6.8 g of a yellow oil (XXII). The IR spectrum showed a peak at 1700 cm^{-1}, indicative of the carbonyl of a carbamate.

The crude oil, without further purification, was reduced by dissolving it in 50 ml of acetic acid and transferred to a three-necked flask fitted with a mechanical stirrer, reflux condenser, and drying tube. After gradual addition of 3.0 g of zinc dust, the mixture was stirred at room temperature for about 60 hr. The zinc mixture was filtered, and the acetic acid was reduced in volume *in vacuo* almost to completion. The residue was made basic with 25% NaOH and extracted with three 30-ml portions of ether. The ether extracts were combined, dried over anhydrous sodium sulfate, and filtered. Hydrogen chloride gas was passed through the ether solution, forming a white precipitate. The precipitate was filtered and recrystallized from ethyl acetate–ethanol (1:1) to yield 2.2 g (51%) of product, decomposition at 230–232°. The IR spectrum showed a broad peak from 2800 to 2600 cm^{-1}, indicative of NH_2^+. The NMR spectrum (dimethyl sulfoxide-d_6) showed peaks at δ 2.3 (m, 2H, $3CH_2$), 3.0 (m, 2H, benzylic), 3.6 (m, 3H, 2CH and $6CH_2$), 3.8 (s, 3H, *p*-methoxy), 3.9 (s, 6H, *m*-methoxy), 5.9 (m, 2H, vinylic), 6.8 (s, 2H, aromatic), and 9.9 (b, 2H, NH_2).

REFERENCES

(1) A. Hoffer and H. Osmond, "The Hallucinogens," Academic, New York, N.Y., 1967, p. 42.

(2) C. A. Winter and L. Plataker, *J. Pharmacol. Exp. Ther.*, **112**, 99(1954).

(3) W. M. Benson, E. O'Gara, and S. Van Winkle, *ibid.*, **106**, 373(1952).

(4) J. Telford, C. N. Papadopoulos, and A. S. Keats, *ibid.*, **133**, 106(1961).

(5) M. Gates and T. A. Montzka, *J. Med. Chem.*, **7**, 127(1964).

(6) M. Gordon, J. J. Laffety, D. H. Tedeschi, N. B. Eddy, and E. L. May, *Nature*, **192**, 1089(1962).

(7) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123(1964).

(8) F. Leuschner, *Arch. Exp. Pathol. Pharmakol.*, **225**, 95(1955).

(9) L. S. Harris, in "Advances in Biochemical Psychopharmacology," vol. 8, M. C. Braude, L. S. Harris, E. L. May, J. P. Smith, and J. E. Villarreal, Eds., Raven, New York, N.Y., 1973, pp. 13–20.

(10) A. T. Shulgin, *Lloydia*, **36**, 46(1973).

(11) J. Lundstrom and S. Agurell, *Acta Pharm. Suec.*, **7**, 247(1970).

(12) R. J. Mayor and K. W. Ohly, *J. Med. Pharm. Chem.*, **4**, 51(1961).

(13) C. S. Weil, *Biometrics*, **8**, 249(1952).

(14) M. E. Koosman, *Proc. Soc. Exp. Biol. Med.*, **115**, 728(1964).

(15) R. M. Pinder, F. A. B. Aldous, B. C. Barrass, K. Brewster, D. A. Buxton, D. M. Green, P. Rich, M. Skeels, and K. J. Tutt, *J. Med. Chem.*, **17**, 1100(1974).

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Dissolution Behavior and Bioavailability of Phenytoin from a Ground Mixture with Microcrystalline Cellulose

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Abstract □ The ground mixture of phenytoin and microcrystalline cellulose was prepared by grinding in a vibrational ball mill. The X-ray diffraction patterns indicated the amorphous nature of the ground mixture. Comparative studies were made concerning the *in vitro* dissolution and *in vivo* absorption of fine phenytoin powder, phenytoin sodium powder, and the ground mixture. The ground mixture showed a greater dissolution rate than the fine powder and attained supersaturation in the pharmacopeial disintegration media at pH 1.2 and 7.4. *In vivo* absorption studies of each preparation were carried out in five subjects, using a crossover design, by measuring the urinary excretion rate of a main metabolite, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin. The blood levels of phenytoin and the corresponding urinary excretion patterns of the metabolite were determined in two subjects. The ground mixtures significantly improved the bioavailability of phenytoin. The drug was completely and rapidly absorbed after oral administration of the ground mixture. The vibrational ball milling technique for a poorly water-soluble drug with microcrystalline cellulose provides a promising way of improving the *in vivo* drug absorption.

