In Vivo–In Vitro Correlations with a Commercial Dissolution Simulator II: Papaverine, Phenytoin, and Sulfisoxazole

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Received February 19, 1982, from the *Division of Biopharmaceutics and Pharmacokinetics, Department of Pharmaceutics, College of Pharmacy, University of Tennessee, Center for the Health Sciences, Memphis, TN 38163.* Accepted for publication June 15, 1982.

Abstract □ The dissolution profiles of 11 commercially available papaverine, phenytoin, and sulfisoxazole dosage forms were determined using a dissolution simulator. The products had been the subject of earlier *in vivo* bioavailability studies with human subjects. The use of an absorption simulator, which is designed to provide an estimate of the optimum sampling scheme for the dissolution simulator, did not provide useful data for this purpose. Good *in vivo–in vitro* correlations were found for the papaverine dosage forms, which included nine controlled-release products. Less satisfactory correlations were obtained for the phenytoin capsules and the sulfisoxazole tablet products.

Keyphrases □ *In vivo–in vitro* correlations—papaverine, phenytoin, and sulfisoxazole using a commercial dissolution simulator □ Papaverine—*in vivo–in vitro* correlations using a commercial dissolution simulator □ Phenytoin—*in vivo–in vitro* correlations using a commercial dissolution simulator □ Sulfisoxazole—*in vivo–in vitro* correlations using a commercial dissolution simulator

An earlier paper (1) described attempts to correlate the *in vitro* dissolution and *in vivo* bioavailability of several solid dosage forms, using commercial absorption[1] and dissolution[2] simulators. That study involved the testing of marketed methenamine, nitrofurantoin, and chlorothiazide dosage forms, which had been the subject of human urinary excretion bioavailability studies. Marketed dosage forms of papaverine, phenytoin, and sulfisoxazole, which were previously evaluated in human bioavailability studies (2–4) using plasma concentration measurements, are the subject of the present study.

EXPERIMENTAL

Absorption Simulator Studies—The design and application of the absorption simulator were described previously (1); the experimental conditions were essentially identical to the earlier study. The initial drug concentrations employed in the absorption studies were as follows: papaverine, 100 and 200 μg/ml; phenytoin, 30 μg/ml; and sulfisoxazole, 200 μg/ml. The surface areas of the artificial lipid barriers[3] were as follows: papaverine, 80 cm^2 and 12 cm^2 for the gastric phase; phenytoin, 40 cm^2 for the gastric phase, 80 cm^2 for the intestinal phase; and sulfisoxazole, 40 cm^2 for both the gastric and intestinal phase studies.

Dissolution Simulator Studies—The experimental approach and the design of the dissolution simulator were discussed previously (1). The following sampling rates were utilized: papaverine, 2.5 ml every 4 min for 56 min in the gastric phase and every 6 min for 123 min in the intestinal phase; sulfisoxazole, 2.5 ml every 2.5 min for 32 min in the gastric phase and 188 min in the intestinal phase; phenytoin, 7.5 ml every 0.5 min for 46 min (gastric phase), using distilled water as the dissolution medium.

The 11 papaverine hydrochloride dosage forms, previously identified (2), consisted of one elixir (150 mg/22.5 ml), eight 150-mg sustained-release capsules, one 200-mg sustained-release tablet, and one 30-mg compressed tablet (with a five-tablet dosage). The 11 phenytoin dosage forms were each 100-mg capsules of sodium phenytoin (3), and the 11 sulfisoxazole tablets each contained 500 mg of drug (4).

Analytical Methods—All drug solutions obtained from the absorption and dissolution studies were assayed spectrophotometrically at a wavelength appropriate for the drug and solvent. Papaverine solutions were diluted with 0.06 *N* hydrochloric acid and measured at 252 nm. Sulfisoxazole solutions, diluted when necessary with the buffer solutions employed in the absorption and dissolution studies, were measured at 253 and 267 nm for the pH 6.5 and 1.3 buffer solutions, respectively. In preliminary studies it was determined that constituents of the phenytoin capsules appeared to interfere in the direct spectrophotometric analysis of dissolution samples. Therefore, dissolution samples were acidified with 3 drops of hydrochloric acid, extracted into 20 ml of chloroform–ethanol (20:1, v/v), and back-extracted into 5 ml of 0.1 *N* sodium hydroxide. The aqueous solution was then measured spectrophotometrically at 230 nm. Phenytoin samples obtained with the absorption simulator were diluted with 0.1 *N* sodium hydroxide and measured directly at 230 nm.

Treatment of Dissolution Data—Two approaches were employed in the analysis of the dissolution rate data: simulated absorption data and general correlations. These procedures were described in detail previously (1), using urinary excretion data.

