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Commentary

The Development of USP Dissolution and Drug Release Standards

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Dissolution tests have been in use in the pharmaceutical industry for over 20 years, and they are official in The *United States Pharmacopeia* since the early 1960s. The dissolution test, reviewed primarily as a quality control tool, replaced the use of disintegration tests which had been official in *The United States Pharmacopeia* since 1950. Refinements in the dissolution test equipment and methodology have occurred over the years in order to enhance its relevance. The Subcommittees of the USP Committee of Revision dealing with these issues have developed and refined compendial dissolution standards and policies for conventional solid-oral dosage forms and modified-release dosage forms.

KEY WORDS: dissolution; drug release; *in vitro; in vivo.*

INTRODUCTION

The purpose of this article is (1) to present a brief review of the historical perspective on the development of public standards for dissolution and drug release, (2) to describe the work of the USP subcommittees (primarily Subcommittees Pharmaceutics 2 and Pharmaceutics 3) in reviewing and establishing compendial standards for conventional tablets and capsules and modified-release dosage forms, and (3) to describe the objectives of the subcommittee in the development of future standards and policies, particularly as they relate to modified-release dosage forms.

HISTORICAL PERSPECTIVE

Immediate-Release Dosage Forms

Disintegration tests, official in the *United States Pharmacopeia* (USP) since 1950 are only indirectly related to drug bioavailability and product performance; thus, a more discriminating test was needed. Dissolved drug was known to be physiologically necessary, and indeed in 1962 a committee of the Pharmaceutical Manufacturers Association seriously considered recommending adding a dissolution requirement to all capsule and tablet monographs in which the active ingredient (drug substance) had a solubility of less than 1% in aqueous media.

During the 5-year period, 1965–1970, only one specific dissolution test was adopted. However, the relationship between dissolution and bioavailability was generally uncertain and the relative importance of pharmaceutical ingredients and processes had yet to be appreciated.

A number of dissolution tests were introduced into the *United States Pharmacopeia* (*USP*) and *National Formulary* (*NF*) in 1970, when 12 monographs incorporated a dissolution standard. This was a consequence of intense interest in the subjects of dissolution and drug absorption, distribution, metabolism, and excretion that later would be incorporated into the general rubric, bioavailability. The USP–NF Joint Panel on Physiological Availability formed in 1967 and, in 1968, recommended adoption of a basket-stirred–flask test apparatus (USP apparatus 1) to determine the dissolution of oral solid dosage forms.

In the subsequent 5-year period leading to the publication in 1975 of *USP XIX/NF XIV*, dissolution requirements were added to several more monographs. Notable was the adoption of a dissolution test in the monograph for Digoxin tablets. In this case a correlation was established between the *in vitro* performance and the *in vivo* performance. This test was based on a collaborative study with industry and government. The adoption of this test was a turning point in demonstrating that an *in vivo* bioavailability USP standard was not necessary to satisfy concern for this article and would not be generally necessary provided a satisfactory *in vivo/in vitro* correlation could be established. This time period was devoted mainly to the introduction of dissolution methodology to a broader base of industry and government. Substantial progress was made in improving the equipment and in standardizing and refining laboratory techniques,

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leading to the development of a larger number of trained analysts.

The paddle apparatus was introduced to complement the basket apparatus and became official in August 1978. The paddle apparatus offered some advantages especially for disintegrating dosage forms. A more sophisticated sampling and decision rule was adopted in May of 1979. The need for calibration had been identified during the 1970–1975 revision period. The use of two standard calibrator tablets, prednisone tablets (disintegrating) and salicylic acid tablets (nondisintegrating) was instituted in late 1978.

A significant development during the 1975–1980 revision cycle was the adoption in January 1976 of a USP policy on dissolution requirements. The policy favored the adoption of dissolution tests in the monographs for all solid-oral dosage forms except where such inclusion specifically was judged scientifically inappropriate (i.e., for nonabsorbed drugs). The comprehensive value of dissolution testing of tablets and capsules was already recognized as a key public standard. Both the value of bioavailability control and the value of general product quality control were recognized at that time. The policy was designed to encourage input from manufacturers regarding their experiences in conducting dissolution tests.

