PERSPECTIVE ON THE HISTORY OF DISSOLUTION TESTING

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"... it would seem that prompt action of certain remedies must be considerably impaired by firm compression. ... the composition of all compressed tablets should be such that they will readily undergo disintegration and solution in the stomach." C. Caspari, *"A Treatise on Pharmacy", **1895**,* Lea Bros., Philad., 344.

Why test at all? Tableting technology has had a century of development, yet the essential problems and advantages of tablets were perceived in bold outlines within the first few decades. Compression, powder flow, granulation, slugging, binders, lubrication and disintegration were all appreciated early on, if not as science, at least as the *art of pharmacy*. Industrial applications of tableting were not limited to drugs, having broad application as well in confections and general chemicals. But poor results were always evident and some items were being called "brick-bats" in the trade at the turn of the 20th Century. Major consideration must be accorded to the fact that the modern era of medicine was yet to come, best dated as starting in 1937. Modern synthetic drugs, being more crystalline, were generally more amenable to presentations as solid dosage forms, and this fact gave more emphasis to these dosage forms.

Tableting technology was still empirical up to 1950 as is evidenced by the literature of the day. Limited work was done before 1950 on drug release from dosage forms, separate from disintegration, partly because convenient and sensitive chemical analyses weren't available. Solution of tablets as a whole was what was discussed, mostly with respect to tablets of simple chemicals or salts, in which the whole could be expected to dissolve. Early interest was shown in the penetration of coatings in the mid-30's.

Official disintegration tests were already adopted in 1945 by the British Pharmacopoeia and in 1950 by the USP. Even then, disintegration was recognized as an incomplete test as evidenced by the USP-NF statement that "disintegration does not imply complete solution of the tablet or even of its active ingredient". A big mistake was made around 1960 when disks (“bone crushers”) were allowed in the test. Real appreciation of the significance of drug release from solid dosage forms with regard to clinical reliability did not develop until there were sporadic reports of product failures in the late 1950's, particularly vitamin products. Work in Canada by Chapman and others had shown that articles with long disintegration times might not be physiologically available.

Two separate developments must be appreciated in discussing events from 1960 and onward. These enabled the field to progress once the issue was raised. First was the increasing availability of instrumental methods of analysis, especially for drugs in biological fluids. Second, and equally important, was the fact that a new generation of pharmaceutical scientists was on hand to apply physical chemistry to pharmacy, a development largely attributable to Takeru Higuchi and his students.

Instances in which tablets that disintegrated were nonetheless clinically inactive came to light. Work in the early 1960's by Campagna, Nelson, and Levy had considerable impact on this fast-dawning consciousness. Sufficient industrial concern had been raised that in 1962 the PMA Quality Control Section's Tablet Committee did a survey of 76 articles to determine the extent of drug dissolved as a function of drug solubility and product disintegration time. They found a significant problem, mostly with drugs of less than 0.3% solubility in water, and came within a hair of recommending that dissolution, rather than disintegration, standards be set on drugs of less than 1% solubility.

Another factor emerged between 1963 and 1968 and continues to be the bane of any scientific discussions of drug release. Drug bioavailability became a marketing issue, a political and economic issue. At first generic articles were seen as falling short on performance. Later, the older formulations, the longest in the marketplace often were seen as short on performance relative to newly formulated articles.

Official testing begins. The USP-NF Joint Panel on Physiological Availability was set up in 1967, see Figure 1, under Rudolph Blythe who already had led industrial attempts at standardization of drug release tests. That effort led to adoption, in 1970, of an official apparatus, the Rotating Basket, derived from one designed by the late M. Pernarowski, long an active force in pharmaceutical science in Canada. A commercial reaction flask was used for cost and ruggedness. The monograph requirements were shepherded by William J. Mader, an industrial expert in analysis and control who directed the APhA Foundation's Drug Standards Laboratory. William A. Hanson prepared apparatus and later commercialized a series of models.

The Joint Panel proposed no in-vivo requirements, but individual requirements were adopted in twelve compendial monographs. USP measured the time to attain a specified amount dissolved, whereas NF used the more workable test for the amount dissolved at a specified time. Considerable controversy was raging at the time of the first official dissolution tests. As more laboratories entered the field, and experiences and mistakes accumulated, the period 1970-80 was one of official test and equipment refinement.

