Commentary

Theme: Landmark Publications in the Pharmaceutical Sciences—The Backstory
Guest Editor: Ho-Leung Fung

Levy G, Hayes B, “Physiochemical Basis of the Buffered Acetylsalicylic Acid Controversy New Engl. J. Med. 262:1053–1058 (1960)”—The Backstory

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During the 1950s, I was a student at the University of California School of Pharmacy in San Francisco. One of my favorite teachers was Dr. Eino Nelson, then a newly appointed assistant professor. I noticed that Eino spent a lot of time in the School's balance room, in front of our only single pan analytical balance. I asked him about that and he told me that he was studying the intrinsic dissolution rate of a number of barbituric acid derivatives and their sodium salts. For this purpose, he prepared highly compressed flat pellets of pure drug and mounted them with wax on a microscope slide such that only one face of the pellet was exposed. The slide, suspended from the balance, was immersed in a beaker of water. The apparent weight loss of the immersed slide was then determined as a function of time, thereby providing the basis for calculating the drug's intrinsic dissolution rate. Eino then explained to me his theory that the rate of gastrointestinal absorption of most drugs, when administered in solid form as tablets or capsules, is determined by their rate of dissolution in gastrointestinal fluids. He subsequently extended his studies to theophylline derivatives and certain antibiotics before eventually turning to research in pharmacokinetics.

When I joined the faculty of the University of Buffalo (now The State University of New York

University at Buffalo) in 1958, I decided to extend this work from drug pellets to conventional tablets. As the first step, it was necessary to develop a dissolution test procedure suitable for such tablets. I had the University's glass blower construct a 400 ml capacity double-walled Griffin beaker with inlet and outlet to permit circulation of temperature-controlled water through the jacket. An electronic controlled speed stirrer and a polyethylene-coated propeller completed the apparatus.

An extensive review of the literature on gastric motility revealed to me that mixing of stomach content was very mild such that different foods ingested consecutively tended to remain in layers until emptied from the stomach. To relate this to the behavior of tablets, I prepared some rapidly disintegrating tablets containing barium sulfate as a radio-opaque indicator and arranged with a medical colleague for serial X-rays after I had taken such a tablet. The images, reproduced in reference 1, showed that the tablet disintegrated promptly in the stomach and remained there as an aggregate rather than as a dispersion of granules and/or particles throughout the gastric fluid.

Consequently, I decided to keep the agitation intensity (stirring rate) very low, just sufficient to attain homogeneity in the dissolution medium for serial sampling. We later conceived of an indirect way to determine the stirring rate equivalent in our *in vitro* system to the typical *in vivo* conditions (2). The result turned out to be very close to the stirring rate that I had selected initially. Moreover, we could demonstrate that

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stirring rates too fast or too slow could produce very misleading results in comparative dissolution studies (1,2). Our beaker dissolution test eventually evolved into the widely used Dissolution Method 2 of the United States Pharmacopeia (USP).

Under conditions of low intensity stirring in our dissolution test, tablets typically form a small mound or aggregate after disintegration. This becomes important for tablets containing two or more interacting components. We showed that aspirin in tablets containing an antacid dissolved much more rapidly than aspirin in tablets without antacid upon mild stirring and that these differences disappeared totally when the dissolution medium is stirred more rapidly so that all the particles are completely dispersed and individually separated in the dissolution medium (2). The pH of the microenvironment of the aggregate of an aspirin-antacid mixture as determined with microelectrodes was several units higher than that in the bulk dissolution medium.

We determined the *in vitro* dissolution rate of aspirin from three different commercial plain aspirin tablet products as well as of calcium aspirin and an aspirin-antacid product and tested their absorption rate in a total of 24 volunteers by a urinary excretion test method. The results revealed a strong positive correlation between dissolution rate and absorption rate (3), the first such published correlation. On the other hand, there was no positive correlation between the disintegration rate of the tablets and their relative absorption rate; the correlation in this particular case was actually negative.

I recommended that the USP disintegration test be replaced by a dissolution test but that took several years to come about. In the meantime, we continued our studies of drug dissolution, including the role of pharmaceutical formulation variables, tablet lubricants and film formation. All this is necessary background for describing the genesis of the manuscript that is the focus of this article.

During the 1950s, there was an intense commercial competition between the manufacturers of the two leading brands of aspirin tablets, one plain and the other "buffered", i.e. with antacid. The "twice as fast" claims for the latter stimulated a number of clinical studies resulting in different conclusions that were of sufficient general interest to achieve publication in a premier medical journal, the New England Journal of Medicine (NEJM). At the same time, there was considerable discussion in the literature about the causes of gastrointestinal intol-

erance and mucosal bleeding associated with aspirin, again with substantial diversity of opinions. Then appeared a report by Rubin *et al.* in a 1959 issue of the NEJM which was thought to have resolved the plain vs. buffered aspirin controversy: it was found that buffered aspirin had no effect on intragastric pH as determined by inserting an electrode into the stomach of volunteer subjects.

Upon reading this report, I decided to set aside for a while my work on several manuscripts describing our dissolution research to prepare a paper that presents (a) the concept of dissolution rate limited gastrointestinal drug absorption and the role of pharmaceutical formulation in this process as applied to aspirin and (b) my analysis of the literature demonstrating that aspirin-induced gastric mucosal damage produced by aspirin is largely a local rather than a systemic effect and that it would be affected by the dosage form in which it is administered. The concept of the microenvironment of dissolving drug aggregates was presented to explain the observations by Rubin *et al.* This manuscript was accepted for publication in NEJM and appeared in 1960 (4).

Even though we subsequently published several other papers in NEJM, I remember this one with particular pleasure, for several reasons. To put the paper in a historic perspective, it was written before the terms bioavailability, bioequivalence, and biopharmaceutics were coined and their concepts and significance were generally appreciated. This was the first manuscript I published after joining the faculty of the University of Buffalo where I remained for about 40 years. My co-author was an undergraduate research participant who with several other undergraduates was involved in my dissolution research as part of a successful program that I started at Buffalo to interest some of our best students in graduate study. The NEJM paper gave me an opportunity to introduce an important concept of pharmaceutical science to a wide readership of physicians at a time when the role of pharmaceuticals, unlike that of medicinal chemistry, was not generally appreciated.

Finally, I must own up to the fact that the NEJM paper was not my first publication on aspirin. The first one was published in 1958 in the Practical Edition of the A.Ph.A. Journal and was co-authored by fellow undergraduate Rod Jones, describing our independent development of a constitutable aspirin suspension of extended stability suitable for pediatric use. Publication of this work without a faculty co-author caused a bit of commotion at the University of California. My

subsequent research activities followed a more conventional path, largely with NIH support.

Aspirin and the salicylates in general continued to engage my interest and efforts for much of the next 20 years. Together with students and clinical collaborators, we elucidated the nonlinear pharmacokinetics of salicylate in humans (the only other saturable pharmacokinetics known at that time was that of ethanol), determined the effect of age from newborns to the elderly and of renal failure on salicylate pharmacokinetics, studied the influence of pharmaceutical dosage form on aspirin-induced gastrointestinal blood loss in humans, demonstrated the efficacy of early administration of activated charcoal for managing acute overdosing of aspirin, and characterized

some drug interactions with salicylate. All this was a great learning experience and a lot of fun.

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