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Meeting Report: AAPS Workshop on Oral Bioperformance and 21st Century Testing

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The AAPS Workshop on Oral Bioperformance and 21st Century Testing was held in Chicago, Illinois, on October 13 and 14, 2012. The main objective of the workshop was to reevaluate and discuss the use of dissolution testing in a more biorelevant scenario. When dissolution testing was introduced in the early 1970s, there was a debate whether the test should be a development or a quality control tool, and it ended up as a QC tool. With the knowledge of in vivo conditions acquired in the last decades, the dissolution test could be better developed to reflect the in vivo behavior of oral solid dosage forms.

SESSION I

Gregory Amidon (University of Michigan, USA) presented the Introductory Comments**.** He gave a historic overview of the evolution of dissolution testing and its role as a quality control tool and highlighted its deficiencies of not better reflecting the in vivo conditions for oral solid dosage forms.

The first presentation, "21st Century Oral Bioperformance," was given by **Gordon Amidon** (University of Michigan). He discussed the lack of progress in dissolution testing showing that there is very little difference in the most used dissolution apparatus. He pointed out that one of the most used dissolution media, pH 6.8 phosphate buffer, is not simulated intestinal fluid, and it is not biorelevant. One of the most important buffers in the human GI tract is bicarbonate. He proposed a bioperformance dissolution test that is predictive of in vivo dissolution to be used as a drug product development methodology. His proposal is to subdivide the BCS Classes 2 and 4 into three levels according to the dissolution behavior in different pH conditions. He emphasized that bioequivalence studies should consider the in vivo dissolution since once the drug is absorbed the pharmacokinetics are going to be the same for the innovator and generic products.

The presentation "Role of Dissolution Testing in the Regulatory Agencies: New Ideas" was given by **Mansoor Khan** (FDA). He discussed the progress in the regulatory arena highlighting the guidances for post-approval changes and biowaivers for locally acting drugs and split tablets, among others. In the case of split tablets, the dissolution behavior of the product should be the same before and after splitting. He emphasized that dissolution is always necessary, and it can be replaced by disintegration or other techniques with appropriate justification with emphasis in QbD. He mentioned that an example of correlation between NIR and dissolution was done in a project between FDA and Pfizer. He commented that IVIVC is formulation specific, but the expansion to other products should be considered. One example is the internal validation being done with the generic product. The benefits and limitations of dissolution testing may be product specific, and the main goal is to develop an in vivo-relevant dissolution method.

SESSION II

James Brasseur (Penn State University) discussed "Motility and Absorption in the Small Intestine," showing the hydrodynamics of in vivo dissolution. He presented videos showing the steps involved in the motility and mixing that occur in the small intestine. His group developed imaging software that can map the peristaltic and segmental contractions, control drug absorption, and be used in 2-D and 3-D simulations. Also, he discussed the importance of the moving villi on the absorption rate and the fact that it can be included in the software simulations.

In his presentation entitled "Quantification of Small Bowel Water/Physiology," **Luca Marciani** (University of Nottingham, UK) showed how magnetic resonance imaging (MRI) can be used to better understand in vivo physiology and improve in vitro–in silico testing and modeling for oral dosage forms. Current state-of-the-art MRI provides multiplanar capability, excellent soft tissue contrast, and the possibility of tuning the contrast differently to the organ or test meal examined, and it does not disturb the physiology in the volunteer being examined. It allows repeated scans during the day, for example, to follow the GI effects of a meal or a drug product. In addition, the technique can be used in the estimation of the amount of water in the small intestine and in quantitative methods.

In the presentation "Linking the Lab to the Patient: Coupling Biorelevant Dissolution Testing with PBPK Modeling," **Christos Reppas** (University of Athens, Greece) discussed the newer biopharmaceutical tools (biowaivers, biorelevant dissolution tests, and IVSIVC using physi-

ologically based pharmacokinetic models) that could be used as a bridge between formulation/manufacturing and pharmacokinetics in the patient. This approach could result in time and cost savings required for clinical development. He presented the composition of several biorelevant dissolution media and some examples of dissolution testing using these media. In addition, he presented some in silico tools that can be used for IV–IS–IV modeling with examples of plasma profile simulations and elucidation of food effect for some drug products.

SESSION III

James Brasseur (Penn State University) spoke on "Modeling Hydrodynamics in the Intestine," showing the differences in the hydrodynamics in the intestine when compared with what happens in the dissolution vessel, including Reynolds number, Peclet number, Sherwood number, effect of micronization of drug particles, confinement, and so forth. He presented some mathematical models that can be used to evaluate diffusion-dominated dissolution, confinement, and diffusion layer thickness. He also discussed a computational experiment used to evaluate the influence of shear on dissolution both in vivo and in USP Apparatus 2 (paddle).