The 1976 policy contained the following key factors:

- The USP Subcommittee to review bioavailability/dissolution data from manufacturers—such data were foremost in selecting requirements.
- Dissolution method to use method I or II (basket or paddle)—proliferation of test apparatus was discouraged.
- Consider intended release profile in establishing test times and tolerances.
- Incorporate known bioavailability information.
- In the absence of bioavailability data, establish standards on the basis of therapeutically proven formulations.
- Delete the disintegration test when a dissolution test is added to a monograph, except where a hydroalcoholic medium is proposed.

In January 1977, a set of guidelines was adopted for use by the USP subcommittee in implementing the USP policy on dissolution testing.

The guidelines for selecting test conditions included the following:

- Dissolution medium selection—water preferred; aqueous acid or buffer solutions in the pH 4–8 range; eliminate use of enzymes in simulated intestinal fluid.
- Volume of medium—generally not less than three times the volume required for a saturated solution (typically 500–1000 ml) to provide sink conditions.
- Specifications for amount dissolved—a minimum amount dissolved per specified time interval. First Case, $\geq$75% in 45 min (typically 30–60 min); testing on individual dosage units.
- Apparatus selection—maintain lower apparatus speed to maximize discrimination (basket at 100 rpm and paddle at 50 rpm).

The adoption of this policy and implementation guidelines resulted in a significant increase in the number of dissolution tests added to monographs during the 1975–1980 revision cycle. The strength of dissolution testing as a quality control tool had also gained widespread recognition independent of any valid bioavailability concerns. When published in 1980, *USP XX/NF XV* contained about 60 monographs with dissolution requirements. The majority of these had been developed partly or entirely by either USP's own Drug Research and Testing Laboratory or laboratories of the U.S. Food and Drug Administration.

During the 1980–1985 revision cycle work accelerated in developing dissolution tests for compendial monograph items. This was the first revision cycle in which a separate subcommittee (Pharmaceutics 2 Subcommittee) was formed to deal with issues related to dissolution and bioavailability. There was continued concern about the progress in standards and the bioavailability/physiological availability of formulated products. A new policy was proposed in September of 1980 and adopted in early 1981, which built upon the 1976 policy by establishing a General Standard for dissolution and defining three cases into which articles could fall. All articles were presumed to meet First Case specifications unless demonstrated otherwise to the satisfaction of the USP subcommittee. First Case is defined as 75% dissolved in 45 min in water using one of the two official apparatus (paddle and basket) at their most common speed, 50 and 100 rpm, respectively. Second Case applies where the solubility characteristics of the drug or dosage form design did not permit application of First Case criteria, and other aqueous media (acid or buffers), apparatus speeds, or specifications were required. Generally where acid or buffers are required it is preferable to increase the specification for amount dissolved or shorten the test time, i.e. 75% in 30 min or 80% in 45 min. Case Three applies where Case One or Case Two cannot be utilized—a special standard may be included in the individual monograph. This forceful policy redefined and preempted all prior relationships between the Committee and industry and government. By October 1982, 275 monographs contained dissolution requirements. In 1985 when the *USP XXI/NF XVI* was published it contained almost 400 dissolution tests in monographs. No monograph required an *in vivo* bioavailability test since no case of inequivalence with a USP article was discovered where a dissolution test did not satisfy the concern.

The culmination of the work in incorporating dissolution requirements into existing monographs for conventional dosage forms was essentially completed during the early part of the 1985–1990 revision cycle. Since then, additional dissolution requirements are mostly those included in new dosage form monographs. *USP XXII/NF XVII,* through the *Second Supplement,* contains dissolution tests in 462 monographs, not including modified-release dosage form tests. In addition, there are 137 disintegration tests for articles that are exempt from dissolution requirements. Typically, articles that are nonabsorbed drugs, vitamins, or minerals or are required to be chewed are exempt from dissolution requirements in the monograph.

The most common media, water and 0.1 *N* hydrochloric acid, are consistent with the most common drug chemistry—salts and weak acids or bases. Buffers are used for some drugs, usually to dissolve weak acids. Modified aqueous media are used where the solubility of the drug or the dosage form does not permit the use of standard aqueous media. To

date surfactants such as sodium lauryl sulfate and polysorbates are the most commonly used aqueous modifiers to enhance solubility.

