Drug Information Journal, Vol. 30, pp. 1063–1070, 1996
Printed in the USA.
0092-8615/96

THIRD GENERATION DISSOLUTION TESTING: DISSOLUTION AS A BATCH PHENOMENON

LEE T. GRADY, PHD
US Pharmacopeia, Inc., Rockville, Maryland

This paper provides an historical review of dissolution testing conducted by US Pharmacopeia, Inc. (USP). Current USP initiatives are also covered, including those designed to move USP to where it wants to be five and 10 years from now. There will be a lot happening with dissolution testing in the next few years. It is expected that as many as 80% of USP's 500-plus dissolution requirements will go to a lower total analytical test load mode.

Key Words: Dissolution; US Pharmacopeia; Testing; Batch phenomenon

A REVIEW OF ALL OF US Pharmacopeia, Inc.'s dissolution records on the start of dissolution testing all those years ago was conducted. This was occasioned by the fact that over the years, the US Pharmacopoeia, Inc. (USP) has been looking at data through its subcommittees and at meetings, and observing that there seems to be a lot of data being generated which are not of decisional value. If researchers are going into the laboratory to do an experiment, that experiment should allow them to make some decisions. It was noticed that, especially with respect to individual tablet dissolution, a lot of people were collecting data, promptly making averages of it, and then not looking at it again. This meant it was *non-decisional*. The idea is to have an immediate goal to get a reduction in overall analytical testing, but of course, no loss in the fundamental assumption that a Pharmacopeia defines an article that is acceptable for the intended use, which means medicines as they are actually used.

USP AND DISSOLUTION TESTING

The Joint Panel on Physiologic Availability recommended dissolution for USP and a National Formulary instead of an improved disintegration and deaggregation test which was much talked about. USP picked a Canadian apparatus (a modified Pernarowski rotating basket). At this stage and during this time period, the Canadians had really done a great deal of work in this whole area of dissolution/bioavailability. Thus, this is where the first apparatus essentially came from. That panel decided to test *individual units*. Why did it recommend individual testing? Why not just take 10 or 20 tablets, throw them in a great big beaker, and use a typical lab stirrer and see what happened after some period of time?

People's attention was captured by the things that possibly have bioavailability prob-

Presented at the DIA Workshop "*In Vitro* Dissolution of Immediate Release (IR) Dosage Forms: Development, *In Vivo* Relevance, and Quality Control Issues," June 6–7, 1995, Toronto, Canada.

Reprint address: Lee T. Grady, US Pharmacopeia, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

lems, such as low solubility drugs, both in actual clinical failures and in theoretical terms. Similarly, the panel wanted to be able to get a tablet that dissolved within a reasonable volume, in a convenient flask.

There was also an interesting impact on academic advice to the Pharmacopeia. Everybody said that to accurately measure an intrinsic dissolution rate, which is like a physical constant, one must do it at sink conditions. Well, that is very nice if one is in the business of establishing physical constants, but the fact of it is that there is too much emphasis on sink conditions. One can get a perfectly workable dissolution test running up to 80% saturation. This may slow the test down by five or 10 minutes or so.

In those days, drugs were dosed in higher masses. Remember, over this period of 25 years, there has been a decrease in the doses. One of the reasons that the pharmaceutical industry today has such over-capacity is that where it used to give 250 mg. of a drug for hypertension control, now it is giving five. There has been a basic change in the amount of drug that needs to get dissolved.

Next, analysts saw a great deal of variability in dissolution test results, and this was particularly influential. Content uniformity as a concept in the Pharmacopeia was just being developed on a separate track, by separate people, and it was not at all clear just how widespread it would become as a Pharmacopeia requirement.

The key is that real products in the marketplace in the late 1960s were not formulated or controlled based on dissolution. That is all over with in these 25 years. Products in the marketplace today have had dissolution as part of their product development scheme. Only a foolish person would try to develop an oral solid without doing dissolution testing in choosing among alternate formulations and process conditions, blending conditions, drying conditions, and so forth.

Back in those days, one could find drugs that were showing 10–20% relative standard deviation, most obviously, though, for slow-dissolving drugs. Today, one does not see that in data coming into USP. The Food and Drug Administration's St. Louis Laboratories made results of about 200 different batches of drugs available, and one just does not see that anymore.