Later, a second apparatus was based on Poole's use of available organic synthesis round-bottom flasks as refined by the St. Louis laboratory. Both choices of flasks proved not to be optimal, indeed, better if the two had been reversed. Eventually USP would offer seven apparatuses, three alone for transdermal articles. A flow- through cell and a reciprocating cylinder were adopted by way of harmonization with Ph. Eur., but there are no USP requirements that use either of these.

There were known problems, such as low solubility drugs, both in actual clinical failures and in theoretical terms. Similarly, the Joint Panel wanted to be able to get a tablet that dissolved within a reasonable volume, in a commercial flask. In earlier days, drugs were dosed in higher masses. Over the last 35 years there has been a decrease in doses, e.g., 250 mg. of an antihypertensive now might be replaced by 5 mg. There has been a change in the amount of drug that needs to get dissolved for many categories of drugs. Nevertheless, few monographs (see Digoxin Tablets) presented a challenge to analytical method sensitivity.

Two practical observations of signal importance must be made on the situation as of 1970, when drug release, dissolution, tests first became official through the leadership of USP and NF. First, the plain fact is that marketed tablets or capsules in general simply did not have a defined dissolution character. They were not formulated to achieve a particular dissolution performance. They were not quality-controlled through dissolution testing. The U.S. Food and Drug Administration, moreover, wasn't even prepared to enforce dissolution requirements or to judge their value. [Note: “sustained-release” products were tested, unofficially, in the NF Rotating Bottle apparatus]

The second practical observation is that the tremendous value of dissolution testing to *quality control* had yet to be proven, and this was perceived in 1970 only dimly even by the best placed observers. Until 1970, and even later, discussions of dissolution were restricted to the context of in-vivo - in-vitro correlations with some physiologic parameter. Dissolution testing is sensitive to formulation variables that might be of biological significance because dissolution testing is sensitive to formulation variables in general. Exquisitely sensitive, by some accounts. Rapid awareness developed between 1970 and 1975 of the proper role of dissolution testing in formulation research and product quality control.

A comprehensive need. Consistent with this new awareness of the value of dissolution testing both in quality control and bioavailability, USP adopted a new policy in 1976 that favored the inclusion of dissolution requirements in essentially **all** tablet and capsule monographs. Thomas Medwick chaired the lead Subcommittee. That policy could not achieve full realization in view of industrial non-cooperation, but in July 1980 dissolution had grown to cover 72 monographs, most supplied by USP’s laboratory under Lee T. Grady, or FDA’s laboratory under Thomas P. Layloff. USP also adopted additional apparatuses and refinements between 1975 and 1980, see Figure 1.

Dissolution testing over the years expanded beyond ordinary Tablets and Capsules, first to Extended-release and Delayed-release (enteric-coated) articles, then to transdermals, Multivitamin and Minerals products, and to Class Monographs for non-prescription drug combinations.

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Data variability. Tablets and capsules available in the above timeframe often showed 10-20% relative standard deviation in amounts dissolved, most obviously, though, for slow dissolving drugs a shown by the Food and Drug Administration's St. Louis Laboratories results on about 200 different batches of drugs available. New formulations, developed using dissolution, are much more consistent.

The key problem in dissolution testing was lab-to-lab disagreement. That essentially ended when calibrators were added and averaged values were to be compared. Every calibrator batch was subjected to a PMA/PhRMA Collaborative Study to determine acceptance statistics. Calibrators were adopted to pick up vibration in the equipment and failures in the drive chains and belts and operator error. Wherever perturbations are introduced in USP equipment, one of the calibrators always picks them up. They were not adopted to test either deaeration or temperature control, but that was the actual experience. The instruction at that time was "deaerate," but how was not specified. At present, heat and vacuum are favored. There was constant interest and many literature reports about calibrators and dearation between 1994 and 1999. The number of tests to qualify an apparatus was halved in the late 1990's. Yet even today laboratories can fail, especially on the international scene.

USP over time changed its decision rules. *Batch property* analyses of strength use an assay of a composite precisely to exclude unit variation from the assay. The content of *individual* dosage units is tested as Content uniformity. Dissolution testing always used intermediate decision rules. Originally (1969) USP tested unit values which proved to be unsatisfactory because it caused lab-to-lab numerical discrepancies. But in 1977 USP required averaging the values of units, thereby moving toward the concept of dissolution as a batch characteristic. In 1997, pooling of analytical samples was allowed, another step toward recognition of dissolution as a batch characteristic.

