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Meeting Report: AAPS/USP/CRS Workshop on Dissolution; New Technologies and Regulatory Initiatives

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Day One

On March 29-31, 2004, AAPS, CRS and USP cosponsored an interesting and exciting Workshop on Dissolution/New Technologies and Regulatory Initiatives, in Bethesda, MD. Approximately 198 people attended the meeting from diverse disciplines and cultures. The attendees included engineers, pharmacists, chemists, regulators, and researchers. The presentations provided a wide variety of opinions and insight into dissolution testing and addressed performance testing of dosage forms other than solid orals. Vivian Gray opened the meeting with an outline of the information to be provided on vessel design, apparatus, fiber optics, BCS extensions, comparator studies, and USP initiatives. FDA followed with information on the current test requirements, identifying some areas for future growth. Academic researchers provided state of the art evaluations of the hydrodynamics of the vessel and were followed by presentations on the introduction of fiber optics as a method of detection. The presentations on day two focused on new technologies and new apparatus designs. The last day of the workshop was highlighted by a presentation on USP initiatives and actual case studies for comparator product testing.

Vinod Shah, of the FDA, provided a regulatory opinion of the current status of dissolution testing and insight into agency perspective. "Where are we now and where will we be in the future?" The purpose and role of dissolution testing was discussed. Dr. Shah emphasized that the amount of testing should be based upon the ability to characterize the performance of the product. In all cases, atypical test conditions should be justified. The in vitro release profile should incorporate sufficient data points for characterization of the performance of a particular product; more for modified release, and transdermals; however, he cautioned about the use of overly discriminatory methods. Dr. Shah also discussed the use of a minimal amount of surfactant in dissolution fluids, sodium lauryl sulfate being the most common. The need to add surfactant to the test medium should be correlated with the drug performance.

The Biopharmaceutic classification of the drug helps in the determination of the amount of testing and the qualification for biowaivers. A review of the standards for meeting these classes was provided. The need to standardize the deaeration process and sinkers was indicated. Alternate products such as transdermals were discussed. Future developmental standards were presented with a goal towards assuring product sameness.

The remaining presentations on Tuesday morning focused on the hydrodynamics of the dissolution vessel.

Fernando Muzzio, of Rutgers University, presented a computational fluid dynamics (CFD) understanding of the dissolution process including both low and high shear models. He provided a demonstration of potential problems at low speeds and under laminar flow. He stated that the USP tablet dissolution test is an analytical tool used for the verification of drug release processes and formulation selection within the pharmaceutical industry. Although engineers do not typically perform this analysis, a failed test can strongly impact the work of engineers in the industry. Variability in test results often leads to delays and alterations in formulation research and development. Given the impact of this test, he found it surprising that operating conditions and testing devices have been selected by trial and error rather than through analysis. In fact, he contended that the flow phenomena in the USP test has received little, if any, attention in the past. An examination of the hydrodynamics in the USP Apparatus 2 by his research group showed that the device is highly vulnerable to mixing problems that can affect testing performance and consistency. Experimental and computational techniques revealed that the flow field within the device is not uniform, and dissolution results can vary dramatically with the position of the tablet within the vessel. Specifically, computations predict sharp variations in the shear along the bottom of the vessel where the tablet is most likely to settle. He described how geometric modifications to the USP paddle are evaluated, focusing on how these modifications influence the hydrodynamics and tablet dissolution rates. Specifically, vessel shape, agitator type, and impeller position were explored. He concluded that the peak vessel reduced the shear rate variability, but the high shear rate may result in the inability to distinguish differences in tablets. The other modifications of differing the impeller height and shape did not resolve the hydrodynamic variability. He told the audience that Rutgers would create a consortium of interested parties that will have its first meeting on 5/9/04 to develop dissolution testing technology where test variability is minimized by systematic application of scientific design methods.