Along came Digoxin Tablets (in 1993), which became the *boundary condition* for dissolution/bioavailability. Digoxin is a poorly soluble drug, absorbed high up in the intestinal tract that exists in a low proportion of drug to excipients. The results here, however, were based on three and four patients in the literature. The original results on prednisone were based on one patient. There is a message in there that if it really matters, one does not need 20 or 30 or 100 patients to tell about it. These things were all picked up on very small patient populations. But those patient populations were small enough that they led to the question of: is that based on a single tablet because of the content uniformity issue?

The first question of dissolution testing ended when calibrators were added. Calibrators were there to pick up vibration in the equipment and failures in the drive chains and belts. Wherever perturbations are introduced in USP equipment, the calibrators always pick them up; that is what they are there for. They are not there to test the aeration. The instructions at that time were "deaerate," but how was not specified. At present, heat and vacuum are favored.

USP also came up with some improved decision rules (Figure 1) which created the current tension. There are batch properties which are something like an assay—one takes a composite and assays it. Then there are also factors found in individual dosage units, and content uniformity is for that. Dissolution has always been intermediate in the decision rules. Originally, in 1969 USP decided to use unit values and made some decisions based on that. That really was not very satisfactory. It is still that way in the British Pharmacopoeia. But in 1977 USP went over to average values of units, moving toward the *batch concept*. Extended release, however, came out in 1983 and that was moving still closer to the unit value.

Researchers needed to move out of the

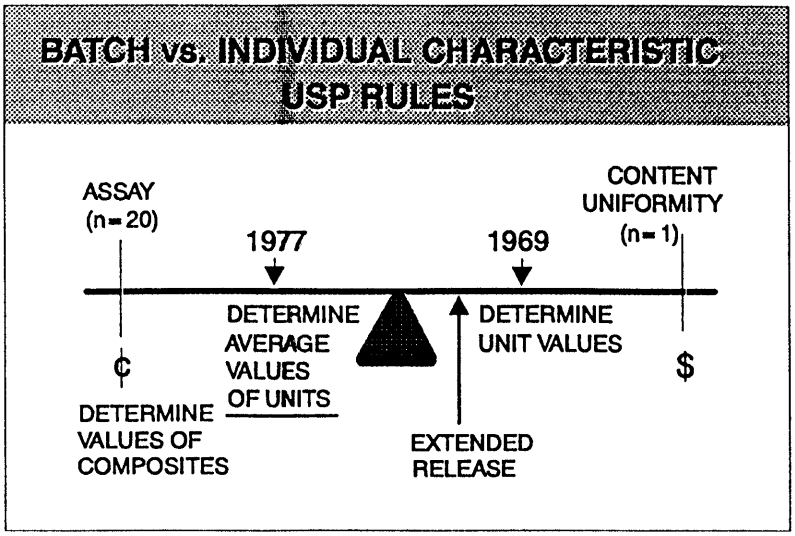

FIGURE 1. Batch versus individual characteristic USP rules.

mist where they were trying to look at dose forms by looking at plasma level data. They needed to go up to the top—if one wants to measure the flow of a waterfall, one does it up there, not down in the mist.

There were dominant causes of diminished bioavailability identified at the time all these decisions were made. There were actual product failures in the marketplace; poor bioavailability and bioinequivalence that showed up in the marketplace. For those things that really caused a problem, what were the *cause and effect* relationships? Recognizing that a tablet or capsule is a physical-chemical entity in time and space, if it caused a problem, there is something within its physical and chemical nature that one ought to be able to determine.

The big thing everybody focused on was *particle size and solubility.* That was obviously influenced by prednisone, nitrofurantoin, and those drugs that were influential at the time. People recognized that when the rate of dissolution was less than the rate of absorption that is where one is most likely going to get a bioavailability correlation.

There was only a little bit of recognition, for example, in the case of phenothiazine, that intestinal metabolism had any matter. At that time, people were not really talking about first-pass metabolism. But if a drug is slow enough dissolving, it can run into trouble in intestinal metabolism. First-pass metabolism, if that is in the cards, requires absorption higher up in the intestinal tract.

So everybody recognized that it is not the solubility of the drug alone that is absolutely critical. It is also the effective surface area from which the drug is dissolving. It is the flux of drug into solution, which is a function (with the Noyes-Whitney equation), of course, of both solubility and particle size, which means surface area. Also, everybody knew that *inadequate disintegration* was going on.

