Dissolution Rate Limited Absorption in Man

Factors Influencing Drug Absorption from Prolonged-Release Dosage Form

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An experimental prolonged-release dosage form of aspirin was used as a biopharmaceutical probe to study dissolution rate limited intestinal absorption in man. This dosage form released drug *in vitro* by an exponential process which was highly sensitive to changes in agitation intensity, but relatively insensitive to pH and pancreatin. Plasma salicylate levels and urinary excretion of salicylate and metabolites were determined in humans after oral administration of 1 Gm. of aspirin in rapidly absorbable form (compressed tablets) and in prolonged-release form. Absorption from the prolonged-release dosage form was determined on two separate occasions in each subject to assess both inter- and intrasubject variations in absorption kinetics. The individual absorption data were found to be describable in most instances as first-order processes preceded by a lag time. In some cases, an initial slow absorption phase preceding the more rapid phase could be noted. It was found also that the averaged data yield a zero-order plot (which is indicative of absorption at a constant rate). This shows that interpretations based on averaged data of the type discussed may lead to erroneous conclusions. The experimental results suggest that the intersubject variation in drug absorption rates from the experimental prolonged-release dosage form studied was due mainly to individual differences in gastric emptying rate and intestinal peristaltic activity and to the pronounced sensitivity (with respect to dissolution rate) of the dosage form to variations in agitation intensity. Intrasubject variation of drug absorption rates appeared to be due primarily to variations in gastric emptying rates.

THE KINETICS of dissolution rate limited gastrointestinal absorption of a drug administered in compressed tablets has been studied intensively (1, 2). Drug absorption was so rapid in these studies, that it is likely that absorption occurred only from the stomach and proximal small intestine. Another study, which dealt with the absorption of a drug administered in enteric-coated tablets, yielded results which indicate that gastric emptying was the major rate-determining process when drugs are administered in this form (3). The availability of an experimental dosage form with prolonged-release characteristics has permitted the authors to extend these studies to cases where dissolution rate limited absorption is sufficiently retarded as to occur mainly from the intestinal tract. The same drug (aspirin) has been used in all of these studies in order to provide a continuum of information on the biopharmaceutical aspects of drug absorption from different types of dosage forms, without introducing the type of drug as an additional variable.

EXPERIMENTAL

Dosage Form.—The prolonged-release dosage form consisted of coated aspirin particles mixed with a hydrophilic gelling agent and compressed into tablets stated to contain 1 Gm. of aspirin. Assay of three individual tablets indicated an average aspirin content of 1.01 Gm., range 1.00–1.02 Gm. The tablets were obtained as an experimental preparation from a pharmaceutical manufacturer. The compressed tablets of aspirin used in this study were a national brand of plain aspirin tablets purchased on the open market. The tablets were stated to contain 325 mg. of aspirin per tablet; assay of six individual tablets indicated an average aspirin content of 328 mg., range 322–337 mg.

Dissolution Rate Determinations.—*In vitro* dissolution rates were determined by the method of Levy and Hayes (4) with the modifications described previously (2). In addition to 0.1 *N* hydrochloric acid, the following were used as dissolution media: (*a*) simulated intestinal fluid U.S.P. XVI (5) and (*b*) pH 7.5 buffer (simulated intestinal fluid U.S.P. XVI without pancreatin).

Clinical Study.—Seven adult male subjects, 36 to 55 years old, ingested 1 Gm. of aspirin in the form of one tablet of the prolonged-release dosage form or in three conventional compressed tablets. The prolonged-release dosage form was given on two different occasions, while the conventional tablets were given only once. The respective aspirin preparations were swallowed whole with 240 ml. of water about 1 hr. after a light standard breakfast. Blood samples were obtained either at 1, 3, 5, 7, 9, and 11 hr. after drug administration (conventional tablets; prolonged-release form, first test) or at 1, 2, 3, 5, and 7 hr. after drug administration (prolonged-release form, second test). Total urines were collected every 2 hr. (compressed tablets) or every 4 hr. (prolonged-release form, second test) for the first 12 hr., and at convenient known intervals thereafter, for at least 60 hr. Serum salicylate levels were determined by the colorimetric method of Trinder (6). Total