According to the manufacturer of the dissolution simulator (5, 6), the cumulative amount of drug withdrawn from the dissolution vessel (*Mi*) is related to the cumulative amount of drug absorbed *in vivo*. Using the

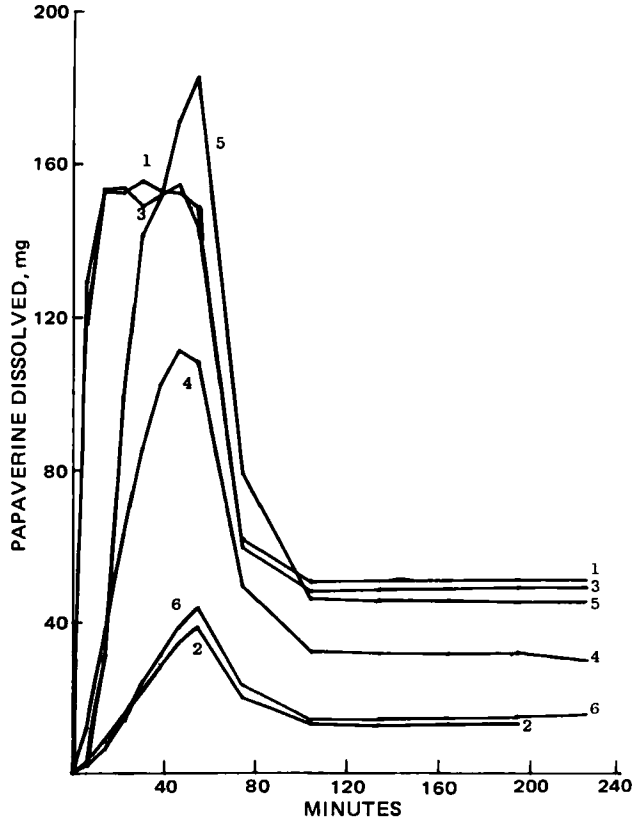

Figure 1—*Dissolution profiles for six papaverine formulations in study group 1. Each data point is the mean of two determinations. The simulated intestinal phase began after 56 min.*

[1] Sartorius Absorption Simulator SM 16753, Sartorius Filters, Inc., San Francisco, Calif.

[2] Sartorius Dissolution Simulator SM 16752, Sartorius Filters, Inc., San Francisco, Calif.

[3] Artificial Gastric Lipid Barrier SM 15701 and Artificial Intestinal Lipid Barrier SM 15702, Sartorius Filters, Inc., San Francisco, Calif.

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Table I—Diffusion Characteristics and Sampling Rates Determined with the Absorption Simulator

Drug	$K_d \times 10^3$, cm/min^{-1} [a]		Time Between Samples, min			
			Calculated [b]		Actual	
	Gastric Phase	Intestinal Phase	Gastric Phase	Intestinal Phase	Gastric Phase	Intestinal Phase
Papaverine	—	—	—	—	4.0	6.0
Phenytoin	12.99	26.60	1.90	0.94	0.5	—
Sulfisoxazole [c]	9.62	10.02	2.6	2.5	2.6	2.5

[a] Diffusion rate constant, calculated according to Stricker (5). [b] Theoretical sampling rates for the dissolution simulator, calculated from absorption simulator diffusion rate according to the method of Stricker (5). [c] Values represent the mean of two determinations.

previously obtained plasma concentration data for each drug, the amount of drug absorbed (A_t) was calculated from:

$$\frac{A_t}{V_d} = C_t + K(\mathrm{AUC})_{0-t}$$

based on the Wagner–Nelson method (7). In this equation, V_d is the apparent volume of distribution; C_t is the plasma concentration at time t; K is the apparent first-order elimination rate constant, assuming a one-compartment model involving first-order absorption and elimination; and $(\mathrm{AUC})_{0-t}$ is the area under the plasma concentration–time curve over the time period 0–t, estimated with the trapezoidal rule. A direct comparison could not be made of the amount of dissolved drug withdrawn from the dissolution fluid (*Mi*) and the amount of drug absorbed *in vivo* (A_t) because the V_d term could not be estimated accurately from the *in vivo* data. To relate the amount dissolved *in vitro* to the *in vivo* plasma drug concentrations, plots were constructed of A_t/V_d *versus Mi*. The slope of the least-squares line forced through the origin was then used to adjust the A_t/V_d data.

A wide variety of correlations were also attempted to relate the *in vitro* and *in vivo* data. Initially, the dissolution rate profiles were examined systematically to determine dissolution rate parameters which exhibited a reasonable rank-order relationship to a given *in vivo* parameter. The correlation was then evaluated further from the statistical analyses of plots of *in vivo versus in vitro* data. The various *in vivo* values considered included the maximum plasma drug concentration, the time of maximum plasma concentration, the total area under the plasma concentration–time curve (AUC) at specific times, the time to achieve a given percent of the total AUC, and the percent of total AUC achieved at a given time. The *in vitro* values tested included the time for a given percentage of drug to be dissolved, the area under the dissolution–time profile at a given time, and the percentage of drug dissolved at a given time.

RESULTS AND DISCUSSION

Analytical Methods—The spectrophotometric methods employed for the analysis of samples obtained with the absorption and dissolution simulator were all relatively simple, and the linearity and reproducibility of the standard curves were excellent. The correlation coefficients describing the various standard curves were all >0.999. The slopes of these curves were reproducible on a daily basis and exhibited relative standard deviations of <3% for three to six determinations.

Absorption Simulator—According to Stricker (5), the diffusion rate constants obtained with the absorption simulator may be employed to determine the optimal sampling rates for the dissolution apparatus. The apparent first-order diffusion rate constants obtained with the absorption simulator are given in Table I, along with the theoretical optimal sampling rates and the sampling rates which were actually employed.

Attempts to study the diffusion of papaverine across the lipid barriers were not successful. The limited solubility of the drug in the receptor fluid (pH 7.5) and the apparent retention of the drug within the membrane resulted in negligible diffusion. Attempts to increase the rate of diffusion with a membrane of smaller surface area (12 cm^2) and a higher papaverine concentration (200 ng/ml) failed to provide adequate diffusion. Thus, the selection of sampling intervals of 4 min (gastric phase) and 6 min (intestinal phase) was based on preliminary trials with the dissolution simulator.

