

Controlled Release Society Annual Meeting Report: Dissolution Highlights

Vivian Gray

Dissolution Technologies
Hockessin, DE

email: vagray@rcn.com

The annual meeting of the Controlled Release Society (CRS) was held in marvelous Honolulu, Hawaii, on June 12-16, 2004. There were 1,200 attendees from many countries. Jennifer Dressman, who is a member of the Editorial Board of Dissolution Technologies and a valued contributor, began her term as President of CRS for the 2004-2005 year. We congratulate her on her new position.

There were many useful presentations and posters, of which a good many were related to in vitro release/dissolution testing. However the most important sessions of the meeting for those interested in Dissolution were the "In Vitro Evaluation of Oral Controlled Release Dosage Forms Workshop" and the "Get up! Get Educated!" education session on In Vitro Drug Release Testing.

The In Vitro Evaluation of Oral Controlled Release Dosage Forms Workshop was co-chaired by **Jennifer Dressman, of the University of Frankfurt**, and **Clive Wilson of the Strathclyde University**. The topic of the first speaker, Professor Wilson, was titled "Gastrointestinal physiology relevant to performance of MR dosage forms". This presentation reviewed the knowledge collected through many years of clinical evaluation of products with regard to transit, pH, mixing and in vitro and in vivo correlations (IVIVC). He explored the limitations on extended and delayed release dosage forms and explained the effects of key gastrointestinal variables. Special topics discussed included the capacity of the elderly to swallow, the volume of liquid needed to adequately assist in gastric motility, dietary habits, including a vegetarian diet, and the effects of other drugs on permeability.

Sandra Klein, of the University of Frankfurt, was the second speaker. Her topic was "Use of BioDis (Type 3) apparatus to distinguish formulation performance". Ms. Klein discussed how to develop predictive dissolution methods using type 3 apparatus, including a description of biorelevant media and a pH gradient method. She presented three case studies including the drug products for Mesalazine, Metoprolol, and Theophylline. Her talk emphasized the advantages of the apparatus 3 type equipment as it offers the ability to simulate the various pH transitions in the GI tract.

Jerry Yeh, of Alza Corporation, gave a presentation on "Use of type 7 apparatus to determine the drug release profile of OROS™ Systems". The OROS™ extended release mechanism was explained. He discussed the development of drug release test methods using the apparatus 7 described in USP General Chapter <724> on Drug Release. This particular apparatus, called the Reciprocating Holder,

has several different design modifications to the sample holder type. The different types presented were the rod (pointed for gluing), spring, cage, claw, and nylon netting. The sample holder used was the rod with the OROS™ Tablet glued to the end of the point. Apparatus 7 with all the modifications are commercially available.

Dr. Christos Reppas, of the National & Kapodistrian University of Athens, presented on the topic, "Use of flow-through methodology in the evaluation of extended release dosage forms". He illustrated the approaches for comparing multi-point dissolution data sets and then went on to describe the key characteristics of the flow through system, USP Apparatus 4. Dr. Reppas gave examples of dissolution test methods using the flow-through cell and biorelevant flow rates and media compositions and explained how the data may be applied to the IVIVC. He pointed out how the intraluminal hydrodynamics are more effectively simulated by the Apparatus 4, especially using the open system.

Bertil Abrahamsson, Ph.D., of AstraZeneca AB, Sweden, gave a talk on the "Industrial experience in the use of dissolution tests in the development of MR dosage forms". Dr. Abrahamsson discussed basic principles to obtain an IVIVC and provided examples using Metoprolol CR and Felodipine ER Tablets. He related the collaboration with Penn State University and Professor Brasseur in a project that studies the shear forces on tablets in the stomach, including a new in vitro test method. The method consists of a beaker with the tablet suspended in medium with constant and predictable laminar flow. He concluded that



Instructors for the Get up! Get Educated! Session, left to right, Sandra Klein, Theresa Shepard, and Jennifer Dressman.

with the need to accomplish good IVIVC, the analyst needs to gain more knowledge in gastro-intestinal forces and hydrodynamics and the dissolution conditions in the colon, the major site for absorption of most ER formulations.

Prof. Reppas gave his second presentation on "Methodologies for comparing dissolution Profiles". He gave an overview of the most frequently used model-dependent and model-independent methods for comparing profiles. He emphasized the application of various indices (i.e. similarity factor, difference factor, and Rescigno index) to the comparison of biorelevant dissolution/release data collected in both closed systems (e.g. rotating paddle and rotation basket) and in an open system such as the flow through cell, Apparatus 4. The general conclusion with Apparatus 4 is that the comparison of data can be safely performed with multivariate model-dependent procedures and with the difference factor or Rescigno index.

The last speaker, **Theresa Shepard, PhD, of Servier Laboratories, Fulmer, UK**, gave a concise and illustrative presentation on "Setting up useful in vitro-in vivo correlations". She explained the process using several case studies illustrating applications in different stages of product development. She discussed the use of simulation studies for initial product specifications and testing the likely success of those specifications- a reality check. She showed how to develop and validate (internal and external) the IVIVC to support a change in manufacturing site for the product. She also explored the application of

simulation exercises appropriate for choosing the batches for an IVIVC study. She concluded with advice to choose batches in the IVIVC study that have large in vitro differences and large predicted in vivo differences also to incorporate a reference formulation early on, and use N=12 for all dissolution testing at time zero. Dr. Shepard summarized with the suggestion that the product development plan include an IVIVC study to track both in vitro dissolution profiles and in vivo plasma levels, continuing to validate the IVIVC when possible.

The workshop concluded with a panel discussion. All agreed that the goals of the workshop, that of enabling the participants to make informed choices about equipment and interpretation of data in light of the GI physiology for MR dosage forms, were met.

On Tuesday morning, the "**Get up! Get Educated!**" education session on In Vitro Drug Release Testing was conducted. The session included three speakers/topics, beginning with **Dr. Jennifer Dressman** discussing the development of in vitro release methods. She emphasized the selection of the appropriate media. Then **Sandra Klein** explored the variety of equipment available for dissolution testing, highlighting those for the MR dosage forms. The topic of IVIVC was presented by **Theresa Shepard**, who gave practical advice on development of these correlations.

The CRS 38th Annual meeting and Exposition will be held on June 16-22, 2005, in Miami, Florida (visit www.controlledrelease.org).