The surprise came for everybody who thought that there could be 100 formulation factors that might affect bioavailability. Well, 100 never showed up. What did show up constantly was *magnesium stearate* as a lubricant, and it is still a problem. What also showed up were sugar-coated tablets because of a shellac subcoat. Then there were also products that were *shellac-coated* for elegance or a better shelf-life.

All of these factors that actually mattered are sensitive to dissolution testing, and wherever there is a bioavailability problem, a dissolution test showed the difference between the nonequivalent test specimens; that still

holds true today. What was lost at the time is that none of those reports really stood or fell on the basis of any single dose unit administration. *It was because the whole batch was slow dissolving, not just one tablet.*

Thus, in 1975, a default standard was proposed. That was because, frankly, industry was not cooperating on getting dissolution into USP because, after all, a lot of dissolution is a political, social, and economic argument. How much competition is there going to be? So there is a scientific aspect and there is a nonscientific aspect. Because of that a default standard was needed.

Originally, dissolution was proposed by the author at 20 minutes for the First Case in water, individual units. That is due to the people who first developed the dissolution tests (Bill Mader and Rudy Blythe took Pernarowski's apparatus and developed it into a compendial test). They demonstrated that at 20 minutes one really should start getting meaningful data. So that was the time that was picked.

In 1981 a subcommittee of USP actually pushed forward the default condition, and that is where all of a sudden USP went from 60 or 70 dissolution tests to 400! USP also went back to 45 minutes, because it gave some room for elegance, for stability, for friability—a lot of things other than dissolution. People always try to push too hard on the one parameter that they really know a lot about. If one wants to travel frequently, when one gets to a destination, one wants the tablets still to be whole tablets and not powder in the bottom of the vial. If one wants to have the choice of the most possible formulations and perhaps humidity stability, one may want to be looking here. Everything done to make a product more elegant makes dissolution poorer.

So the subcommittee at that time adopted this new default policy. The First Case basically said that USP will live with it—it is not necessary to come to USP and provide any data. There were no known products that had bioavailability problems or bioequivalence that would pass that. The Second Case was where there were no known bioavailability problems, but they could not meet First Case, so they had to have some special tests for a monograph, and there are a lot of those. Then there is the Third Case where there is actually documented bioinequivalence. With USP if there is a bioavailability correlation available that will always be the basis of the monograph test.

CURRENT USP INITIATIVES

All of that experience was combined. In the case of First Case, there are no reasonable examples so far of true medically significant inequivalence. The subcommittee is taking a look and saying that differences within the envelope of meeting the First Case dissolution are insignificant in terms of fitness for use. On a macro scale, it does not matter which batch of drug or which source is tested—the differences are medically insignificant—so the Pharmacopeia can assure the public that it is an acceptable article. On a micro basis, unit-to-unit differences must be insignificant. So unit-to-unit data have no public significance. Therefore, the test load can be reduced by not running all those individual values.

As a first step, the subcommittee has come up with what is in *Pharmacopeial Forum* now, which would allow one to pool the individual specimens from six vessels and do a single analysis. For automated ultraviolet (UV) methods, that is no big savings. The idea, however, is to get the Pharmacopeia to where it wants to be five years from now. That is what this is all about, to get everybody psychologically thinking about what can be done to reduce the test loads.

The second step is that one can validate that testing multiple units per vessel—6, 10, whatever—essentially gives the same mean dissolution or some reasonable value close to it. One can then switch to running multiple units *per vessel*. A few of them have been checked in USP's lab and basically many of them are likely to come out with about the same *mean* if they are smaller tablets. With

the larger amounts of tablet material being stirred around, the multiple tablets give lower *mean* dissolution, but this can possibly be solved by going up to 75 rpm with the paddle.

Next, the subcommittee recognized that for less soluble materials, there may be some *new apparatus* needed because running 6–10 in one kettle with a one-liter flask may not be enough. All these years—USP has over 500 dissolution requirements—there have been as many times when the subcommittees have wished that they had a dissolution apparatus that had a low volume, maybe 100 ml or less, as the number of the times sodium laurylsulfate and so forth had to be used to get a test for less soluble materials. But the subcommittee does not want to waste capital investments, so it tried to keep the existing baths, stirring heads, electronics, computer interfaces, and so forth. Software might need to be changed; that is no problem. What may have to be changed would be the mounting boards. The manufacturers of dissolution equipment are already looking at four-liter flasks, and at how they can come in line with this proposal and make some contribution to it. So over the next several years, there is going to be a lot happening. It is to people's advantage to work along with that and to validate these replacements.

