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Commentary

Commentary on AAPS Workshop
Dissolution Testing for the Twenty-first Century: Linking Critical Quality Attributes and Critical Process Parameters to Clinically Relevant Dissolution

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Abstract. This is a summary report of the workshop entitled "Dissolution Testing for the Twenty-first Century: Linking Critical Quality Attributes and Critical Process Parameters to Clinically Relevant Dissolution," organized by the *In Vitro* Release and Dissolution Testing Focus Group of the American Association of Pharmaceutical Scientists. Participants from the pharmaceutical industry, regulatory authorities, and academia in the US, Europe, and Japan attended this workshop to review, discuss, and explore the role of traditional dissolution testing in the new arena of Quality by Design (QbD) and Process Analytical Technology (PAT). Other areas of discussion were the use of the dissolution test to evaluate drug release from novel dosage forms, challenges in dissolution testing and specification setting, and dissolution apparatus calibration using performance verification tablets versus mechanical calibration. The workshop identified areas where further research and collaboration are needed to advance knowledge and understanding of the science of dissolution. Views expressed in this report are those of the authors and do not necessarily reflect those of the FDA and USP.

KEY WORDS: AAPS; commentary; dissolution; process analytical technology; quality by design; workshop.

INTRODUCTION

This report summarizes the proceedings and outcome of the workshop on "Challenges for Dissolution Testing in the Twenty-first Century: Linking Critical Quality Attributes and Critical Process Parameters to Clinically Relevant Dissolution," sponsored by the American Association of Pharmaceutical Scientists (AAPS), organized by AAPS *In Vitro* Release and Dissolution Testing (IVRDT) Focus Group, and held on May 1–3, 2006 in Arlington, VA.[1] This two-and-a-half-day workshop provided an opportunity to bring together participants and experts from the pharmaceutical industry, the regulatory authorities, and academia in the U.S., Europe, and Japan to review, discuss, and explore the role of dissolution testing and identify future directions in the following areas:

1. Relevance of dissolution testing to Quality by Design and Process Analytical Technology (Sessions 1 and 2)
2. Dissolution of novel dosage forms (Session 3)
3. Challenges in dissolution testing (Session 4)
4. Dissolution—hot topics (Session 5)

There were five sessions that consisted of presentations and a Q&A session at the end of each presentation. Each session was followed by a candid panel discussion. Highlights of the dissolution workshop have been published.[2] The slide presentations are available online at the IVRDT Focus Group website.t[3] This summary report is based on the panel discussions including clarification, consensus or disagreement, and necessary background information on the emerging subjects of interest. The report is divided into four sections, one for each of the above-mentioned topics.

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[2] Highlights of the AAPS Workshop on Dissolution Testing for the 21st Century, Jan Parker and Vivian Gray, Dissolution Technologies, Volume 13, Issue 3, August 2006
[3] http://www.aapspharmaceutica.com/meetings/meeting.asp?id=63

SESSIONS 1 AND 2—RELEVANCE OF DISSOLUTION TESTING TO QUALITY BY DESIGN AND PROCESS ANALYTICAL TECHNOLOGY

Dissolution in Quality by Design

A dissolution method along with acceptance criteria should be defined to deliver desired performance of a product in the intended *in vivo* environment. In a QbD system, product formulation and manufacturing processes are designed to achieve the desired dissolution characteristics for a product. Dissolution may relate product attributes to clinical performance. Based on an understanding of how variability in formulations and manufacturing processes impact product performance, dissolution methods and acceptance criteria are established to provide continued assurance of clinical performance. Dissolution acceptance criteria are proposed using appropriate statistical methods and verified by relevant clinical information (e.g., pharmacokinetic/pharmacodynamic and clinical observations). Formulations and manufacturing processes should be optimized to consistently manufacture product with the desired dissolution performance. It should be noted that different dissolution methods may be used for drug product development and quality control purposes.

