Historical Perspectives on Dissolution Technology

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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."[1]

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, there being 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 century. Disintegration was an issue throughout this period and, indeed, is still seen as an underlying problem in present day product failures. A substantial weight variation problem also was a constant feature, and as blending problems became more recognized, the scope of this issue recently was broadened to include content uniformity. Governmental interest in tablet shortcomings led to the establishment, in 1924, of the Contact Committee, predecessor to today's Pharmaceutical Manufacturing Association (PMA)[2] Quality Control Section. As late as 1936, United States Pharmacopeia (USP) had seen its way clear to only four monographs for tablets, in contrast to the forty-eight in National Formulary (NF). Major consideration must be accorded to the fact that the modern era of pharmacy was yet to come, best dated as starting in 1937. Modern synthetic drugs, being more crystalline, were generally 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 on drug release from dosage forms, separate from disintegration, was done through 1940, partly because convenient and sensitive analyses weren't available and partly because the issue was still undefined. 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. Some interest was shown in the mid-30's already in the penetration of coatings.

Official disintegration tests were already adopted in 1945 by the British Pharmacopeia and in 1950 by the USP. USP adopted the StollGershberg apparatus used in the Army-Navy Procurement Laboratory and which was commended to USP by E. B. Vliet representing the Contact Committee. 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.

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[1] "A Treatise on Pharmacy," Gaspari C, Lea Bros., Philadelphia, 1895, page 344.

[2] Currently named the Pharmaceutical Research and Manufacturers Association (PhRMA).

Real appreciation of the significance of drug release from solid dosage forms to clinical reliability did not develop until the late 1950's when sporadic reports of product failures began to attract the attention of a core of pharmaceutical scientists. Vitamin products were under particular scrutiny at that time. Work in Canada by Chapman and others had shown that articles with long disintegration times may not be physiologically available. Other studies, however, found that poor disintegration was not a widespread problem.

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 which supplied the necessary speed, sensitivity and selectivity. Second, and equally important, was the fact that a new generation of pharmaceutical scientists was on hand. The application of physical chemistry to pharmacy, a development largely attributable to T. Higuchi and his students, was bound to redefine any problems of dosage forms in terms of the science of pharmacy instead of the art of the pharmacy. Much of the work since 1960 has been, therefore, by way of a scientific retrospective on the history of solid dosage forms as the new generation of pharmaceutical scientists defined, with chemical and mathematical precision, the cumulative variables of dosage form technology and the significance of these which had eluded the previous pharmacists and artisans.

Instances in which tablets that disintegrated were nonetheless clinically inactive came to light. Work by Campagna, Nelson, and Levy had considerable impact on this fast-dawning consciousness. Sufficient concern had been raised that in 1962 the PMA Quality Control Sections 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. But in early 1963 they decided that not enough time remained to get this into the 1965 editions of USP or NF. Instead, disintegration times were shortened. The period 1960 - 1970 saw a proliferation of designs for dissolution apparatuses.

Another factor that was established between 1963 and 1968 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. Now the older formulations, the longest in the marketplace, are being seen as short on performance relative to newly formulated articles. The result in 1963 -1968 was to shift the focus of attempts at standardization away from industry and to the world's compendia and governments.
The USP-NF Joint Panel on Physiological Availability was set up in 1967 under R. Blythe who already had led industrial attempts at standardization of drug release tests. That effort led to adoption, in 1970, of an official apparatus and individual requirements in twelve compendial monographs. The apparatus was derived from one designed by the late M. Pernarowski, long on active force in pharmaceutical science in Canada. The monograph requirements were shepherded by W. Mader, an industrial expert in analysis and control who directed the APhA Foundation's Drug Standards Laboratory. No in-vivo requirements were proposed by the Joint Panel.

Most laboratories had to learn their first exercises in dissolution testing using that official apparatus. This first generation of testing drugs in a new way led to our current appreciation of

the principles of dissolution testing. Add to this the factors peculiar to this apparatus which had to be learned. But first and foremost came the establishment of the true role of dissolution technology in pharmaceuticals.

Considerable controversy was raging at the time of the first official dissolution tests. At one extreme individuals discounted bioequivalence, and to a lesser extent bioavailability, as significant components of the general therapeutic scene. At the other extreme individuals used these issues to cast aspersions upon the general therapeutic scene. Economic factors were apparent in both extremes, and it is unremarkable that our present understanding eschews either. Authoritative lists are available of drugs with potential or proven problems either in bioequivalence or in the wider sense of bioavailability. Although the problem drugs represent a minority of all drugs, these do include some critical drugs with narrow therapeutic indices.

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 (with the exception of sustained release forms). They were not formulated to demonstrate a particular dissolution performance. They were not quality controlled through dissolution testing. Our U.S. Food and Drug Administration (FDA), moreover, wasn't even prepared to enforce dissolution requirements or to judge their value. No one can state, with certainty, how many of these originally undefined products still are being presented to the public even at this late date.

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. That is to say, as a crystallization within the bioavailability milieu. This reflects the fact that dissolution technology was developed in response to problems in bioavailability and the need to have sensitive tests with which to work in-vitro.

Dissolution testing is sensitive to formulation variables which 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. There are few today who would limit this technology to in-vivo/in-vitro experiments.

Consistent with this new awareness of the value of dissolution technology, USP adopted a new policy in 1976 which favored the inclusion of dissolution requirements in essentially all tablet and capsule monographs. That policy did not achieve full realization, but in July 1980 dissolution had grown to cover 72 monographs. It should be noted that other pharmacopeias have even yet to accord this importance to dissolution, or to bioavailability in the first instance, and have neither such a comprehensive policy nor large numbers of monograph requirements. USP also adopted additional apparatuses and refinements between 1975 and 1980, and these are discussed in detail in other parts of this paper.

Bioavailability issues continued to be raised throughout the 1970 -1980 period, as best illustrated by the well-known problems with Digoxin dissolution and bioavailability. Significant signposts were pointed out by the 1974 Office of Technology Assessment Report on Drug Bioequivalence. Dissolution technology was recognized in all this as a critical component of any response to the bioavailability and bioequivalence issues. In January 1973, FDA proposed bioavailability regulations which were not made final but were followed in January 1975 by detailed bioequivalence and bioavailability regulations which became final in February 1977. 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 comes not from a recent urgent interest in the interaction of foods with drugs, but rather from the issue of bioequivalence of drugs as this relates to drug substitution. That is, the economic angle sets the grid for these discussions.

No pharmacopeial monograph, USP or worldwide, 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 explanation would seem to be that no known bioequivalence problem existed which could not be settled either by a monograph dissolution requirement, or the splitting of a former monograph to create two distinct pharmacopeial articles.

On the other hand, bioavailability concerns also justified the adoption of X-ray diffraction as a compendial method to approach the problem from a second direction in addition to dissolution. Developments in international commerce in drug substances may call for more widespread application of X-ray and particle size specifications.

Researches on sustained release formulations, other than the newer "delivery systems", have been almost obscured over the last ten years in contrast to their relative prominence in the 1955 - 1965 period. Presently official dissolution technology may or may not be suitable for formulation research and quality control of these articles. Wholly distinctive technologies may arise in response to the more recent excursions into sophisticated drug delivery systems.