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John Mauger, of the University of Utah, presented theoretical models of tablet erosion with the calibrator coated on one side. He provided a clear illustration using a graphical display of the dissolution distribution pattern in the vessel. He stressed the importance of using a visual display and not relying on analytical data points alone in the evaluation of a product. The use of a dye with salicylic acid tablets provided further support for his position. The visualization studies emphasized the importance of density gradients in areas where the fluid flow is slower. The dissolution data he presented on model salicylic acid tablets correlates well with a convective-diffusion model based on a stationary disk in a rotating fluid. This correlation indicated that the USP Apparatus operates within known fluid mechanical and physicochemical parameters between 50-100 rpm. He also stressed the importance of the micro-environmental region of the testing process as dependent upon the solubility of the compound and its pKa, the pKa of the buffer species, and the pH of the buffer and its buffer capacity.

Anne Marie Healy, of Trinity College in Dublin, Ireland, presented variations in hydrodynamics and dissolution rate with changing positions of the paddle dissolution apparatus. She reported that different hydrodynamics in different regions of the apparatus may be responsible for reported high variability in test results. She showed that the apparent diffusion boundary layer and dissolution rate constant can vary significantly depending on the surface of the compact form upon which dissolution takes place and also on the location and size of the compact. CFD modeling of the test apparatus revealed large variations in fluid velocity magnitudes with position in the vessel and low-velocity domain directly below the center of the rotating paddle. The fluid shear rates were shown to vary depending on the tablet surface and the location on the surface and were consistent with observed asymmetrical dissolution of model tablets. The dissolution rate was found to increase when drug compacts were positioned off-center. She concluded by stating that an accurate model of dissolution from a solid dosage form should take into account the variability in the hydrodynamics of the apparatus, which may result in variable flow velocities and apparent diffusion boundary layer thickness at different sites of the dosage form. Different mass transfer rates may be observed for different surfaces or positions of the dosage form. The movement of the dosage form during the dissolution test will further complicate matters as dissolution rate may vary not only with location but also with time.

Peter Scott, of AstraZeneca, used mathematical/ geometrical considerations to explain the impact of the glass vessel on the performance of the dosage form in the test. After a brief history of the evolution of the test equipment, and explaining the methods of molding glass when manufacturing the vessel, he focused on the asymmetry of the vessel and its influence on the variability of results. While variability in the vessel specifications appears to lie within the acceptable range provided in USP, the impact of irregularities can still negatively effect testing and lead to erroneous results. He urged the participants to visually inspect the vessels for irregularities and reiterated that the calibrator tablets will pick up the flaws. He suggests that the dissolution analyst not mix brands of vessels in the testing equipment and that the onus is still on the manufacturers to come up with a more uniform way of manufacturing the vessels.

James Polli, of the University of Maryland, provided a report summarizing the AAPS/FDA sponsored workshop on the Biopharmaceutics Classification System, extension opportunities and implementation challenges. The classification system is based upon solubility and permeability. Its purpose is to aid in the prediction of bioequivalence through the use of in vitro models and tools and aid in the qualification for bioequivalence waivers of in vivo studies. The workshop included a review and discussion of the industrial and regulatory experiences, as well as perspectives on the use of the BCS guidance. It provided a forum to discuss the challenges and opportunities in predicting bioavailability/ bioequivalence using in vitro and in situ tools. It also included the identification of issues and explored appropriate strategies to address them. In the workshop there were breakout discussion sessions. Consensus was achieved in the following areas: method suitability of permeability classification, solubility classification, dissolution classification, potential biowaivers for BCS Class 2 drugs, and potential biowaivers for BCS Class 3 Drugs. Most notably, there was a broad consensus supporting biowaivers for at least some Class 3 drugs whose formulations exhibit very rapid dissolution and the effect of excipients are well known. His presentation was based on an article called the "Commentary, Summary Workshop Report: Biopharmaceutics classification System – Implementation and Challenges and Extension Opportunities" that was published in the Journal of Pharmaceutical Sciences, Vol. 91, No. 6, June 2004, pgs 1375-1381.

The afternoon speakers focused on the use of fiber optics as the mode of detection in the dissolution test. This innovative method of detecting allows for the determination of the percent dissolved in the vessel without having to sample or further manipulate the vessel's hydrodynamics. No solution needs to be added to compensate for material removed during the testing. All of the presenters agreed that there are limitations to the method when it comes to interference, but that situation already exists with UV being replaced by HPLC.

