Testing Dissolution of Pharmaceutical Tablets for Litigation Purposes
A technical primer for attorneys

By Dr. Fernando J. Muzzio,
Distinguished Professor, Rutgers University
Co-Founder, Acumen Biopharma

1. Introduction: What is Dissolution Testing?

The dissolution test, also called "in vitro dissolution" or "in vitro drug release" test, is a laboratory test where a pharmaceutical tablet is dissolved in one of several standardized pieces of equipment using one of several solutions known as "dissolution media".

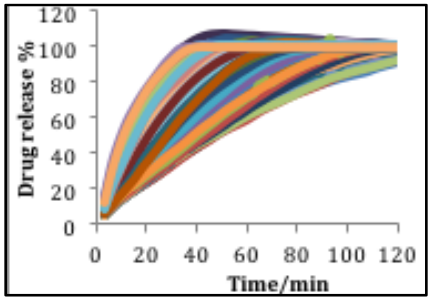

Figure 1: Dissolution profiles for a family of formulations gradually transitioning from immediate release to extended release

In general, the purpose of a dissolution test is to measure (or more appropriately, estimate) the amount of drug that is released by the tablet as a function of time. This result is called the "dissolution profile) (See figure 1). In the pharmaceutical industry, this information result is used for several purposes.

- During product development, dissolution profiles are used to select ingredients (or amounts of ingredients) that speed up or slow down the release of the drug. Pharmaceutical formulations are designed to exhibit various types of release: profile, e.g., "immediate release" (when most of the drug is released in a short period of time), sustained release, delayed release, etc.
- In quality control, the dissolution profile is used to detect unwanted changes to the product, which could occur because of changes to the ingredients or to the process.
- For generic drugs, generic companies typically seek to match the dissolution profile of the innovator drug as one of the criteria for pursuing an FDA approval.

Figure 2: USP 2 dissolution apparatus at one of our partner laboratories

Dissolution equipment has been standardized by the Unites States Pharmacopeia. Several options exist, and while the most common are the USP 1 (basket method) and USP 2 (paddle method) geometries (see Figure 2), some other options are sometimes used. Even within these two common systems, many variations can be employed. For example, within the "USP 2" test, companies use different media, different speeds (50, 75, and 100 RPM), "peak vessels", different size vessels (900 ml, 200 ml and 100 ml), etc.

In the typical test, a number of pharmaceutical product units is placed in the selected apparatus, which contains the media pre-warmed to a specified temperature of 37 °C, and the solution is sampled and tested at various pre-determined intervals, depending on the type of formulation.

Over the years, in addition to USP standards for performing the tests, the FDA has issued several "guidances" regarding the proper performance of the test and the proper use of the data. However, these guidances are not strictly compulsory, because companies sometimes need to modify the standard test to address specific formulation issues (such us, for example, using "sinkers" for formulations that tend to float) and also because of advances in the field, such as the introduction of standardized media compositions to simulate gastric and intestinal fluids, the invention of devices that more closely simulate the GI tract, etc.

2. Dissolution testing in pharmaceutical patent litigation

In our experience, *in vitro* dissolution is one of the most common tests used in pharmaceutical patent litigation. This is due to several reasons:

- The inventive concept of formulation patents is often related to achieving a given dissolution performance

- Patent claims often contain elements that refer to dissolution behavior, e.g. "a sustained release formulation", "no less than 50 % of the drug released after 30 minutes", etc.

- Dissolution performance is one of the criteria used to establish that a generic product is "equivalent" to a brand product

Different aspects of pharmaceutical litigation can use dissolution test results:

- Literal Infringement: When the patent claims contain explicit language regarding in vitro drug release profiles, tests performed on an accused product can support arguments of literal infringement, or, alternatively, non-Infringement.

- DOE Infringement: even when explicit language is not present in the claim, dissolution test results can be used to support arguments that two formulations, or two manufacturing processes, are "equivalent", because , for example, the accused manufacturing process is insubstantially different from the patented process, or whether the accused process performs substantially the same function in substantially the same way to obtain the same result.

- Invalidity due to anticipation or obviousness: If the claim contains explicit language about a dissolution profile defining the "product of the invention", dissolution results can demonstrate that prior art formulations were already achieving, or could be expected to achieve, the "inventive" result.

- Invalidity due to indefiniteness: As mentioned, the dissolution test can be performed in a variety of equipment, using a wide range of media and test conditions. Patents often neglect to specify all the relevant conditions, and as a result, the outcome of a dissolution test can vary widely depending on how the test is performed. This can give rise to strong indefiniteness (or lack of written description) arguments.

