

Proof of concept

The efficacy of these novel delivery systems have been verified in various animal models and in clinical trials. Utilizing the thiomer technology an absolute pharmacological efficacy of 1.3% was gained by the oral administration of salmon calcitonin (7). In case of orally administered insulin a relative pharmacological efficacy of 7% versus s.c. injection could be achieved as shown in Fig. 2 (8).

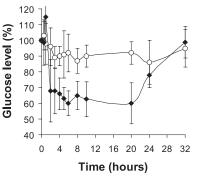


Fig. 2. Blood glucose level in diabetic mice after single oral administration of PEGylated insulin loaded minitablets comprising thiolated poly(acrylic acid) (") and of a PEG-ylated insulin solution (o). Each point represents the mean ± SD of ten experiments. (8)

(Scientifically continued on page 10)





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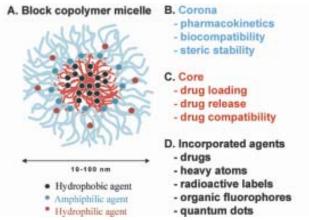


Intracellular Fate of Block Copolymer Micelles

by Radoslav Saviæ and Dusica Maysinger McGill University, Canada

Block copolymer micelles are nanosized (10-100 nm), typically spherical particles made from synthetic, amphiphilic block copolymers. The hydrophobic portion of the block copolymer forms the core of the micelle providing a loading site for hydrophobic drugs. The hydrophilic segment of the block copolymer forms the water-soluble corona ensuring water-solubility and keeping the micelle particles in suspension (Figure 1). Micelles release the incorporated drug into physiological fluids at a rate that is influenced by the physical and chemical properties of the block copolymer and that of the incorporated agent [1]. Micelles can also deliver drugs to sub-cellular compartments.

Figure 1. Schematic cross section of a block copolymer micelle



The cellular fate of the micelles and the incorporated agent(s) [2] becomes important in evaluating and optimizing the efficacy of the delivery system [3]. Obstacles encountered in following micelles within cells include the labeling of the polymer and the detection of the micelles. The label, covalently attached to the block copolymer, must not prevent the formation of micelles. Possible labels include radioactive probes, heavy atoms, and fluorescent molecules. Radioactive probes can provide quantitative results with low backgrounds as compared to fluorescent markers. Heavy atom probes are analyzed by electron microscopy and they provide the greatest resolution. Fluorescent probes provide the advantages of both of heavy atoms and radioligands: they can be measured quantitatively and imaged with high resolution by confocal microscopy. A major advantage of fluorescent probes is live cell imaging [2].

Confocal microscopy is relatively simple and fast as compared to electron microscopy, and organelle selective fluorescent probes enable colocalization with labeled micelles [2]. Electron microscopy of heavy atom labeled micelles is significantly longer requiring hours for sample preparation and days before the first images can

be obtained. Once the challenges of labeling and imaging the micelles have been overcome, the interpretation of data requires particular attention to the origin of the signal. Does the signal originate from the probe that is in the micelles or from the free probe? This issue can be addressed in part by using covalently attached fluorescent probes to the block copolymer. Ideally, both the micelles and the micelle-incorporated probes would be visualized in the biological sample. In this regard, visualization of phospholipid micelles with micelle-incorporated quantum dots has been achieved. Both the incorporated probe (quantum dots) and phospholipid corona were visualized on a single micelle level [4]. This approach may not be possible for traditional non-metalic micelle-incorporated fluorescent probes. Another way of addressing the origin of the signal capitalizes on quenching of the fluorescence of incorporated probes by micelles. Comparisons of fluorescence measured in lysed and non-lysed cells reveal several fold greater signal intenisty in lysed cells treated with micelles than with free probe (unpublished observation). This suggests that micelles quench the probe's fluorescence in the cells until the cells (and micelles inside the cells) are lysed.

What are the future directions of research involving block copolymer micelles and the delivery of small molecular weight drugs at the cellular level? In light of the goal of delivering drugs to the cell surface or intracellular organelles, degradation of the polymer inside the cells and the toxicity of the polymer byproducts needs to be addressed. An additional important question is the residence time of micelles in cells and its effects on cell viability. Ultimately the toxicity of the polymer and the intended pharmacological intervention will determine the applicability of the micelles and incorporated drugs – cell killing or cell rescue.

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Pharm News

Applications of Controlled Release Science and Technology: Progesterone

Some drugs just demand to be delivered via a controlled release technology. One such drug is progesterone. Progesterone has a short biological half life (15 minutes), undergoes extensive liver metabolism (first pass effect) and needs to be repeatedly administered by injection to elicit its effect as it cannot be administered via the oral route. Biologically it plays an important role as an endocrinological hormone in the estrous cycle of most animals [1]. In the mid Seventies it was successfully incorporated into a silicone based matrix-type intravaginal delivery system to control the estrous cycle of cattle (PRID; Figure 1). The PRID



Figure 1: PRID. Manufactured by injection molding, the PRID comprises a strip of stainless steel covered on both sides with a matrix of silicone and progesterone (1.55 g) in the form of a coil with a diameter of 4 cm and length of 12 cm.

became the forerunner to several similar silicone based technologies (CIDR 1900, CIDR 1380, CueMate; Figures 2-4,

Figure 2: CIDR 1900. T-shaped delivery system with a wing tip-to-tip distance of 15 cm and body length of 13 cm comprising a silicone/progesterone (1.9 g) matrix that is injection molded over a nylon spine that affords the shape and retention characteristics of the insert.





Figure 3: CIDR 1380. An injection molded T-shaped delivery system that is bioequivalent to the CIDR 1900. In the CIDR 1380 the silicone/progesterone skin has been optimized to result in a lower progesterone load (1.38 g) and exhibit a smaller residual progesterone content after removal.

Figure 4: CueMate. Fluted pods of progesterone (1.56 g) homogenously distributed throughout silicone that are manufactured by injection molding and then attached onto a wishbone shaped spine to facilitate their administration, retention and removal.



respectively) [2-6]. More recently, an alternative polymer (poly a caprolactone) has successfully been combined with progesterone and fabricated into a commercially viable intravaginal delivery system (Figure 5) [7]. However, no one could have foreseen the

by Michael J Rathbone - InterAg, New Zealand and Keith L Macmillan - Melbourne University, Australia

Figure 5: PCL Intravaginal Insert. A Tshaped insert comprising 1.38 g progesterone homogenously distributed throughout poly (&-caprolactone). The PCL Intravaginal Insert offers the cost advantage of being manufactured by a single step injection molding process. Developed to be bioequivalent to the CIDR 1380.



impact that these intravaginal delivery systems would have on endocrinological and physiological knowledge of the estrous cycle of cattle, or on the advanced drug delivery systems that would subsequently result from the expansion of that knowledge (Smartt1, InterAg Electronic DDS; Figures 6 and 7 [1-4]).

Progesterone is used to synchronize the estrous cycle of farmed animals. Normally any cow in a particular herd could be at any stage of its 21-day estrous cycle. Each cow within a herd would be observed to display behavioural symptoms of estrus for about 12 to 24 hours with a proportion of animals continuously coming onto and out of heat (exhibit estrous). Such a situation would require daily need for the farmer to present a small proportion of his herd to the bull or present it for artificial insemination; a timeconsuming and costly process. The controlled delivery of progesterone to herd members allows the entire herd to be brought into estrus at the same time thereby offering a valuable farm management tool when combined with artificial insemination.

Back in the Seventies it all seemed so simple. A review of the literature at that time revealed the early pioneering controlled release studies using silicone for the delivery of steroids to women in the form of vaginal rings. Animal scientists identified the opportunity to utilize silicone as an inert matrix for the continuous delivery of progesterone via the intravaginal route and designed intravaginal inserts that slowly delivered progesterone at the right rate to cattle. Progesterone appeared to be well absorbed via the vaginal route and offered the advantage of easy termination of treatment (by insert removal) that caused a sudden drop in progesterone that initiated estrus. The approach resulted in excellent synchronization of the herd, but the original 12-day treatment period resulted in inadequate fertility; an unexpected and unsatisfactory outcome. However, extensive studies by animal scientists using progesterone containing intravaginal inserts resulted in greater insights into the endocrinology and physiology of the estrous cycle allowing them to identify the roles, timings and complex interrelationship between the naturally occurring compounds responsible for estrous cycle control. Using this approach animal scientists identified the problem as 'stale follicles';

(Pharm News continued from previous page)

administration of a progesterone-containing insert late in the estrous cycle prevented existing follicles ovulating causing them to over develop and become infertile. Shorter insertion periods were not the answer, however. The solution, based on the animal scientists' increased knowledge, was the introduction of 'treatment programs' that involved not only the administration of a progesterone-containing insert but also integrated administration of estradiol and prostaglandins at strategic points within the program to induce follicular turnover, follicle atresia, and luteolysis followed by the onset of estrus and the ovulation of a recently developed, fertile follicle. However, a once simple delivery regime for progesterone now required additional injections resulting in extra veterinarian visits and additional costs to the farmers.

Despite the additional drug administrations and veterinary visits, the treatment programs are economically viable. However, the increased knowledge and identification of treatment programs have resulted in new challenges for the formulation scientist. Could a drug delivery technology be developed where all the required drugs were incorporated into a single delivery system that was capable of sustaining release of progesterone for 7 or 8 days, as well as providing an immediate release of estradiol followed by a delayed release of a prostaglandin one day before removal of the device? A demanding challenge! However, drug delivery scientists have recently developed solutions using electronically controlled drug delivery technologies (Smartt1, InterAg Electronic DDS; Figures 6 and 7 [1-4]).



Figure 6: Smartt1 or 'Intelligent Breeding Device'. A sophisticated microchip controlled device capable of delivering multiple drugs at various times and patterns. At the base of the device progesterone is stored in a small (~5 mL) concertina bladder that lies adjacent to a coiled spring. An outlet from the bladder leads via a solenoid to the head of the device. Progesterone release is

controlled by opening and closing of the solenoid. When in the open position the coiled spring forces the progesterone formulation out of the orifice. In the closed position, release is prevented. Thus continual on/off operation of the solenoid, controlled by the electronics in the device, results in a continuous, prolonged release of progesterone. At the head of the device are several chambers in which formulations of estradiol and prostaglandin are housed. Within these chambers are spring loaded pistons that are attached to a plastic cord that is pulled back and tethered over a resistor. The resistor is connected to a microchip controller. At the appropriate time current is passed through the resistor, causing it to heat up making the plastic tether melt and -resulting in the spring loaded piston pulsing out its contents.