Several monographs will be affected. Whether or not any savings will result remains to be seen. This single proposal based on First Case—a majority of USP monographs are First Case—affects 272 monographs (Table 1). This affects several thousand shelf-keeping units—nearly 1,000 different formulations.

First Case now encompasses water, acid, or buffer less than 6pH. That is specifically meant to exclude pH6.8, 7.2, and so forth because a dose form is already getting a lot of help when those are used. That may not be a reliable thing to do.

Of the 272, a third of them use liquid chromotographic (HPLC) assays, and that is where some savings will be seen. The automated UV methods do not offer much savings. The savings are seen where there are combination products, all the ones using HPLC because of a sensitivity problem. One may be able to get out of HPLC entirely and go over to UV because one may now be up into a sensitive enough range using multiple units.

TABLE 1
Monographs Affected by Previews: *Pharmacopeial Forum* 21(1) January–February 1995

	272
Media:	water, acid, buffer pH ≤ 6.0
Apparatus:	1–100 rpm 2–50 rpm
Time:	≤ 45 minutes
Tolerance:	≥ 75% disolved
Monograph <711> change:	Using a pooled sample . . ."

The official acceptance table, though, adds 5% at each stage to allow for the fact that now only the composite is being looked at. Individual units have been thrown away. Based on the surveys of the marketplace, nothing is being lost. In the 1995 *Pharmacopeial Forum* there is an article generated at Ayerst statistically showing some operating curves that will support S1 and S2 at 10% at Q+5, which is 5% higher than the <711> plan. The industry out in Chicago thinks Stage 3—Q+5—should be just Q.

The subcommittee is getting all the data. USP is already getting response to the January 1995 *Pharmacopeial Forum*, not just letters, but actual computer exercises, and some dissolution data. So over the next few months, the 1995–2000 Subcommittee on Dissolution and Bioavailability will take all of that information together and see what proposal it wishes to come up with based on it. What appears in *Pharmacopeial Forum* (PF) is based on the 1990–1995 subcommittee's choices; it is not a done deed. Remember, PF is open for public comment. Do not make plans based on what appears in PF because it can change. The subcommittees are very responsive to public comment. They are very responsive to the comments they get

at USP Open Conferences. There was a great deal of discussion. It will be months before staff and the subcommittee members can boil down all the comments that have been received.

THE FUTURE AT USP

What about the future application of *batch phenomenon* thinking? For First Case, how about adding the paddle up to 75 rpm? It is probable that the initial people pushing the paddle as an official apparatus were holding to the 50 rpm based on a famous academic consultant. That probably was unnecessary. Seventy-five rpm gives less coning under the paddle. The coning is entirely an artifact of the test. There is no reason that one really cannot go up to 75 rpm for most paddle work.

USP has a new subcommittee that is going to establish standards for many over-the-counter products. These are combination products where there are three or more active ingredients, creating much more difficult analytic situations, perhaps several analyses per monograph. There may not be one HPLC system that picks up four chemically dissimilar molecules. So that will be a big savings there.

The boundary condition, Digoxin Tablets, is still medically significant; it is the single-most important bioavailability problem after all these years. At one hour a dissolution/bioavailability correlation can be picked up. That is a boundary circumstance. So then the question is: how much faster dissolving does it have to be? When USP proposed that First Case condition back in those years, typical hallway conversations would be: "Well, it should dissolve in the duodenum. Well no, make it dissolve in the dissolve stomach. Maybe in the esophagus." Then one person was even saying, "Well, all right, how about in the moisture on the tip of a finger?" At what point does early dissolution exceed what is generally a concept of the Law of Diminishing Returns?

One of the things that might be considered for batch phenomenon is going after all the things that dissolve at one hour or less because Digoxin provides a back-up as a boundary condition. That is the fall-back position.

Next would be to take a look at things that have cumulative plasma profiles, no narrow therapeutic index, and accumulated where it is two or three weeks before steady-state level is reached. There is not much difference in individual doses unless there is a very narrow therapeutic index. Phenytoin, perhaps, would be an exception there.

There are no rewards in titrating a patient up with an antibiotic, such as there are with an antihypertensive. All the antibiotics are given in more of a dose than is necessary, so the individual dose-to-dose variation does not mean anything. As a group one could probably apply batch phenomenon thinking, getting rid of testing of individual units of all antibiotics. There will be a few exceptions where antibiotics overlap with anti-cancer properties—a separate subcommittee will take a look at that.

