Interpretation of *In Vitro* Dissolution Data Relative to the Gastrointestinal Absorption Characteristics of Drugs in Tablets

Sir:

The recognition that the gastrointestinal absorption of drugs administered in the form of compressed tablets is frequently rate-limited by the process of dissolution (1–3) has led to numerous studies of the effect of tablet formulation factors on the *in vitro* dissolution rate(s) of the active ingredient(s). The difficulty and expense of clinical trials, and the desirability of utilizing the eventually marketed dosage form as early as possible in clinical studies of a new drug, have resulted in the use of *in vitro* dissolution tests as a means for selecting the most promising tablet formulation(s) from among several experimental preparations. It is the purpose of this communication to outline some hazards in the interpretation of results obtained from *in vitro* dissolution test procedures which have not been calibrated exactly on the basis of *in vivo* data.

Two experimental tablet formulations of aspirin (0.32 Gm. per tablet) were recently made available to the authors.[1] These were conventional compressed tablets, differing essentially only in the particle size of aspirin, and designed to yield gastrointestinal absorption characteristics in the upper and lower range of rates ordinarily encountered with commercial products. The tablets designated as type *A* were prepared with finely milled aspirin (80-mesh and finer) while the type *B* tablets contained relatively coarse aspirin (all particles larger than 20-mesh). Gastrointestinal absorption studies were carried out on 6 ambulatory subjects (trial *1*); the early phase of this clinical trial was repeated once with these 6 subjects and 2 others (trial *2*) in order to obtain additional data and to assess the degree of intrasubject variability. The tablets were swallowed whole, with 200 ml. water, in the morning on an empty stomach. No food was permitted for 2 hr. following tablet ingestion. Blood samples were obtained at various times and the concentration of total salicylate in the plasma was determined by the method of Brodie *et al.* (4) after heating the plasma with 2 *N* hydrochloric acid at 100° for 10 min. The results are summarized in Table I[2] and indicate that aspirin in type *A* tablets is absorbed about 3 times as rapidly *on the average* as it is when given in type *B* tablets.

TABLE I—TOTAL SALICYLATE CONCENTRATION (mg./L.) IN THE PLASMA AS A FUNCTION OF TIME AFTER ORAL ADMINISTRATION OF 0.65 GM. ASPIRIN AS TWO TABLETS OF TYPE *A* AND TYPE *B* IN TWO TRIALS

Time, min.	Tablets *A* Mean	S.D.[a]	Tablets *B* Mean	S.D.
		Trial 1[b]		
10	24.7	13.9	5.5[c]	1.8
20	41.0	17.8	12.8[c]	4.7
30	46.1	14.8	18.7[c]	6.2
60	48.7	10.7	32.0[c]	7.1
120	48.0	9.0	43.8	8.2
240	34.7	8.0	34.5	6.0
360	23.0	6.5	24.2	6.2
		Trial 2[d]		
10	17.8 (15.5)[e]	8.3	7.2[c] (7.8)[e]	4.1
20	41.0 (38.5)	16.5	15.0[c] (16.7)	5.7
30	51.4 (49.7)	19.9	21.5[c] (24.3)	9.0

[a] Standard deviation (the meaningfulness of this value is limited due to inter-subject variations in apparent volume of distribution). [b] Average of 6 subjects (5 F, 1 M); av wt., 67.5 Kg.; av. age, 27.7 yr. [c] Significantly different from tablets *A* ($p < 0.01$). [d] Average of 8 subjects (5 F, 3 M); av. wt., 70.0 Kg.; av. age, 28.0 yr. [e] Figures in parentheses are data for the 6 subjects who participated in trial *1*.