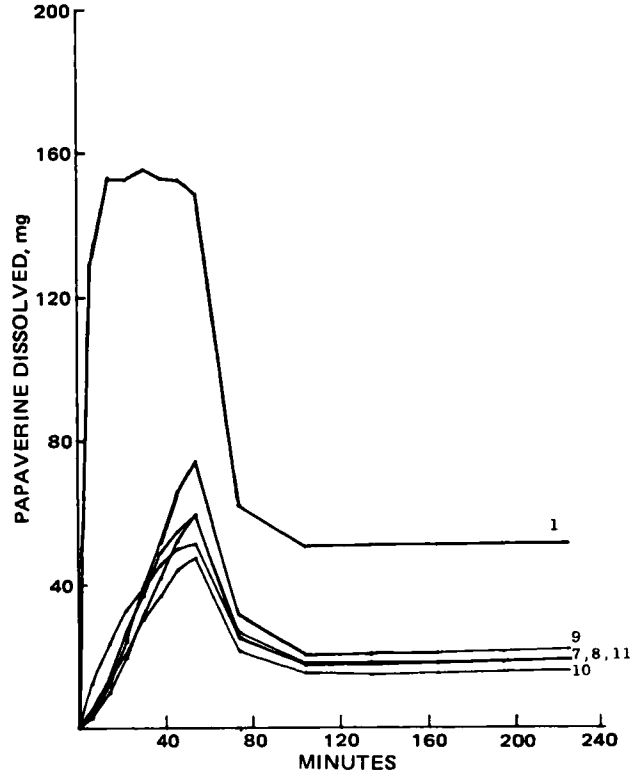

Figure 2—*Dissolution profiles for six papaverine formulations in study group 2. Each data point is the mean of two determinations. The simulated intestinal phase began after 56 min.*

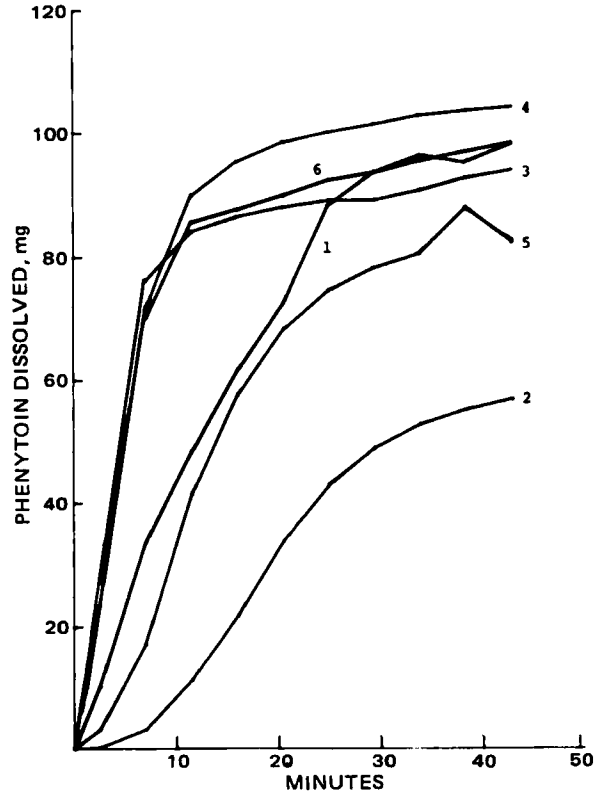

Figure 3—*Dissolution profiles for six phenytoin formulations in study group 1. Each data point is the mean of two determinations.*

Table II—Reproducibility of the Dissolution Simulator [a]

Sample Time, min	Total Amount of Dissolved Drug, mg											
	Sulfisoxazole (Group 1)				Phenytoin (Group 1)				Papaverine (Group 1)			
	Product 2		Product 5		Product 2		Product 4		Product 2		Product 3	
	A	B	A	B	A	B	A	B	A	B	A	B
6	—	—	—	—	—	—	—	—	5	1	120	116
7	49	40	3	3	1	5	61	83	—	—	—	—
14	—	—	—	—	—	—	—	—	11	6	115	150
16	—	—	—	—	16	28	91	101	—	—	—	—
18	63	58	26	18	—	—	—	—	—	—	—	—
29	70	64	45	46	—	—	—	—	—	—	—	—
30	—	—	—	—	46	53	99	105	27	16	151	147
43	—	—	—	—	57	58	103	107	—	—	—	—
46	—	—	—	—	—	—	—	—	40	29	158	151
64	396	432	268	290	—	—	—	—	—	—	—	—
74	—	—	—	—	—	—	—	—	19	21	61	59
134	—	—	—	—	—	—	—	—	13	12	49	49
139	539	539	377	375	—	—	—	—	—	—	—	—

[a] A and B represent duplicate determinations.

The diffusion of the phenytoin across the lipid barriers was quite rapid from both gastric and intestinal media. The theoretical sampling intervals were 1.9 and 0.9 min for dissolution in the simulated gastric and intestinal fluids, respectively, based on the diffusion data. However, phenytoin was poorly soluble in the gastric and intestinal fluids of the dissolution apparatus, and the dissolution fluid was rapidly saturated as the 100-mg dosage form dissolved in 100 ml of the fluid. As a result, the sampling rate was changed to the maximum rate possible with the apparatus: 7.5 ml every 30 sec, for 45 min. In addition, distilled water was employed as the dissolution medium, as currently used in the USP XX dissolution procedure.