The second presentation of this section, "Physiologically Relevant Parameters for In Vitro Testing Including Bicarbonate Buffer and Surface pH," was given by **Gregory Amidon** (University of Michigan). He discussed the physiological and drug properties that affect dissolution and highlighted the role that bicarbonate buffer plays in the GI tract. He showed some predicted and experimental results obtained using the film model with bicarbonate buffer and the rotating disk dissolution apparatus with several drug substances. The buffer most used in dissolution is phosphate buffer, and he gave some considerations on the concentration and ionic strength that should be used with phosphate buffers to simulate what would happen with bicarbonate buffers.

SESSION IV

The presentation "Using In Vitro Lipolysis Testing to Explore the Utility of Lipid Based Formulations" was given by **Chris Porter** (Monash University, Australia). He explained the principles for solubilization using lipid-based formulations with highly dispersed colloidal species where drug is in rapid equilibrium with drug in "true" solution, with the intent of avoiding drug precipitation. These formulations are tested using a standard pH titration apparatus, in most cases employing simulated intestinal fluid with the addition of digestive enzymes (porcine pancreatin). This apparatus can be used to assess formulation performance, and the formulations that retain more drug in solubilized state are preferred. Profiles can be obtained, and they can be compared with in vivo bioavailability in animals or volunteers. A consortium across academia and industry was formed to validate standard operating procedures to assess lipid-based formulations and to identify key performance criteria for lipid-based formulations.

Hans Lennernas (Uppsala University, Sweden), in his presentation "In Vitro Computational Biopharmaceutical Aspects of Two Drug Absorption Processes: Precipitation and Intestinal Permeability," discussed a new oral bioavailability tool (OrBiTo) created through a pan-European biopharmaceutics project with extensive international collaboration. This project will evaluate novel theoretical and experimental methods to investigate oral drug delivery. The key outputs of this project will be establishment of a common database, new tools for identification of drug targets, standardization of models and assays for drug efficacy and safety, patient-reported outcomes, and classification of diseases. The impact of this project on the R&D process will be: improved early risk–developability assessment of candidate drugs, selection of optimal formulations/form with respect to clinical performance in a time- and resource-efficient manner, reduction and refinement of animal experimentation, extended opportunities for biowaivers, and clinically relevant pharmaceutical quality criteria in the context of quality by design.

The last presentation of the day, "Rotating Disk Dissolution to Understand and Predict Bioperformance," was by **Michael Hawley** (Boehringer Ingelheim GmbH). He gave an overview of rotating disk dissolution, including details about the most common apparatus and the possibilities of working with miniaturized equipment. To understand dissolution and bioperformance, it is very helpful to understand how materials dissolve, which can be accomplished by this technique because it removes the impact of particle size and formulation variables and focuses on specific properties of the compound. He discussed diffusion-layer theory and showed some examples of its application in the selection of solid form, salt, and cocrystals.

SESSION V

The first presentation of the second day of the workshop was by **David Sperry** (Eli Lilly Co.). He discussed the "Artificial Stomach Duodenum" apparatus. This equipment does not have quality control or regulatory applications but is a very useful tool to guide the product development process. The most important parameter is pH. The procedure does not simulate the entire transit time of the human GI tract, and it does not take absorption into account. He presented a decision tree that can be used to evaluate product candidates. Drugs that are BCS 2a and 2b are the most suitable for this approach.

Dwayne Friesen (Bend Research) gave the presentation entitled "Membrane Permeation Test: In Vitro Evaluation of Formulations of Low Solubility Compounds" where he discussed how this test can model the in vivo absorption mechanisms through the epithelium into

the blood circulation by simulating the mucus layer in the epithelium. The test can be used to quantify the free drug level provided by a formulation, the amount of drug present in micelles, and the sustainment of free drug over time (precipitation–crystallization rate). The membrane mimics the mucous boundary layer but not the in vivo intestinal wall. The system consists of an inner permeate container where the permeated drug is collected with the membrane attached at the bottom and an outer reservoir where the feed solution is located. The liquid-filled membrane (decanol in decane) acts as sink for the drug. The hydrophilic membrane surface and small pore size (0.1 µm) prevents direct transport of drug-containing particles to the permeate. The key to the success of the test is the hydrophilic treatment of the membrane surface. A water vapor plasma treatment attaches hydroxyl groups to one membrane surface (and a few µm into the pores). This technique is very helpful for low aqueous solubility compounds, for the evaluation of the impact of the crystal form, and for formulations where crystallization may occur in vivo. In conjunction with other in vitro tests, critical compound and formulation properties can be quantified and used as inputs to allow prediction of in vivo pharmacokinetics.