Based on the monographs in *USP XXII/NFXVII* the breakdown of the number of monographs by type of test is given in Table I.

Modified-Release Dosage Forms

In September 1982, the USP Subcommittee on Pharmaceutics—Dosage Forms and Systems developed and presented a proposed policy on modified-release dosage forms. This subcommittee was formed to address these articles separately from conventional immediate-release tablets and capsules. An unencumbered look was then possible for modified-release preparations based on priorities established by a survey of the medical experts on the USP Drug Information Advisory Panels. This coincided with a renewed interest on the part of USP in this type of product following years of exclusion on the basis of negative medical merit judgments by the USP Scope Subcommittee.

The initial focus of the policy, adopted in early 1983, was the definition of terminology for dosage forms designed to alter the timing and rate of release of drug from the dosage form. Modified-release dosage forms were defined as those for which the drug release characteristics of time course and or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

The proposed policy defined three types of modified-release dosage forms.

(1) *Extended release*—a dosage form which allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release dosage form.

(2) *Delayed release*—a dosage form that releases a discrete portion or portions of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

(3) *Targeted release*—a dosage form that releases drug at or near the intended physiological site of action—it may have either immediate- or extended-release characteristics.

Table I. Breakdown of the Number of Monographs by Type of Test

Medium	Apparatus	Tolerances	No. of monographs
Water	1:100 rpm	≥75%; ≤45 min	79
Water	2:50 rpm	≥75%; ≤45 min	76
Aqueous hydrochloric acid	1:100 rpm	≥75%; ≤45 min	44
Aqueous hydrochloric acid	2:50 rpm	≥75%; ≤45 min	33
Aqueous buffer (pH 4.0–6.0)	1:100 rpm	≥75%; ≤45 min	3
Aqueous buffer (pH 4.0–6.0)	2:50 rpm	≥75%; ≤45 min	16
Aqueous buffer (pH <4.0)	Any	Any	4
Aqueous buffer (pH 6.4–8.0)	1:100 rpm	≥75%; ≤45 min	7
Aqueous buffer (pH 6.4–8.0)	2:50 rpm	≥75%; ≤45 min	9
Aqueous buffer (pH >8.0)	Any	Any	11

Implementation of the policy in individual monographs called for each monograph title to include the designation of the type of modified release (i.e., indomethacin extended-release capsules). Also, an article using the USP title was required to conform to the *in vitro* drug release requirements specified in the monograph. Finally, implementation was to be done on a monograph by monograph basis.

The policy also described three general cases for developing initial compendial drug release standards. All cases specify the use of official USP apparatus as defined in the USP General Chapters on *Dissolution* ⟨*711*⟩ and *Drug Release* ⟨*724*⟩. The individual monographs may define the details of the *in vitro* test either directly in the monograph or by inclusion within product labeling. The acceptance criteria are defined in terms of the labeled dosing interval, *D* (where two or more dosing intervals are given, the shorter time interval is used). For example, a product labeled for dosing every 8 to 12 hr would have a *D* value of 8, and a test time of 0.500 *D* represents a 4-hr test time.

Case One describes the "ideal" or formulation-objective dosage form which conforms to following the standard criteria.

- The *in vitro* drug release test utilizes apparatus 1 at 100 rpm or apparatus 2 at 50 rpm.
- Five hundred to one thousand milliliters of water is the medium—900 ml is the most common volume, as the dissolution vessel which has a nominal capacity of about 1200 ml can reasonably accommodate that volume. The first kettles used in the early days of dissolution work had a nominal capacity of only about 1000 ml, and any volume greater than 900 ml resulted in potential problems with loss of media due to physical limitations of the vessel.
- A test of pH independence is also a feature of Case One.
- Acceptance criteria are as follows:
  0.25 *D*—between 20 and 50% dissolved;
  0.50 *D*—between 45 and 75% dissolved;
  1.00 *D*—not less than 75% dissolved.

The first time point was chosen to establish whether or not dose dumping exists; the second to characterize the release profile and show extension of release; and the third to show that most of the intended complete dose is delivered. The subcommittee did not anticipate a priori that many, if any, of the already marketed dosage forms would conform to the Case One standard. However, this standard does provide initial guidance to scientists in the United States and internationally.