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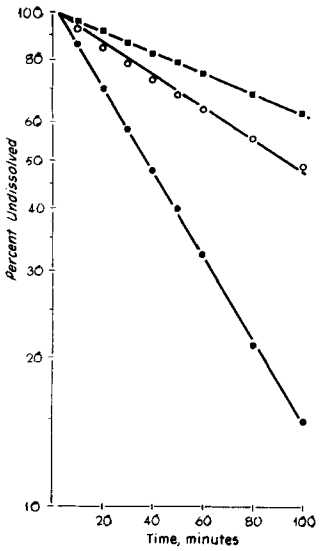

Fig. 1.—Effect of agitation intensity on dissolution rate of aspirin contained in an experimental prolonged - release dosage form. Dissolution medium: pH 7.5 buffer at 37°. Key: ■, 30 r.p.m. (average of two tablets); ○, 45 r.p.m. (average of three tablets); ●, 60 r.p.m. (average of eight tablets).

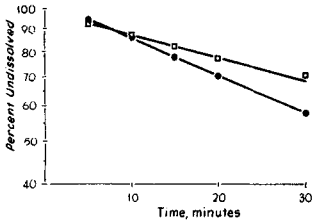

Fig. 2.—Effect of pH on dissolution rate of aspirin contained in an experimental prolonged-release dosage form. Stirring rate, 60 r.p.m. Key: □, 0.1 *N* hydrochloric acid, pH ≃ 1.1 (average of two tablets); ●, pH 7.5 buffer (average of eight tablets).

salicylates in the urine were determined by the method of Smith *et al.* (7) as modified by Levy (8).

Calculations.—The per cent of the dose absorbed at various times after drug administration was calculated by the procedure of Wagner and Nelson (9). Details of the application of this procedure to the salicylates have been presented elsewhere (1, 2).[1]

RESULTS AND DISCUSSION

Dissolution Properties of Dosage Forms.—The dissolution of aspirin from the prolonged-release dosage form followed apparent first-order kinetics in the *in vitro* test procedure used (Fig. 1). Half-life for dissolution in pH 7.5 buffer solution, using the standard agitation intensity of 60 r.p.m. [50 r.p.m. rotating disk equivalent (10)], was 0.60 hr., standard deviation 0.090 hr. The dissolution process was very sensitive to agitation intensity, as evident from the data shown in Fig. 1. Half-life for dissolution at 45 r.p.m. was 1.6 hr., and it increased to 2.3 hr. when agitation intensity was decreased to 30 r.p.m. The effect of pH on dissolution was small, as can be noted from Fig. 2 which depicts dissolution of aspirin in 0.1 *N* hydrochloric acid and pH 7.5 buffer, respectively. Dissolution rates in simulated intestinal fluid U.S.P. and pH 7.5 buffer solution (consisting of simulated intestinal fluid U.S.P. without pancreatin) were the same, which indicates that the rate of release of aspirin from the sustained-release dosage form was not affected by pancreatic enzymes.

Dissolution of aspirin from the compressed tablets used in this study was rapid, with an average half-life of 0.05 hr. in 0.1 *N* hydrochloric acid and 60 r.p.m. agitation intensity. No detailed dissolution data are presented since the compressed tablets were used only as a standard for determination of physiologic availability, and for comparison of the metabolic fate of aspirin administered in rapidly absorbed and prolonged-release dosage form, respectively (11). Results of a study of absorption kinetics of aspirin administered in compressed tablets with similar rapid dissolution characteristics as the tablets used in this investigation have already been reported (2).

Physiologic Availability of Aspirin in Prolonged-Release Dosage Form.—The urinary recovery of total salicylates (salicylate, salicylurate, salicylic glucuronides) after administration of aspirin in conventional compressed tablets and in prolonged-release dosage form is shown in Table I, which lists individual recovery data for seven subjects. These data are expressed in terms of per cent of the dose given, in order to account for a small difference between the aspirin content of three conventional tablets and of one unit of the prolonged-release form. The data show that absorption of aspirin given in the prolonged-release dosage form used in this study was as complete as when the drug was given in conventional tablets with rapid release characteristics.

