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Studies on Dissolution Tests of Solid Dosage Forms. IV.[1] Relation of Absorption Sites of Sulfonamides administered orally in Solid Dosage Form to Their Solubilities and Dissolution Rates

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The relation of absorption sites of sulfonamides administered orally in uncoated tablets to their solubilities and dissolution rates was studied. Eight sulfonamides, sulfisomidine, sulfamethoxypyridazine, sulfamethizole, sulfamethoxazole, sulfisoxazole, sulfamonomethoxine, sulfaphenazole and sulfadimethoxine, were tested to determine their solubilities, dissolution rates and absorption rates following oral administration to humans. As a marker of gastric emptying time, the lag time of the urinary excretion of total salicylate was determined after the concurrent administration of enteric tablets of aspirin.

A new parameter, RAAS (Relative Amount Absorbed in the Stomach) is proposed in order to represent the relative amount absorbed in the stomach region. RAAS values showed good correlations with the solubilities and dissolution rates of sulfonamides determined by means of the Sartorius solubility simulator with continuous pH change under non-sink conditions.

It was concluded that:

1) The critical value of the solubility which distinguishes drugs according to their absorption sites, stomach or intestine, is about 3 mg/ml in 0.1 N HCl at 37° when 1 g of the drug is administered to humans orally with 200 ml of water after overnight fasting.

2) A drug having a solubility larger than the critical value can reasonably be tested for dissolution rate in an acidic medium, and a drug having a solubility less than the critical value should be tested under neutral conditions after pretreatment in acidic conditions.

Keywords——dissolution test; bioavailability in human; sulfonamide tablet; solubility; dissolution rate; gastric emptying time; enteric coated tablet of aspirin; pH value of test solution

In this series of studies,[1,3,4] various conditions to be attached to the dissolution test have been studied from the view point of the secondary means for testing the bioavailability of solid dosage forms.

pH values of about 1 and 7 are usually used for dissolution tests to simulate the stomach region and the intestine, respectively. However, it is not clear which pH should be chosen for testing a particular drug, and whether the volume and pH value should be kept constant during the test.

1) Part III: H. Ogata, T. Shibazaki, T. Inoue, and A. Ejima, *J. Pharm. Sci.*, in press.
2) Location: *1-18-1 Kamiyoga, Setagayaku, Tokyo.*
3) H. Ogata, S. Suzuki, T. Shibazaki, A. Ejima, and T. Inoue, *Yakugaku Zasshi*, **98**, 823 (1978).
4) H. Ogata, T. Shibazaki, T. Inoue, and A. Ejima, *J. Pharm. Sci.*, in press.

The purpose of this paper is to clarify the factors to be considered in selecting a pH value for the medium and other conditions for dissolution tests. Sulfonamides were used in this study because they have many derivatives with various solubilities, are absorbed passively from both the stomach and intestine,[5] and are commercially available as uncoated tablets which can be disintegrated and dispersed easily.

Experimental

Materials——Sulfonamide: Commercially available uncoated tablets used were as follows; sulfisomidine (SIM; 500 mg),[6] sulfamethoxypyridazine (SMP; 250 mg), sulfamethizole (SMZ; 250 mg), sulfamethoxazole (SMX; 500 mg), sulfisoxazole (SIX; 500 mg), sulfamonomethoxine (SMM; 500 mg), sulfaphenazole (SPZ; 500 mg), sulfadimethoxine (SDM; 250 mg). These tablets disintegrated in a few minutes. Powders used were commercially available in Japan. Enteric coated aspirin tablets were also used (Shionogi Co., Ltd.; 250 mg of aspirin, 25 mg of ascorbic acid). Other chemicals used were of reagent grade.

Determination of the Solubility of Sulfonamide——A centrifuge tube containing 30 ml of 0.1 N HCl and 0.5 to 3.0 g of a sulfonamide powder was tightly sealed and shaken at 37°. The concentration of the dissolved drug was determined spectrophotometrically following filtration with a Millipore filter (type EH; pore size 0.5 μm), and the procedures were repeated every 24 hr until a constant concentration was obtained.