In vitro dissolution rates were determined by the beaker method of Levy and Hayes (5) with recently described modifications (2), using the precision stirring apparatus of Levy and Tanski (6). The times required for dissolution of one third, one half, and two thirds of the drug content of one tablet (*i.e.*, $t_{1/3}$, $t_{1/2}$, and $t_{2/3}$) were determined graphically from cumulative dissolution plots. These measurements were made at stirring rates of 50, 60, and 75 r.p.m., using an average of six tablets each. The results of these experiments are shown in Fig. 1. The inset in the figure shows the $t_{1/3}$ ratios (type *B*:type *A*) for the tablets as a function of stirring rate. It can be noted that this ratio changed from less than unity at 50 r.p.m. to almost 15 at 75 r.p.m.[3]

This striking sensitivity of relative dissolution rates to small changes in stirring intensity has profound implications. Only at about 55 r.p.m. (by interpolation) is the ratio of *in vitro* dissolution rates similar to the ratio of the *average in vivo* absorption rates. A small change in agitation intensity (such as is obtained by a change in stirring rate by ±10 r.p.m. or by a change in the dimensions of the dissolution apparatus) can yield results either contrary to those obtained *in vivo* or showing much greater differences from those observed in the clinical

[1] The authors thank Dr. John H. Wood and the Bristol-Myers Products Division for preparing the experimental tablet preparations used in this study.

[2] A tabulation of individual data is available upon request.

[3] The reader is referred to *References 7* and *8* for a discussion of the physicochemical basis of these observations.

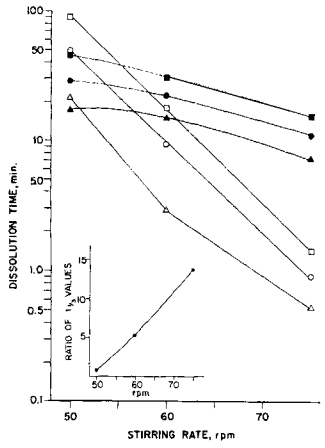

Fig. 1—Dissolution rate of aspirin from type A *(open symbols) and type* B *(solid symbols) tablets as a function of stirring rate. Triangles,* $t_{1/3}$; *circles,* $t_{1/2}$; *squares,* $t_{2/3}$. *Inset: ratio of* $t_{1/3}$, *type* B : *type* A *tablets, as a function of stirring rate.*

study. It must be emphasized that the preparations studied were conventional type tablet preparations rather than specialty dosage forms such as sustained-release or "buffered" formulations. The results of the investigation described here show clearly that dissolution test procedures which have not been calibrated *exactly* on the basis of *in vivo* measurements are unlikely to reflect the gastrointestinal absorption characteristics of the preparations tested and may in fact yield very misleading data.

The pronounced sensitivity of the dissolution rate of a drug in tablet form to agitation intensity has some interesting clinical implications. It suggests that subjects who are consistently rapid or slow absorbers, such as were noted in a previous study from this laboratory (2), may be individuals who by reason of certain anatomic or physiological characteristics of their gastroin testinal tract cause ingested tablets to be subjected to relatively intensive or mild agitation, respectively. As a corollary, one would expect to find the same type of differences in *in vivo* absorption kinetics with rapid and slow absorbers as were noted in *in vitro* dissolution kinetics at high and low stirring rates, respectively. Accordingly, plasma salicylate levels obtained after administration of type *A* and type *B* tablets were compared in a consistently rapid and a consistently slow absorber (as judged on the basis of data obtained in two tests with type *A* tablets) from among the group of subjects who participated in this study. The results, expressed as ratios of plasma salicylate concentration after type *A* to those obtained after type *B* tablets, are listed in Table II. They show, as predicted, that

Table II—Relative Absorption Rate of Aspirin from Type *A* and Type *B* Tablets in a Rapid and a Slow Absorber[a]

Subject	Ratio of Salicylate Concn. in Plasma Type *A* : Type *B* Time, min. 10	20	30
Rapid absorber	2.7	3.1	2.6
Slow absorber	0.8	1.0	1.1

[a] Based on data obtained in 2 trials per subject per tablet type.

differences in absorption rate of drug in the two types of tablets are clearly evident in the rapid absorber, but are essentially absent in the slow absorber.

Extending this reasoning one step further, one would expect less inter-subject variation in the rate of drug absorption from type *B* tablets (which show very little dissolution rate dependency on agitation intensity) than from type *A* tablets (which show a pronounced dissolution rate dependency on agitation intensity). These effects are indeed evident in the clinical results obtained from the cross-over study in 6 subjects. The time of occurrence of peak salicylate levels in the plasma following administration of type *B* tablets was 120 min. in 5 subjects and 240 min. in the sixth subject. On the other hand, these times varied markedly following administration of type *A* tablets: 20 min. (1 subject), 30 min. (1 subject), 60 min. (2 subjects), and 120 min. (2 subjects). It should be noted, however, that there may be some bias in these results because of the longer sampling intervals at the later times.