Case Two applies where (a) the physical properties of the drug or the formulation do not allow application of Case One conditions such as the media or times and tolerances or (b) the drug was actually released over a time period less than the labeled dosing interval as in the case of drugs with longer biological half-lives or drugs acting over a short time interval. The individual monograph will contain details of the

specific drug release test to be applied. For dispensing purposes all such products from various manufacturers are intended to exhibit similar bioavailability and are expected to carry AB ratings in the FDA Approved Drug Products list (the Orange Book).

The subcommittee anticipated that multisource products using similar release mechanisms might fall into this case, as well as any single source products that did not meet Case One requirements.

Case Three is applicable where the chemistry or physical properties of formulations from different manufacturers differ to an extent such that a single set of *in vitro* drug release specifications, or test conditions, is not feasible. In this situation the monograph will contain multiple *in vitro* drug release tests, and the labeling of a product will designate with which drug release test a product complies.

The Case Three approach represents a major advance in thinking for the USP whereby practitioners would gain immediate access to relevant *in vitro* and/or *in vivo* information for product selection decisions. it also represents a departure from the establishment of laboratory standards only and gets the USP involved in performance standards as well. Note that fundamental to the use of dissolution standards, as has occurred with immediate release products, is the existence of a meaningful *in vitro/in vivo* correlation for each product or class of products.

In May 1984, a revised policy was published. The revised policy deleted the term targeted release because no examples of a specific product existed at the time. The other definitions and Case One, Two, and Three guidelines remained essentially the same. The addition of a third footnote gave the subcommittee the latitude necessary to achieve the goal of developing compendial standards for modified-release dosage forms.

A general chapter, *Drug Release* ⟨*724*⟩, was proposed in the May–June 1983 issue of *Pharmacopeial Forum*. It specified the use of USP apparatus 1 or 2 and provided methodology and acceptance criteria for extended-release and delayed-release products. The general chapter was adopted by supplement to *USP XXI/NF/XVI*. Because of the short time between the adoption of the test and the publication of *USP XXI*, only one monograph, that for diazepam extended-release capsules, was included in the hardbound book.

Based on their initial experience with modified-release dosage form, the subcommittee anticipated that the time necessary to develop these standards would be much greater than now required for contemporaneous conventional dosage forms. By the end of 1988 there were 16 official monographs for modified-release dosage forms. The hardbound *USP XXII/NF XVII* has 23 monographs for modified-release dosage forms. Of these, 5 are for delayed-release dosage forms, and 18 are for Extended-release dosage forms.

OTHER SUBCOMMITTEE ACTIVITIES

In addition to the efforts already described the subcommittee initiated several other major projects during the 1985–1990 revision cycle.

Enteric-Coated Tablets

In September 1986, in light of the controversy surrounding enteric-coated dosage forms, the subcommittee published a stimuli article expressing some of their concerns about such dosage forms. Their concerns were centered mainly around known variability in the gastric pH and stomach-emptying time in fasted and fed states, in contrast to the often simplistic assumptions underlying existing formulations.

The *Pharmacopeial Forum* article requested comments regarding the following:

- Potential retropulsion of an enteric-coated tablet in the stomach under nonfasted conditions could lead to two or more tablets leaving the stomach simultaneously, possibly subjecting the patient to an overdose of medication (in addition to an undosed condition prior to this).
- Potential for erratic plasma-level profiles as a result of varying stomach-emptying times.
- A rising stomach pH value which could cause premature release of the drug in the stomach from retained units. Alternatively, prolongation of the residence time in the acidic stomach might lead to delays in establishing therapeutic blood levels.

In Vitro/in Vivo Correlations

An issue in establishing dissolution specifications for extended-release dosage forms is the validity and design of *in vitro/in vivo* correlation studies. In July 1988 the USP subcommittee published a *Pharmacopeial Forum* stimuli article to encourage discussion on this issue. An *in vitro/in vivo* correlation is defined as the establishment of a relationship between measurable biological consequence (or a parameter derived from a biological activity) produced by a dosage form and a measurable physicochemical characteristic of the dosage form. The article discusses several possible correlative methods and categorizes them with respect to their meaningful application to extended-release dosage forms.

