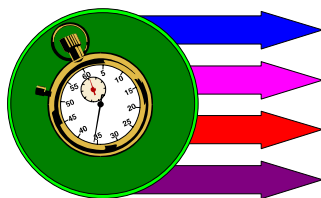


Sustained Delivery

April 2006



Newsletter of the AAPS Modified Release Focus Group (MRFG) Membership

Newsletter Editor's Note – Dr. Dave Wallick

“Hope springs eternal,” they say, but I hope that Spring stays for a few more weeks here in Michigan. The warmth of the sun – we haven’t seen that for a few months – is helping me forget the travails of snow and ice of Winter recently past.

While Winter was generous to the MRFG – you can see on the next page the Final Report of the 2006 Arden Conference organized and run by our Group – it’s time to Spring into the rest of the year. Check out, as well, our regular feature – *Modified Release Technology Corner* – which is an update & overview of recent literature highlights for a variety of MR methods and techniques. Let your MRFG Newsletter help keep you on top of the literature in this active field of knowledge.

Enjoy this new issue of *Sustained Delivery* – the communication focal point of our Modified Release Focus Group.

MRFG Chair's Corner – Dr. Dave Wallick

One of the best things about having a MRFG Newsletter is that recognition of our members for wonderful accomplishments and activities can now be done in a fashion that all of us can see. It is my privilege as MRFG Chair to recognize the efforts of the 2006 AAPS Arden Conference Organizing Committee. All are members of MRFG. There are not many professional activities that would top pulling off a prestigious scientific conference like the AAPS Arden Conference. This week-long meeting of like-minded pharmaceutical scientists was focused on MR technology, and was a wonderful success for MRFG and for AAPS. Please

read the Final Report from the Conference, which is included on the next page of this Newsletter.

Congratulations to all of the Organizing Committee members for assembling and implementing this year’s program – and it took all of a year to plan it and get it right.



The 2006 Arden Conference Organizing Committee – (from left to right) Linda Felton, Dave Wallick, Steve Howard, Avi Thombre (in back), Ping Lee, Jian-Xin Li, and Esteban Bornancini. Missing from the photo, but appreciated no less, are Samir Mehta and Vicki Penn.

Look for more recognitions later this year as MRFG members are busily involved in planning WebCasts, Symposia for the upcoming AAPS National Meeting, updates to our MRFG Homepage Website and Discussion Board, and an update of the MRFG Charter and reorganization of MRFG Leadership structure. More to come – keep watching your *Sustained Delivery* newsletter.

Meet Your MRFG Steering Team Leadership

Your Steering Team is ready to meet the needs of the MRFG membership. Feel free to contact them for answers to your questions or to share your ideas for a better MRFG.

Chair: Dr. Dave Wallick, Dow Chemical, dewallick@dow.com, phone 989-636-1018

Co-Chair: Dr. Jian-Xin Li, FMC BioPolymer, jianxin_li@fmc.com, phone 609-951-3783

Past-Chair: Dr. Ping Lee, Univ. of Toronto, ping.lee@utoronto.ca, phone 416-946-0606

Past Chair: Dr. Samir Mehta, Intas Pharmaceuticals, samir_mehta@intaspharma.com, phone 919-870-0597

Dr. Esteban Bornancini, GlaxoSmithKline, esteban.r.bornancini@gsk.com, phone 610-917-5909

Dr. Hye-Ok Choi, 3M, hhchoi@mmm.com, phone 651-733-0412

Dr. Steve Howard, Howard Consulting, jshoward.1@sbcglobal.net, phone 203-797-1991

Dr. Avi Thombre, Pfizer, avinash.g.thombre@pfizer.com, phone 860-441-8734

Dr. Samantha Lai, Pfizer, samantha.lai@pfizer.com, phone 973-385-5969

Mission and Plans for the MRFG – MRFG Steering Team

Some of the chartered activities of the Modified Release Focus Group (MRFG) are to:

- Solicit and submit programming ideas related to modified release topics for AAPS annual meetings.
- Organize educational events such as workshops and symposia, as appropriate.
- Pose questions or answer those of others' in the MRFG Forum, a chat board for Focus Group members (non-confidential information, only, please).
- Bring together scientists interested in this area via email distribution lists, newsletters, face to face meeting at the annual meeting, etc.