***In Vitro* Dissolution Test**——The dissolution rates of sulfonamides from uncoated tablets were determined by the following two methods.

a) Levy's Beaker Method (BE)[7]: This method was used to obtain the dissolution rate under sink conditions. A tablet was cut to an appropriate cube containing about 20 mg of the drug (cut tablet). The test was performed in a 500 ml beaker with a flat bottom (8 cm inner diamter) containing 400 ml of the medium at 37°. The medium was stirred by means of a three-bladed impeller (4.5 cm × 1.5 cm) at 48 rpm at a distance of 4.5 cm from the bottom of the beaker. A cut tablet was placed freely on the bottom. The medium used was 0.1 N HCl containing 0.01% polysorbate 80 (PS-80). The concentration of the drug dissolved in the medium was determined spectrophotometrically after filtration through cotton.

b) Sartorius Solubility Simulator Method (SSS): The procedures were the same as those reported previously,[4] with some exceptions. The test was carried out with a tablet containing 250 mg of a sulfonamide using 0.1 N HCl containing 0.01% PS-80 for 110 min. If the drug had not dissolved completely by that time, 1.55 g of Tris(hydroxymethyl)aminomethane was added to the dissolution chamber, and the medium was replaced with pH 7.6 Tris buffer containing 0.01% PS-80. It took ten to fifteen minutes for the pH value in the chamber to adjust to 7.6.

Absorption Test in Humans——Six healthy male volunteers, aged 22—48 years and weighing 52—72 kg, participated. After fasting overnight the subjects took tablets containing 1.0 g of a sulfonamide and an enteric coated tablet of aspirin (250 mg) with 200 ml of water. They took 100 ml of water at 2 hr and had lunch at 4 hr after administration. From 4 hr after drug dosing, food and beverages (non-alcoholic) were taken *adlibitum*. Urine samples were collected just before and at about 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hr after dosing.

Determination of Sulfonamide in Urine——For sulfonamides other than SDM, the concentration of the drug in the urine was determined by the colorimetric method.[5] N^1-conjugated sulfonamide may also be determined by this method, in addition to the parent compound. However it is reasonable to presume that the unchanged compound was predominantly determined in these cases, because very little of the N^1-conjugated form of these sulfonamides was detected in human urine.[8] In the case of SDM, the unchanged form must be determined after separation from its N^1-glucuronide since about 80% of SDM is excreted as that form in humans.[8] The separation procedure was as follows. One ml of urine was diluted to fifty ml with pH 4.0 phosphate buffer. Thirty ml of chloroform was added to 25 ml of the diluted urine, and the mixture was shaken vigorously for 30 min. Twenty-five ml of the organic layer was shaken with 5 ml of 3 N HCl, then 4 ml of the acidic aqueous layer was taken for assay of the unchanged form by the colorimetric method.[5]

Determination of Total Salicylate in Urine——Total salicylate excreted in the urine was determined by the colorimetric method.[9]

5) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.* (Tokyo), **12**, 413 (1964); *idem*, *ibid.*, **12**, 421 (1964).
6) The numbers in parentheses are the dose per tablet.
7) G. Levy and B.A. Hayes, *New England J. Med.*, **262**, 1053 (1960).
8) T. Uno and R. Konishi, "Drug Transfer in Biological Systems," ed. by M. Nakagaki, Nankodo Co., Ltd., Tokyo, 1968, pp. 227—285.
9) W.L. Chiou and I. Onyemelukwe, *J. Pharm. Sci.*, **63**, 630 (1974).

Results

Table I shows the solubilities of sulfonamides in 0.1 N HCl at 37°.

Table I. Solubility of Sulfonamides in 0.1 N HCl at 37°

Sulfonamide	Solubility (mg/ml)
Sulfisomidine	49.418
Sulfamethoxypyridazine	17.243
Sulfamethizole	9.172
Sulfamethoxazole	3.140
Sulfisoxazole	1.440
Sulfamonomethoxine	1.336
Sulfaphenazole	1.199
Sulfadimethoxine	0.606

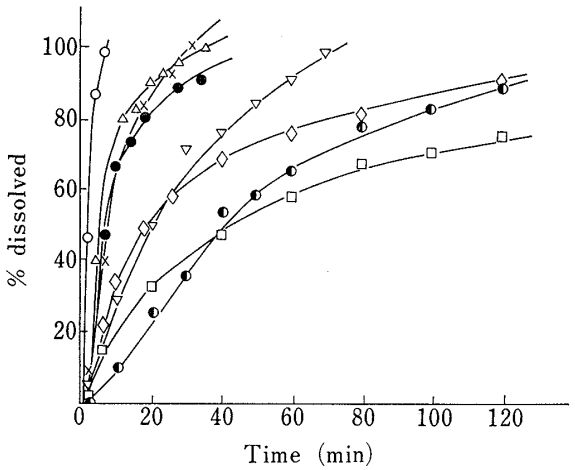

Fig. 1. Dissolution Rate Curves of Sulfonamides from Uncoated Tablets measured by the BE Method under Sink Conditions in 0.1 N HCl Containing 0.01% PS-80

Sulfonamides: ○, SIM; ×, SMP; △, SMZ; ▽, SMX; ●, SIX; □, SMM; ◇, SPZ; ◐, SDM.