This article has shown how the demands of the clinician can be met through controlled release science and how the resultant delivery systems can impact upon the clinicians knowledge, resulting in new demands, that are subsequently addressed, and met, by the controlled release scientist. Figure 7: InterAgs Electronic DDS. A gas controlled delivery system, simple in design, offering the ability to deliver multiple drugs at various times and patterns. The device comprises a winged barrel, plunger, a gas generating battery and a resistor. The resistor controls the amount of gas production, which in turn controls the travel distance of the plunger, which in



turn dictates the rate of delivery of the progesterone formulation. At the head of the device are two chambers that incorporate a solid or liquid formulation. A second small piston protrudes a given distance out from the base of these chamber into the progesterone formulation. As the main piston moves along the barrel, it contacts with the secondary piston causing it to move and force out the formulation contained within the small chamber. Tailoring the length of the secondary piston results in an accurately timed pulse. The advantages of this device are the large reservoir volumes and simple mechanisms for timed, pulsed release.

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(Scientifically continued from page 5)

In 2003 the thiomer technology was evaluated by the Massachussets Institute of Technology, USA and found to be '*extremely promising*' in the oral delivery of protein therapeutics (9). In further studies, for instance, an absolute nasal bioavailability of 2.6% (Fig. 3) was reached for human growth hormone, when the drug was incorporated in a thiomer (10). Additionally ocular drug delivery mucoadhesive inserts provided a sustained drug release of drug for several hours in a clinical evaluation of the technology (4,11).

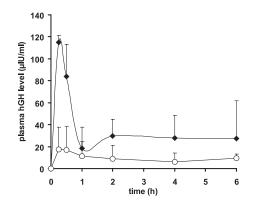


Fig. 3. Concentration- time profiles of human growth hormone (hGH) in rat plasma obtained after nasal administration of hGH incorporated a thiolated polyacrylate gel ($^{\circ}$) and in the corresponding unmodified polyacrylate gel (O). Data represent the mean \pm S.D. of 4-5 experiments (10)

In contrast to many other technologies, the thiomer technology can be easily combined with further technologies. As the permeation enhancing properties of thiomers follow a mechanism, that is completely different to other permeation enhancers, they can be easily combined with small molecule permeation enhancers such as medium chain fatty acids. In addition, nano- and microparticles may be prepared or coated with thiomers in order to improve their mucoadhesive properties and consequently in vivo performance. The residence time of poly(acrylate) microparticles on the intestinal mucosa, for instance, was increased 3-fold by using the corresponding thiolated polymer (12).



Drug delivery companies utilizing thiomers

Meanwhile the drug delivery company ThioMatrix GmbH (<u>www.thiomatrix.com</u>), which owns the main patents on thiomers is utilizing the thiomer-technology for the development of various non-invasive drug delivery systems. Currently oral formulations for calcitonin and insulin as well as a nasal formulation for human growth hormone are in development. In addition, ThioMatrix is willing to undertake co-development projects with big pharmaceutical companies utilizing the thiomer-technology as well as participate in the research and development of all kinds of non-invasive drug delivery systems.

Another company called MucoBiomer (<u>www.mucobiomer.com</u>) has gained the patent rights on this new technology for ocular drug delivery systems and as mentioned above the first mucoadhesive controlled release systems based on thiomers have already been successfully tested in the clinic (4,10).

The result of various studies focusing on the thiomer-technology will be presented at the next CRS meeting in Honolulu.

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SPOTLIGHT Celator Technologies

by Marcel B. Bally, Paul Tardi, Troy Harasym, Natashia Harasym, Christine Swenson, Andrew Janoff, and Lawrence D. Mayer Celator Technologies Inc., Canada

"Celator Technologies Inc. is developing technology that utilizes synergistic combinations of rationally selected chemotherapeutic agents to improve the treatment of cancer."

Combination chemotherapy is a major component of cancer treatment for most tumor types. When cancer is cured it nearly always involves the use of drug combinations. These combinations are typically developed by first introducing the drugs to patients as single agents. After a maximum tolerated dose is determined for one agent, a second agent is added and the dose of one or both agents is adjusted on the basis of toxicity. The development of these combination regimens is therefore determined empirically on the basis of tolerability.

In vitra, where the ratio of drugs used in combination can be controlled, we have demonstrated that drug combinations providing synergy at one ratio may be simply additive or even antagonistic at other ratios. Celator's proprietary platform technology termed CombiPlexTM is based on the findings that in vitro synergistic activity of antineoplastic drugs depends on specific drug ratios and that the optimal in vivo activity of a combination depends on maintaining the synergistic ratio in vivo. Celator rationally selects agents based on synergistic efficacy in rapid, cell-based assay systems. Ratios proven to be synergistic in killing tumor cells are then fixed in pharmaceutical carriers so they remain true after injection and can arrive at the tumor in optimal proportions. In this way, the development of a particular chemotherapeutic regimen can be based on the most efficacious ratio rather than empirically based on toxicity.

Celator scientists have recognized expertise in formulating drug combinations into single pharmaceutical products that use lipidbased or polymer-based carriers. This technology is unique because it embodies carrier properties that control the incorporation and release of therapeutic agents with markedly different chemical properties. These carriers are formulated to deliver controlled levels of the combined drugs so that tumor cells are exposed to drug ratios that will provide maximum effectiveness.

Utilizing off-patent compounds in ratios selected for synergistic activity, Celator is designing products that will be active against major tumors such as lung, colorectal, breast, and ovarian cancer. Results obtained by Celator to date indicate that dramatic improvements in antitumor efficacy can be achieved using the CombiPlex[™] approach. This is illustrated in Figure 1, which shows the antitumor activity against a difficult to treat human xenograft model of pancreatic cancer for a drug combination administered as a cocktail (1:1 mole ratio) at its maximum tolerated dose (MTD) versus the activity of a 4-fold lower dose of the same drug combination in a fixed ratio CombiPlex^{\rm TM} formulation. There has also been a great deal of excitement generated around the potential of using Celator's fixed ratio formulations in combination with conventional therapeutics and radiation, where a single pharmaceutical formulation comprising two or more agents becomes a component of a broader strategy developed to treat cancer patients.

FIGURE 1: In vivo 1200 therapeutic activity depends on 1000 maintaining drug ratios. CPX-1, a 800 $CombiPlex^{\rm TM}$ formulation cktail (1:1) 600 containing a 1:1 molar ratio of a 400 Tumor Weight (mg topoisomerase I inhibitor and 200 antimetabolite is CombiPlex[™] (1:1) significantly more 40 60 80 active against a Day post tumor cell inoculation human xenograft

model of pancreatic cancer than a cocktail of the same drugs at a 1:1 molar ratio. IV treatment is indicated by the arrows. The dose of the cocktail was 4-fold higher than for the CombiPlexTM formulation.

Celator Technologies arose from the research conducted in the laboratories of Dr. Marcel Bally and Dr. Lawrence Mayer at the British Columbia Cancer Agency in Vancouver (B.C., Canada) and has become a North American biotechnology company with operations in Vancouver and Princeton (New Jersey, USA). Under the direction of Celator's CEO, Dr. Andrew Janoff (formerly VP of Research at Elan), Celator is developing drug carrier formulations designed to incorporate and deliver two or more therapeutic agents in fixed, synergistic ratios to treat major tumor types with unmet medical need. Initially, Celator is developing drug combinations already approved for use in humans. This approach will provide critical proof-of-concept data demonstrating the therapeutic value of utilizing co-formulated drugs as compared to the free agents cocktails. Celator has recently initiated a formal development program of its first product candidate, CPX-1, which is being developed for the treatment of colorectal cancer.

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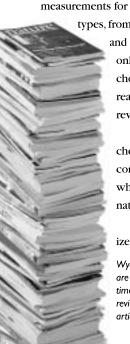
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Flavour-Matrix Interactions in Food Products

by A.E.M. Boelrijk, K.C.G. Weel, M.J.M. Burgering NIZO Food Research and J.J. Burger, Quest International, The Netherlands

In vivo flavour release measurements, the MS Nose

Present-day flavour research extends beyond finding the right key flavour ingredients. The contribution of flavour ingredients to the total flavour perception is strongly determined by the rate and the degree of their release from the food product and arrival at the receptors in the nose. They may use the (external) nasal route, when the consumer smells the product before taking it in his mouth, or the (internal) retronasal route, when he is eating it. Many factors influence the release pattern of aroma compounds from foods: e.g. the ingredients themselves such as fats, proteins, carbohydrates and alcohol. Additionally structural factors such as product hardness, viscosity and elasticity may play a role. Also specific encapsulation techniques may change the release pattern of flavour compounds. In recent years techniques have been developed to measure flavour release *in vivo* while a person is eating a product.



Figure 1. APCI-MS Nose, in vivo measurement of flavour release during consumption

APCI-MS (also called MS Nose, see figure 1) is a technique in which exhaled air from the nose of a panellist is directly (in real time) analysed by mass spectrometry. By resting one nostril on a plastic tip, attached to an open tube, the tidal flow of air from the nostril is allowed to pass back and forth through this tube. In this way, the panellist can inhale and exhale freely, without experiencing hindrance from the air sampling. Together with this analytical measurement a sensory evaluation can be performed by the panellist. In this way both sensory and analytical flavour effects caused by modifications in the product matrix can be established directly and under the most relevant conditions. For instance, the effect that the replacement of fat has on the release of aroma compounds in 'light' products or the effect that the type of encapsulation has on the release of flavours during chewing (for instance in chewing gum).

Flavour-matrix interactions in beverages

Variation between replicates and between individual panellists is inherent in *in vivo* measurements. For solid products, the relative long *in vivo* sampling time overcomes a high variability in results, especially for products like chewing gum. For beverages however, small irregularities in swallowing, breathing and chewing can easily disturb the measurement of flavour release. With the use of a strict protocol to control breathing and swallowing, a trained panel was able to significantly discriminate between flavour solutions with a concentration difference down to 17% (see figure 2A).