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Availability concerns. Bioavailability issues continued to be raised throughout the 1970 - 1980 period, as best illustrated by well-known clinical problems with various oral solid products dissolution and bioavailability. In January 1973, FDA proposed bioavailability regulations that were not made final but were followed in January 1975 by detailed bioequivalence and bioavailability regulations that became final in February 1977. A big mistake was made in requiring measure of *rate of absorption*, which seldom has any medical significance and led to many false negatives because of error and imprecision in measurement. In contrast to the 1975 proposal, the 1973 proposal did not contain the in-vitro bioequivalence requirement concept, and this contrast reflects the then growing awareness of the general utility of official dissolution requirements. Much of the impetus behind the bioavailability issue came from the issue of bioequivalence of drugs as this relates to generic substitution. Bernard E. Cabana was the primary formulator of these regulatory initiatives. Jerome P. Skelly continued and expanded them.

A major wave of introduction of generic equivalents to the USA market followed the Hatch-Waxman legislation. The leadership of Shrikant V. Dighe was pivotal to this accomplishment. FDA continued to be the source of the great majority of *in vivo / in vitro* correlations available to USP for non-First Case standards setting.

Digoxin Tablets became and remained the *boundary condition* for dissolution/bioavailability. Correlation between dissolution and absorption was shown in 1973. Digoxin is a life-saving and maintaining drug, it has a low therapeutic index, it is poorly soluble, it is absorbed high up in the intestinal tract (narrow window) and it is formulated as a low proportion of drug to excipients. The official standard that followed was the watershed for the entire field. Note that the

published decisive clinical observations results were based on merely three and four patients. The original concern for Prednisone Tablets was based by Wagner on one patient. There is a message--if it really matters, one does not need 30 or 100 patients to see it. Decisive bioinequivalences were all picked up on very small patient populations!

No USP monograph has an in-vivo bioequivalence or bioavailability requirement, whether in humans or in animals. This is in stark contrast to the decades-old use of bioassays as compendial requirements. The reason is that no known bioequivalence problem emerged that could not be settled either by a monograph dissolution requirement, or the splitting of a former monograph to create two distinct pharmacopeial articles.

Cause and Effect. There were dominant causes of examples of diminished bioavailability identified at the time all these critical decisions were made. There were actual product failures in the marketplace, either poor bioavailability or bioinequivalence. For actual clinical problems, what were the cause and effect relationships? Tablets or capsules are physical-chemical entities, and the *dose is the final bioassay*. Bioinequivalencies all were traced to formulation specifics. If there is a problem, there must be something within its physical and chemical nature that one ought to be able to determine.

Scientists early recognized that when the rate of dissolution was less than the rate of absorption then is when one is most likely going to get a bioavailability or clinical correlation. There was only a little early recognition (for example, phenothiazines) that intestinal metabolism mattered, or of the problem of first-pass metabolism.

The first focus was on particle size and solubility. Prednisone, nitrofurantoin, digoxin, and such low solubility drugs were pivotal at the time, based on clinical data. Scientists recognized that it is not the solubility of the drug alone that is critical; it is the effective surface area from which the drug is dissolving. It is the **flux** of drug into solution, which is a function (Noyes-Whitney equation) of both solubility and particle size. USP later adopted a test for intrinsic dissolution rate.

The surprise came for everybody who said in the mid-70's that there could be 100 formulation factors that might affect bioavailability or bioequivalence. Well, 100 never showed up. What did show up constantly was hydrophobic **magnesium stearate** as a **lubricant**, and it is still a problem. What also showed up were sugarcoated tablets because of a hydrophobic **shellac** subcoat. Products then were shellac-coated also both for elegance or for longer shelf life.

Everybody already knew that inadequate **disintegration** was a problem, as discussed above. Disintegrant integrity and force of compression are operational here.

All four of these proven factors are sensitive to dissolution testing. Wherever there was a medically significant problem, a dissolution test showed the difference between the nonequivalent formulations and that still holds true today.