MRFG Goals for 2006 are to:

- Implement 2006 PT Arden Conference program on **Oral Controlled Release Development and Technology** and special edition of

PharmSciTech e-journal dedicated to the Conference in 2006.

- *Dr. Steve Howard to lead overall.*
- Facilitate membership participation in MRFG.
 - continue to publish regular editions of the membership e-newsletter, "*Sustained Delivery*."
 - expand MRFG outreach to student-members.
 - continue efforts to engage FG membership via MRFG Discussion Board.
 - seek cooperation from other Focus Groups on planning and conducting joint meetings
 - *Dr. Dave Wallick to lead overall.*
- Continue to provide new and high quality MR programming ideas to AAPS membership:
 - submit proposal and implement Parenteral MR Delivery WebCast in 2006.
 - solicit programming topics, seminars, symposia, workshops, and roundtables from MRFG for all AAPS National meetings
 - seek cooperation from other Focus Groups on developing joint programming topics
 - *Dr. Jian-Xin Li to lead overall.*

FINAL REPORT: 41ST Annual Pharmaceutical Technologies Arden Conference: "Oral Controlled Release Development and Technology"

Dr. Stephen A. Howard, Chairman

The 41st Annual Pharmaceutical Technologies Arden Conference was held January 22 – 27, 2006 at the Thayer Hotel in West Point, NY. The conference was proposed by the Modified Release Focus Group and developed by a committee consisting of Stephen Howard (Chair), Jian-Xin Li (co-chair), Esteban Borancini, Linda Felton, Ping Lee, Samir Mehta, Vicki Penn, Avinash Thombre, and Dave Wallick.

This program was designed to update pharmaceutical scientists on the latest technologies in developing controlled release products. The program gave an overview of controlled and sustained release development. Detailed presentations discussed modeling for the design of controlled release products, regulatory and legal aspects of controlled release, material selection including a discussion of the availability of new polymer materials and the latest technologies to develop and manufacture controlled release products.

The conference participants rated the Conference as highly successful. One hundred percent of the respondents responding to a post-Conference survey indicated that the speakers' talks were valuable and the vast majority answered positively on all aspects of the conference. Each speaker generated excellent discussions and the attendees were truly active participants. The vast majority of the comments during the Conference were very positive regarding the meeting and the facility.

There were a number of firsts for this conference. It was the first conference to be held at the Thayer Hotel, rather than Arden House Conference Center which closed last year. Another first for this meeting was the inclusion of vendors in the Conference program. Vendor participation provided valuable information regarding new polymer excipients and MR technologies, which complemented the presentations offered by speakers. The vendor booths were well attended and the vendor workshops generated a great deal of discussion. An online discussion board was also added to the Conference for the first time. Its purpose was to allow speaker and attendee discourse both before and after the Conference as a means of extending communication and information exchange.

Joint Secretary (Pharmaceuticals) Gurdial Singh Sandu, of the Ministry of Chemicals and Fertilizers in the Government of India, visited the conference and briefly addressed the conference regarding the present and future state of the pharmaceutical industry in India.

The 2006 Arden Conference achieved its goals of updating the dynamic field of oral controlled release technology and development, and doing so in a highly interactive fashion eliciting participation of all participants. Thanks to the MRFG for organizing and supporting the 2006 Arden Conference.