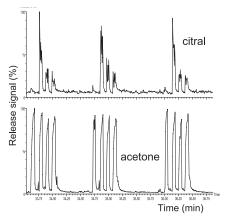


Figure 2A. Triplicate measurement of citral release from 3 ppm aqueous citral solutions. Acetone, resulting from the fatty acid metabolism and present in the breath, is used as breathing indicator.

The effect of sweeteners on flavour release from a lemon flavoured beverage has been studied by means of this beverage protocol. The release of lemon flavour was compared between 10% w/v sucrose and an equisweet mixture of sodium cyclamate and sodium saccharinate. At these concentrations, which are relevant to the beverage industry, no differences were observed in flavour release (see figure 2B). Differences in flavour release between bulk and intense sweeteners have been hypothesized to account for differences in perception of regular and intense sweetened beverages. The present results suggest that the change in flavour perception due to the use of intense sweeteners cannot be attributed to flavour release.

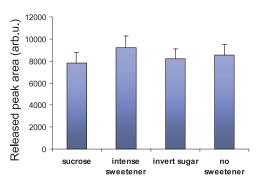


Figure 2B. Averaged in vivo released peak area (3 panellists, 4 replicates) of 3 ppm citral solutions, sweetened with various types of sweetener (error bars indicate standard errors).

(C&DP continued on page 19)



People on the Move

Hayat Onyuksel named University of Illinois 2003 Inventor of the Year

University of Illinois-Chicago, U.S.A.

In 1985, College of Pharmacy Professor Hayat Onyuksel, PhD, made a difficult choice. When given the opportunity to extend her summer-long visit to the United States and continue her temporary University of Illinois, Chicago research project in the area of pharmaceutics and bioengineering, she took a risk and opted to stay - leaving behind her extended family, friends and a permanent faculty position at Ankara University, in Turkey.

Years later, Hayat Onyuksel's tough decision appears to be one of the best she has made.

Within her first three years of living in the United States, Onyuksel married, had a son and accepted a demanding, full-time position as an assistant professor in the UIC College of Pharmacy. And this year, now with eight patents under her belt and several more pending, an option on her technology by Baxter Health Corporation, and two start-up companies (VipoGen and MedLipids), the University of Illinois in Chicago has named Onyuksel as its 2003 Inventor of the Year.

"Getting this award puts everything into perspective. It was not easy at all, things worked out really fine and did not stop me from doing my innovative research" she said. "I don't have any reservations or concerns about whether I should have done things differently."

The prestigious Inventor of the Year award recognizes UIC faculty researchers who demonstrate outstanding achievement and leadership in the advancement of science and useful arts.



Minimally, nominees for this distinction must be a primary inventor or creator of a UIC technology which is patented or copyrighted, that contributes significantly to the advancement or knowledge in the field, and that has been developed into a product or process that has benefited or will benefit society.

In addition to serving as Professor of Pharmaceutics and Bioengineering, Onyuksel is also Assistant Head of the Department of



Dr. Onyuksel (second from right) with her research team.



Dr. Onyuksel (center) receiving her award.

Biopharmaceutical Sciences and Director of Graduate Studies. She is behind the development of novel drug delivery systems that can improve drug solubility and targeted delivery to a cell, organ or tumor for treatment of numerous conditions, including breast cancer and rheumatoid arthritis. Her research efforts in this area involve collaboration with UIC College of Medicine Professor Israel Rubinstein, MD. Onyuksel and Rubinstein were recently awarded almost \$1 million by the Department of Defense and the Department of Veterans Affairs to explore two of the most promising applications of these drug delivery systems: targeted drug delivery and advanced imaging techniques for breast cancer treatment and detection.

"Dr. Onyuksel is the third member of the UIC College of Pharmacy faculty and the first woman to receive this esteemed recognition since it was created in 1985. We are very proud of Dr. Onyuksel's outstanding achievement and celebrate her success," said College of Pharmacy Dean Rosalie Sagraves.

Onyuksel was selected to receive this distinction by a committee of UIC scholars. She credits her family, her UIC administrators and colleagues with providing a supportive environment that allowed her to focus her creative energies on research.

"It's always nice to be recognized and appreciated," Onyuksel says. However, she is most excited about reaching the point where her long-term research efforts are resulting in novel drug products that visibly impact the lives of patients.

Journal of Controlled Release

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

Four upcoming articles appearing in the *Journal of Controlled Release* are highlighted herein. The first article is by Lee and coworkers, and it describes a multifunctional hydrogel-based delivery system. This complex dosage form is a bilayered device with a folding gate, which permits unidirectional drug release. It can potentially be held against a mucosal surface using a bioadhesive material. The "gate" is opened and closed through changes in local pH permitting pulsed drug release. The delivery system is prepared using traditional polymer chemistry and microfabrication techniques.

Another relatively simple approach to pulsed release for oral delivery applications is presented by Sungthongjeen *et al.* A compressed tablet (core) containing the active is coated sequentially with a material composed of a swellable substance (e.g., a superdisintegrant) followed by a layer of ethylcellulose. The outer layer ruptures after the inner swellable layer expands in the presence of water. Depending on the thickness of the two layers, the lag time before drug dissolution begins can be controlled and

ranges from 1 to 8 hours. Dissolution of the model drug buflomedil HCl was rapid once the lag time expired.

Bot and coworkers describe the design and testing of solid aerosols for the delivery of immunoglobulins. IgG was co-spray dried with lipid; some formulations also included a biocompatible surfactant. Biologic data from mice showed that nonretentive (immediate release) particles, but not slow release particles, effectively curbed virus replication. These data suggest that pulmonary (and possibly systemic) administration of antibodies is possible.

A self-assembling three component, modular DNA delivery system based on silica nanoparticles is described by Saltzman and coworkers. The silica particles are used to enhance uptake at the cell surface. A range of transfection agents were tested to enhance cellular uptake of the particles. Silica nanoparticle-enhanced transfection also was dependent on particle size. The silica nanoparticles and transfection agents showed little toxicity in the cell lines tested.

Chapter Update

by M. Jayne Lawrence King's College, United Kingdom Lance Shaw GlaxoSmithKline, United Kingdom

January 13th 2004, GSK House, Brentford

A joint one day meeting was held between the Royal Society of Chemistry and Society of Chemistry Industry (SCI) Colloid Group and the United Kingdom and Ireland Chapter of the Controlled Release Society (UKICRS) entitled 'Macromolecular Drug Delivery: Big Molecules, Big Problems'. The aim was to discuss the problems associated with the formulation of macromolecular drugs such as antibodies and heparin. The meeting with 65 delegates, was generously hosted by the Pharmaceutical Company, GlaxoSmithKline (GSK) in their new corporate headquarters in Brentford, Middlesex.

The morning session commenced with **Professor Randy Mrsny** (University of Cardiff) describing his research group's attempts to modulate the barrier properties of the intestinal membrane by selectively opening up the junctions between the cells constituting the membrane in a controlled and reversible manner. If this goal proves to be achievable then it opens up a whole new avenue for drug delivery as it may then be possible to deliver realistic amounts of drug encapsulated in a colloidal vehicle across the small intestine; the major site of drug absorption after oral administration.

Professor Mrsny was followed by **Professor Sandy Florence** (School of Pharmacy, University of London) who detailed efforts to use colloidal particles (particularly those in the 5-500nm size range) as oral drug delivery vehicles. A whole plethora of colloidal systems have been studied including dendrimers, microemulsions and hydrophobic nanoparticles but with varying degrees of success. It is now generally accepted that it is only possible to deliver very low

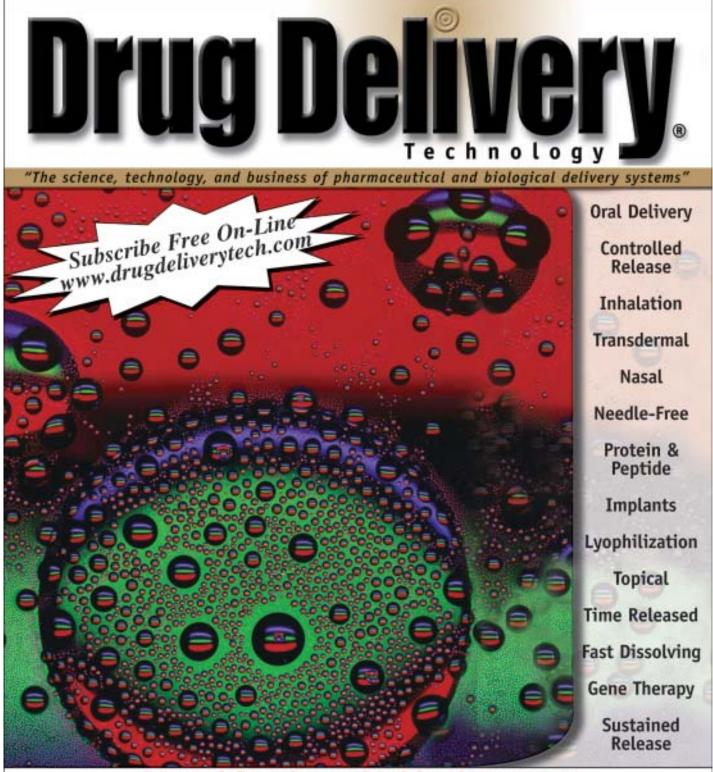


Speakers from left to right: Professor Sandy Florence, Professor Bob Laughlin, Dr. Marian Ashford, Dr. Giuliano Siligardi, Professor Randy Mrsny, Professor Steve Harding, Professor Tudor Arvinte

levels of therapeutic molecules across the intestine using colloidal carriers, such as those suitable for vaccine delivery. However this may change if Professor Mrsny's approach is successful. Realising the fact that many of the barriers facing the successful formulation of drugs for oral delivery are colloidal in nature, Professor Florence called upon colloid and surface chemists to become involved in the drug delivery process. Professor Florence also highlighted that many of the macromolecular drugs available are themselves small colloidal particles and may be able to act as their own delivery vehicle.

The final speaker of the morning, **Dr Giuliano Siligardi** (King's College London) told the audience how his work successfully exploited the naturally-occurring blood colloid, human serum albumin (HSA) as a drug delivery vehicle. Dr Siligardi exploits the natural ability of HSA to bind fatty acids. By modifying a drug molecule to contain a





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Patent Watch

Our patent search for the calendar year 2003, uncovered 106 granted patents and published patent applications. From these 27 were U.S. issued patents and 46 U.S. patent applications. There were also 16 World patents issued and 17 European patent or patent applications.