Per Nielsen, of Delphian, started the session by describing the test and its advantages. He emphasized the tremendous increase in data points that can be recorded using continuous monitoring and the reproducibility over multiple days with multiple chemists. The agency and USP are open to considering the method. As with all methods, it must be validated, personnel must be trained, and there is a cost for new technology.

Ishai Nir, of C Technologies, gave his perspective on

the use of fiber optics with all USP methods, citing PAT as a new driving force. The use of thin fine probes for a wide range in concentrations increases the versatility and desirability of the method. He also highlighted the ability to obtain a full spectrum of the profile through constant monitoring. He provided an interesting and informative temporal profile of the dissolution, and applied the testing to stability, as well as NIR, UV correlation.

Eric Wethington, of LEAP Technologies, started his presentation with a brief history of the development of fiber optics. Listing the advantages, he also went into greater detail on the configurations of the probes and detection methods and how they worked. Interference was discussed, and the methods for dealing with it through changes in design. He proposed mathematical calculations to compute the correction factor.

John Burmicz, of PharmaTest GmbH, discussed how the hollow shaft technology has already been successfully applied to the direct measurement of dissolution products, in situ. He stated that equivalence in measured dissolution profiles between this method and more traditional manual / semi-automated systems has been established. The development of hardware or standard apparatus is primarily governed by the USP / EP and other Pharmacopeial bodies. However, he described alternative routes to be taken in radiation (light) transmission hardware, data acquisition, background / particle (excipient) scattering corrections and detection hardware, which can simplify handling and data quality. He concluded with discussing vibration elimination and other mechanical considerations that may lead to improvements in the day-to-day use of such instrumentation, not only in R&D, but also for QC applications.

Day one ended with a **panel discussion**, where all the speakers of the day were assembled. The focus of the questions came back to vessel hydrodynamics and pressing for the details of fiber optic testing. The BCS biowaiver extensions were clarified. Then the participants attended the exhibits, which included many equipment vendors that had fiber optics capability.

Day Two

Ruben Lozano, of Bristol-Myers Squibb Company, moderated the Second Day with sessions on new technology and new apparatus design.

Xujin Lu, of Bristol-Myers Squibb Company, opened the session on New Technologies, where he discussed fiber optic technology. To implement this technology, a number of challenges have to be faced: dissolution is a restrictively regulated test so it takes time for scientists, managers, and regulatory agencies in the pharmaceutical industry to gradually accept a new technique. Fiber optics is a cutting edge technology for dissolution applications with a relatively short history; the instrumentation is not yet mature and optimization of the hardware and software is still in progress. To most users, the different spectroscopic designs and probe types among the commercial

instruments complicate its selection and implementation. Users have to learn these differences and their impact in order to develop a fiber optic method and conduct a successful dissolution test. He described studies performed to clarify these instrumental characteristics. Parameters evaluated included hydrodynamics, linear range, light scattering, particulate accumulation, detection frequency etc. Based on the studies, strategies were established to develop, validate, and implement fiber optic dissolution methods for various solid dosage formulations. This presentation focused on those efforts and demonstrated these strategies with examples of real drug products.

Frauke G. Russell, a Ph.D. student at F. Hoffmann-La Roche, Ltd., Basel, Switzerland and the Department of Pharmaceutical Sciences, University of Basel, Switzerland, discussed dissolution testing by NIR Transmittance Spectroscopy. She pointed out that commonly used dissolution testing methods, such as the paddle stirrer model, feature high material consumption, time exposure, and destruction of the tested dosage forms. Analysis is performed after the complete batch is produced and only a few samples are tested. She detailed how Near-Infrared Spectroscopy (NIRS) represents a new approach in quality control analysis of tablets. This fast and non-destructive vibrational spectroscopic technique allows measurements of dosage forms as a whole, and reveals information about chemical and physical properties, (e.g., tablet hardness and density). Analysis can be conducted in the laboratory, as well as on-line, during production processes and requires little to no sample preparation. Data is evaluated by using multivariate regression techniques. Yet calibration complexity is high and depends on conventional analytical methods as a reference. In her research, NIRS was used to determine the active substance release level of intact immediate-release tablets after a defined period of time. Several optimization tools were applied to improve the Partial Least Squares (PLS) Calibration.