Modified Release Technology Corner

Dr. Dave Wallick

Controlled release of drugs is a vibrant, important technology for drug formulators. This is best exemplified by a survey of the scientific literature, revealing 392 citations so far this year (by end of March, and it's just First Quarter). The following is an overview of some CR technical highlights:

General CR

Meredith, Hans L.; *et. al.*, "Daily to annual biodegradable drug delivery strategies for psychoactive compounds," Handbook of Biodegradable Polymeric Materials and Their Applications (2006), 2 77-102, editors: Surya K. Mallapragada and Balaji Narasimhan; publisher: American Scientific Publishers, Stevenson Ranch, CA.

This review discusses the principles behind the long-term delivery of pharmaceutical agents, the biodegradable polymers available for such applications, the mechanisms of drug release from biodegradable polymers, and the various applications of biodegradable polymers for long-term administration. It also considers the important contributions in the area of long-term release of psychoactive compounds from biodegradable polymers, with emphasis on biodegradable microparticles for the delivery of risperidone, naltrexone, thioridazine HCl, haloperidol, clonazepam, chlorpromazine, and fluphenazine. Biodegradable implants for the delivery of haloperidol are also discussed as well as some of the new technologies available for long-term drug release from biodegradable systems.

Jacob, Jules S.; Edith Mahiowitz; Avinash Nangia; Ze'ev Shaked; and Peyman Moslemy, "Controlled regional oral drug delivery," **US 2006045865** Patent Application (2006).

A composite formulation has been developed for selective, high efficacy delivery to specific regions of the mouth and gastrointestinal tract. The formulation uses bioadhesive and CR elements to direct drug release to specific regions. The bioadhesive polymer may be either dispersed in the matrix of the tablet or applied as a direct compressed coating to the solid oral dosage form. By selecting for both release and retention at a specific site, typically based on time of transit through the GI tract, enhanced efficiency of drug uptake is obtained. This is particularly useful for drugs with narrow windows of absorption and for drugs with poor solubility, such as BCE class II and class IV drugs. *Congratulations to Peyman Moslemy for this patent; Peyman attended the recent 2006 Arden Conference on "Oral CR Development and Technology."*

Berg, Michael C., *et. al.*, "Controlled Drug Release from Porous Polyelectrolyte Multilayers," *Biomacromolecules* (2006) 7(1), 357-364.

Microporous and nanoporous polyelectrolyte multilayer films have been explored as ultrathin coatings for controlled drug release. In addition to homogeneous porous multilayers, heterostructures comprising porous regions stacked alternately with nonporous regions were assembled. The amount of drug released could be tuned by varying the number of layers in the porous regions of films, and the release rate depended on the pore size in the films. Ketoprofen and cytochalasin D were successfully loaded into nanoporous films and showed zero-order release over a period of many days.

CR Coatings

A major theme for recently published literature is CR coatings for use on implanted medical devices, particularly for cardiovascular stents. An overview of these includes:

Weber, Jan, "Stents with drug eluting coatings," **US 2006045901** Patent Application (2006).

Jerome, Christine, *et. al.*, "Surface modification of metallic cardiovascular stents by strongly adhering aliphatic polyester coatings," *Journal of Biomedical Materials Research, Part A* (2006) **76A**(3), 521-529.

Stenzel, Eric B., "Drug-coated medical devices having an increased coating surface area," **US 2006034884** Patent Application (2006).

Domb, Abraham J., "Electropolymerizable monomers and polymeric coatings on implantable devices prepared therefrom," **US 2006013850** Patent Application (2006).

Tan, Sharon Mi Lyn, "Ultrasound-activated anti-infective coatings for medical devices," **WO 2006019848** PCT Intl Application (2006).

An implantable medical device is provided including a vascular access device and a coating on at least one of an inner surface and an outer surface of the vascular access device. The coating includes: (a) a polymeric component including at least one of a light reactive moiety and a sound reactive moiety; and (b) at least one therapeutic agent releasable associated with the polymeric component. Rate of release of the therapeutic agent is controlled *in situ* by exposure of the device to at least one of a light energy source and an ultrasound energy source.