Keyphrases □ Phenytoin—dissolution and bioavailability, ground mixture with microcrystalline cellulose compared to fine powder □ Dissolution—phenytoin, ground mixture with microcrystalline cellulose □ Bioavailability—phenytoin, ground mixture with microcrystalline cellulose □ Dosage forms—phenytoin and microcrystalline cellulose ground mixture, dissolution and bioavailability, compared to fine powder □ Cellulose, microcrystalline—ground mixture with phenytoin, effect on dissolution and bioavailability □ Anticonvulsant agents—phenytoin, dissolution and bioavailability, ground mixture with microcrystalline cellulose

When a relatively insoluble drug is administered orally, the rate of absorption and/or the extent of bioavailability are controlled by its dissolution rate in the GI fluids (1). Therefore, efforts have been made to increase the dissolution rate of poorly soluble drugs (2–5).

In an earlier study (6), a ground mixture of griseofulvin and microcrystalline cellulose significantly im-

proved the dissolution rate and bioavailability of griseofulvin compared with a micronized griseofulvin powder. Since microcrystalline cellulose is considered to be innocuous when taken orally, ground mixtures of poorly soluble drugs and the cellulose have been proposed to be biopharmaceutically useful formulations (6).

Phenytoin, a poorly water-soluble anticonvulsant, is incompletely and irregularly absorbed after oral administration (7). Significant variations in blood levels were reported recently when phenytoin capsules made by different manufacturers were administered (8, 9). In addition to dissolution rate-limited absorption, marked differences in biological half-lives among individuals and the closeness of the therapeutic and toxic levels (10) make phenytoin therapy very complicated and difficult. Therefore, phenytoin bioavailability recently has become a matter of great importance.

This paper describes the bioavailability of phenytoin and the physicochemical properties of the ground mixture of the drug and microcrystalline cellulose. Dissolution studies were carried out on the following preparations: the ground mixture of phenytoin and the cellulose, a fine powder, and a phenytoin sodium powder. The *in vivo* evaluation of each preparation after oral administration to healthy human volunteers also is described.

EXPERIMENTAL

Materials—Phenytoin[1] JP and phenytoin sodium[1] were used as received. The mean particle size of a phenytoin sample, as measured by nitrogen gas adsorption, was 5.3 μm. 5-(*p*-Methylphenyl)-5-phenylhydantoin[2], 5-(*p*-hydroxyphenyl)-5-phenylhydantoin[2], and microcrystalline cellulose[3] also were used. Phenyltrimethylammonium hydroxide[4] was a 20–25% solution in methanol. All other chemicals were of reagent grade, except *n*-heptane which was of spectroscopic grade.

Preparation of Ground Mixture—The ground mixture was prepared by adding 10 g of phenytoin to 90 g of microcrystalline cellulose and grinding for 2 hr with a ceramic vibrational ball mill[5]. Amorphous cellulose was similarly prepared by milling microcrystalline cellulose alone.

The X-ray powder diffraction[6] patterns of the mixture were obtained before and after the grinding process. A physical mixture (simple blend) was prepared by tumbling the fine powder with a ninefold excess of the cellulose in a bottle.

Dissolution Rate Studies—Dissolution rates of phenytoin from the different forms into 1 liter of JP VIII disintegration medium No. 1 (pH 1.2) or No. 2 (pH 7.4) were measured at 37° in a constant-temperature water bath. The amount of the drug used was 100 mg of the free acid equivalent: 100 mg of the fine powder, 109 mg of the sodium salt powder, or 1000 mg of the ground mixture.

Each preparation was transferred directly into the dissolution medium and stirred with a three-bladed stainless steel propeller at 100 rpm. A suitable aliquot was removed at the specified time using a membrane filter[7] (0.2 μm) and analyzed for drug by a UV spectrophotometric[8] method (11).

Nonequilibrium Solubility Studies—The amount of phenytoin dissolved in the disintegration medium No. 1 from the simple blend of 5 mg of the fine powder and 45 mg of amorphous cellulose and 50 or 150 mg of the ground mixture was determined at daily intervals. These preparations were weighed into 50-ml erlenmeyer flasks, which were then immersed in a constant-temperature bath. Thirty-milliliter portions of the medium, prewarmed to 37°, were added to the flasks. These flasks were immediately shaken horizontally at 70 strokes/min.

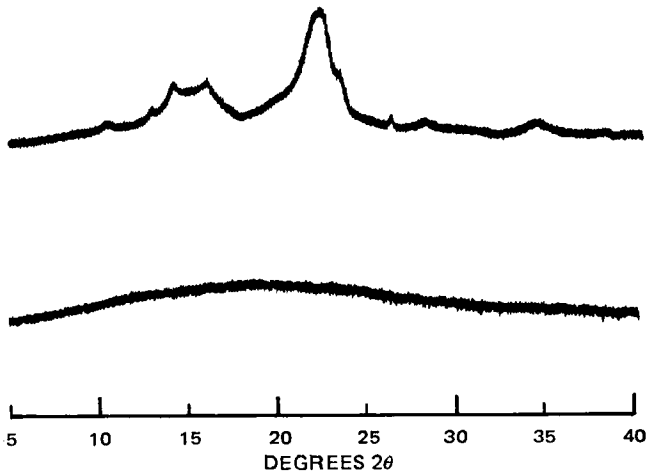

Figure 1—*X-ray powder diffraction patterns of a simple blend (upper) and the ground mixture (lower) of phenytoin and microcrystalline cellulose (1:9).*