For drug product development using a quality-by-design approach, dissolution is a powerful tool for evaluating multivariate processes and factors that can affect drug product performance. To understand and identify critical quality attributes of the product and the processing parameters that impact dissolution performance, design of experiment (DoE) should be utilized by taking dissolution failures into consideration. When a reliable prediction of dissolution from critical quality attributes is established and demonstrated in a design space, dissolution testing may not be needed as a routine finished product specification when these critical quality attributes are controlled by critical process parameters. Control of a critical quality attribute may be more relevant than a dissolution test in ensuring product quality. For immediate-release (IR) dosage forms, often a single parameter related to drug product performance can be identified. Dissolution can be a dependent variable of a critical quality attribute such as API particle size distribution, excipients, or tablet film-coating, if found to be relevant. In these cases, an API particle size or a disintegration test may replace a dissolution test to ensure drug product performance when scientific justification is provided.

More complicated dosage forms involving devices, implants, API polymorphs, and so forth would require examining multiple parameters that may affect drug product performance. Thus, QbD principles are perhaps even more important for modified-release (MR) dosage forms than for IR. It is also recognized that only limited knowledge and experience are available during the research and early development phase of a product's life cycle, and for QbD, it is important to utilize information and knowledge gained from later phase development and commercialization. With respect to assessing post approval changes (e.g., level 3) within a design space, there was a concern that SUPAC may be the appropriate approach because it could lead to performing dissolution only on the end products without understanding the changes. As an alternative, the use of a comparability protocol with study design may be appropriate.

It was agreed that dissolution will continue to play an important role in stability testing due to potential changes in drug product as a result of temperature and relative humidity effects.

For drug product performance, there is a great emphasis on the attainment of *in vitro-in vivo* correlation or relationship (IVIVC or IVIVR). Although QbD does not necessarily directly link to clinical relevance, a thorough understanding of the product through QbD enables the sponsor to choose a dissolution test that may provide the desirable IVIVR for drug release. Even if IVIVR study results do not meet FDA guidance, sponsors are encouraged to submit the data and discuss the results with the regulatory agency during the submission process. Depending on the overall evaluation, the product may still be granted regulatory approval.

Real-time Release

If product performance is within the design space, dissolution testing may not be needed as a routine test for a finished product specification or could be replaced by other testing. Real-time release (RTR) replacing end product testing becomes possible. Other surrogate tests that could be considered for release testing of immediate-release products include hardness, disintegration, and NIR for particle-size testing. Some work has also been done in collaboration with FDA to develop and evaluate vibrational spectroscopic chemical imaging, a technique that has been used successfully as a trouble-shooting tool.

Data is required to demonstrate that dissolution can be replaced by a surrogate test. Challenges lie in how to generate necessary scientific data from the formulation and process development to ensure product quality through QbD. The method used to collect data must be based on sound science. The amount of data depends on how well one understands the science of the drug product and process.

Process Analytical Technology (PAT)

Dissolution detects changes in drug products, but does not indicate the cause for the changes. In many dissolution failures, it is often easy to look at dissolution testing rather than the materials in formulation and manufacturing processes. QbD is established on a scientific basis with an understanding of PAT such as NIR and imaging tools. PAT is able to assess both quality of materials and manufacturing process in real time and in more depth. NIR as the core PAT method in the pharmaceutical industry is able to predict multiple dosage form properties in a non-destructive manner. Dissolution characteristics of both IR and MR formulations can be predicted from the spectra of intact dosage forms. NIR can often monitor many drug product properties and could be used as a valuable resource to provide information on critical quality attributes to isolate probable causes for dissolution failures. NIR can be a complementary tool to dissolution for a better understanding of quality and process control. For example, NIR could be used to establish a relationship between API particle size and the percentage of drug dissolved for a drug product involving Biopharmaceutics

Classification Systems (BCS) IV API. Nevertheless, NIR variability associated with sampling should be carefully addressed.

Setting product specifications for an NIR test would require looking at clinical data. In the case involving a BCS IV drug, although the relationship between the NIR results and the dissolution results was known, the NIR results could not be used to demonstrate IVIVR because IVIVR had not been established. Dissolution cannot be completely replaced by PAT because it provides valuable assurance of the overall quality of the drug product. Many PAT techniques focus on single critical quality attribute when in reality multiple factors can modify dissolution and bioavailability.

NIR is a good qualitative tool for troubleshooting and assessing unit operation but not necessarily suitable for assessing product performance. For instance, NIR was shown to be a better or less variable predictor of hardness than the crushing test. However, NIR would not be able to detect all types of critical process parameters. For instance, overmixing a formulation with a large amount of magnesium stearate could negatively impact dissolution, but NIR would not detect a problem.