We only covered in our review the forty six issued patents. Eleven of these patents pertained to transdermal devices and methods and thirteen to chemical enhancers. There were also eighteen patents pertaining to electrophysical methods (iontophoresis, electroporation, skin ablation) and four pertaining to the abrogation of skin irritation and sensitization. The most pertinent of these are discussed in our review.

During 2003 there were several commercial activities of interest. Oxytrol [™], Watson's transdermal patch for oxybutynin was approved in the USA in February for the treatment of overactive bladder, including symptoms of urge incontinence, urgency and frequency. Oxytrol is a clear patch that releases 3.9 mgs/day of oxybutynin and it is applied twice weekly. The product was introduced in the USA at a 10% discount to its oral competition, Detrol LA[™] and Ditropan XL[™]. It was filed for approval in the European Union in March 2003 and it will be marketed by UCB Pharma in Europe and Paladin Labs in Canada.

In April 2003, Noven and its worldwide marketing partner, Shire Pharmaceuticals, received a non-approvable letter from the FDA on their MethylPatch[™] (methyl phenidate). MethylPatch is indicated for the once-daily treatment of attention deficit hyperactivity disorder.

In November 2003, Berlex Laboratories obtained FDA approval of the Climara Pro[™] patch for the relief of moderate-tosevere symptoms associated with menopause. The once weekly patch was developed using 3M technologies and delivers 0.015 mgs levonorgestrel and 0.045 mgs per day estradiol.

by Agis Kydonieus and Bozena Michniak UMDNJ - New Jersey Medical School, U.S.A.

In the summer of 2003, Nitto Americas, Inc acquired 100% of the stock of Elan Transdermal Technologies, Inc, including its 110 employees. In another business development, Adolor obtained exclusive rights for North America of EpiCept's topical lidocaine patch, LidoPAIN SP[™], which is indicated as a treatment for controlling postoperative incisional pain. EpiCept also licensed its LidoPAIN BP[™] patch to Endo for the treatment of acute lower back pain. Endo continues to develop LidoDerm[™], its own 5% lidocaine patch for treatment of chronic back pain.

Positive results were presented by Somerset Pharma on the use of its monoamine oxidase patch for depression, Altea for a skin patch delivering an opiate for managing severe pain, and Neuroges X on the use of high concentration capsaisin patches for the long-term pain relief of post-shingles pain.

Here below some of the more interesting patents are discussed.

DEVICES / METHODS

Non-contact Printing Method for Pressure Sensitive Adhesive (PSA) Devices (3M) WO 0224373 A method of preparing a patch is claimed where a base layer (PSA) is coated onto a substrate and a liquid composition

substrate and a liquid composition containing the drug is non-contact printed onto the base layer. At least part of the liquid composition is allowed to diffuse into the PSA.

Pyrrolidonoethyl Acrylate Containing PSA (3M) WO 006568 The invention pertains to PSA

compositions comprising copolymers of pyrrolidonoethyl acrylate and pyrrolidonoethyl methacrylate that can be used to prepare transdermal devices.

Transdermal Device with Improved Drug Stability (Alza) US 6660295 The invention pertains to methods of increasing the stability of drugs, such as oxybutinin. The patch containing the drug is enclosed in a hermetically sealed protective pouch, and should have a nonocclusive backing or release liner. Within the protective pouch a degradation protectant is enclosed. The degradation protectant could be a water scavenger, such as a dessicant, or an oxygen scavenger.

Method of Fabricating Epidermal Abrasion Device (University of California) US 6610235

A method of preparing an injection molded epidermal abrasion device is disclosed, comprising the deposition of a mold material on an epidermal abrasion device, removal of the mold and forming an epidermal abrasion device. The abrasion device may include isotropically etched structures with vertical height of at least 20 micron, suitable for abrading the epidermis.

Flushable Disposable Polymeric Products (Tepha) US 6592892

Naturally occurring polyhydroxyalkanoates, such as polyhydroxybutyrate and polyhydroxyvalerate are described as biodegradable polymers from which backing layers, controlled membranes and pressure sensitive adhesives can be prepared. Due to their biodegradable properties, these transdermal devices can be flushed and they will disappear within a year. Method for Preventing Crystal Formation (Alza) US 6569448 A method of manufacturing transdermal devices is claimed, comprising liquid dispersions of a liquid in aqueous or nonaqueous matrices. The recrystallization of these dispersions is prevented by annealing the films and laminates containing such dispersions, in-line immediately following the film or laminate formation.

Preparation of Hydrophilic Pressure Sensitive Adhesives having Optimized Adhesive Properties (Corium) US 6576712

The invention relates to the preparation of adhesive compositions for topical, transdermal, transmucosal or iontophoretic delivery devices or other products adhering to the skin such as wound dressings. This would be a hydrophilic pressure sensitive adhesive (PSA) using a hydrophilic polymer and a hydroxyl-terminated or carboxyl-terminated short chain plasticizing agent. The optimum adhesive properties are obtained through the hydrogen

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(Patent continued from page 17)

bonding or electrostatic bonding between the PSA and plasticizer.

Penetration Enhancing and Irritation Reducing Systems (Cellegy) US 6579865 Various selected penetration enhancing systems are described that may be used in topical and transdermal formulations such as creams, lotions, ointments, gels, etc. An example may be oleic acid with Carbon 1 to Carbon 4 alcohol and a glycol with or without a gelling agent (Carbopol 940, Klucel, Klucel HF etc.). The enhancers are especially appropriate for the delivery of testosterone.

CHEMICAL ENHANCERS

Hydroxide-releasing Agents as Skin Permeation Enhancers (Dermatrends) US 6586000, 6582724, 6645520, 6562368, 6562369, 6562370, 6558695 There are seven related patents pertaining to drug permeation enhancement by the use of hydroxide-releasing agents. US patent 6586000 contains broad claims to the use of inorganic hydroxides, inorganic oxides and metal salts of weak acids, as enhancers. Many individual hydroxide releasing agents are disclosed including ammonium, sodium, calcium, and potassium hydroxides, as well as sodium phosphate, sodium acetate and potassium carbonate among others. The agents increase the skin pH to between 8.5 and 13 and are used in quantities not to exceed 25% of the formulation. US patent 6582724 claims dual enhancers,

hydroxide releasing agents and lipophilic co-enhancers, such as fatty alcohols, fatty ethers and fatty acid esters. The other five patents cover specific drug families, which are respectively, antiinflammatoties, oxybutynin, androgenic

drugs, steroidal drugs, and peptidyl drugs.

Combination of Fatty Acids or Alcohols as Penetration Enhancers (Permatec) EP 0913158

A chemical enhancer composition is described to be used with a variety of pressure sensitive adhesives which are tackified with rosin or its esters. The enhancer system comprises saturated straight chain fatty acids or alcohols with 8 to 18 carbon atoms and unsaturated straight chain fatty acids or alcohols with 10 to 24 carbon atoms. Lauric acid and lauryl alcohol, as well as oleic acid and oleic alcohol are specifically claimed.

Permeation Enhancers for Transdermal Delivery (Alza) EP 0934078

Monoalkyl ethers of polyethyleneglycol and their alkyl or aryl carboxylic acid esters and carboxymethyl ethers are claimed as enhancers for increased transdermal permeation.

Topical Delivery Using Phosphatidylcholine (Pericone) WO 101480

Crystalline phosphatidylcholine is described as the carrier for entrapping peptides, such as oxytonin, vasopressin, insulin, calcitonin, gonadotropin and others. The preferred composition comprises 85% soybean lecithin as the phosphatidylcholine, together with ascorbyl palmitate or lipoic acid. It is claimed that the loosely packed lipid bilayers of the crystalline carrier-drug composition, integrate into the cell membranes and thus transport the peptides to the bloodstream.

Chaperone Moiety Transdermal Delivery (MIT) WO 066130

A transdermal system is presented, where a chaperone moiety reversibly associates with the drug, so as to increase its permeation through skin and releasing the drug after crossing the dermal tissue. The association can be ionic, hydrophilic, hydrogen bonding or through electrostatic interactions. N-methyl pyrrolidone, octadecene, isopropyl myristate, oleyl alcohol and oleic acid are shown as chaperone molecules.

ELECTROPHYSICAL ENHANCERS

Matrix for Iontophoresis (Hisamitsu) EP 0747092

An interface for an iontophoretic device is claimed comprising a porous matrix holding the drug in a dissolution liquid containing a humectant, selected from the group of polyhydric alcohols, sugar alcohols, amino acids and acidic mucopolysaccharides. Glycerin, proline and hydroxyproline are disclosed as humectants. The innovation is more appropriate for the delivery of peptides and proteins.

Iontophoretic Drug Delivery Device having High-efficiency DC to DC Energy Converting Current (Vyteris) US 6522919

An iontophoretic system is described comprising a patch and an anode and a cathode electrode that holds the electrolyte and the medication. A controller includes a DC to DC converter circuit that generates an output voltage and an adjustable current regulator circuit. The DC to DC converter circuit is responsive to the voltage drop across the electrodes and adjusts its output voltage in response to this voltage drop.

Integrated Transdermal Drug Delivery (Transpharma) WO 039620

A system is presented where a cartridge comprising at least one electrode and a patch containing the drug substance and where the electrodes are positioned in such a way so that when current is applied through them, they are able to create at least one microchannel through the stratum corneum.

Trandermal Delivery and Analyte Extraction (Elecsys and Transpharma) US 6615079, 6611706, 6597946

Devices for ablating the stratum corneum are disclosed, so as to increase the transdermal permeation of drugs or receive body fluids for analysis. In general electrodes are provided and a power source that applies electrical energy between the electrodes, which is sufficient to cause ablation of the stratum corneum. In some claims a control unit detects the generation of at least one spark and adjusts the current appropriately.

Polymeric Foam Reservoirs for Electrotransport Delivery (Murdock) US 6650934

A method is provided for preparing a drug containing reservoir for use in electrotransport. A polymeric matrix containing the drug is foamed and then crosslinked to form a closed cell foam. This allows for smaller amounts of the drug to be incorporated into the electrotransport reservoir and it is especially useful for the delivery of peptides and proteins, as well as other costly drugs.