Fischer, Frank J., *et. al.*, "Implantable medical device with anti-neoplastic drug," **US 2006030826** Patent Application (2006).

Asymmetrically-coated tablets are also represented with some literature examples:

Kim, Cherng-ju, "Controlled release: asymmetrically coated tablets," *Drug Delivery Technology* (2006) **6**(1) 38, 40-43.

Asymmetrically coated tablets (ACTs) are developed so that immediate- or time-delayed times can be precisely controlled, and the CR core may provide zero-order or first-order extended and pulsatile release depending on the excipients used in the tablet formulations. The core of the tablet is coated with an asymmetric coating, i.e., a coating with regions having different properties and different rates of dissolution.

Altinkaya, Sacide Alsoy, and Hacer Yenil, "In vitro drug release rates from asymmetric-membrane tablet coatings: Prediction of phase-inversion dynamics," *Biochemical Engineering Journal* (2006) **28**(2), 131-139. Most of the CR systems developed for drug delivery applications depend on membrane technology. The dense structure of some membranes used in CR systems can excessively prolong the release of drug due to the low permeability of the coating to drug. To increase the drug release rate, asymmetric-membrane

tablet coatings were prepared by a phase-inversion technique using cellulose acetate/acetone/water solution. Results show that drug release from asymmetric-membrane based tablet coatings is primarily governed by the dynamics of the phase-inversion process, with zero-order or near zero-order release easily achievable.

Gastroretentive Drug Delivery

Bakker, Johan A.; Marius L. DeWinter; and Santa Fabiano, "Oral sustained release formulation of tedisamil with gastric retention properties," **WO 2006000583** PCT Intl. Application (2006).

The invention relates to a novel SR formulation with gastric retention properties comprising tedisamil or a pharmaceutically acceptable salt thereof and the use of the formulation in the prevention and treatment of atrial fibrillation, atrial flutter, and cardiac ischemia.

Odidi, Isa, and Amina Odidi, "Controlled extended drug release technology," **US 2006003007** Patent Application (2006).

Controlled extended release of hydrophobic or hydrophilic drugs or therapeutically-active agents is accomplished by use of hydrodynamically-buoyant dosage forms which allow for longer resident times in the stomach.

Streubel, Alexander; Juergen Siepmann; and Roland Bodmeier, "Gastroretentive drug delivery systems," *Expert Opinion on Drug Delivery* (2006) **3**(2), 217-233. A CR delivery system with prolonged residence time in the stomach is of particular interest for drugs that i) are locally active in the stomach, ii) have an absorption window in the stomach or in the upper small intestine, iii) are unstable in the intestinal or colonic environment, or iv) exhibit low solubility at high pH. This article gives an overview of the parameters affecting gastric emptying in humans as well as on the main concepts used to design pharmaceutical dosage forms with prolonged gastric residence times. In particular, bioadhesive, size-increasing, and floating drug delivery systems are presented and their major advantages and shortcomings are discussed. Both single- and multiple-unit dosage forms are reviewed and, if available, results from *in vivo* trials are reported.

Patil, J. M., *et. al.*, "Trends in floating drug delivery systems," *Journal of Scientific & Industrial Research* (2006) **65**(1), 11-21.

Several approaches are currently utilized in the prolongation of the gastroretention time (GRT), including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. This review covers the current developments in the FDDS family, including patented delivery systems and marketed products. The pharmaceutical basis of their design, their

advantages, and future potential for oral controlled drug delivery are discussed.

Small Intestinal Drug Delivery

Saekinen, Mia, et. al., "Are chitosan formulations mucoadhesive in the human small intestine? An evaluation based on gamma scintigraphy." International Journal of Pharmaceutics (2006) **307**(2), 285-291. Rapid passage through the proximal intestine can result in low bioavailability of drugs with site-specific absorption characteristics in the upper GI tract. Mucoadhesive polymer excipients are used to overcome this by increasing gastro-retentive or small intestine-retentive drug formulation characteristics. This study assessing the *in vivo* performance of a chitosan-based drug delivery system showed that the bioavailability of furosemide was not increased in the small intestine.

