

Dissolution Method Development for Immediate Release Solid Oral Dosage Forms

“Quick Start Guidelines for Early Phase Development Compounds”

David Fortunato

Johnson and Johnson Pharmaceutical Research and Development
Spring House, PA

email: dfortuna@prdus.jnj.com

Introduction

In the Pharmaceutical Industry, as product development continues to multiply at increasingly faster rates, dissolution method development must be able to keep pace with the increased number of products that are entering the pipeline. For many of these products, initial dissolution methods and their corresponding assays must be developed as “living processes” which must be able to adapt to change as the product changes. Even though many of these early formulations may not survive to full development, the Dissolution Scientist must be assured that the data obtained from these initial methods is accurate. The Dissolution Scientist may use the following techniques to develop both the dissolution and “assay” methods when quick answers are required for initial formulations. In this article, “assay” is defined, as an assay for dissolution use only, not an HPLC assay for impurities.

Communication between the Dissolution Scientist and the Early Phase Development Teams is essential for the expedient development of usable dissolution and assay methods. The Early Phase Development Teams may be comprised of formulators and the chemists who have developed the drug substance assay methods. Any information supplied to the Dissolution Scientist prior to start of the work greatly facilitates the dissolution method development process. Specific information about the drug substance solubility, drug substance stability as a function of pH, and BCS Classification will direct the Dissolution Scientist to the expedient selection of a proper dissolution medium. For example, the drug substance may be highly soluble in 0.1 N HCl, but was the solubility determined immediately or over a 24-hour period with constant sonication? The dissolved drug substance may be stable over a 7-day period, but was the solution stored at 4 °C or at room temperature? The details are important! Additional information such as potential dosage strengths, potential formulations, the type and range of excipients, the type (hard gelatin or soft gelatin) and sizes of capsule shells, reference standard information including purity values, and any current analytical methodologies will allow the Dissolution Scientist to determine the direction of both the initial dissolu-

tion and analytical method development processes. For example, does the label claim for the proposed dosage strengths reflect free base or salt formulations? Quickest results are obtained when the Early Phase Development Teams are able to supply the Dissolution Scientist with excipients, placebo granulations and capsule shells.

Analytical Assay Development

Preliminary analytical assay development must be initiated prior to the assay of any samples. The Dissolution Scientist must have some way of analyzing the samples. Since this is at the beginning of the method and assay development processes, this work does not require a lot of time. The initial assay parameters may be determined with drug substance dissolved in a dissolution medium. Hopefully, the preliminary information received from the Early Phase Development Teams would include specific UV or HPLC assay parameters. If a UV assay, important parameters would be wavelength of detection and cell path length. If an HPLC assay, important parameters would be column type, mobile phase and method of detection. The Dissolution Scientist must understand that assay parameters and dissolution medium may change as the formulations evolve.

Generally, the simplest assay method to develop utilizes UV/VIS Spectrophotometry. This assay method may be used provided the API has a UV chromophore and no UV interference is observed with the proposed excipients and/or capsules shells used in the formulations. The Dissolution Scientist may run a series of UV scans to determine the proper wavelength for the assay. Generally, several scans are run which include a blank of the dissolution medium alone, a standard solution, and a placebo formulation dissolved in either the dissolution medium or a standard solution. A UV assay may be used if the Dissolution Scientist is able to choose a wavelength region where the excipients and/or capsule shell do not absorb and a reasonable response is obtained from the API. Once a wavelength has been chosen, the Dissolution Scientist must choose the most appropriate cell path length that covers a wide linear range. If no wavelength is available which meets these criteria, then an HPLC assay must be developed.

Communication with the Early Phase Development Teams facilitates the development of an HPLC assay. Hopefully, information such as column type, mobile phase and method of detection may be obtained from preliminary assay development with the drug substance. Generally, dissolution HPLC assays are developed for one peak; consequently, shorter columns could be used to develop assays with 1 to 2 minute run times. A variety of detection methods may include UV, Refractive Index and Fluorescence.

Very often, the Early Phase Development Teams require quick answers, which will guide their next steps; consequently, minimum analytical validation work is required for very early, initial batches. The Dissolution Scientist must be assured the parameters are rugged enough to provide confident answers for even the earliest of batches. Again, the Dissolution Scientist must realize the assay parameters may change as the formulation evolves. More comprehensive assay validation may be completed once the final formulations have been determined. Once a usable analytical assay has been determined, the initial parameters for filtration and solution stability must be established prior to the completion of any dissolution samples.

Initially, the Dissolution Scientist must complete a successful filtration experiment. The Dissolution Scientist must first determine the volume of filtrate that must be discarded to obtain complete recovery of the API. Generally, a different filter should be used if the discard volume exceeds 20 mL. The filtered samples should be obtained with separate filters using a solution equivalent to 20% of the lowest dosage form dissolved in the volume of dissolution medium proposed for the dissolution method. The filtered samples are compared against an unfiltered portion of the same solution. The goal is to achieve 98.0% to 102.0% recovery of the API for a minimum of six replicate samples. Centrifugation may be used if adequate recovery cannot be achieved.