Transdermal Enhancement with Electrically Induced Poration (Altea) WO 101507 and WO 077971 The innovation provides for the formation of at least one micropore in a tissue membrane (skin) for transdermal delivery. A woven fabric is described comprising

structural fibers and electrically conductive fibers and at least one porator formed by the conductive fibers acting as a heat resistive element. Transdermal systems using porators, electrodes, and attachment mechanisms are also described.

Transdermal Active Delivery System (Electromagnetic Bracing) US 6564093 An electrotransport device is presented comprising an electro-osmotic electroporous membrane, which becomes actively electroosmotic when an electric charge is passed through the membrane, thus enabling a drug solution passing through to a skin surface to create an electrotransport effect. Also included are an energy source, generating an electric current and means of generating an electromagnetic field having one predetermined frequency.

Transdermal Delivery of Analyte Extraction (Transpharma) WO 089043 An apparatus is described comprising a board, attached onto which is a plurality of ablating electrodes. Energy is delivered to the ablation electrodes through driving electrodes attached to pads, which are coupled to the ablating electrodes. The current is able of ablating at least a portion of the stratum corneum in the vicinity of the ablating electrodes to facilitate transdermal transport.

Cutaneous Administration System (Hewlett-Packard) WO 028797 Bioactive agents are cutaneously delivered by a thermal of piezoelectric jet injector. The dispenser propels precise volumes of droplets toward the skin, where they exert a

ANTI-IRRITANTS / COUNTERSENSITIZERS

local or topical effect.

Composition for Inhibiting Hypersensitivity (Purdue Research Foundation)

WO 059284 and WO 059221 A method of inhibiting skin sensitization in transdermal delivery is claimed, comprised of matrix compositions, extracts, or hydrolysates of liver basement membrane, urinary bladder submucosa, stomach submucosa, or processed collagen from other vertebrate non-submucosal sources.

Transdermal or Transmucosal Delivery Device (Hisamitsu) US 6564092 An iontophoretic device is disclosed with an energization pattern controller, which can supply combination patterns comprising two or more patterns containing at least a pulse depolarized type among three types of energization; the other two types being direct current and pulse. There are at least one dozen combination patterns presented. All of these combinations give excellent results with peptides (calcitonin), but more importantly they give substantially lower irritation scores than, for example, direct current type alone.

Formulation for the Administration of Fluoxetine (Alza) US 6512010 A transdermal device, less than 60 sq. centimeters in size, is claimed for the delivery of fluoxetine acetate. The device comprises a reservoir containing the fluoxetine and a corticosteroid, such as hydrocortisone. The fluoxetine is delivered at the rate of 250 to 3500 micrograms per hour. The rate of delivery of hydrocortisone is in excess of 0.1 micrograms per hour per sq. centimeter, but does not exceed 5 mgs per 24 hours. The hydrocortisone is codelivered with the fluoxetine and it is shown to reduce its skin irritation.

(C&DP continued from page 13)

Sucrose however does have an effect on flavour release at higher concentrations. The size and direction of the effect differs between flavour compounds. This is important for products that contain higher amounts of sucrose, for instance hard boiled sweets. Usually an increase in sucrose concentration, which leads to a higher concentration of flavour in the water phase, gives an increased flavour release.

Flavour release from chewing gum, the importance of delivery systems A typical application of flavour release measurements can be the study of mint flavour in chewing gums as presented in figure 3. Shown are average release curves of three different panellists in duplicate. Panellists were monitored by the MS Nose for 6 minutes while chewing on one of the gums. In the present study, three gums are compared; the gums were all prepared with different delivery systems.

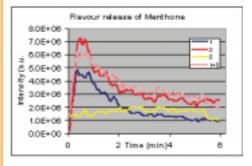


Figure 3. Flavour release from different types of chewing gum.

Gum number 5 is a traditional flavoured mint gum (yellow curve) while gum number 1 (blue curve) is a gum with an encapsulated mint flavour to give a flavour burst. Gum number 2 (red curve) contains both the delivery systems of number 1 and number 5. The question raised was whether release properties from gum number 2 is a superposition of the results of the other two individual gums. This appeared to be true. In fact, 1+5 is 2! For illustration, the calculated curve in which the measurements of gum number 1 and number 5 are combined, is also presented in the figure (shaded red curve) and it shows that the results can indeed be added up. The calculated curve matches the actual measured curve quite well. These flavour release results can clearly accelerate product development of new types of chewing gum by giving analytical feedback with respect to sensory panel data.

(Chapter continued from page 15)

fatty acid it is possible to get up to 9 drug molecules binding to a molecule of HSA. The use of HSA as a delivery vehicle offers a number of advantages, including increasing both the plasma half-life and safety margin of the drug, and acting as a solubiliser of the drug. This novel technology is now being commercially developed by an international pharmaceutical company.

After an excellent lunch during which the audience were able to view the posters and exhibition, **Dr Marian Ashford** (AstraZeneca) gave a personal view of the need to identify potential drugs with a view to fitting into a particular drug delivery system, rather than developing supposedly 'universal' drug delivery vehicles. Recent advances in high throughput screening and combinatorial chemistry meant that many thousands of putative drugs are being identified, many of which however exhibit physico-chemical properties that make them difficult, if not impossible, to formulate successfully using conventional methods. In order to successfully develop new medicines therefore Dr Ashford argued, that the selection procedure should not be based solely on consideration of therapeutic activity of the drug but also its ability to be incorporated into existing drug delivery vehicles.

Professor Bob Laughlin (Cinncinati, USA) then detailed his work concerned with development of a vaginal controlled release betweenmenstrual period contraceptive technology. This technology consists of a silicone diaphragm-like devices from which it is possible to control the release of the spermicidal non-ionic surfactant, C10E5. This novel contraceptive device offers the advantage that the spermicidal C10E5 is non-hormonal and is released at its intended site of action and consequently should not produce any major side effects. The device was well accepted by patients in a clinical trial. Unfortunately due to Company policy this exciting technology was not commercialised. The final two sessions of the day outlined the development of physicochemical techniques to characterise antibodies. Antibodies are potentially very important therapeutic molecules and recent advances in biotechnology mean that it is now possible to manufacture them at a cost that makes them realistic candidates as drugs. In his paper **Professor Tudor Arvinte** (University of Geneva) showed how he has successfully combined the use of quantitative electron microscopy (where image analysis is used to quantify changes in the morphology of various proteins) with a wide variety of spectroscopic techniques including fluorescence and circular dichroism to determine subtle changes in antibody conformation. Of particular interest was his work showing how these techniques could be used to explain the inactivity of an antibody preparation after freeze drying.

The final presentation of the day was by **Professor Steve Harding** (University of Nottingham) who outlined to the audience how analytical ultracentrifugation techniques can be successfully combined with molecular modelling to determine the solution conformation of a whole range of antibodies. Ultracentrifugation is one of the best ways to determine antibody structure in solution as antibodies are currently too large to be successfully studied using high resolution NMR. The only other technique employed to successfully look at antibody solution structure is neutron scattering (again in combination with X-ray structure determination and molecular modelling), but this technique is not currently widely accessible, requiring the use of national facilities and deuterated molecules.

After the scientific part of the meeting was concluded, delegates were taken on a short tour of the new GSK headquarters. The meeting was well attended and all papers enthusiastically discussed by the delegates.



Reviewer 3 regrets

by Ijeoma Uchegbu University of Strathclyde, United Kingdom

you ask. Well a negative

impact at this point in the

tale. The impact factor is a

really good measure of the

frequency and so in a world

journal's *previous* citation

where high numbers are

some bizarre guilt by

good and low numbers are very bad, it means that, by

association ritual, if you get in after all those great

must be really good, I mean really really good!! But

seriously impact factors are a

good measure, so long as we

are talking about the same

area of specialisation and so

just as we cannot compare

scientists have been and most definitely gone, you

Now how could you respond to Reviewer 3, the only reviewer who had found time to read and append his comments as responses from Reviewer's 1 and 2 were, to put it quite simply, not received. *Technology*? How about all three – thank you very much. Why is it so important to be seen in the *Journal of Must Read Technology*? Because it has an impact factor of 1,500! Impact on whom, I hear

The author should comment on..., and then he, or perhaps it was a she, had launched into an incomprehensible monologue. Oh the exquisite joys of peer review, a system that must have been set up with good intentions but which has led many an author to hell. The Editor in Chief of the Journal of Must Read Technology had expressed his regrets and using the first person singular (a nice - I am taking responsibility for your wrath touch) had declined to accept the manuscript "on this occasion". Space, you were told "was at a



Can we read them all?

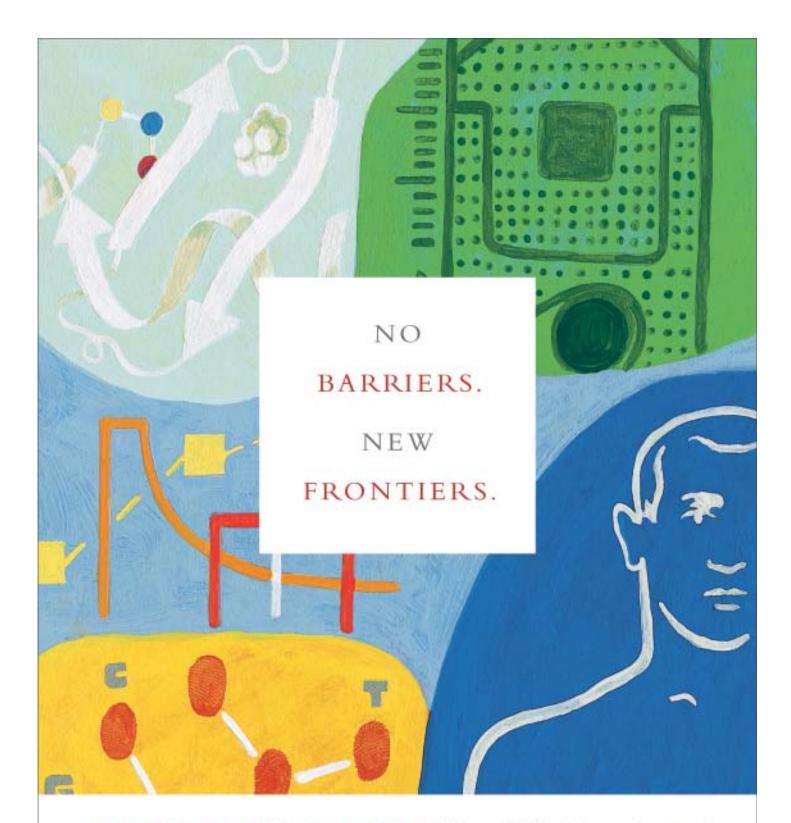
premium" and hence the journal had to be "selective". Rejection does cause actual physical pain, you note. What do you do next? Well you gather yourself together with the shreds of your self esteem and gently tap the rage button. It works wonderfully and very soon you are feeling much better. Begin again, from Square one or a square a little further along, summon up a re-write, another journal perhaps, another study even? Vowing to emphasise the fundamentalness, the genericness, the everyoneought-to-read-this-ness, a re-run commences.