TABLE I.—PHYSIOLOGIC AVAILABILITY OF ASPIRIN IN EXPERIMENTAL PROLONGED-RELEASE DOSAGE FORM

Subject	% of Dose Excreted: Compressed Tablets[a]	% of Dose Excreted: Prolonged-Release Form[b]
A	84.6	90.0
B	85.5	85.9
C	89.8	92.6
D	85.5	82.7
E	86.1	91.9
F	90.3	85.0
G	87.2	83.7
Mean	87.0	87.2

[a] Based on 0.984-Gm. dose. [b] Based on 1.01-Gm. dose.

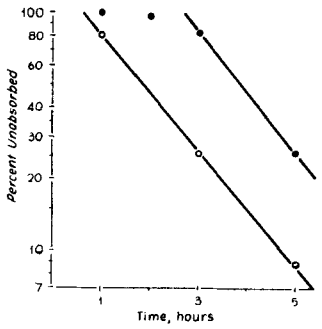

Fig. 3.—Absorption of 1 Gm. of aspirin administered in an experimental prolonged - release dosage form. (Subject *C*.) Key: ●, first test; ○, second test.

[1] Some of the data were recalculated by a recently developed method which permits determination of absorption rates from drug metabolite levels (16). The results of these calculations were within 5% of those obtained by use of the Wagner-Nelson method. This is as expected (16), since the *in vivo* hydrolysis of aspirin is very much more rapid than the *in vivo* elimination of salicylate (15).

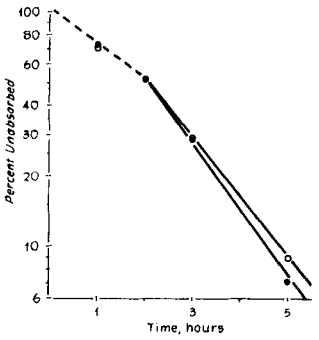

Fig. 4.—Absorption of 1 Gm. of aspirin administered in an experimental prolonged - release dosage form. (Subject *G*.) Key: ●, first test; O, second test.

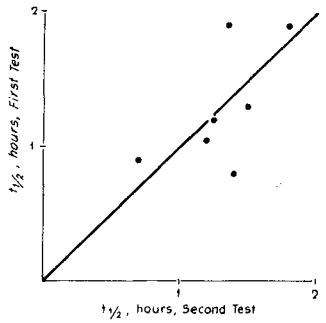

Fig. 5.—Scatter plot of individual half-lives for aspirin absorption from an experimental prolonged-release dosage form determined in two separate tests on seven subjects. Line (slope 1.0) indicates position of points if correlation between tests had been perfect.

Kinetics of Absorption from Prolonged-Release Dosage Form.—The absorption of aspirin from the prolonged-release dosage form was describable in most instances as a first-order process which was preceded by an initial apparent lag phase. A typical example is shown in Fig. 3, which represents a semilogarithmic plot of per cent of dose unabsorbed as a function of time. The slope of the line was based on at least three experimental points in 10 out of 14 experiments. In four experiments, only two experimental points were available for this purpose. However, each of these cases involved subjects who had yielded three or more experimental points to characterize at least one out of the two sets of experimental data as being describable by first-order kinetics. It will be appreciated that relatively slow and variable absorption makes it very difficult to obtain blood samples always at times which are ideal for subsequent kinetic analysis.

The lag time preceding absorption probably is only an apparent characteristic representative of an initial slow absorption phase. The latter could be noted definitely in four out of 14 experiments [subjects *G* (both times), *E*, and *F*] and is exemplified in Fig. 4.

Apparent lag times (based on extrapolation of the line fitted to data points depicting the major phase of drug absorption) and half-lives for drug absorption are listed in Table II for 14 experiments on seven subjects. There was a pronounced inter- and intrasubject variation in apparent lag times but a much smaller variation in absorption half-lives. A scatter plot of the latter (Fig. 5) suggests a consistency of values in any one subject, thereby indicating the possible existence of "slow" and "rapid" absorbers. However, the correlation was not statistically significant (correlation coefficient = 0.62), possibly due to the limited number of test subjects participating in the study. There was good reproducibility of the *average* lag times and absorption half-lives in the two experiments despite the variability of individual data. Similar good reproducibility of average data (despite pronounced variation of individual values) has been observed in a previously reported study (2) and in other unpublished investigations.