Vivian A. Gray, of V.A. Gray Consulting, discussed her view of the regulatory and USP aspects related to fiber optic testing. She indicated that there appears to be resistance to using fiber optics in dissolution testing because it is not yet accepted as a regulatory method. There is no official position on fiber optic dissolution testing by USP or FDA; however, she pointed out that there are some indications that neither regulators nor the compendia discourage this technology, along with other new technologies. She suggested ways to demonstrate the equivalency of the dissolution test comparing fiber optics to other analytical techniques, for a mature product or in method development of a new product. The unique validation aspects of fiber optics were discussed in addition to the utility of the technique in newer dosage forms, types, and special testing. A checklist of parameters was provided for consideration when purchasing fiber optic equipment.

Kailas D. Thakker, of Analytical Solutions, discussed

dissolution of semisolids and the automation of diffusion cell analysis. She stated that dissolution of active ingredient from a semisolid product is determined by developing an In Vitro Release Test (IVRT). She stated that, in some cases, this test could be used to monitor the quality and consistency of manufacture. She emphasized that the test could serve as the single most important tool to assure product uniformity, due to its dependence on several physical characteristics of the product and the active ingredient. Since the FDA, SUPAC-SS guidance has been in effect; the IVRT has now become a very important developmental tool. It is used to develop and screen formulations, and to develop a database for use when changes are necessary for post approval of a semisolid product. She pointed out some considerations in developing *In Vitro* Release tests such as: consistency and reproducibility among different batches of product; the ability to discern between "good" and "bad or failed" batches; the ability to differentiate between batches when key changes in concentration/quality of excipients are altered; and ideally, the test should be able to show some correlation with a biological parameter. She described the critical aspects of development of IVRT method. These included the development of an assay for the active ingredient in the receiving medium if necessary, and selecting appropriate receiving medium and a membrane filter that will allow adequate diffusion of the active ingredient into the receiving medium while maintaining sink conditions. The validation of the IVRT was carried out with attention to attributes such as precision, reproducibility, and correlation of release rate with strength of the dosage form. Release rate dependence on temperature, though not essential, may be included. Examples were given of a typical IVRT method development and validation.

James G. Brasseur, of Pennsylvania State University, discussed combining computer simulation with an *In Vitro* experiment to evaluate extended-release tablet attrition in the fed stomach. He explained how the rate of release of low-solubility pharmaceuticals from polymer hydrophilic extended release (ER) tablets is determined by shear stress on the tablet surface. He stressed that it is important to mimic *in vitro* the physiological shear stresses and flow patterns over ER tablets if measurements of mass loss rate are to be physiologically meaningful. Since surface shear stress is not measurable *in vitro*, he stated that it could be predicted with high accuracy using specified tablet geometries and flows by combining the laws of physics with appropriate numerical algorithms and computer models. In contrast, he pointed out that the rates of mass loss from ER tablets cannot be predicted accurately, but they can be measured *in vitro*. His work combined computer simulation with *in vitro* experiments to analyze surface shear and tablet mass loss rate in the gastric fed state for specific ER formulations. He described an *in vitro* experiment that was designed and replicated in a separate series of accurate computer simulations to determine the experimental parameters required to produce the physiological ranges of tablet surface stress. To accurately control the flow around ER tablet *in vitro*, an apparatus was designed in which the tablet was held rigidly within a beaker in solid body rotation-avoiding secondary and non-steady flow patterns in standard USP devices. Three media at different viscosity were combined with the RPM range to produce physiological shear and flow "Reynolds numbers". From this unique combination of experimental and numerical data, his laboratory quantified surface stress and mass loss rate for two ER formulations. He also showed some very interesting video simulations of the actions of the stomach.