Figure 1 shows the dissolution curves of sulfonamides from uncoated tablets in 0.1 N HCl containing 0.01% PS-80, measured by the BE method under sink conditions.

Figure 2 shows the dissolution curves of sulfonamides from uncoated tablets measured by the SSS method. As the amount of drug was 250 mg and the volume of the medium was 100 ml, it is reasonable to consider that the drug was dissolved under non-sink conditions. Saturation was observed with SIX, SPZ, SMM and SDM under acidic conditions, and they dissolved faster after the pH of the medium was increased to 7.6. SIX showed an apparent

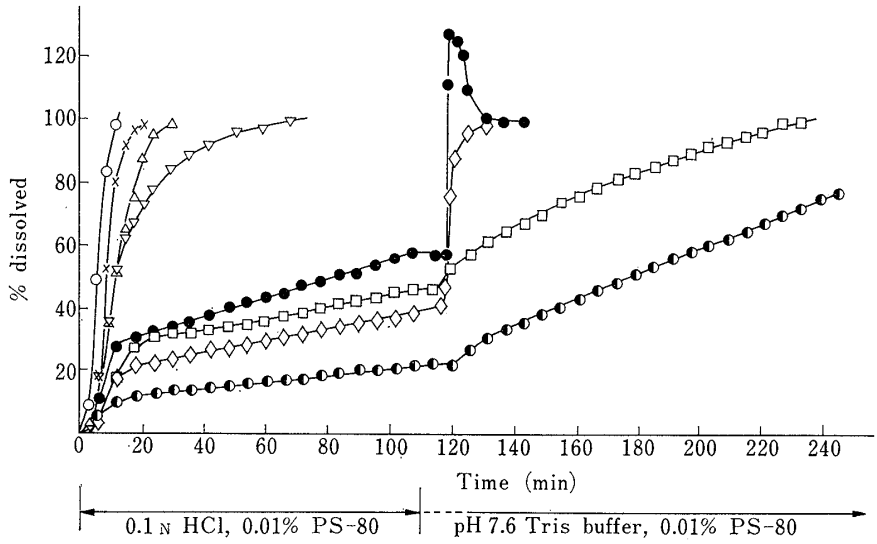

Fig. 2. Dissolution Rate Curves of the Sulfonamides from Uncoated Tablets measured by the SSS Method under Non-Sink Conditions with Continuous pH Change

Sulfonamides: ○, SIM; ×, SMP; △, SMZ; ▽, SMX; ●, SIX; □, SMM; ◇, SPZ; ◐, SDM.

increase in concentration to 120% solubility just after the change of pH of the medium, seeming to become supersaturated. However, this concentration of SIX is far less than the saturation concentration at pH 7.6. This phenomenon may be attributed to an apparent localized increase of drug concentration due to the poor agitation in the SSS method.[4]

The urinary excretion rate-time curves of SIM and total salicylate, and of SDM and total salicylate in one subject are shown in Fig. 3. In all the total salicylate excretion curves, a lag period was observed because the aspirin was administered orally as an enteric coated tablet. The lag time may be considered as a marker representing the gastric emptying time, though it may be affected by other factors. As shown in Fig. 3, SIM and SDM, which have

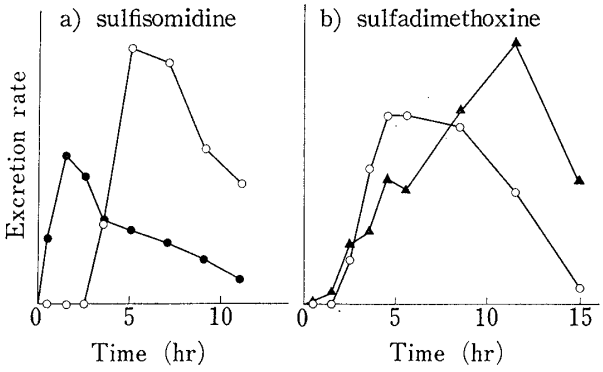

Fig. 3 Examples of Urinary Excretion Rates of Sulfonamide and Total Salicylate after Oral Administration of Uncoated Tablets of Sulfonamide (1.0 g) and Enteric Coated Tablets of Aspirin (250 mg)

●, sulfisomidine; ▲, sulfadimethoxine; ○, total salicylate.