Relationship Between Absorption and Dissolution Rates.—The range of individual absorption half-lives (0.70 to 1.9 hr.) falls in the range of the *in vitro* dissolution half-lives obtained by using agitation intensities of from 30 to 60 r.p.m. (0.60 to 2.3 hr.). The mean absorption half-life (1.3 hr.) is equivalent to the *in vitro* dissolution half-life obtained by using an agitation intensity of about 50 r.p.m. in the Levy-Hayes procedure. The ratio of the average *in vitro* dissolution rate constant at 60 r.p.m. to the average *in vivo* absorption rate constant is about 2.2. In previous studies, which probably involved aspirin absorption mainly from the stomach and proximal small intestine, *in vitro* : *in vivo* ratios of 3.0 and 8.5 were obtained (1, 2).

Interpretations of these results are, of necessity, somewhat equivocal. The pronounced intersubject variations of absorption half-lives may be due to differences in intestinal agitation intensity. (Such differences can reflect variations in peristaltic activity and/or in the diameter of the intestinal lumen.) This interpretation is based on the marked sensitivity of drug dissolution from the prolonged-release dosage form to changes in agitation intensity and on the relative insensitivity of the dissolution process to changes in pH. The average *in vitro*: *in vivo* ratio [also called intensity factor (2)] of 2.2 is lower than the ratios obtained in other studies (1, 2) where *in vivo* dissolution probably occurred mainly in the stomach. These results are in agreement with the substance of a previous discussion by Levy (12) who, in considering gastric and intestinal absorption of aspirin, stated that "much greater agitative forces are brought to bear upon aspirin solids in the intestine due to the greater proximity of peristaltic waves by reason of the small intestinal lumen." Since *in vivo* dissolution of aspirin from the prolonged-release dosage form occurred mainly in the intestine rather than in the stomach, the difference in *in vitro* : *in vivo* ratios is to be expected.

The apparent absorption lag times (Table II) probably reflect the time required for the dosage form to be transferred from stomach to intestine. It is known that the gastric emptying rate of solid objects is extremely variable between individuals as well as between tests in any one individual (3, 13, 14), and the pronounced variability of the apparent lag times is consistent with these findings. The initial slow absorption phase evident in four experiments on three subjects is interpreted to be an indication of the slower drug dissolution in the stomach due to milder agitation conditions and lower pH. Such gastric emptying effects are not as noticeable with dosage forms which release drug relatively rapidly in the gastric environment.

TABLE II.—APPARENT LAG TIMES AND ABSORPTION HALF-LIVES OF ASPIRIN ADMINISTERED IN EXPERIMENTAL PROLONGED-RELEASE DOSAGE FORM ON TWO DIFFERENT OCCASIONS

Subject	Lag Time, hr. First Test	Lag Time, hr. Second Test	Absorption Half-Life, hr. First Test	Absorption Half-Life, hr. Second Test
A	1.20	0.72	0.80	1.4
B	0.03	2.90	1.3	1.5
C	2.67	0.56	1.2	1.25
D	1.66	0.95	1.9	1.35
E	1.95	0.60	0.90	0.70
F	0.65	1.52	1.9	1.8
G	1.03	0.86	1.05	1.2
Mean	1.31	1.16	1.29	1.31
Mean of both tests	1.23		1.30	

tests, with 46 out of 60 data points being within ± 15% of perfect correlation. Comparison of the data shown in Figs. 6 and 7 is limited somewhat since (*a*) different subjects were used, and (*b*) the prolonged-release dosage form was given 1 hr. after a light breakfast, while the conventional tablets were given on empty stomachs. However, interpretation of the results is not hindered appreciably by these differences since it is *not* suggested that aspirin absorption from the rapidly available dosage form was more reproducible than from the prolonged-release dosage form. Inspection of actual absorption data (Fig. 5 and Table II in the present paper and Fig. 12 in *Reference 2*) shows that absorption kinetics were quite variable with both dosage forms. However, absorption was completed before the third hour when conventional tablets were given, but took considerably longer when the drug was administered