During the **panel discussion** questions were focused on NIR analysis, further clarification of the apparatus used in the in vitro experiment used to generate surface stress, and some validation aspects of IVRT. There was also a call to form an **AAPS focus group on dissolution**. The participants were reminded that if they were AAPS members they could sign up at this meeting. The response of the participants was highly favorable to the formation of this focus group and over 60 signatures were collected.

Saeed A. Qureshi, of Health Canada, reported on the deficiencies of the USP paddle apparatus and a possible solution. The presentation focused on the issues facing the current dissolution testing technique, in particular using USP paddle apparatus 2 and a discussion on problems with the technique. The potential causes of the high variability were listed as analytical methodology, product quality, dissolution technique, and relevance of the method to the in vivo environment. Based on experimental studies conducted in his laboratory, it appears that a combination of the spindle (Paddle) and the round bottom shaped vessel is the source of the problem. His final conclusion was that the highly variable results are due to the hydrodynamics in the dissolution vessel. Keeping this observation in mind, a modified or crescent shaped spindle was developed which appears to address the issues adequately and provide bio-relevant dissolution results. It is anticipated that the use of such a spindle may help in developing simpler dissolution testing procedures and saving in financial and human resources for both product development and regulatory assessments.

Harry G. Brittain, of the Center for Pharmaceutical Physics, discussed alternative means for the observation of dissolution phenomena. He stated that dissolution rates are usually followed by removing a sample from the dissolution bath, and then using either an absorption spectroscopic or chromatographic method to determine the dissolved concentration. His view was that the process could be considerably more efficient by obtaining concentration information without withdrawing the sample, and pointed out that the development of such methodology is ongoing at many facilities. He reported that there were several, *in situ* ways that may be used to follow the dissolved concentration of a substance. For

instance, the concentration of a salt can be determined by means of the conductivity developed as the substance dissolves, and such measurements are easily performed in a dissolution vessel. When the dissolving drug substance happens to exhibit fluorescence, then *in situ* emission spectroscopy can be used to follow its dissolution kinetics. Even the time evolution of tablet disintegration can be followed by using *in situ* turbidity or *in situ* nephelometry as a means of detection. The use of such methodology for observing dissolution and disintegration phenomena was presented.

Martin Wunderlich, of the J.W. Goethe-Universität, presented a transfer model that predicted the precipitation of poorly soluble weak bases upon entry in the small intestine. He began by describing how solubility and dissolution relationships in the gastrointestinal tract can be critical for the oral bioavailability of poorly soluble drugs. In the case of poorly soluble weak bases, the possibility of drug precipitation upon entry into the small intestine may also affect the amount of drug available for uptake through the intestinal mucosa. To simulate the transfer out of the stomach into the intestine, a "transfer model" was devised. He described the apparatus that was used to perform this testing. The drug is dissolved in simulated gastric fluid and is then continuously pumped into a container of acceptor phase media, in this case, simulated intestinal fluid. Drug precipitation in the acceptor medium is examined via concentration/time measurements. The *in vitro* precipitation of a poorly soluble weakly basic drug was investigated. Extensive super saturation was achieved in the acceptor medium. Under simulated fasted state conditions, precipitation of the drug occurred, whereas under simulated fed state conditions, the higher concentrations of bile components and the lower pH value in the acceptor medium inhibited precipitation at concentrations corresponding to usual doses. Comparison of these results with pharmacokinetic data indicated that a combination of transfer model data with solubility and dissolution profiles could lead to better predictions of *in vivo* behavior of poorly soluble weak bases. He concluded that the transfer model could allow for prediction of precipitation after oral administration and allow for investigation of various factors, such as food intake or formulation. The model could assist in investigations of crystallization –inhibitory effects of excipients and give a more physiological simulation of the concurrent processes in the GI tract.