QbD is an evolving process. Therefore, new models may be needed to avoid being too aggressive or conservative in designing meaningful specifications. Traditional validation may be not meaningful for PAT under QbD. NIR models used for API properties such as particle size distribution and formulation are not necessarily suitable for drug product release. One should be cautious in choosing appropriate models to predict or control the process. Different models (i.e., simulation, control, and predictive model) are used for PAT and QbD. Clarification and justification are needed regarding what models are appropriate to use. Chemometric models intended for quality control are not suitable for predicting dissolution conditions for bioavailability and bioequivalence.

The lack of a validation procedure for NIR methodology is a concern expressed by the audience. It was a consensus that a general method validation approach is applicable but should be more NIR specific and determined on a case-by-case basis.

In addition to NIR, novel PAT methodologies such as fiber optic (FO) dissolution testing and focused beam reflectance measurement (FBRM) probe have been applied to obtain a mechanistic understanding of drug release. Fiber optics dissolution testing has high time resolution with good reproducibility. FBRM measures changes in particle size distribution. By combining both technologies, FO dissolution testing yields information about drug release kinetics, while FBRM obtains the kinetics of non-dissolved excipients due to disintegration of tablets.

SESSION 3—DISSOLUTION OF NOVEL DOSAGE FORMS

Many innovative drug delivery systems have been developed in the last decade; these dosage forms have advantages over conventional oral dosage units, including increased patient compliance and the ability to target drugs to specific sites in the body. Examples of novel dosage forms include suspensions, orally disintegrating tablets, chewable tablets and medicated gums, semisolid topical preparations, suppositories, liposomes, injectable microparticulate formulations, transdermal delivery systems (TDS), subcutaneous implants, drug-eluting stents (DES), and steroid-eluting leads for pacemakers. Even though many of these dosage forms do not dissolve *in vivo*, drug is released from them and the rate of this release is critical in determining if the product is safe and effective in patients. It was generally agreed that dissolution testing, or more accurately drug elution or release testing, is needed at all stages of the product life cycle.

General dissolution method principles apply to methods that are developed and validated for measuring drug release from novel drug delivery dosage forms. A balance has to be struck between conditions that provide for a fast release (desirable from a quality control point of view) and those that discriminate among batches that are not bioequivalent. The ultimate goal for the elution method is the same as for a dissolution method for a conventional oral dosage form: a demonstration of an *in vitro-in vivo* relationship (IVIVR.)

Because the drugs used in many novel dosage forms have little or no solubility in aqueous media, the use of non-traditional media in drug release methods for these products may be required. Examples of non-traditional media include those with high concentrations of surfactant and hydro-alcoholic media. These media can present challenges in routine use, such as the possibility of leaching compounds when certain types of material are used in the equipment or loss of volume due to evaporation. The effects of leaching and evaporation are of special concern with novel dosage forms because an *in vitro* test, which requires several days to reach a release plateau, may be necessary.

Validating a drug release method for a novel dosage form can present challenges not found with conventional dosage forms. For example, there may be a very limited number of samples available for testing. This is because batches are small and manufactured infrequently. A polymer-coated device may require careful handling because the polymer can be physically damaged by excessive agitation. The use of non-aqueous dissolution media can also damage devices with polymer coatings.

It may be difficult to demonstrate IVIVR with drug devices such as DES because the drug is released at a specific site in the body and not systemically. It is often impossible to determine how much drug is released *in vivo* in humans, so animal test subjects are substituted, and the amount of drug released over time is determined through serial sacrifice. Instead of trying to extract the released drug from tissue samples, the amount of unreleased drug remaining on the removed DES is determined, and the amount released is calculated by subtracting what remains on the DES from the label claim.

The FDA representative stated that the FDA does not prefer one type of medium to another or one apparatus to the other. Supporting data that justifies the chosen conditions should be included in a submission. The requirements are that the final method be scientifically sound and adequately validated. The FDA representative stated the general expectations for drug release profiles are that profiles should reach 80% released, or reach a plateau, and sampling points should capture 25, 50, and 80% of label claim released. Clinical data, stability data, and release data must be evaluated when setting specifications, and communication with FDA through-

out the drug development process is crucial. One caution that was given in setting specifications is that although there may be greater variability in novel dosage forms, it is not acceptable to set extraordinarily wide specifications on dissolution results to mask this variability. In addition, drug released from a drug device must be expressed as percent of label claim, not of an individual unit.