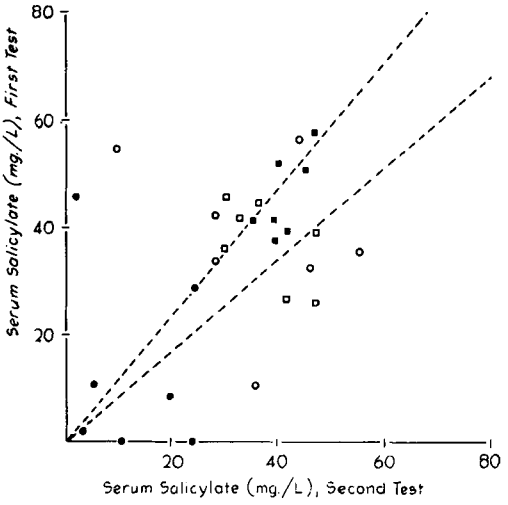

Fig. 6.—Plot of individual serum salicylate concentrations at various times after oral administration of 1 Gm. of aspirin in prolonged-release form in two separate tests on seven subjects. Key: ●, 1 hr.; ○, 3 hr.; ■, 5 hr.; □, 7 hr. after drug administration; – – – enclose data points within ±15% of perfect correlation.

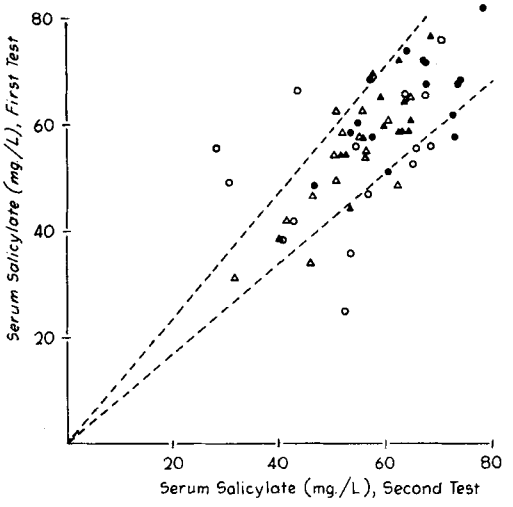

Fig. 7.—Plot of individual serum salicylate concentrations at various times after oral administration of 1 Gm. of aspirin in compressed tablets in two separate tests on 15 subjects. Key: ○, 1 hr.; ●, 2 hr.; ▲, 3 hr.; △, 4 hr.; – – – enclose data points within ±15% of perfect correlation.

Effect of Absorption Rate on Intrasubject Variation of Salicylate Blood Levels.—The clinical importance of variations in drug absorption rates is related largely to the resulting variability in the blood and tissue levels of the drug. A plot of individual serum salicylate concentrations obtained 1, 3, 5, and 7 hr. after administration of aspirin in prolonged-release form in two separate tests (Fig. 6) shows a pronounced variability between tests. Only five out of 28 points are within ± 15% of perfect correlation. Unfortunately, similar data on rapidly absorbable compressed tablets were not available for comparison since only one absorption test could be carried out with compressed tablets. However, data are available from a previous study (2) where aspirin was given twice in the form of rapidly dissolving compressed tablets. These data, presented in Fig. 7, show much better reproducibility between

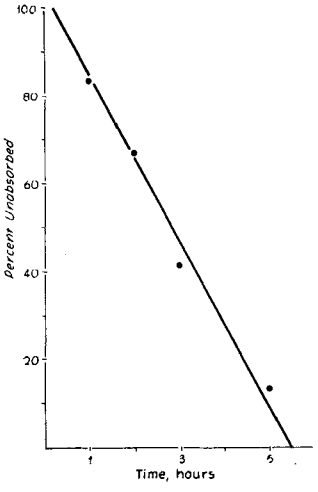

Fig. 8.—Plot of average per cent aspirin unabsorbed as a function of time after administration of 1 Gm. of aspirin in experimental prolonged - release dosage form. Based on 14 experiments on seven subjects.