Four levels of correlation are defined.

Correlation Level A. This level represents the highest level of correlation, demonstrating a 1:1 relationship between the *in vitro* dissolution and the *in vivo* profile. The *in vitro* dissolution and the *in vivo* curves are superimposable.

Correlation Level B. This presently is the most commonly encountered type of correlation. It uses the principles of statistical moment analysis, e.g., comparing the mean *in vitro* dissolution time to either the *in vivo* mean dissolution time or the *in vivo* residence time. This level is not considered a 1:1 correlation as it does not reflect the actual *in vivo* plasma level curves.

Correlation Level C. This level of correlation relates one dissolution parameter ($T_{50\%}$, $T_{90\%}$, etc.) to one pharmacokinetic parameter such as AUC, C_{max}, or T_{max}. It represents a single-point correlation and does not really reflect the complete blood-level curve shape. This type of correlation is useful for manufacturing of the product. It should not be relied upon to justify changes such as a formulation modification or a manufacturing site change.

Correlation Level D. This level includes such procedures as relating disintegration to *in vivo* performance or more qualitative *in vitro/in vivo* relationships. The USP subcommittee does not consider this a very viable or useful correlation level.

CURRENT WORK EFFORT

Case Three Requirements

In October 1988 the subcommittee discussed the application of Case Three requirements to prescription (Rx) and nonprescription (OTC) products. Comments had been received that expressed concern over presumed inclusion of biological release profile data in the labeling for OTC products. After a review of the issue the SC determined that only *in vitro* drug release requirements will be included in the USP monographs for OTC products. The subcommittee nevertheless encourages manufacturers to supply *in vivo* data on their products for inclusion in the USP Drug Information database. The proposed USP monograph for aspirin extended-release tablets exemplifies application of Case Three requirements to an OTC product.

For Rx products the subcommittee reaffirmed its position on the application of Case Three-type requirements with the *in vitro* drug release profiles of each different product to be included in the USP monograph with appropriate labeling requirements. The *in vitro* drug release tests should be supported by *in vivo* data demonstrating the bioavailability of the product. The proposed monograph for indomethacin extended-release capsules is an example of how this is implemented in a monograph.

In order to simplify labeling requirements the monograph will contain the various *in vitro* test methods required for different products. Thus, a monograph might include three *in vitro* tests, defining them as Test 1, Test 2, and Test 3. Product labeling need specify only which test applies (for example, "Meets USP Drug Release Test 1"). While this clearly represents a departure from previous practices it is intended to alleviate the need to develop multiple monographs for a single drug product that is produced by different manufacturers. This approach also minimizes the need for established NDA drug release criteria to be altered to comply with a single set of conditions. The monograph on drug release test will contain the media, apparatus, analytical method, and specifications for the ranges at the time points given.

Acceptance Criteria

The acceptance criteria remain those given in the general chapter on *Drug Release* ⟨*724*⟩. There are three levels of replicate testing, with Level One acceptance based on individual values and testing of 6 units. This level is designed to allow products with optimum *in vitro* performance to pass with a minimum of testing. Level Two is designed as the usual acceptance level. It defines acceptance criteria both for the average value of 12 units and for the individual values. If a product does not pass at Level Two, a third level of testing is conducted on an additional 12 units. Level Three gives acceptance criteria for the average value of 24 units and the individual values as in Level Two and, also, defines and places limits on the individual outliers.

The subcommittee anticipates that the majority of extended-release products will fall into Case Three. The use of different formulation mechanisms for achieving similar extension of drug release is likely to result in different *in vitro* tests being used to characterize the products.

FUTURE ACTIVITIES

The meeting of the USP Convention in March 1990 gave direction to the newly elected Committee of Revision. It is likely that the following issues will be of interest and the subject of further work by USP subcommittee.

- Further work in establishing *in vitro/in vivo* correlation techniques, especially for modified-release dosage forms.
- The development of standard protocols for conducting bioavailability/bioequivalence studies.
- Evaluation of alternative apparatus for determining the *in vitro* drug release profile of modified-release dosage forms.
- Developing compendial monograph standards for new types of dosage forms as they emerge in the marketplace.

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