Diane J. Burgess, of the University of Connecticut, described new apparatus designs used with dispersed systems, stents and other implantable devices. She pointed out that *In vitro* release testing of dispersed systems (such as, microspheres, emulsions, liposomes and nanoparticles) is complicated by separation of the dispersed system from the dissolution media. In addition, current USP methods were designed for oral and transdermal routes, whereas dispersed systems are often intended for parenteral applications. She further explained that a similar situation occurs for stents and other implantable devices. Her lab has been investigating different apparatus, in particular those using sample and separate, *in situ*, and continuous flow and dialysis techniques. Problems that have been identified include: violation of sink conditions, particle aggregation, apparatus blockage, and variation in flow rates. She presented data using bulk equilibrium reverse dialysis bag technique, the sample and separate technique, miniature methods, and continuous flow techniques. The USP Apparatus 4 flow through cell method was described in detail and seems to be the most promising to date.

The **panel discussion** focused on the contention that high variability was a present and recurring problem in dissolution. Some of the participants felt that the problem was not as prevalent as suggested. More details were given on the Transfer Model. The meeting was adjourned to a reception and more time to examine the instruments that were exhibited.

Day Three

Pankaj Shah, of Bristol Myers Squibb Company moderated the last day of the workshop with sessions devoted to Compendial initiatives and method development challenges.

Eric Sheinin, of USP, substituting for Dr. Roger Williams, opened the Wednesday session with a general discussion of the current USP process and explained the interrelationship of the USP with ICH, FDA, and the harmonization process. Dr. Sheinin described the USP monograph performance test as a critical quality control tool. He outlined procedural changes in the USP such as the yearly update of the book with 2 supplements replacing the 5-year update with more supplements. The USP is extending its scope by adding vaccines and blood products, as well as dietary supplements to the USP section. Based on route of administration and taxonomy, the USP is approaching the following classes of drugs: mucosal, injection, topical, inhalation, and oral. USP is actively studying these classes of drugs with the intention that these products will eventually have performance tests.

Margareth R. Marques, of USP, gave an extensive presentation on the current USP Informational Dissolution Chapter called <1092> The Dissolution Procedure: Development and Validation. The USP Biopharmaceutics Committee activities included pooled sampling deletions and labeling a drug where there are multiple dissolution standards (example Levothyroxine). Now when more than one Dissolution/Drug release test is given the labeling states the Dissolution/Drug Release test is used only if Test 1 is not used. A working group has been put in place to examine method development for liquid filled capsules. The group intends to write a stimuli article on the subject which may eventually lead to a USP informational General Chapter.

William E. Brown, of USP, presented information on the calibrators as a gauge of the system's suitability. Reference was made to USP <1225> and <711> and the need to demonstrate controls. Each unit must conform to a performance standard. The process includes the equipment and the analyst. A brief history of the calibrators was provided. The calibrators must meet standards including content uniformity. An ideal calibrator should be poorly soluble, nontoxic, stable, readily analyzed, and not react with the medium.

Lyn Hughes, of Rohm and Haas, spoke on a new technology, using stirred flow through cells in series. He described the apparatus as three separate cells for gastric, intestinal, and systemic simulations. The goal of the data from this apparatus is to develop a test that gives Level A IVIVC correlation without a mathematical model. The same conditions and controls could be used for all drugs manufactured with the same drug substance. There is constant volume, flow, and no filter. The smaller particles evacuate the cell and move to the next stage, simulating the in vivo process. No solids leave the intestinal cell. There has been a high correlation for the products that have been tested. HPLC pumps are used to maintain the proper flow. An algorithm is used for the calculation. These techniques are not yet accepted for use as a QC tool, but can be useful in the development stage. He concluded that the benefits of the system would be a decrease in development time, screen more options, decrease time to market and reduce cost and human testing.

Kimloan Huynh-Ba, of Huynh-Ba Consulting, discussed the difficulties of blinding clinical trial samples without changing their dissolution properties. In her practical presentation, she provided real world situations with actual test examples of encapsulated tablets and scenarios and challenges they faced with the solutions they found. There are no regulatory guidances to address this issue. The same issues when developing a new generic product are faced when modifying an existing product for blinded studies. That is one of disintegration, dissolution, stability, and validation. The development process was discussed and actual case studies were presented. The f2 similarity factor was used in all cases to show if encapsulation changed the dissolution results.

The **panel discussion** brought up the new website from FDA that will give the dissolution test for reference products. Mr. Tran of the FDA addressed the concerns of the participants.