SESSION VI

In the presentation "Two-phase In Vitro Dissolution System: Characterization of In Vitro Release Attributes of Supersaturable Formulations and their Relevance to In Vivo Absorption," **Yi Shi** (Abbott Labs) discussed the advantages of using two-phase (biphasic) systems in dissolution testing. It allows the evaluation of dissolution and permeation processes and is a very useful tool to evaluate formulations containing BCS Class 2 drugs. In the biphasic system, drug dissolves in the aqueous phase then partitions into the organic phase. This simultaneous "dissolution–partition" kinetics model mimics drug dissolution–absorption in vivo. The biphasic system can be used in USP Apparatus 2 (paddle) and Apparatus 4 (flow-through cell), in conjunction allowing the determination of the drug concentration in the organic phase without analytical burden. This presentation was complemented by the next one, "Modeling Two Phase Dissolution System," given by **Gregory Amidon** (University of Michigan) who discussed the diffusion-based model and the effect of interfacial permeability in more detail. He showed some experimental data obtained for ibuprofen. Also, he discussed how the two-phase dissolution apparatus simulates in vivo conditions. This system can be used in non-sink conditions in the aqueous phase that may be more representative of in vivo conditions. Volumes more physiologically relevant (<900 mL) are feasible for a wider range of drugs and offer greater flexibility. This technique may be useful for unconventional dosage forms such as supersaturable systems and precipitation inhibiting systems.

The next presentation in this session was "Two Compartment Caco2 Model / Mini-scale Dissolution" by **Shinji Yamashita** (Setsunan University, Japan). He presented some projects that are being coordinated through the Consortium of Oral Drug Absorption Screening. One of them is the classification of around 300 drugs on the market according to BCS and fraction-absorbed values. The other two projects presented were the dissolution/permeation (D/P) system that mimics the in vivo absorption process and a combination of it with small-scale dissolution test. The D/P system allows the prediction of the fraction absorbed considering the food effect. The small-scale dissolution test will be used for predicting the oral absorption of BCS Class 2 drugs, understanding the rate-limiting factor in the drug oral absorption, and helping in formulation design to improve oral absorption. Fasted State Simulated Intestinal Fluid (FaSSIF) can give a better prediction of fraction absorbed for poorly soluble drugs.

SESSION VII

This section started with the presentation "In Vitro Characterization of Precipitation Kinetics of Poorly Soluble Drugs under Supersaturated State and the Effect of Polymeric Precipitation Inhibitors with the Use of FBRM Technology" by **Ping Gao** (Abbott Labs). He discussed the phenomena of supersaturation and crystallization that can occur in vivo with certain drugs and the use of certain polymeric substances to retard the drug precipitation process. The incorporation of a polymeric crystallization inhibitor can stabilize the supersaturated state. The use of focused-beam reflective measurement (FBRM) allows a particle size distribution–time profile of the precipitated drug to be obtained. The FBRM probe can get real-time measurement of both the dimension and number of solid precipitate particles. Some examples showing the effect of using certain excipients in developing supersaturable formulations were discussed.

John Sagartz (Seventh Wave Labs) discussed the "Dynamic Dissolution (TIM-1)." The simulated gastrointestinal tract model 1 (TIM-1) is a multicompartmental, dynamic, computer-controlled system that simulates the human upper GI tract. This in vitro system closely simulates all of the in vivo dynamic physiological processes that occur within the lumen of the stomach and small intestine of humans including secretion of enzymes, cofactors, and bile salts in physiological amounts; appropriate pH control; appropriate mixing and physiological transit times for each step of digestion; and removal of the products of digestion. All test parameters can be controlled to mimic various human GI (patho-)physiologies. The system is highly predictive of the in vivo behavior of the formulation and is a useful tool in formulation selection, API physical form evaluation, prediction of food effects, and establishment of an in vivo–in vitro correlation.

SESSION VII

Mike Bolger (Simulations Plus) gave the presentation "In Silico Models for Simulation of In Vivo Gastrointestinal Supersaturation and Precipitation" where he discussed the mechanism of nucleation and crystal growth theory. Some in silico models that can be used to evaluate the effects of supersaturation and precipitation were presented and discussed. Also, he discussed the stirring model of precipitation that uses FaSSIF and mini vessels to generate dissolution profiles.

The last presentation of the workshop, "Combining Experimental and Computational Approaches for Predicting Oral Bioperformance," was given by **Peter Langguth** (Johannes Gutenberg University, Germany). He discussed how experimental and computational methods can be combined to predict pharmacokinetics for oral products. Some examples were presented of compounds that undergo carrier-mediated intestinal transport and how carrier affinity and segmental distribution can affect the drug performance. The design of simulations is composed of four steps: optimization of in vitro parameters, development of physiologically based absorption model, simulation of nonlinear pharmacokinetics from immediate-release dosage forms, and simulation of drug pharmacokinetics from modified-release dosage forms. These simulations studies can be useful in the design of dosage forms containing drug substances with complex absorption, in the adjustment of the parameters of in vitro tests, and in the mechanistic analysis of drug–drug and food–drug interactions.