Apparatus 4 was mentioned by several speakers in conjunction with the release testing of novel dosage forms. Applications included screening engineered API particle size for sustained release and quality control method for DES. There is currently no performance verification tablet for Apparatus 4. The physical parameters that are controlled on Apparatus 4 are flow rate and temperature, and mechanical calibration to date consists of verifying these settings on a periodic basis. There was some disagreement about how often flow rate needs to be verified. It was agreed that the newer style digital pumps need less scrutiny than the older style piston pumps.

There was a discussion on whether or not drugs that have a low solubility are considered controlled release. It was agreed that to be a controlled-release product, a dosage form must be designed to release drug slowly, for example, by using a matrix. Drugs that simply have a low solubility in vitro are not considered controlled release. A question was raised as to whether the traditional requirement of demonstrating IVIVR by showing three lots having three different profiles was applicable to TDS. An FDA representative stated that she was not aware of any such submissions and indicated that one lot of transdermal product with IVIVR submitted to FDA could very well be sufficient.

SESSION 4—CHALLENGES IN DISSOLUTION TESTING

Currently, the dissolution test is used as an indicator of product performance. However, in some instances, the test may be "non- or over-discriminating" or not sufficient to ensure product quality/bioavailability, especially when a single-point criterion is used. The FDA representative challenged the audience to make the dissolution test more biologically relevant. Work toward this goal has been ongoing for nearly 15 years with no significant progress. Another challenge is to increase an understanding of the mechanisms governing dissolution. While the current paradigm focuses on a data-driven approach, the shift is toward understanding dissolution from a knowledge-driven perspective. There has to be a mechanistic understanding of the dissolution phenomenon using critical quality attributes to increase the predictive power of this method. In cases where IVIVC/R is obtained, the focus should be on knowing the scientific rationale behind this relationship.

One approach to furthering knowledge and allowing a better comparison of dissolution testing across product lines and laboratories is to adopt a single medium, for example, pH 6.8 buffer for highly soluble drugs, with certain exceptions. The rationale for a single dissolution medium stems from the fact that intestinal transit time is independent of gender, race, fed/fasted state, and dosage form. A single dissolution medium would also eliminate the use of clinically irrelevant media (e.g., pH>10).

The FDA representative was agreeable to the development of two kinds of dissolution tests for a product, one that is QC-friendly and one that is used in formulation development and to establish IVIVR. This would be acceptable because they serve different purposes. The agency verified that longer dissolutions (90–120 min) with lower Q values (<80%) may be acceptable if properly justified. If the method is truly bio-relevant, the drug does not have to be 100% dissolved.

The option of filing an alternate dissolution test method for generic products was discussed, since a single method and acceptance criterion may not fit all formulations of a product. Given that generic manufacturers are not able to obtain Q values from the FDA's Office of Generic Drugs (OGD) database, it is not clear if the dissolution method developed is clinically relevant. They are often faced with a "catch-22" situation in which an alternate dissolution method that is selected for filing with the regulatory agency is not accepted by the USP without the FDA's approval. A similar situation was discussed wherein the innovator uses design space to release its product. Since this is proprietary information, the FDA representative recommended that generic companies develop their own methods.

Another challenge discussed at length was the setting of specifications. The USP defers this to the FDA as it does not receive all the submitted data (due to confidentiality issues) and does not have access to the justification offered for any changes. The FDA responded by saying that the agency will provide specifications based on data if none are included in the submission. Toward this end, generic companies need to provide a scientifically justified method along with proposed specifications. However, this process is long and may result in delaying drug approval.

The FDA representative emphasized that analytical method development reports are valuable in submissions because they provide more justification for the parameters chosen in the final method. To expedite the review process of post-market submissions, the agency advised that industry provide all the documents submitted during the initial filing and any new information.

It was stressed that pre-validation testing is necessary to verify that method development phase is complete. For analytical method development, DoE could be used to identify critical parameters for method robustness. Atypical dissolution results need to be studied carefully; decisions based on poorly understood dissolution results can lead to erroneous conclusions. In addition to plotting test results, it is critical to observe and record any phenomena that occur inside the dissolution vessel. In short, "One look is worth a half-dozen theories."