Colonic Drug Delivery

Haddish-Berhane, Nahor, et. al., "A multi-scale stochastic drug release model for polymer-coated targeted drug delivery systems," Journal of Controlled Release (2006) **110**(2), 314-322.

A multi-scale mathematical model for drug release of oral targeted drug delivery systems was developed and applied to a commercially-available delayed release tablet (Asacol) that delivers 5-aminosalicylic acid (5-ASA) to the colon.

Van der Mooter, Gary, "Colon drug delivery," Expert Opinion on Drug Delivery (2006) **3**(1), 111-125. Colon targeting for oral drug delivery has several therapeutic advantages, such as delivery of drugs that are destroyed by the stomach acid and/or metabolized by pancreatic enzymes. Sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina, and arthritis. Local treatment of colonic pathologies, such as ulcerative colitis, colorectal cancer, and Crohn's disease, is more effective with targeted delivery of drugs to the colon. This article provides insights into the design and manufacturing considerations of colonic drug delivery systems, as well as an analysis as to why few of these systems have reached the market despite intensive research into the field.

Katsuma, Masataka, et. al., "Effects of absorption promoters on insulin absorption through colon-targeted delivery," International Journal of Pharmaceutics (2006) **307**(2), 156-162.

The results of this study demonstrated that colon-specific delivery of insulin with sodium glycocholate was effective in increasing hypoglycemic effects after oral administration, and the combination of sodium glycocholate and poly(ethylene oxide) gelling agent tended to prolong the colonic absorption of insulin and might be more effective.

Request for Contributions of Technical Content to the Sustained Delivery Newsletter – Dr. Dave Wallick, Newsletter Editor

Students, professors, researchers, retired scientists, business colleagues - Share your views on what's hot in the world of CR / MR technology or commercial highlights or happenings. If you have views about new breakthroughs – yours or those of others - that you are willing to share, about people receiving recognition for their work in drug delivery, about new drug approvals that use CR or MR delivery, or about your learnings from drug delivery meetings or courses through the year, please submit them for publishing in *Sustained Delivery*, the Newsletter of our MRFG. Contact the Newsletter Editor at dewallick@dow.com.

Increase Student Participation in MRFG

Student members of AAPS represent those who are often the most energetic, the most enthusiastic, the most driven to learn, and the most in need of the experience and insight that MRFG has to offer. In MRFG itself, student members comprise 20% of our membership, but often a silent contingent as we plan our activities or report our successes.

One of the MRFG Goals for 2006 will be to increase our outreach to student and post-doc members. As AAPS student members, join the MRFG (http://www.aapspharmaceutica.com/inside/focus_group_s/fgap.asp) and sign up for the listserv (<http://www.aapspharmaceutica.com/inside/listserves/index.asp>) to keep current on your MRFG newsletter, *Sustained Delivery*, and other Focus Group communications.

As MRFG members, students are encouraged to participate in MRFG activities - for instance, check out the MRFG Discussion Board (http://www.aapspharmaceutica.com/forums/forum.asp?forum_id=16&forum_title=General+Chat) to ask a question, start a topic, or share your expertise for the enrichment of others - and learn, share, or serve, as you like. MRFG needs your inquisitiveness and your knowledge.

As a professional and scientist, encourage your student colleagues to join AAPS, MRFG, and your AAPS student affiliate to gain the benefit of learning, of networking, and of expanding interests.

As a MRFG member, support your local AAPS student affiliate chapter. Share your career experiences with those just starting on the path, give a presentation on your drug delivery work to one of the most attentive and appreciative audiences that you may ever address. What a great way to get further mileage out of your

AAPS meeting posters and public publications than by sharing them with a student affiliate. Find the location and contacts at your nearest AAPS student affiliate chapter by perusing:

http://www.aapspharmaceutica.com/careercenter/student_center/chapters.asp. And, let the *Sustained Delivery* Newsletter know the results of your outreach, to recognize your effort to help others and to benefit those who would like to do the same on behalf of our students.