We ought to be able to take rejection in our stride as we do know that it even happens to the very best. J.K. Rowling went from a pile of rejection letters to being an *overnight* publishing phenomenon of the Harry Potter series of novels and Paul Lauterbur, the 2003 Nobel Prize winner for Physiology or Medicine, had his seminal magnetic resonance imaging paper initially turned down by Nature, only to be accepted on appeal. Nature also famously rejected Hans Krebs letter describing his citric acid cycle for which Krebs later won the Nobel Prize for Physiology or Medicine in 1953. The list goes on. It fails to make you feel any better though.

There you were, thinking that you had converted 3 years of hard work, numerous experiments of which only a fraction could be presented, your blood, sweat and maybe even a few tears into something simply marked "ACCEPT"? If only life were so simple. What will you ask of the Research Fairy next time you meet? Good ideas, lots of funding or the ability to turn ideas and cash into a manuscript suitable for publication in the *Journal of Must Read* apples with oranges, we cannot compare ... erm ... journals with erm ... journals but we can compare some journals with some other journals. It makes perfect sense to me as well.

When is it sensible to give up trying to get published in the Journal of Must Read Technology? I know a group who spent 3 years battling with a single sceptic in order to get their precious work into one of our finest publications. Three years! Over one thousand days!! There were 4 of them so over four thousand days!!! Well what do you do if Reviewer 3 requires more experiments? Totally irrelevant ones of course, they always are. What if Reviewer 3 asks you why you failed to examine the impact (!) of parameter XYZ on response ABC?? Do you go back to the laboratory and look for the postdoc who has long gone to take up an offer of employment in Reykjavik or do you check the bench at the back for the PhD student who has since left to join your rival's laboratory in New Mexico, taking all your secrets and plans for the future along with him? No you boldly step into the laboratory and work the equipment, which has changed so much since you last were at the bench that the dials have been replaced with sound activated technology. Sound activated technology? Every time you swear, solvents and samples spill resolutely to the floor. You learn to whisper your way through the start up menu and then panic repeatedly as you realise how long it will take you to get to grips with the sophisticated piece of metal which cost you squillions and squillions of man hours to fund. You struggle to turn the equipment on for 3 months; struggle to understand how it works

(Reviewer continued on page 24)



COMPLEX CHALLENGES, INNOVATIVE SOLUTIONS. For 35 years, ALZA has led the drug delivery industry in developing extraordinary products based on our transdermal, oral, implantable, and liposomal delivery platforms. More than 30 products in 80 countries are based on ALZA's novel drug delivery and targeting technologies. Today, ALZA's dedicated researchers and scientists are addressing the complex challenges of delivering small molecules and biopharmaceuticals, with the commitment to create better medicines that improve healthcare for patients worldwide. Visit www.alza.com to learn more.



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LEADING THE NEXT GENERATION OF DRUG DELIVERY

IntheNews

Connetics' New Drug Application for Extina Has Been Accepted for Filing by the FDA

PR Newswire via NewsEdge Corporation: Palo Alto, CA, April 8/ — Connetics Corporation (Nasdaq: CNCT), a specialty pharmaceutical company focused on dermatology, announced today that it has received confirmation that the U.S. Food and Drug Administration (FDA) has accepted for filing the Company's New Drug Application (NDA) for Extina[™], as of January 26, 2004 with a user fee goal date of September 24, 2004. Extina is an investigational new drug formulation of 2% ketoconazole delivered in the Company's proprietary VersaFoam[™] delivery system, as a potential new treatment for seborrheic dermatitis.

Orally disintegrating drug receives FDA approval for schizophrenia -Schizophrenia

NewsRxCDC-FDA via NewsEdge Corporation: April 11/ — Cima Labs Inc. (CIMA) announced that Fazaclo, a new product in its collaborative pipeline, has received U.S. Food and Drug Administration (FDA) approval for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment. Under the terms of its agreement with Alamo Pharmaceuticals, Cima will receive revenue from the sale of the product to Alamo Pharmaceuticals and royalty payments based on Alamo Pharmaceuticals' commercial sales volume.

Cima develops and manufactures prescription and over-the-counter products based upon its proprietary, orally disintegrating drug delivery technologies. They are manufacturing Fazaclo, which contains the active ingredient clozapine, for Alamo Pharmaceuticals in an orally disintegrating tablet (ODT) formulation based on the company's OraSolv technology. Cima's OraSolv ODT formulation dissolves quickly in the mouth without chewing or the need for water. Cima Chairman and Interim Chief **Executive Officer Steven Ratoff** commented, "Upon its launch, Fazaclo will be the seventh commercially available ODT product manufactured by Cima. Our ODT technologies are becoming increasingly recognized across the pharmaceutical industry as offering

compelling product life cycle and patient benefits."

Phase I trial for Oxybutynin gel completed - Overactive Bladder NewsRxWomensHealth via NewsEdge Corporation: April 8/ — Antares Pharma, Inc., (ANTR) announced the successful completion of the phase I clinical trial for its oxybutynin topical gel product. The reported product is intended for the treatment of overactive bladder (OAB), characterized by involuntary muscle contractions leading to loss of urine. This transdermal gel formulation of oxybutynin provides therapeutic levels of oxybutynin along with a significant reduction of the initial drug metabolism in the liver.

Antares Pharma's phase I trial showed that the oxybutynin gel delivers therapeutic doses of oxybutynin with a significant reduction of the main metabolite, Ndesethyloxybutynin. This metabolite is believed to be responsible for several of the adverse effects of the oral drug; transdermal delivery from a gel formulation may, therefore, offer an improved alternative in the treatment of OAB. No skin reactions were reported during the study.

The product utilizes Antares Pharma's proprietary ATD gel technology designed to allow delivery of active substances across the skin. The oxybutynin formulation is a cosmetic quality, clear and odorless gel designed to be rapidly absorbed through the skin after once-a-day application on the abdomen, shoulders or thighs. Commenting on the results, Dario Carrara, managing director for Antares Pharma's European operations, said, "Antares Pharma's ATD transdermal gel technology has already been clinically proven in the field of transdermal drug delivery of several hormone products, and the very promising results obtained now from our phase I study support our belief that Antares Pharma's proprietary technology can be successfully applied in other therapeutic fields.

Method produces uniform, selfassembled nanocells - Drug Delivery NewsRxDrugs via NewsEdge Corporation: 2004 April 9/ — Nanotechnology is about making improved products by building them from components hundreds of times

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

smaller than a human blood cell. But how do you put things together at such a tiny scale? One way is to create the right conditions, so that they assemble themselves.

For example, a new method for producing uniform, self-assembled nanocells has been developed by researchers at the National Institute of Standards and Technology (NIST). Reported in the Journal of the American Chemical Society (2004;126(9)), the method may have applications as an improved method for encapsulating drug therapies. A patent application has been filed.

Current bulk methods for producing nanocells - a type of artificial cell - produce particles in a wide range of sizes. The sizes must be sorted and filtered before being used for drug delivery, since dosage depends critically on size. The new NIST method uses micrometer-size channels etched into a device to produce selfassembled liposomes of specific sizes from as large as about 240 nanometers (nm) to as small as about 100 nm. Medicine-filled liposomes made in nanosizes should allow for more accurate drug delivery. In particular, liposomes have been studied for years as a way to concentrate the effectiveness of cancer chemotherapy while minimizing harmful side effects.

LAB International announces Phase I results for Fentanyl TAIFUN^o LAVAL, QC, April 1 /CNW/ - LAB International Inc. (TSX: LAB), a fullyintegrated product development organization specializing in inhalation delivery, announced on April 1, further details of a successful phase I study on Fentanyl TAIFUN - the Company's inhaled opiate analgesic for the treatment of break-through cancer pain. The study was designed to assess the pharmacokinetic profile of Fentanyl TAIF UN^o and to compare the bioavailability of the inhaled formulation with intravenous administration of fentanyl.

The results of the study, performed in 16 healthy volunteers, demonstrated that the absorption of fentanyl from Fentanyl TAIFUN was very rapid. Only 5 minutes after administration, the plasma

(News continued on page 25)

Hawaii CRS: Veterinary Controlled Release Programming

by David Brayden, University College Dublin, Ireland and Terry Bowersock, Pfizer, U.S.A.

The veterinary committee of CRS has been active on your behalf to ensure an excellent programme that will interest both veterinary and "human" researchers alike. Last year, we started a policy of having joint sessions with speakers from human and veterinary drug delivery in order to emphasise that the two branches have much in common. In Hawaii, we continue this approach; and therefore, veterinary speakers will be prominent at the podium session entitled, "Appropriate animal models for evaluation of human and veterinary therapeutics, " which will be co-chaired by Dr. Terry Bowersock of Pfizer and Dr. Lorne Babiuk (University of Saskatchewan). In an invited lecture, Dr. Babiuk will speak on CpG adjuvant evaluation in large animals. Our second invitee, Dr. Greg Russell-Jones (Access Pharma, Australia), will then review the oral delivery of targeted peptides to dogs and pigs. Following the invited presentations, selected podium abstracts will cover several very innovative delivery devices and mechanisms of drug transport. These include immunoliposome therapy in rabbits, electronic drug delivery via intravaginal inserts in cattle, and the discovery that the anti-parasitic agent, selamectin, is a P-glycoprotein substrates in dogs. This session should be one of the highlights of the conference.

Secondly, we have arranged Aan amusing and provocative topic for one of the Pearls debating sessions, namely, "*Veterinary drug delivery is just human delivery on four legs.*" Dr. David Brayden from University College Dublin will propose the topic, and Dr. Michael Rathbone from InterAg, New Zealand, will oppose.