The *in vitro* results illustrate the limitations and possible hazards in the use and interpretation of dissolution rate data derived from tests carried out under arbitrary conditions. It is now evident that small differences in agitation intensity or in the pH of the solvent (9) can have a pronounced effect on the relative dissolution rate of a drug in different tablet formulations. These problems are of course obviated by administering drugs such as aspirin in solution (10). Where it becomes necessary to select the most promising tablet formulation from among several experimental formulations available for clinical study, it would appear prudent to base this selection on dissolution rate data obtained over a range of agitation intensities and solvent pH.

The clinical data suggest that differences in absorption rates may, in the case of dissolution rate limited drug absorption, be due to differences in the intensity of agitation of the gastrointestinal content. Therefore, disease and environmental conditions (including stress, physical activity, food, and medication) which affect gastro-

intestinal motility (and gastric pH) may have a corresponding effect on dissolution rate limited drug absorption. It is possible, therefore, that 2 types of tablet formulations of a given drug may show pronounced dissolution rate differences in one kind of population or clinical environment, but not in another. However, it must be emphasized that the conclusions concerning these *in vivo* implications are clearly preliminary and require confirmation in a large population sample containing significant numbers of consistently rapid and slow absorbers.

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Diffusional Model for Transport Rate Studies Across Membranes

Sir:

There has been much in the literature in recent years concerning the so-called "three-phase" model of drug absorption. Absorption studies in this area have concentrated mainly on the passive or diffusional transport of drugs. Most models currently proposed are kinetic outgrowths of the original Brodie-Shore-Hogben pH-partition thesis. In recent communications to this journal authors (1, 2) have proposed equations based on first-order kinetics, which give the amount of drug in each of the three phases *versus* time.

The importance of diffusion in drug absorption has been recognized (3). However, no strictly diffusional model of drug absorption has been proposed for the three-phase multicomponent diffusion problem that can physically describe, for example, pH effects.

The authors in these laboratories are exploring general diffusional models for gastrointestinal absorption of ionizing and nonionizing drugs. A proposed steady-state model, shown in Fig. 1 for the case of a weak base, RN, which can become protonated to give RNH^+, allows for intestinal and blood buffers. It is assumed here also that only the uncharged drug species can diffuse in the lipid phase. An important feature of this model is the inclusion of aqueous diffusional barriers on each side of the lipoidal membrane.

Preliminary results (Fig. 2) obtained for the steady-state case *via* computer correlate the combined effects of varying pKa and the partition coefficient (KLH). The units of G, the transport rate, are mmoles cm.$^{-2}$ sec.$^{-1}$. TH1 and TH3, the effective aqueous diffusion layer thicknesses on the left and right side of the membrane, respectively, are taken as equal for these calculations. TH2 is the effective thickness of the lipid phase. For low to moderate agitation conditions, TH1 should be around 50 to 200 μ (4). The authors would estimate TH2 to be effective somewhere between tens of microns to few millimeters.

In Fig. 2 most noticeable is the fact that steady-state transport rates are linear with increasing partition coefficients only up to a certain point

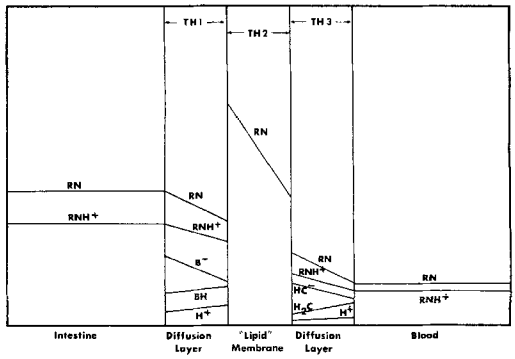

Fig. 1—The steady-state diffusional model for the transport of a weak amine drug, RN, *across the intestinal barrier. Concentration profiles are schematically given for all species:* RNH^+ *= protonated drug;* BH *and* B^- *= the buffer molecule and its anion in the intestinal fluids;* H^+ *= hydrogen ion;* H_2C *and* HC^- *= carbonic acid and bicarbonate in the blood.* TH1, TH2, *and* TH3 *are the diffusion layer thicknesses in the three phases.*