In preliminary trials with the dissolution of the sulfisoxazole tablets, it was determined that the theoretical sampling rates suggested by the absorption simulator were satisfactory for the study of these dosage forms. Duplicate determinations were made for sulfisoxazole, and the mean values are given in Table I.

Individual diffusion rate constants differed from the mean by < 3% for both the gastric and intestinal phase studies. Only single determinations were made for phenytoin and papaverine because of the limited value of the absorption simulator for these drugs. As noted in the previous study (1), data obtained with the absorption simulator generally was not applicable to the selection of appropriate conditions for the dissolution tests.

Dissolution Profiles—The dissolution rate profiles of the various formulations of the three drugs are shown in Figs. 1–6. Each data point represents the mean of two dosage forms, except for the papaverine elixir (product 1). Too little of the elixir remained from the earlier studies to permit duplicate dissolution studies. The reference to groups 1 and 2 in each of the dissolution study profiles relates to the fact that each *in vivo* bioavailability study involved two groups of subjects, with a reference (product 1) being common to both groups; e.g., six subjects received each of five papaverine dosage forms and the elixir, and an additional six

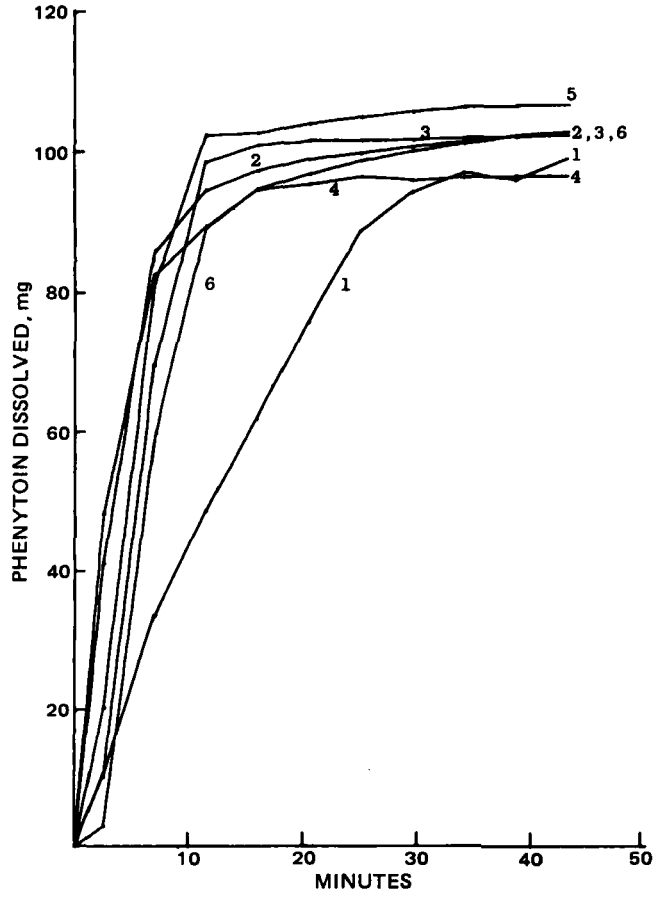

Figure 4—*Dissolution profiles for six phenytoin formulations in study group 2. Each data point is the mean of two determinations.*

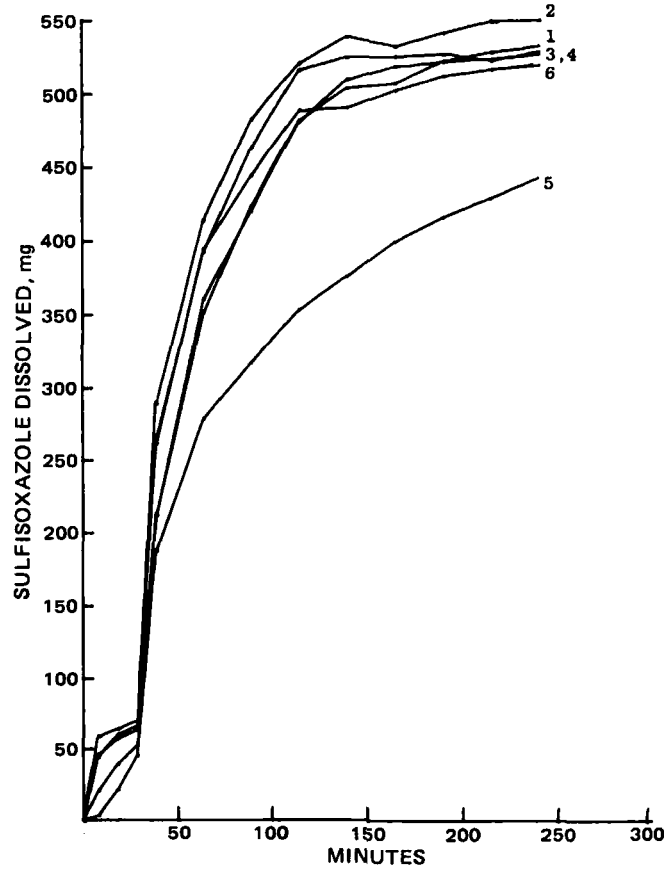

Figure 5—*Dissolution profiles for six sulfisoxazole formulations in study group 1. Each data point is the mean of two determinations. The simulated intestinal phase began after 32 min.*