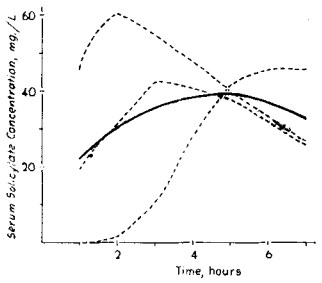

Fig. 9.—Apparent plateau serum salicylate level (——) obtained by averaging individual levels (– – –) resulting from rapid, intermediate, and slow absorption of aspirin.

in prolonged-release form. As a result, almost all the blood level data points shown in Fig. 6 are affected by absorption rate. On the other hand, only the first hour blood levels presented in Fig. 7 are affected significantly by absorption rate, and only these data points show pronounced variability. The reproducibility of blood levels of a drug in any one individual depends largely on the variability of absorption and elimination rates,[2] and the effect of the former on postabsorption blood levels increases as the ratio of the rate constant for absorption to the rate constant for elimination decreases (15).

Errors in Interpretation Which May be Introduced by Use of Average Data.—The authors have pointed out previously that a kinetic model based on average data is meaningful only if all or the majority of individual data can be fitted satisfactorily to that model (2). When the individual absorption data obtained in the presented study are averaged, one obtains values which indicate absorption by zero-order kinetics (Fig. 8). This artifact resulting from averaging individual data reflecting different first-order rate constants and lag times could be misinterpreted as being indicative of constant rate absorption, a characteristic which (were it actually existing) would make the dosage form a potentially good sustained-release preparation which could be used to maintain drug levels obtained initially by administration of drug in rapidly absorbed form.

Another example of how average data can be misleading is illustrated in Fig. 9. Dosage forms exhibiting wide variations in apparent lag times for absorption (due, for example, to variations in gastric emptying rate) will yield maximum blood levels at widely different times. When blood levels obtained after administration of such dosage forms are averaged, one obtains a relatively flat curve or plateau for an appreciable time. The average serum salicylate curve shown in Fig. 9 shows this effect—the example was not biased by use of the particular three sets of data since the average curve thus obtained is quite similar to the average curve based on all 14 sets of data (which cannot be depicted adequately in a single figure). The examples presented here argue strongly against the evaluation of potential or purported sustained-release products on the basis only of average data; it is necessary to examine individual data in order to establish the presence or absence of the required or desired sustained-release characteristics.

[2] Possible changes in volume of distribution (due to disease or administration of other drugs) are not being considered in the present discussion.

REFERENCES

(1) Levy, G., *Arch. Intern. Pharmacodyn.*, **152**, 59(1964).
(2) Levy, G., and Hollister, L. E., *J. Pharm. Sci.*, **53**, 1446(1964).
(3) Leonards, J. R., and Levy, G., *J. Am. Med. Assoc.*, to be published.
(4) Levy, G., and Hayes, B. A., *New Engl. J. Med.*, **262**, 1053(1960).
(5) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 1073.
(6) Trinder, P., *Biochem. J.*, **57**, 39(1954).
(7) Smith, P. K., *et al.*, *J. Pharmacol. Exptl. Therap.*, **87** 237(1946).
(8) Levy, G., to be published.
(9) Wagner, J. G., and Nelson, E., *J. Pharm. Sci.*, **52**, 610 (1963).
(10) Levy, G., and Procknal, J. A., *ibid.*, **53**, 656(1964).
(11) Hollister, L. E., and Levy, G., *ibid.*, **54**, 1126(1965).
(12) Levy, G., *ibid.*, **50**, 388(1961).
(13) Blythe, R. H., Grass, G. M., and MacDonnell, D. R., *Am. J. Pharm.*, **131**, 206(1959).
(14) Nelson, E., *Clin. Pharmacol. Therap.*, **4**, 238(1963).
(15) Levy, G., *Anesthesia Analgesia Current Res.*, to be published.
(16) Nelson, E., *J. Pharm. Sci.*, **54**, 1075(1965).