Thirdly, the annual get- together of veterinary controlled release researchers will take place as part of a social gathering with those attending the Young Scientist and Student Highlights parts of the programme.

Finally, we will have an informal veterinary committee meeting, for which an agenda will be circulated at the meeting to members of the veterinary sub-group.

We hope that the veterinary members enjoy the meeting and look forward to feedback as to how we can make further constructive programming arrangements for Miami in 2005.

(Reviewer continued from page 21)

for another 6 months and then re-write in 3 days as this latter part is the part that you do best. You browse your inbox just before you fire away your re-worked, re-worded masterpiece and then ever so casually check out the Table of Contents that have just been mailed to you by the *Journal of Must Read Technology*. Then you see it. You pause, read the title slowly and realise that the paper you were just about to resubmit has already been published by your rival in New Mexico!!! Now you decide that rage will not do and so you quietly kill yourself!

How do I review? Fairly of course because *we* are fair but *they* are always unfair. Journal editors know that some reviewers want the earth and I am not talking just geologists. They also know that other reviewers fearfully ACCEPT everything and yet other reviewers simply return manuscripts marked REJECT, no other words being deemed necessary, the work being so foul. The system is not perfect; remember all those questionable Schön papers which had the great and the good spinning on their impacts. Journal editors do try their best though, it must be said. They know that busy scientists who are struggling to find the extremely important sample, which was last seen in the top left compartment of the freezer are quite willing to take up to 3 hours per paper to write a detailed critique and tick a box in a final flourish of achievement for nothing more than a thank you note. *Dear Dr*

Kindness, the Editor in Chief writes, I am writing to ask if you will be willing to review the under noted manuscript which has been submitted for publication to the Journal of Must Read Technology. Should you agree to review this manuscript, I will ask that you return your review in 3hours and 30 minutes as this will enable me to communicate a timely decision to the author. The Journal of Must Read Technology relies on reviewers such as yourself who are willing to give up their weekends and work unwaged to support the Journal. Yours sincerely, he signs off, Dr Knows the Most, Editor in Chief of the Journal of Must Read Technology. Of course you agree, after all someone reviews your articles, do they not and even if you do not get a free subscription to the journal you will getwhat will you get? You dismiss such wicked and thoroughly unaltruistic thoughts from your head and proceed to fairly review the submitted work, knowing deep down that someone somewhere has just got the better of you, but you are not quite sure who, how or why.

If you have never had a paper rejected you will not have the foggiest idea what this is all about, but I suspect that you were never very truthful, even as a toddler. Would I do anything else but be an overworked, underpaid and emotionally spent scientist. What do you think? It still is my dream job and when I grow up I still want to be a scientist!

(News continued from page 23)

concentrations reached an average of 73% of the respective maximum concentrations. The rapid absorption was well reflected in the appearance of the first opiate related effects, observed 6.5 minutes (median) after the administration of Fentanyl TAIF UN^o, as compared with 4 minutes (median) after the start of intravenous infusion. The absolute bioavailability was on average 80%. Fentanyl TAIF UN^o was well tolerated and safety data did not reveal any safety concerns for the inhaler.

These results compare very favorably with the reported data on the pharmacokinetics and bioavailability of the commercially available fentanyl lozenge. Whereas the onset of efficacy with the lozenge is reported to be between 15 and 45 minutes, the onset of efficacy using Fentanyl TAIF UNTM is expected to be within a few minutes.

"This study was crucial for demonstrating that our formulation will bring relief to patients much quicker than available formulations and has the potential to be the fastest delivered fentanyl product on the market, reinforcing our confidence as we advance this product into Phase II trials," said Dr. Halvor Jaeger, CEO of LAB. "The strong data also demonstrate the superiority of our regulatory approved TAIF UNTM platform for systemic delivery of drugs. This puts us in a good position to further leverage our platform for additional products and co-development deals, since it offers significant advantages over currently marketed inhalers."

Micro Laboratories, Inc. Completes Research on Sublingual Spray for Pain Relief

Business Wire via NewsEdge Corporation: Johnston, RI — March 30/ - Micro Laboratories, Inc. (OTCBB:MLAR), a leading manufacturer of oral spray vitamins and breath spray, announced today the completion of research on a new sublingual spray for pain relief. Micro Laboratories has developed a non-aspirin pain reliever that can be sprayed under the tongue for immediate relief of headaches, muscle pain, etc.

"It has long been known that sublingual absorption in the form of a spray is the most efficient, effective and convenient method of delivering vitamins and nutrients to the body," stated Robert Thistle, CEO of Micro Laboratories. "This same delivery system," he continued, "can be utilized in the pharmaceutical arena for many of the existing pain relievers and narcotics. In fact, it requires a much smaller dose in the form of a sublingual spray because you're putting the product directly into the bloodstream. For example, nitroglycerin has been administered under the tongue for many years for heart patients. Micro Sprays' sublingual delivery system will offer a tremendous advantage for the pharmaceutical industry because it bypasses the entire gastro-intestinal system and therefore eliminates many of the problems associated with ingesting many pharmaceutical products."

The proposed new product for pain relief will undergo clinical trails the same way that Micro Sprays' "Stop Smoking" product did and may also require FDA approval.

Micro Laboratories, Inc. has developed and patented (US pat #6,071,500) an entire line of oral spray vitamins and supplements. The products are sprayed under the tongue and absorbed directly into the bloodstream, bypassing the gastrointestinal tract altogether.

Micro Spray vitamins and minerals utilize a unique delivery system that provides the consumer with a nutrient retention rate of approximately 90%. Of all today's methods of ingesting nutrients, the oral spray method consistently provides the highest absorption rate, combined with the most effective and efficient delivery system available.

Robert Thistle stated, "The future belongs to spray. This will certainly be the preferred method of ingesting vitamins and nutrients and will revolutionize market and meet the rising demands both here and abroad well into the 21st Century." Already available for sale in spray form are Micro Spray Adult Multiple Vitamin, Micro Spray Children's Multiple Vitamin, Micro Spray Adult B Complex, Micro Spray Children's B Complex, Micro Spray Vitamin B12, Micro Spray Zinc with Vitamin C (for colds and allergies), and now Micro Spray Osteo Care

NexMed to launch Femprox clinical study in China - Female Sexual Arousal Disorder

NewsRxWomensHealth via NewsEdge Corporation : April 1/ — NexMed, Inc., (NEXM), a developer of transdermal treatments based on its proprietary drug delivery technology, announced its plans to initiate a 400-patient phase III study for Femprox in China. The design of this study is based on results from NexMed's clinical studies to date, and is double-blind, placebo-controlled, and randomized, and will test the efficacy and safety of Femprox cream in patients diagnosed with female sexual arousal disorder (FSAD).

Femprox is topically applied, and incorporates alprostadil, a vasodilator that is administered through the NexACT transdermal enhancer. In NexMed's U.S. phase II study for Femprox, 98 premenopausal women diagnosed with FSAD completed the 4-week clinical study in an "at-home" setting. The trial results demonstrated positive dose-related trends, with up to 77% mean percent success rate reported at the highest dose vs. 55% reported for the placebo. The side effects observed in the study were mild in nature and short in duration.

These results were presented at the 2002 annual meeting of the American Urological Association and were published in the October-December 2003 issue of Journal of Sex & Marital Therapy, a peer-reviewed specialty medical journal.

Atrix Receives FDA Approval for Erythromycin/Benzoyl Peroxide PR Newswire via NewsEdge Corporation : Fort Collins, CO, March 30/ — Atrix Laboratories, Inc. (Nasdaq: ATRX) announced today the company received approval from the U.S. Food and Drug Administration (FDA) for its Abbreviated New Drug Application (ANDA) for 3% erythromycin / 5% benzoyl peroxide (E/ BP). In August 2003, the company announced that they had received a nonapproval for this product. This approval is a reversal of that previous decision.

Atrix's product is the AB-rated generic to Benzamycin(R) topical gel (3% erythromycin / 5% benzoyl peroxide), which is marketed by Dermik Laboratories. This AB-rated product represents the first approval for a generic version of the popular anti-acne medication. The Novartis company, Sandoz Inc. (formerly Geneva Pharmaceuticals) will market this new E/BP product.

"This is a major victory for Atrix," said David R. Bethune, Atrix's chairman and chief executive officer. "E/BP represented not only great challenges in formulation and in demonstrating clinical bioequivalency but also represented major regulatory challenges. We are pleased we

(News continued on page 27)

SCOLR, Inc.

SCOLR's suite of 3 patented self-correcting oral delivery systems utilize conventional pharmaceutical manufacturing processes and equipment to form swellable, erodible matrix tablets, caplets and capsules. These systems can potentially yield first-order, bimodal and zero-order drug release profiles. In addition a large variety of



soluble, insoluble, low drug dose, high drug load and drug combinations can be rapidly formulated with these self-correcting systems.



US Patent #6,337,091: Referred to as the "Dual Polymer" platform - APIs with poor flow properties may be combined with better flowing controlling polymers and excipients during the granulation step to yield a more manufacturable tablet. APIs with poor compression characteristics or those formulations that require a large drug load to be therapeutically effective may also be combined with more compressible materials and high-viscosity polymers to allow for the manufacture of a lower-volume dosage form than is possible with other matrix technologies.

US Patent #6,090,411: Referred to as the "Electrolyte" platform - This system is capable of zero-order, pH-independent release of an API for up to 24-hours, without regard to the solubility of the API itself. Because the system consists of a non-covalently bonded matrix, the manufacturing process is fundamentally a two-step process of simple dryblending and direct compression. This two-step process allows for the manufacture of a monolithic tablet with cost advantages comparable to a simple wax-matrix, yet provides release profiles comparable to an osmotic pump, or other high-end delivery system.



US Patent #6,517,868: Referred to as the "Amino Acid" platform - API's with solubility issues are formulated in a matrix comprised of the API granulated with one or more ionic resins or polysaccharide gums and one or more amino acids, within a second dry-blended matrix of similar composition for the production of simple monolithic dosage forms. The ionic interaction between the granulated and dry-blended constituents allows for the controlled release of an API over 24-hours, independent of its solubility.

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3625 132nd Ave SE, suite 300 Bellevue, WA. 98006 (425) 373-0171 WWW.SCOLR.COM were able to satisfy the FDA's requirements for approval."