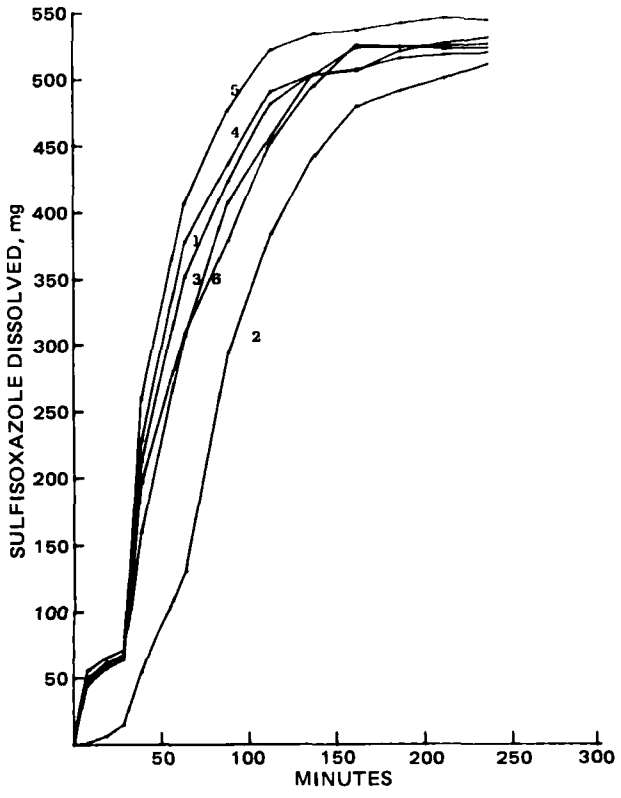

Figure 6—*Dissolution profiles for six sulfisoxazole formulations in study group 2. Each data point is the mean of two determinations. The simulated intestinal phase began after 32 min.*

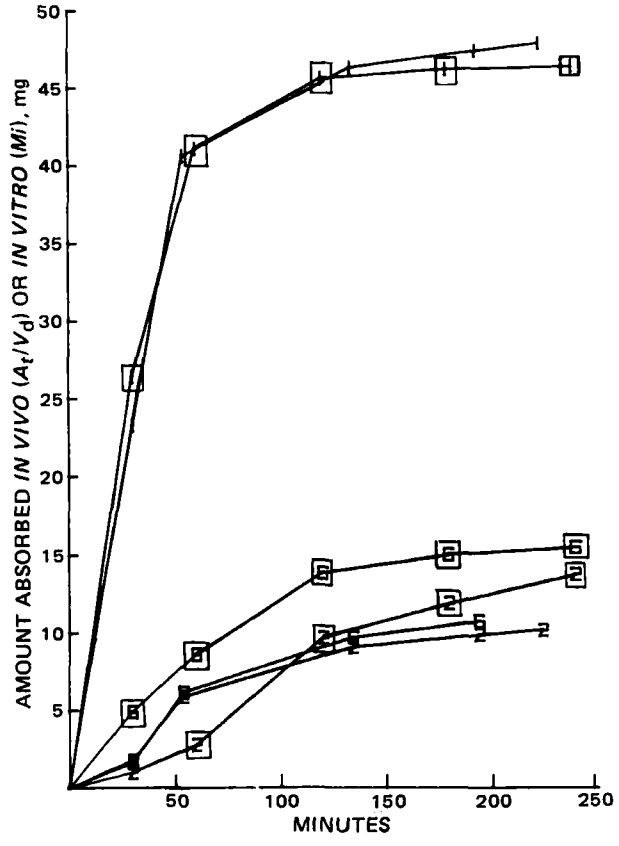

Figure 7—*Comparison of the total amount of papaverine withdrawn from the* in vitro *dissolution system (*Mi*) and the adjusted* in vivo *absorption profiles (A_t/V_d) for three papaverine formulations in study group 1. Each* in vitro *data point is the mean of two determinations for products 2 and 6 and a single determination for product 1. Each* in vivo *data point (□) is the mean of six subjects.*

subjects received the other five papaverine dosage forms and the elixir (2).

The data for the papaverine formulations (Figs. 1–2) demonstrated rapid dissolution for both the elixir (product 1) and the compressed tablets (product 3). Each of the sustained-release dosage forms dissolved more slowly, including product 5 which was a 200-mg tablet. The amount of drug dissolved for each product decreased when the pH of the dissolution medium was increased to 6.5 after 56 min, suggesting precipitation of the papaverine under these conditions.

The dissolution of the majority of the phenytoin capsules was quite rapid, with all but 3 of the 11 products being at least 85% dissolved within 10 min. Product 2 in group 1 was slowly and incompletely dissolved even after 45 min, and this product also exhibited the poorest *in vivo* bioavailability (3).

The dissolution of each of the sulfisoxazole tablet products (Figs. 5 and 6) proceeded more rapidly after 32 min when the pH of the dissolution fluid was increased to 6.5. The two products which dissolved the slowest, product 5 (group 1) and product 2 (group 2), also failed the USP XVIII dissolution specifications (applicable at the time the *in vivo* studies were conducted).

In general, the reproducibility of the duplicate determinations was reasonably good. Table II summarizes individual dosage form values for the fastest and slowest dissolving formulation of each of the three drugs. By comparison, relative standard deviations for 12 replicate determinations of the dissolution of the phenytoin capsules, using the USP XX method (8), were <5% at each sampling time[4]. At the time of the sulfisoxazole bioavailability study, the various tablets were also subjected to the USP XVIII dissolution test, using six replicates. Samples were obtained only at 30 min. The dissolution values obtained for products 2 and 5 (Table II) were 475–511 mg and 90–125 mg, respectively. There is no official dissolution test for controlled-release papaverine dosage forms; therefore, these products were only studied with the dissolution simulator.

