dx.doi.org/10.14227/DT050298P5

Two-Tier Dissolution Testing*

Vivian A. Gray
DuPont Merck Pharmaceuticals
Wilmington, DE

In early 1993, the USP Subcommittee on Dissolution and Bioavailability (DBA) decided that the soft gelatin capsules dissolution test exemption in the USP <711> Dissolution General Chapter should be deleted. It was determined that there should be a dissolution test for all types of capsules. For capsules where a dissolution test could not be developed, a rupture test was proposed in Pharmacopeial Forum (PF), the revision journal of the USP.

In July 1993, at a DBA Subcommittee meeting it was decided that "aged capsules" that did not pass the dissolution test would undergo a second dissolution test using medium containing enzyme. However, this was only allowed providing that there was no evidence that the bioavailabilty of the capsules had been adversely changed. The change was proposed in the USP <711> Dissolution General Chapter in the Previews section of the PF in early 1994. This was a fairly stringent standard, requiring in most cases a bioequivalence study, and objections were raised by the pharmaceutical industry.

At this point, the FDA/Industry Gelatin Capsules Working Group was formed and USP became a participant. The USP DBA Subcommittee decided to defer the "aged capsules" proposal until the Working Group had completed its bioequivalence studies. The bioequivalence studies showed that the stressed hard gelatin capsules were bioequivalent to unstressed capsules.

In early 1997, a PF proposal, recommended by the Working Group and the DBA Subcommittee, allowed for a two tier dissolution test, in which a second dissolution test could be performed using enzyme in the medium if a hard gelatin capsule failed the official dissolution test. The proposal stated that the second dissolution test would be shown in the individual monograph. However, a revised proposal, shown in PF 23 (5) {Sept.-Oct. 1997], describes the appropriate second dissolution test medium in the General Chapter <711> Dissolution eliminating the need to include a second dissolution test in the individual monograph. The proposal reads as follows: "Hard gelatin capsules that do not conform to the dissolution specification may be tested, except when the medium is water, using the same medium as indicated in the monograph for the drug product with the addition of 3.2 grams of purified pepsin or less, with an activity of 800 to 2500 units per mg of protein, or 5 grams of pancreatin or less, per 1000 mL of

Two-Tier Dissolution Testing...continued

medium, as appropriate. Pepsin should normally be added to acidic media, while pancreatin is appropriate for media at or above pH 6.8. If the initial test is water, the second test medium could be either 0.1 N hydrochloric acid with pepsin or pH 6.8 phosphate buffer with pancreatin, depending on the drug solubility. Conformance to the specification upon testing in one of these media is acceptable."

There are certain aspects of the proposal that should be noted. It does not address the use of surfactants. The product can fail any time—that is even at release. However, the analyst should be warned that if the product fails at the time of release—on stability the added enzyme may not be sufficient to overcome the crosslinking problem.

This proposal was adopted as an Interim Revision Announcement and was official on December 1, 1997. It is the legal standard put forth by USP and enforced and followed by the FDA. The FDA has not given guidance as to how using the second dissolution test is to be documented, whether it will be in an annual report as any USP change, or by some other mechanism.

The two tiered test will be revised again to add the application to soft gelatin capsules. With soft gelatin capsules the current information suggests that a different activity of pepsin or a different concentration of pancreatin will be needed. The standard for products that are gelatin coated tablets will also be addressed.

USP was glad to be a part of the efforts of the Working Group and was pleased with the outcome. It is hoped that this kind of interaction involving USP, FDA, and industry will continue.

* Excerpts from a talk in the Invited Podium Session, Hard and Soft Gelatin Capsules: Issues, Research and Outcome, AAPS National Meeting, November 5, 1997, given on behalf of the USP as part of the FDA/Industry Gelatin Capsule Working Group