USP strategy. Much about dissolution and bioequivalence really was and 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. Frankly, industry was not cooperating with USP. Thus, in 1975, Lee T. Grady proposed a default standard to USP. Originally, it called for 60% dissolved at 20 minutes for the First Case in water, testing individual units in the official apparatus. Bill Mader and Rudy Blythe in 1968-70 had demonstrated that at 20 minutes one could start getting meaningful data, consistent with the then typical disintegration times.

In 1981 a USP Subcommittee chaired by Jane Sheridan from industry actually pushed forward the default condition, and that is why USP went promptly from 70 dissolution tests to 400 in 1985, a five-fold increase in four years! Here USP selection of a higher amount dissolved, 75%, made for tighter data and has the advantage of meeting any pharmacological response curve, i.e., essentially complete. And a later test time, 45 minutes, was chosen because it gave formulators some room for elegance, for stability, for friability--a lot of things other than dissolution. Everything done to make a product more elegant seemed to make dissolution poorer. Subsequently, industrial cooperation improved, and later the FDA Office of Generic Drugs supplied both dissolution and bioavailability data and information to USP's elected experts for standards-setting.

. There were no known products that had bioavailability problems or bioinequivalence that would pass First Case. The boundary drug, Digoxin, would have allowed a less-demanding test, 60% at 60 minutes, and it was the *fall-back standard*. There is no known medically significant bioinequivalence problem with articles where 75 percent is dissolved in water at 37° in 45 minutes with the use of either official apparatus at usual speed. With USP whenever there was a bioavailability correlation available that always was the basis of the monograph test. FDA supplied many and those always supported a less demanding requirement.

At the end of the day. Experience has demonstrated that where a medically significant difference in bioavailability has been found among supposedly identical articles, a dissolution test has been efficacious in discriminating among these articles. Because the USP sets forth attributes of an acceptable article, such a discriminating test is satisfactory because the dissolution standard can exclude definitively any unacceptable article. Therefore, no compendial requirements for animal or human tests of bioavailability were necessary. The practical problem has been the obverse, that is, dissolution tests are so discriminating of formulation factors that may only sometimes affect bioavailability that it is not uncommon for a clinically acceptable article to perform poorly in a typical dissolution test. In such cases, the Committee of Revision has been mindful of including as many acceptable articles as possible, but at the same time not setting forth dissolution specifications so generous as to raise reasonable scientific concern for bioinequivalence.

ACKNOWLEDMENTS. The author and our public are indebted to Barbara B. Hubert, Vivian A. Gray and Will E. Brown for their extensive contributions in making USP initiatives into accomplishments. Each standard required their coordination of elected experts with industrial and governmental scientists and laboratories.

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Figure 1. USP TIMELINE

1945, 1950 Disintegration official in *Brit. Pharmacop.* and USP

1962 PMA Tablet Committee proposes 1% solubility invert threshold

1967 USP and NF Joint Panel on Physiological Availability chooses Dissolution as a test, chooses an apparatus.

1970 Initial twelve monograph standards official

1971-4 Variables assessment; more laboratories, three Collaborative Studies by PMA and Acad. Pharm. Sci. 1975 First calibrator tablets pressed; First Case default proposed to USP

1976 USP Policy—comprehensive need; calibrators (3) Collab. Study

1977 USP Guidelines for setting Dissolution standards

1978 Appar. 2—Paddle adopted; two Calibrator Tablets adopted

1979 New decision rule and acceptance criteria

1980 Three case Policy proposed; USP Guidelines revised; 70 monographs now have standards

1981 New policy adopted January, includes the default First Case, monograph proposals published in June

1982 USP Policy proposed for Modified-release dosage forms

1984 Revised policy adopted for Modified-release.forms

1985 Standards now in nearly 400 monographs; field considered mature; Chapter <724> covers Extended-release and Enteric-coated

1990 Harmonization: Appar 4—Flow- through adopted; Appar 3 Appar 5, 6, 7 for transdermal articles.

1991 USP chapter on in vivo/in vitro Correlations published

1995 Third Generation testing proposed—batch phenomenon; propose reduction in calibration test number

1997 FIP Guidelines for Dissolution Testing of Solid Oral Products; pooled analytical samples allowed

1999	Enzymes allowed for gelatin capsules; reduction from 0.1 N to 0.01 N HCl to begin for 112 monographs .