Simulated Absorption Profiles—Using the approach described earlier, attempts were made to relate the amount of drug dissolved *in vitro* and the amount in the body during the *in vivo* studies. This approach was not successful with data from either the phenytoin or the sulfisoxazole studies. Since the dissolution rate determinations for the phenytoin capsules were terminated after only 45 min, comparisons of the *in vitro* and *in vivo* absorption profiles were not meaningful. With the sulfisoxazole tablets, it was determined that the amount dissolved *in vitro*, in general, greatly underestimated the amount of drug absorbed *in vivo* for all products. Thus, no useful relationships could be discerned. However, there was a reasonably good correlation between the *in vitro* and *in vivo* data for the papaverine products, except for products 4 and 5 of group 1. Representative data are shown in Figs. 7 and 8. Since the two *in vivo* study groups differed significantly in the plasma papaverine concentrations obtained with the reference elixir, the data were analyzed separately for the two groups. Plots of A_t/V_d *versus Mi* yielded slopes of 1.77×10^{-5} and 1.15×10^{-5} ml^{-1} for groups 1 and 2, respectively. The slope value can be considered as a correction factor incorporating the V_d term and other *in vivo* variables not present in the *in vitro* system.

General Correlations—This data treatment represents a more classical approach which attempts to relate an *in vitro* parameter, such as percent dissolved at a given time, to an *in vivo* parameter, such as area under the plasma concentration–time curve (AUC), maximum plasma concentration (C_{max}), or time of maximum plasma concentration (t_{max}). Although a wide variety of potential correlations were tested, only those resulting in the best correlation are presented herein.

Papaverine—Good correlations were observed for plots of C_{max} *versus* percent dissolved in 30 min *in vitro*, $r = 0.917$ ($p < 0.01$), and the 0–10 hr AUC, $r = 0.899$ ($p < 0.01$), or C_{max}, $r = 0.869$ ($p < 0.01$), *versus* area under the dissolution–time curve for 3.2 hr. The best correlation (Fig. 9) related the 0–10 hr AUC to the percent dissolved in 30 min, $r = 0.922$ ($p < 0.01$). The group 1 and group 2 data were plotted together by normalizing the group 2 AUC values by the ratio of the AUC values for the reference elixir which was common to both study groups.

Phenytoin—The best correlations resulted when *in vivo* t_{max} values were plotted *versus* the time for 50% dissolution *in vitro* ($t_{50\%}$), $r = 0.909$ ($p < 0.01$), or the percent dissolved in 7 min, $r = 0.827$ ($p < 0.01$). The t_{max} values for the group 2 subjects were normalized by the ratio of the t_{max} values for reference (product 1), which was common to both groups.

[4] Personal communication from V. P. Shah, Division of Biopharmaceutics, Food and Drug Administration, Rockville, MD 20857, on April 14, 1982.

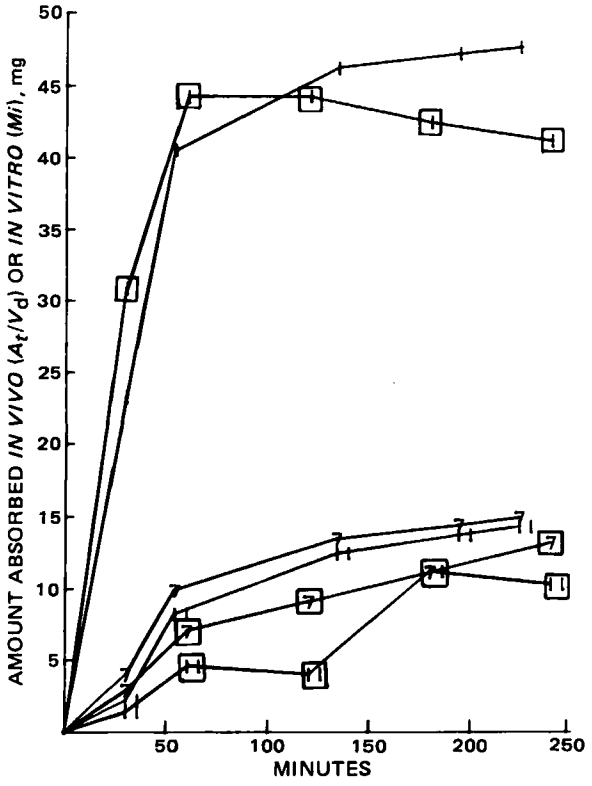

Figure 8—*Comparison of the total amount of papaverine withdrawn from the* in vitro *dissolution system* (Mi) *and the adjusted* in vivo *absorption profiles* (A_t/V_d) *for three papaverine formulations in study group 2. Each* in vitro *data point is the mean of two determinations for products 7 and 11 and a single determination for product 1. Each* in vivo *data point* (□) *is the mean of six subjects.*