The Dissolution Scientist must be assured the sample and standard solutions are stable at least long enough for the assay to be completed. As time permits, the stability of a 100% standard solution stored at ambient room temperature may be determined from 1 to 7 days. The aging standard solution may be compared against fresh standards prepared daily or to the same solution stored at 2 – 8 °C. The absolute difference between the results at time 0 and the time indicated for stability must be less than or equal to 3.0%. A different dissolution medium may need to be chosen if the standard solutions are not stable for at least 24 hours at ambient room temperature.

Dissolution Method Development

Dissolution method development may begin once the analytical assay, sample filtration and stability parameters have been established. The Dissolution Scientist and the

Early Phase Development Teams that are developing the products have similar expectations for dissolution methods. The primary goal for both groups is the development of a discriminating method, which must be able to provide the ability to detect small changes in the formulation or manufacturing processes.

Discriminating dissolution methods may be difficult to develop for BCS Class 1 compounds. These compounds are highly permeable and highly soluble. The development of a discriminating method and the determination of a QTime and QValue are not limited by poor solubility. Several types of dissolution media may be used which will provide acceptable results. Complete recovery of the API may be achieved for a variety of formulations within 10 minutes with several types of dissolution media.

Discriminating dissolution methods are the most difficult to develop for BCS Class 4 compounds. These compounds are poorly permeable and poorly soluble. The poor solubility limits media selection, apparatus type and speed, QTime and QValue selection.

Once the initial dissolution medium has been chosen based upon the solubility and stability information of the drug substance, the development of the dissolution method may begin. The dissolution apparatus and rotational speed must be chosen. Generally, paddles at 50 RPM are used for tablets and baskets at 100 RPM are used for capsules. However, this is only a starting point. Remember, the goal is to develop a discriminating method. If the dissolution proceeds too quickly, the dissolution test may produce a profile that levels off too early to show discrimination between the formulations. If the dissolution proceeds too slowly, the dissolution apparatus, rotational speed or dissolution medium may have to be changed to produce a discriminating dissolution profile. For immediate release products, an ideal profile approaches 100% recovery of the API within 45 to 60 minutes.

Generally, the Early Phase Development Teams require information on the very earliest of formulations. If this is the case, the Teams may supply the Dissolution Scientist with several dosage forms produced with various formulations and/or manufacturing processes. Useful information may be obtained from testing just three dosage units of each formula variation. Apparatus type, rotational speed, volume and type of dissolution medium should be consistent for all dosage forms to maximize the usefulness of information, but it is understood that any or all dissolution parameters may change at a later date. The Early Phase Development Teams are interested not only in the comparative dissolution results, but also on the behavior of the various formulations. Visual observations such as incomplete dosage form disintegration, erosion or pellicle formation may provide the formulators with useful information to direct their future efforts.

Challenges

The greatest challenge for the Dissolution Scientist occurs when poor results are obtained with these early batches. If suspect or poor results are observed from early batches, the Dissolution Scientist must try to determine if the suspect results occurred because of a poor formulation, poor dissolution and/or assay methods, or perhaps a combination of all three. This determination may be difficult! If the Dissolution Scientist is confident with the assay method, media selection, filtration and stability parameters, then additional efforts must be directed toward the dissolution method. Dissolution experiments may be repeated with baskets at 100 RPM instead of paddles at 50 RPM or vice versa. Additionally, dissolution experiments may be repeated with paddles at 75 RPM or with a different volume and type of dissolution media. Even though the dissolution test should not exceed 60 minutes for an immediate release product, useful information may be obtained from sampling at an infinity time point (dissolution samples are obtained after an additional 30 minutes at 250 rpm). Dissolution results should be close to 100% at the infinity time point. Useful infinity time point information is obtained only if dissolution method parameters are identical for each formulation tested.

Conclusions

If dissolution results do not improve after all these trials, the Dissolution Scientist must not hesitate to inform the Early Phase Development Teams that future formulations may need to follow a different path. Remember, this is a "Living Process" which requires a collaborative effort from everyone. Success can be achieved only if the lines of communication are open on both sides. Each group must understand that processes must evolve as product development evolves.

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Ron Mamajek, Manager, Dissolution Laboratory, J&J PRD, Spring House, PA.

Lola Araba, Research Associate, Dissolution Laboratory, J&J PRD, Spring House, PA.

Dana Stallings, Research Associate, Dissolution Laboratory, J&J PRD, Spring House, PA.

Gregory Worosila, Senior Director, Analytical Development, J&J PRD, Raritan N.J.