Table II. Relative Amount absorbed in the Stomach (RAAS) for Sulfonamides

Sulfonamide	RAAS
Sulfisomidine	1.592
Sulfamethoxypyridazine	0.735
Sulfamethizole	1.000
Sulfamethoxazole	0.406
Sulfisoxazole	0.101
Sulfamonomethoxine	0.319
Sulfaphenazole	0.063
Sulfadimethoxine	0.008

widely different solubilities, show a marked difference in their absorption patterns. SIM (high solubility) was absorbed very fast and showed the maximum excretion rate at 1.5 hours, though total salicylate had not appeared by this time. On the other hand, SDM (low solubility) was absorbed slowly, and reached the maximum excretion rate more than 12 hours after dosing. The absorption patterns of SDM and total salicylate seem to parallel each other, especially until 2 hours after dosing. SDM must be absorbed faster than SIM conversely if the difference of their intrinsic absorption rates were attributable to the difference of their absorption patterns. The results observed in Fig. 3 show clearly that absorption of drugs administered orally in solid dosage form is rate-limited by the dissolution process. SIM may be absorbed mainly from the stomach region because of its high solubility under acidic conditions. On the other hand, SDM may be absorbed mainly from the intestinal region after transfer from the stomach because of its very poor solubility under acidic conditions.

If it is considered that the lag time observed in the urinary excretion of salicylate dosed in enteric form represents the gastric emptying time of a sulfonamide administered concurrently with the enteric coated aspirin tablet, a new parameter (RAAS) can be proposed to represent the relative amount absorbed in the stomach of a drug administered orally in solid dosage form, as follows;

$$\text{RAAS (Relative Amount Absorbed in the Stomach)} = \frac{M_{\text{stomach}}}{M_{\text{peak}}}$$

where M_{stomach} and M_{peak} represent the amount of the drug excreted in urine during the lag time of excretion of total salicylate, and that by the time of maximum excretion rate, respectively. Table II shows the values of the proposed parameter, RAAS. These are mean values of two or three experiments.

Discussion

The pharmacokinetic profiles of sulfonamides may be changed by concurrent administration of aspirin,[10] and the time of the maximum urinary excretion rate is a rather vague value because it is determined as the time when the rates of absorption and elimination become equal, and these rates are variable among different drugs. No simple methodology has been developed to study the absorption process in the human gastro-intestinal tract without causing discomfort to the subject, and studies in humans have been difficult. Thus, even though there may be some problems in connection with the parameter, RAAS, it should be valuable in studying the absorption profiles of drugs administered orally in solid dosage form.

The values of RAAS, which represent the relative absorption rates related to gastric emptying time, did not correlated well with the dissolution rates determined in 0.1 N HCl

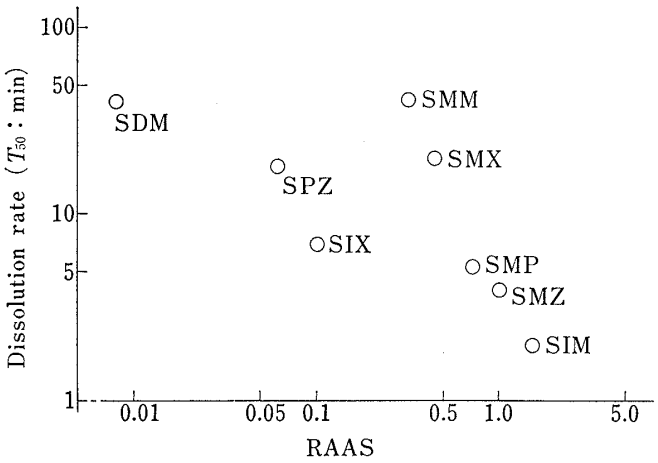

Fig. 4. Correlation of RAAS with Dissolution Rates of Sulfonamides measured in 0.1 N HCl under Sink Conditions