It is unlikely that batch phenomenon thinking to reduce the cost of testing will likely ever be applied to narrow therapeutic index drugs. Extended release and delayed release are unlikely. For these, people will still get data on individual units.

Over the next 5–10 years, however, as many as 80% of USP's 500-and-some dissolution requirements are expected to switch over to a lower total analytical test load mode. That is a reasonable presumption. That is where USP wants to be 5–10 years from now. This is what the subcommittees are doing today to get that started to make that happen. All of this will be done without any loss to the public of an assurance that something that passes the Pharmacopeia's requirement is an acceptable article.

Another place where this may be seen is nutritional supplements. As there is no necessary dose interval and no significant dose-response curve, USP went to pooled dissolution specimens. For all other drugs that do not have a really sharp dose-response curve, there is an obvious place where one can go over to batch phenomenon tests.

USP also has subcommittees active in the area of toxicity and cell cultures. There is already a policy statement out in *Pharmaco-*

peial Forum about pushing into USP cell culture and tissue culture methods, whole cell, or perhaps some biochemical methods. This has come together since the (subcommittee) policy statement and there has been a World Congress on Alternatives to Animal Testing pushing getting out of animals using tissue culture methods. A recent National Institutes of Health Workshop on Oral Drug Delivery was excellent on the prospects, for example, of cells for absorption studies.

The future is in more *in vitro* methods in culture and tissue culture. This should reduce some of the preclinical study time. That is what the subcommittee's policy statement is meant to do. Earlier identification of physiological challenges to formulation—gut and liver metabolism—is desired. One does not necessarily have to use humans to find this out if one can do it in cell culture. That is the idea: get earlier formulation selection, bioavailability, and bioequivalence thinking. Then bioavailability and bioequivalence studies in the future should only be confirmatory tests with no more than 10 patients.

At a recent meeting on bioavailability, a new metric for doing bioavailability studies was called for by Professor Benet. There is a new definition of bioavailability/bioequivalence working its way through—it was given out at a meeting of Biopharma. The net result of this should reduce some of the unnecessary testing that is going on.

There is a *residual problem* with dissolution—and that is the effect of humid storage on dissolution. This usually gets involved with questions of packaging, repackaging, and a subject called "beyond-use dating." Sure enough, in *Pharmacopeial Forum*, USP again trotted out another proposal on beyond-use dating. What is happening in the United States is that pharmacies are buying by the thousands, and then they are making up three to four months of medication for a patient, because of cost control. The whole push is on cost control. Some of this is being sent through the mail. Some of it is just being given to a patient. They are down there in the Gulf Coast states in high-humidity environments, opening and closing containers for three to four months. The whole system of stability testing in the industry has been testing in the market pack. But the market pack is no longer 100% of the way drugs get used. What needs to be done is to take a look at data on those things that have had some difficulties. Dissolution is a big one in stability and contact with humid environments. Some guidance must be given to pharmacists and physicians and patients as to whether or not their medication is appropriate exposed to higher humidity environments.

This is a problem of the entire industry, and right now companies have a letter asking for data on drugs where difficultly in the existing stability data has been experienced. USP is not asking anybody to do any new experiments. It knows there is a lot of data in the folders. There is a USP Convention resolution to pursue this, a project of the Subcommittee on Packaging and Stability—because this is a packaging issue; this is not considered bioavailability. If tablet or capsule dissolution is decreased, that will probably in many cases, certainly with prednisone, result in less bioavailable and, therefore, bioinequivalent materials. It certainly does with nadolol and a couple of other drugs. What USP is looking to do is to give advice to patients, physicians, and pharmacists as to what reasonable storage conditions for their drugs are. Right now in the United States in the medicated population there is no bioavailability/bioequivalence problem, except for this problem which can be solved.

The next thing USP is asking its subcommittees to do is to come up with a chapter on Bayesian statistics which will help in compendial testing. It would also be a great help in interpreting biostudies and letting researchers do previous biostudies and accumulate data. The trouble with Bayesian statistics is that maybe only Bayes understood it, and that is a problem when working with statisticians.

Similarly, for diminishing testing of intensity, right now the general chapter subcommittee is looking at a very large database on content uniformity to see whether or not the current rules for when content uniformity is applied can be changed, which would result in less total content uniformity testing.