NeoPharm Announces New Approach for Combination Therapy by Entrapping Two Drugs in Single Liposome Using NeoLipid Technology Business Wire via NewsEdge Corporation, Lake Forest. IL. - March 29/— NeoPharm. Inc. (Nasdaq/NM:NEOL) announced today that data for its new technology for entrapping two drugs in a single liposome for combination therapy was presented via poster presentation on Sunday, March 28th at the 2004 American Association for Cancer Research (AACR) in Orlando, Florida. The Company refers to its new technology as "Tandem Technology." A copy of abstract #643 is available on the NeoPharm website, http:// www.neophrm.com.

"Simultaneous delivery of two or more cytotoxic agents in a single liposome for chemotherapy treatment for cancer is a new approach that holds great promise," said James M. Hussey, NeoPharm's President and Chief Executive Officer. "The ability to deliver two cytotoxic agents simultaneously in a single delivery system via infusion is further evidence of the potential and flexibility of our unique NeoLipidä technology. We are very excited about potential applications of the new `tandem technology."

The research poster describes the combination of liposomal paclitaxel (LEP) and either doxorubicin (DOX) or mitoxantrone (MTO) into a single liposomal delivery system using NeoPharm's proprietary NeoLipid(tm) technology. Combination therapy is designed to exploit the different mechanisms of action of the two administered drugs. In the present study, the Company has presented evidence that two anti-cancer drugs can be co-entrapped without any compromise in the stability or entrapment efficiencies of the loaded drugs. Preliminary studies of LEP-DOX on tumor-bearing mice showed promising results in overcoming resistant cancers.

Access Pharmaceuticals, Inc. Enters Research Collaboration on Nanoparticle Aggrigate Drug Delivery Technology DALLAS, TX, March 23/ Access Pharmaceuticals, Inc. (AMEX: AKC) today provided an update of progress in the development of its proprietary Nanoparticle Aggregate Drug Delivery System ("Nanoparticle Aggregate Technology."). The Company also disclosed that it has entered into a research collaboration with a US major drug delivery company to assess the Nanoparticle Aggregate Technology. Due to confidentiality provisions in the Agreement, Access cannot disclose the name of the strategic partner. The goal of the collaboration is to evaluate the utilization of Access' versatile Nanoparticle Aggregate Technology for the delivery of therapeutic proteins. The focus of the initial development project is to formulate proteins which are susceptible to degradation in the presence of solvents. The Nanoparticle Aggregate Technology is being developed primarily for the controlled release of water-soluble proteins. Access has demonstrated that these proteins can be incorporated into the aggregate in a simple cost effective manufacturing process using aqueous solutions at room temperature. Release of the protein from the nanoparticle aggregate can be tailored to meet the desired profile, allowing delivery lasting from several days, up to a projected six-month period.

Depomed Announces Positive Phase III Clinical Trial Results for Ciprofloxacin GR; Once-daily Formulation Shows Comparable Efficacy, Fewer Gastrointestinal Side Effects Business Wire via NewsEdge Corporation: Menlo Park, CA, March 18/ Depomed, Inc. (Nasdaq:DEPO) today announced top line results from the Phase III clinical trial of its Ciprofloxacin GR, an extended release formulation of ciprofloxacin HCl, which is used to treat urinary tract infections. The data confirmed Phase II results, demonstrating that Depomed's once-daily Ciprofloxacin GR eliminated the organisms responsible for urinary tract infections as effectively as twice-daily CIPRO^o, but with fewer gastrointestinal side effects, specifically fewer incidences of nausea and diarrhea.

"As we expected, our once-daily, extended release formulation of ciprofloxacin HCl has demonstrated positive pivotal clinical trial results which differentiate it from the existing twice-daily, immediate release CIPRO product," said John W. Fara, president, chief executive officer and chairman of Depomed. "We expect our once-daily formulation will improve patient convenience and compliance and now, with these results, believe that patients will also benefit from fewer gastrointestinal complications. The randomized, double-blind Phase III trial involved 580 evaluable patients with uncomplicated urinary tract infections (UTI). The trial was designed to evaluate the efficacy and safety of a three-day course of treatment with Depomed's oncedaily Ciprofloxacin GR compared to a three-day course of treatment with twicedaily CIPRO, an immediate release formulation. The preliminary analysis showed a microbial eradication rate of 93.5 percent in the Ciprofloxacin GR arm compared with 89.6 percent with CIPRO.

CYPHER® Sirolimus-eluting Coronary Stent Approved for Marketing in Japan PRNewswire-FirstCall, Miami, FL, March 31/ — Cordis Corporation, a Johnson & Johnson company, reported today it has received approval from the Japanese Ministry of Health, Labor and Welfare (MHLW) to market its CYPHER® Sirolimus-eluting Coronary Stent in Japan. CYPHER[®] Stent distribution in Japan is expected to begin mid-year, coincident with government approval of reimbursement. Japan is the world's second largest interventional cardiology market with approximately 166,000 angioplasties performed annually, 70% of which involve stent placement.

"The CYPHER Stent will provide Japanese interventional cardiologists with an important new tool to safely treat coronary artery disease," said Akira Matsumoto, President, Johnson & Johnson K.K. "We will be working closely with Japanese physicians to optimize patient outcomes with the CYPHER Stent."

The CYPHER Stent is Japan's first approved drug-device combination to significantly reduce the incidence of restenosis (reblockage) of a treated coronary artery — one of the greatest challenges in long-term management of patients with heart disease. The CYPHER Stent has been shown to reduce restenosis by 90% compared with a conventional bare metal stent.

"The CYPHER Stent is the only drugeluting coronary artery stent whose performance is supported by four largescale, randomized, double-blind, controlled clinical trials involving approximately 1,800 patients," said Jeffrey W. Moses, M.D., of Lenox Hill Hospital, New York, a principal investigator in the U.S. clinical trial, SIRIUS, which was also used for the

(News continued from page 27)

Japanese regulatory submission for approval. "No other stent in this category has been studied as extensively in clinical trials and registries across such a broad range of patients, including some high-risk patients with difficult- to-treat lesions."

Paradigm shifts in cardiovascular medicine

Holmes, D. R. Jr, Firth, B. G. & Wood, D. L. Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota 55905, USA. holmes.david@mayo.edu Cardiovascular medicine is changing rapidly with the development, testing, and introduction of new diagnostic and therapeutic methods. New interventional techniques such as the use of drug-eluting stents have important implications for the care of individual patients and the delivery and economics of health care in general. Drug-eluting stents have been shown to improve outcomes among patients undergoing percutaneous coronary intervention by significantly reducing restenosis rates. Two randomized trials have documented that per 100 patients treated with the sirolimus drug-eluting

stent, 12.5 to 13.6 patients avoided the need for subsequent target lesion revascularization, when compared with patients treated with conventional stents. The economic effect of the introduction of these stents, which are projected to be two to three times as expensive as conventional stents, is complex and depends on which segment of health care is considered. Drug-eluting stents will be favorably received by patients, physicians, employers, and society, as well as payers. However, hospitals may be adversely affected by having increased procedural costs for the stents, along with fewer procedures for evaluation and treatment of restenosis and probably decreased surgical volumes. Drug-eluting stents are only the first of many new technologic advances that will affect cardiovascular care. These procedures have many features in common, including: 1). replacement of major surgical procedures with less invasive approaches; and 2). redistribution of costs, with a decrease in hospital profits but potentially lower costs of health care delivery for society as a whole. J Am Coll Cardiol. 2004 Feb

18;43(4):507-12.

Current Status and Future Potential of Transdermal Drug Delivery Prausnitz, M. R., Mitragotri, S. & Langer R. School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332, USA. mark.prausnitz@chbe.gatech.edu The past twenty-five years have seen an explosion in the creation and discovery of new medicinal agents. Related innovations in drug delivery systems have not only enabled the successful implementation of many of these novel pharmaceuticals, but have also permitted the development of new medical treatments with existing drugs. The creation of transdermal delivery systems has been one of the most important of these innovations, offering a number of advantages over the oral route. In this article, the authors discuss the already significant impact this field has made on the administration of various pharmaceuticals; explore limitations of the current technology; and discuss methods under exploration for overcoming these

limitations and the challenges ahead. Nat Rev Drug Discov. 2004 Feb; 3(2):115-24. ■

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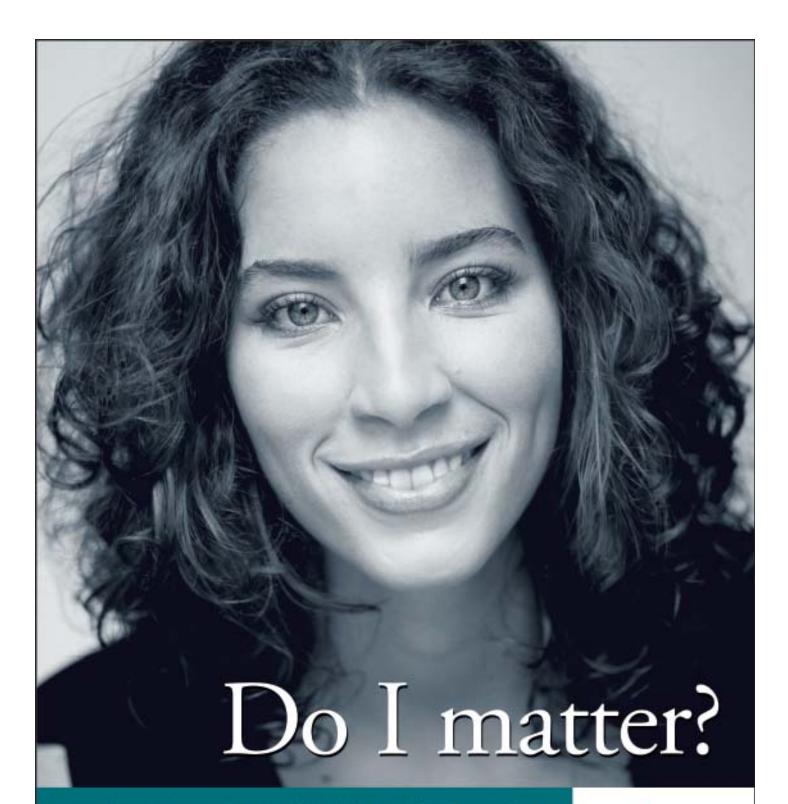
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