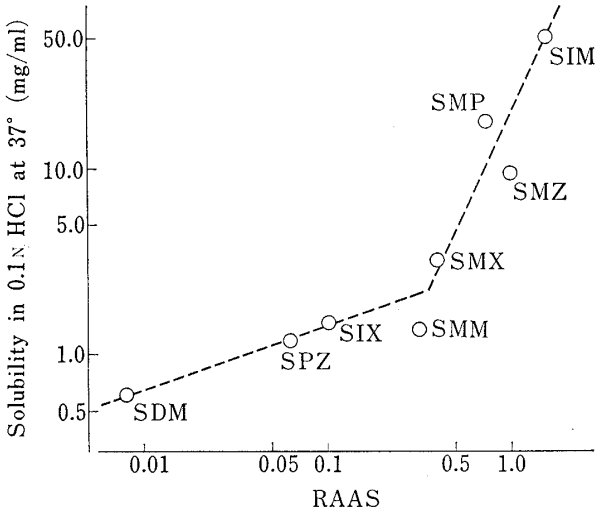

Fig. 5. Correlation of RAAS with the Solubility of Sulfonamides

under sink conditions by the BE method (r=0.6924), as shown in Fig. 4. On the other hand, the sulfonamides studied seem to show good correlations between RAAS values and solubilities (Fig. 5), and between RAAS and the dissolution rates determined by the SSS method under non-sink conditions with a continuous pH change (Fig. 6). As the time period under acidic conditions is arbitrary, two different values of the rates were taken in Fig. 6. One was T_{50} (the time of 50% dissolution) from Fig. 3, in which the acidic period was 120 minutes, and the

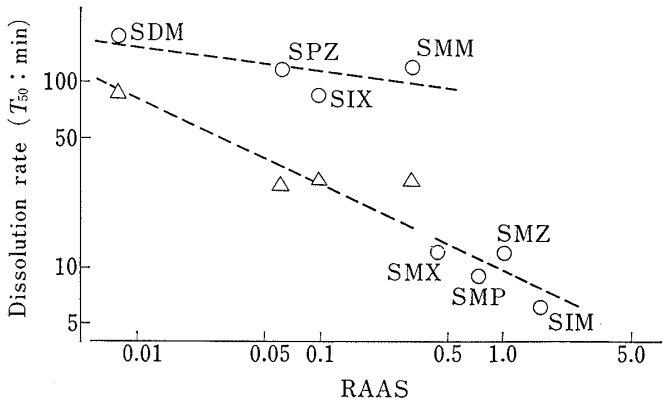

Fig. 6. Correlation of RAAS with Dissolution Rates of Sulfonamides measured by the SSS Method

○; the dissolution rate measured with an acidic period of 120 minutes, △; the rate corrected on the assumption that the acidic period was 30 minutes.

10) Y. Imamura, K. Shigemori, and H. Ichibagase, *Chem. Pharm. Bull.* (Tokyo), **22**, 2324 (1974).

other was the value corrected by subtracting 90 minutes from the former values for SDM, SPZ, SIX and SMM, assuming that the acidic period is 30 minutes, which corresponds to the time when the saturation phenomena appeared.

Judging from Fig. 5, sulfonamides having solubilities of more than 3 mg/ml in 0.1 N HCl seem to be absorbed mainly from the stomach, and ones having lower solubilities seem to be absorbed mainly after transfer to the intestine. This classification is also reflected in the rates of dissolution determined by the SSS method (Fig. 6). The conditions of the SSS method seem suitable to get *in vitro* dissolution rates that correlate well with *in vivo* data. As shown in Fig. 6. when the acidic period was 120 minutes, two different regression lines were obtained and two groups could be classified clearly according to their solubilities (Fig. 5). However, with a 30 minute period, all the sulfonamides fitted a single regression line (r=0.9400).

In summary, 1) The critical value of solubility which distinguishes drugs according to their absorption sites, stomach or intestine, is about 3 mg/ml in 0.1 N HCl at 37° when 1 g of the drug is administered orally with 200 ml of water after overnight fasting in humans. 2) Considering the solubility of the drug, the conditions for dissolution tests must be appropriate. A drug having a solubility larger than the critical value can reasonably be tested for dissolution rate in an acidic medium, while a drug having a solubility less than the critical value should be tested under neutral conditions after pretreatment in acidic conditions.

These conclusions are based on intrinsic physical properties of drugs, and it may be difficult to correlate the dissolution test data for a drug in various dosage forms with the bioavailability. However, these conclusions should aid in selecting suitable conditions for dissolution tests as a first step.

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