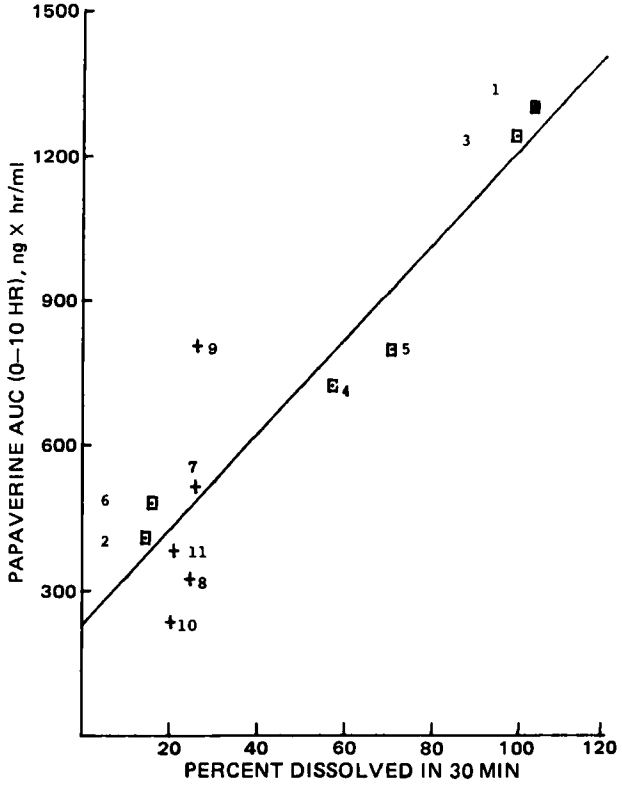

Figure 9—In vivo–in vitro *correlation for 11 papaverine formulations,* r = *0.922* (p < *0.01*). *Each data point represents the mean of two* in vitro *and six* in vivo *values, except the* in vitro *value of product 1 which is the result of a single dissolution study. Key:* (⊡) *data from group 1;* (+) *data from group 2* (⊞) *product 1.*

As shown in Fig. 10, products 2 and 5 of group 1 did not fit the correlation employed to describe the other nine dosage forms.

Since the completion of these studies, new USP dissolution specifications have been published for phenytoin capsules (9). These dosage forms have been divided into two types, based on dissolution characteristics. "Prompt" capsules must dissolve ≥85% within 30 min, using 900 ml of water and the USP Apparatus I at 50 rpm. "Extended" capsules must dissolve ≤35% in 30 min, 30–70% at 60 min, and ≥80% in 120 min, using the same dissolution system. As shown in Fig. 3, only products 2 and 5 of group 1 failed to dissolve at least 85% in 30 min using the dissolution simulator. However, both products were >35% dissolved at 30 min. Thus, these two products dissolved too slowly to be considered "prompt" and too fast to be considered "extended" using the USP XX criteria. Product 1, which is a formulation that meets the USP XX specifications of "extended," also dissolved ~90% in 30 min using the dissolution simulator. With the exception of product 5 (group 1), the relationship illustrated in Fig. 10 could be employed. This suggests that if the time for 50% dissolution exceeded 5 min, the t_{max} value *in vivo* would exceed 4.5 hr. On the basis of dissolution testing, as well as *in vivo* bioavailability studies, current phenytoin products may be employed in different dosage regimens, depending on whether they are labeled "prompt" or "extended." The "prompt" formulations are recommended for three times a day (TID) administration, while the "extended" capsules may be given once a day after an initial period to reach the optimal titer.

Thus if the data from the dissolution simulator were to be employed to establish such specifications, products 1, 2, and 5 (group 1) and 6 (group 2) each would be considered "extended." However, the t_{max} for product 5, which exhibited the second longest dissolution time, was not appreciably different from that for the majority of the other products. The *in vitro* studies carried out with some of these products using the USP XX method (8) found products 1 and 2 (group 1) and 6 (group 2) to be the slowest dissolving, which is consistent with the present data. However, product 5 (group 1) was one of the more rapidly dissolving products. Thus the USP XX method provided dissolution data which were more consistent with the *in vivo* observations than that obtained with the dissolution simulator employed in the present study.

Sulfisoxazole—As part of the previous *in vivo* studies, all of the tablets

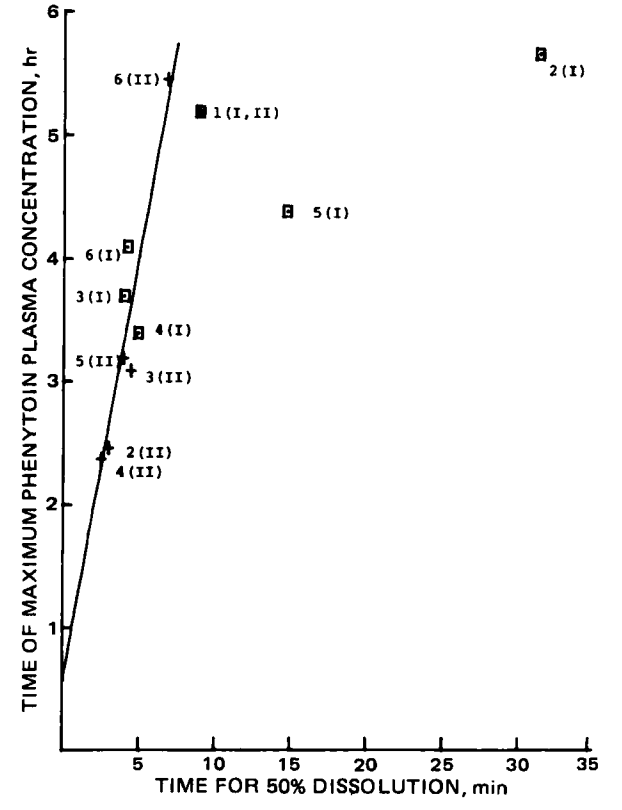

Figure 10—In vivo–in vitro *correlation for 11 phenytoin formulations,* r = *0.909* (p < *0.01*). *Each data point represents the mean of two* in vitro *and six* in vivo *values. Products 2 and 5 (group 1) were omitted from the correlation. Key: (I) group 1; (II) group 2.*