Pulsatile Delivery – bullets of useful information

▪ **Announcements:**

- The 33rd Controlled Release Society (CRS) Annual Meeting & Exposition will be held in Vienna, Austria, 22-26 July 2006. An innovative and exciting scientific line up has been planned by the Programme Chairs that includes multiple plenary speakers, over 40 invited speakers, 5 mini-symposia, and more than 30 scientific sessions. The highly successful Young Scientist Sessions, Pearls of Wisdom Sessions, Educational Workshops, Releasing Technologies, Soapbox Sessions, and Industrial Session will all be included in the Vienna programme.
<http://www.controlledreleasesociety.org>.
- *New Report on the Future of Nanomedicine* - Ruth Duncan for Cardiff University has chaired a major new Forward Look exercise on behalf of the European Science Foundation. This is the first such exercise to define "Nanomedicine," examine the current status of the field, and make strategic recommendations regarding funding priorities. View a copy of this report at: <http://www.controlledreleasesociety.org/main/about/pdfs/nano.pdf>
- *2006 AAPS National Biotechnology Conference (NBC) June 16 – 21, 2006* - The 2006 AAPS National Biotechnology Conference is an annual conference devoted to the science of pharmaceutical biotechnology. It offers rich scientific programming designed to stimulate interaction and provoke discussion; cutting-edge poster sessions; the AAPS Career Center dedicated to biotech jobs; plus, an exhibit hall showcasing the major biotech suppliers. It will be held in Boston, MA at the John B. Hynes Veterans Memorial Convention Center. For more information, see: <http://www.aapspharmaceutica.com/nationalbiotech/>
- *AAPS Workshop on Challenges in Developing Fixed-dose Combination Oral Solid Dose Products, Sept. 13 – 14, 2006* - Combination products are becoming increasingly important, both as new products and as line extensions of approved products for synergistic therapeutic effects and/or to improve patient compliance. Oral solid dosage forms comprise the vast majority of pharmaceutical dosage forms. Developing combination oral solid dose products presents a set of unique challenges arising from stability, process development, and mechanical properties of the constituents. Given the growing number of combination products in development pipelines, and the meager amount of published information on the challenges in developing these products, there is a need for a forum for elucidating and discussing these challenges and means to address them. The workshop will be held at Hyatt Crystal City Arlington, VA. For more information, see: <mailto:http://www.aapspharmaceutica.com/meetings>
- To receive regular copies of *Sustained Delivery*, the newsletter of the AAPS Modified Release Focus Group, join the MRFG (http://www.aapspharmaceutica.com/inside/focus_groups/fgap.asp) and sign up for the listserv (<http://www.aapspharmaceutica.com/inside/listserve/index.asp>) to keep current on your MRFG newsletter, *Sustained Delivery*, and other Focus Group communications.
- As a MRFG member, participate in MRFG activities - for instance, check out the MRFG Discussion Board (http://www.aapspharmaceutica.com/forums/forum.asp?forum_id=16&forum_title=General+Chat) to ask a question, start a topic, or share your expertise for the enrichment of others - and learn, share, or serve, as you like. New discussion topics have been added recently. Check it out.
- Pass this Newsletter issue to your friends and colleagues, and encourage them to share in the information exchange and networking opportunities by joining AAPS and the Modified Release Focus Group.
- Send your questions or comments about the new MRFG *Sustained Delivery* newsletter to the Editor: Dr. Dave Wallick, dewallick@dow.com. Your topics or contributions for the next newsletter, scheduled for Jul/Aug 2006, are welcome. Let us know:
 - about upcoming meetings of interest to the MRFG membership
 - about recognitions and awards for MRFG members
 - about your new technical or commercial MR highlights (public info only)
 - your program ideas for future AAPS meetings.