3. Dissolution testing in other types of pharmaceutical litigation

In addition to patent litigation, dissolution testing (or analysis of testing results) can be important to a number of other types of litigation. For example, in product liability cases, a product that fails to achieve the target profile under a specific set of relevant conditions can support arguments that the product might have been harmful. For example, if a product that is intended to be "sustained release" would instead release a large fraction of the drug at short times (this is known as "dumping") patients can experience overdose, adverse clinical effects, harm, and even death.

4. Analyzing and comparing dissolution test results

In almost every situation involving dissolution test results (whether new lab results or data from documents), the need will emerge to compare dissolution profiles,

either with other test results, or with pre-determined specifications. Such comparisons can be performed in multiple ways, to various degrees of statistical rigor.

Comparison to specifications is in principle straightforward, although results can be affected by methodology issues, such as, for example, the number of tablets used to conduct the test, the accuracy of the test itself, etc.

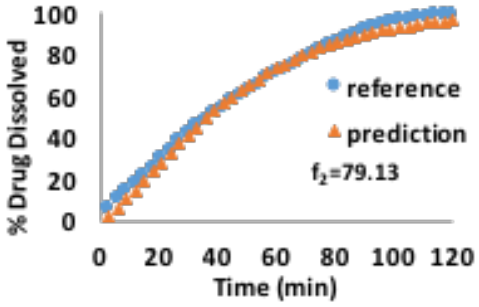

Figure 3: Comparison between two profiles, "reference" and "predicted" based on the f2 index. Profiles are considered "similar", as evidenced by a value of F2 above 50.

A more common issue is the need to compare two profiles (see figure 3). The most common comparison between profiles is to use the f_2 index, which uses a mathematical formula to evaluate how similar two profiles are. While commonly used, this test does not have a rigorous statistical foundation, and the outcome is affected by the number of data points used to describe the profile, the number of tablets used to perform the test, etc. FDA has issued guidance language seeking to decrease these sources of uncertainty.

In recent years, other methodologies have emerged, including model-dependent comparisons, model-independent comparisons, MANOVA, etc. While these methods are slowly growing in acceptance, the most common practice is still to rely on the f_2 criterion.

A special case, also illustrated in figure 3, is when the result of the test is "predicted" based on models that describe the expected dissolution results. This situation can arise in cases where a specific test result does not exist or cannot be obtained (for example if drug product is not available to perform the test) but can be predicted based on results obtained during development of historic manufacturing of an older product.

5. Common pitfalls and errors in performing the dissolution test

When dissolution test results are used in litigation, a number of common criticisms can emerge, including:

- *Was the analytical method properly developed, calibrated, and implemented?* The dissolution test relies on a second method to assay the amount of drug in

solution, most commonly a combination of chromatography and spectroscopy (UV, IR, Raman, etc.). All variations of these methods rely on properly functioning sensors, properly selected and maintained chromatography columns, etc.

- *Was the test properly performed?* A number of errors can occur during test performance, including errors in medium composition, temperature, agitation speed, sampling time, excessive medium evaporation, correct filter size, incomplete release of drug from polymer matrix, clogging of lines and filters, etc. One common problem is for tests that require different pH at various times during the test; pH can be highly variable and is not always carefully controlled. Another common pitfall is to use too few tablets to perform the test in a meaningful manner.
- *Was the proper test implemented?* Since the test can be implemented in a variety of ways, often leading to quite different results, a common concern is whether the test has been implemented in a fair and representative manner, or alternatively, whether the specific method selected is idiosyncratic and is selected to achieve a pre-determined result.

6. Resources Available at Acumen Biopharma

Our experts have extensive experience regarding the role of dissolution testing in formulation, quality control, and litigation. We can assist attorneys in understanding the role of dissolution test results in a given case, both for background purposes or for litigation.

When tests are needed, we can typically specify the testing that is required, and perform the test, in as little as two weeks. Given the wide range of issues relevant to dissolution test results and their use in litigation, Acumen Biopharma maintains service agreements with multiple academic and industrial laboratories to enable us to specify and perform dissolution tests quickly and reliably, including DEA licensed labs that can handle controlled substances. We have developed protocols to support the selection of the proper test for a given purpose.

Moreover, since our experts have assisted many law firms in analyzing and performing test results, our protocols include effective methods for ensuring data quality and integrity, including chain of custody protocols, equipment and method calibration, and extensive documentation practices that include electronic record keeping, laboratory notebooks, photographs and videos.

We are always happy to discuss technical issues. Many more details are available upon request. For more information, please contact us.

www.AcumenBioPharma.com|
PO box 304 Oceanport, NJ 07757
Phone : +1609-285-8344|