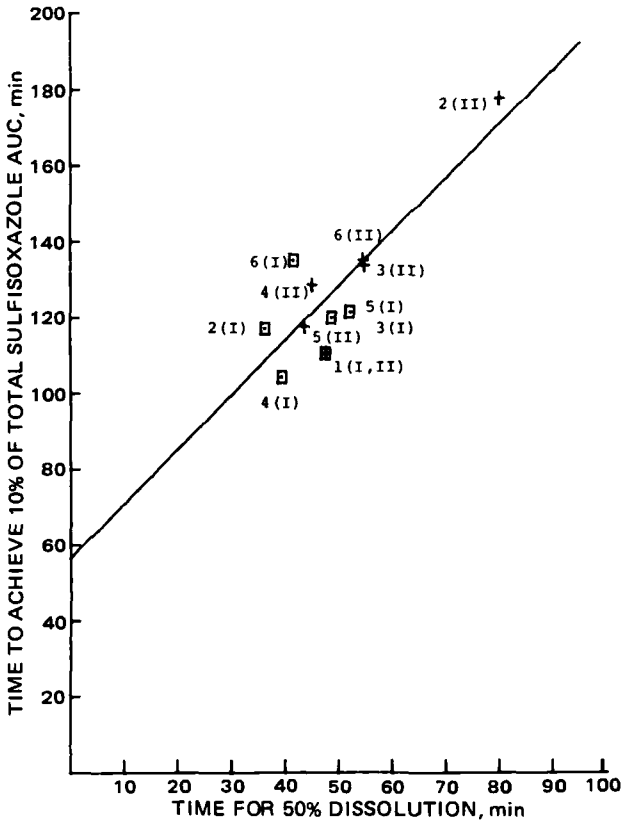

Figure 11—In vivo–in vitro *correlation for 11 sulfisoxazole formulations,* r = *0.870 (*p < *0.01). Each data point represents the mean of two* in vitro *and six* in vivo *values. Key: (I) group 1; (II) group 2.*

were evaluated using the USP XVIII dissolution method. Products 3 and 5 of group 1 and product 2 of group 2 failed the USP requirement of ≥60% dissolution in 30 min. The extent of dissolution was 12.6, 21.4, and 49% after 30 min for products 2, 5, and 3, respectively. Figure 11 illustrates the best correlation obtained in the present study, $r = 0.87$ ($p < 0.01$), relating time for 50% dissolution to the time to achieve 10% of the total AUC. Attempts to relate more conventional parameters such as total AUC, t_{max}, or C_{max} did not result in meaningful correlations, due in part to the relatively narrow range of *in vivo* bioavailability characteristics. The data of the *in vivo* studies resulted in a conclusion that the 11 dosage forms did not differ significantly in terms of any of the usual bioavailability parameters. Since product 5 (group 1) and product 2 (group 2) were the slowest dissolving tablets with both the USP method and the dissolution simulator, and yet did not differ significantly *in vivo*, there did not appear to be any advantage to the use of the dissolution simulator.

Study Limitations—As with the previous study (1), the expiration dates for several of the products had passed prior to the completion of the dissolution studies. Furthermore, too few dosage units remained to permit a determination of content uniformity. However, 90–100% of the labeled product content was dissolved during the period of the dissolution test for the papaverine elixir and compressed tablets, the majority of the phenytoin capsules, and the sulfisoxazole tablets, indicating no significant degradation had occurred during storage of these products. In addition, the slow dissolution of two of the sulfisoxazole tablets and three of the phenytoin capsules was consistent with other results obtained using USP methodology.

CONCLUSIONS

As was determined in the previous study (1), the use of the absorption simulator did not always provide useful information for establishing the optimum sampling rates for the dissolution simulator. Of the three drugs studied with the dissolution simulator, only the papaverine dosage forms resulted in a reasonable correlation between the *in vivo* bioavailability and the *in vitro* dissolution data. For the phenytoin capsules a reasonable correlation was obtained between the *in vitro* t_{max} and dissolution, except for two slowly dissolving capsules, thus limiting the general applicability of the relationship. Furthermore, other studies of these phenytoin capsules have indicated the present USP XX dissolution method provides better *in vivo–in vitro* correlations. The lack of suitable correlations was probably due, in part, to the limited fluid volume of the dissolution chamber, which was rapidly saturated with phenytoin. Finally, studies involving the sulfisoxazole tablets also failed to provide any significant *in vivo–in vitro* correlations, due in part to the similar *in vivo* characteristics of the 11 products. As with most, if not all *in vitro* dissolution systems, it is not possible to assume *a priori* that data obtained with the dissolution simulator will relate to the *in vivo* performance of a given dosage form.

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ACKNOWLEDGMENTS

This work was adapted in part from a thesis submitted by M. K. T. Yau to the University of Tennessee Center for the Health Sciences, in partial fulfillment of the MS degree requirements, and was supported in part by contracts from the Food and Drug Administration (FDA No. 223-74-3097 and FDA No. 223-77-3011) and the Tennessee Department of Public Health.

The use of the Sartorius Absorption and Dissolution Simulators, provided by Sartorius Filters, Inc., is gratefully acknowledged.