SESSION 5—HOT TOPICS

Much of the discussion in Session 5 revolved around performance verification (PV) tablets and mechanical calibration. PV tablets, formerly referred to as calibrator tablets, continue to generate controversy. Some participants advocate abandoning PV tablets altogether in favor of additional mechanical calibration requirements, such as measuring the distance from the shaft to the vessel wall at two points instead of one. However, there is also support for maintaining a PV

tablet due to its value as a performance qualification tool. Because of the complexity of the dissolution test, many feel strongly that some kind of performance verification is needed, not only to ensure the suitability of the equipment but also to demonstrate proficiency of the analyst. The PV tablet provides an independent public standard that works across manufacturers to ensure a common proficiency. Thus, the running of PV tablets is a valuable part of routine analyst training. It was suggested that within an individual laboratory, dissolution analysts rather than metrology specialists could analyze the PV tablets so that the results reflect what is being done when samples are being analyzed on a day-to-day basis.

One of the arguments against relying on the PV tablets is their inherent variability. However, since the limits are established in a large collaborative study, this variability should be accounted for in the specifications. The collaborative effort for setting the specifications on PV tablets includes "good" labs, not just the "best" labs, so that attainable specifications that accurately reflect the dissolution characteristics of the product are obtained.

It was pointed out that it might be useful to separate the issue of the use of the USP prednisone tablet as the PV tablet from the usefulness of a PV tablet in general. It was suggested that a commercially available tablet that would serve instead of the current USP prednisone tablet might be identified. The attributes for the ideal PV tablet were presented; the tablet chosen should be a stable, easily handled product, produced in a GMP environment, and accepted by ICH. The audience was reminded that the USP prednisone tablet was developed to be sensitive to the effects of inadequate deaeration and vibration, although proponents of mechanical calibration argue that deaeration at least can be measured mechanically. There was also discussion over the possibility that an in-house standard be used as an alternate to a universal PV tablet because it would be more relevant to the sponsor's marketed product. However, it was not clear what would be required to prove the suitability of the in-house product for this purpose.

The relevance of PV tablets was questioned in some cases, such as with extended-release (ER) products where the dissolution test extends over a much longer period than the 30-min test for the current PV tablet. There is still no PV tablet specified for Apparatus 4, and it was pointed out that it could be very complicated to choose one due to the wide variety of cells employed with this apparatus. A USP advisory panel continues to evaluate an appropriate Apparatus 4 PV tablet.

Whether or not mechanical calibration alone would be sufficient, it has been demonstrated that performing mechanical calibration prior to testing PV tablets yields more consistent results. Specifications for vibration continue to be discussed, and experiments indicate that the frequency of the vibration may be more critical than the overall displacement. Experiments have also shown that the measurement needs to be taken at the point of release within the vessel. There are devices being developed, but none is yet commercially available. Another area that needs improvement is the measurement of vessel eccentricity. This is a frequently overlooked source of dissolution bias. Currently, trending of results may be necessary to uncover eccentricities that are difficult to detect by inspection.

As part of its PAT initiative, FDA is working with interested parties through the American Society for Testing and Materials (ASTM) to develop standards for various pieces of laboratory equipment. One of the standards under development is for dissolution Apparatus 1 and 2. This standard will rely only on mechanical calibration and will not specify the use of the USP PV tablet as part of instrument qualification. A USP representative summed up the views of many of the conference participants when he stated that although USP is supportive of the mechanical calibration initiative, it will oppose a standard that undercuts proficiency testing.

CONCLUSION

Dissolution is an integral test utilized in establishing the quality of solid dosage forms. For some drugs, dissolution can serve as a test of both pharmaceutical as well as biopharmaceutical product quality. However, for most drug products, dissolution serves as a test of pharmaceutical quality only (i.e., a QC test). The dissolution specifications should be set keeping the objective in mind. In the context of PAT and QbD, dissolution may serve a more important role in some cases, while in others, if other critical parameters are more relevant, dissolution may not be needed as a test. For instance, for a low solubility drug, the API particle size may be an equally good indicator of dissolution behavior. Hence, particle size monitoring and control may eliminate the need for dissolution testing of the end product. In conclusion, it is fair to assume that the role of dissolution in pharmaceutical testing will continue to evolve as has been the case since it was first introduced about 30 years ago.