At appropriate intervals, the samples were withdrawn through the membrane filters (0.2 μm). An aliquot was analyzed by a reported GLC method (12) with the following modifications. Phenyltrimethylammonium hydroxide (13) was employed instead of tetramethylammonium hydroxide as a methylating reagent, and 1.5% OV-101 on a solid support[9] (80–100 mesh) was used instead of DC-200 as a stationary phase.

***In Vivo* Absorption Studies**—The fine powder (250 mg), the sodium salt powder (272 mg), or the ground mixture (2500 mg) was orally administered to five normal subjects. The subjects were 21–27 years old, and the average body weight was 63 kg (range of 48–75 kg). Preparations were administered to each subject with 200 ml of water at approximately 9 am following an overnight fast using a crossover design. No food was taken for 6 hr postadministration. A minimum of 1 week was allowed between experiments.

Urine samples were collected at hourly intervals for the first 8 hr and at convenient time intervals up to 120 hr after administration. The volume and pH of each urine sample were recorded, and small portions of the urine samples were refrigerated until analyzed. In addition to the urine collection, blood samples were taken from two subjects at 0, 2, 4, 6, 8, and 24 hr. The blood samples, collected in heparinized test tubes, were centrifuged, and the plasma was stored in a refrigerator until assayed.

The amount of *p*-hydroxylated phenytoin and its conjugate, the main metabolite in humans (14), in the urine and the levels of the intact drug in the plasma were assayed by the same GLC method described for solubility measurements.

RESULTS AND DISCUSSION

Physicochemical Properties of Ground Mixture—The X-ray diffraction patterns of phenytoin–microcrystalline cellulose mixtures (1:9) before and after the grinding process are shown in Fig. 1. Before grinding (simple blend), sharp diffractional peaks derived from the drug crystals and broad diffractional peaks derived from the crystalline portions of the cellulose were observed. As the grinding progressed, however, these diffractional peaks disappeared; only the halo was observed in the X-ray diffraction pattern when complete grinding was achieved.

The changes in the X-ray diffraction patterns upon grinding indicate the decrease in the proportion of crystalline forms in the drug and the cellulose and the increase in the proportion of amorphous forms. The previous report (6) described some possible mechanisms

[1] Aleviatin, Dainippon Pharmaceutical Co., Osaka, Japan.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] Avicel PH-101, Asahi Kasei Industrial Co., Tokyo, Japan.
[4] Tokyo Kasei Industy Co., Tokyo, Japan.
[5] Type B1, Chuokakoki Co., Toyoake, Aichi Pref, Japan.
[6] Model D-3F, Rigakudenki Co., Tokyo, Japan.
[7] Nuclepore, General Electric, Pleasanton, Calif.
[8] Spectrophotometer model 139, Hitachi Manufacturing Co., Tokyo, Japan.
[9] Shimalite W, Wako Pure Chemical Industry, Osaka, Japan.

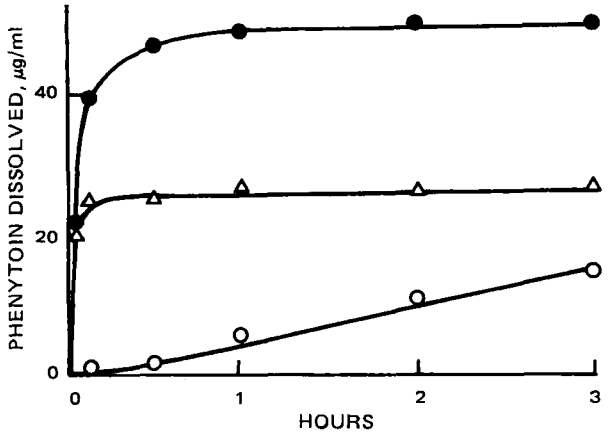

Figure 2—*Dissolution profiles of phenytoin from three preparations in 1 liter of JP VIII disintegration medium No. 1 (pH 1.2) at 37°. Each data point represents the mean of three determinations. Key: ●, 1000 mg of the ground mixture (1:9); △, 109 mg of a sodium salt powder; and ○, 100 mg of a fine powder.*

in the transition from the crystalline state to the amorphous state. IR spectra and melting-point measurements (295°) indicated no chemical change of the drug during the milling process.

Dissolution Behavior—The dissolution behavior of the fine powder, the sodium salt powder, and the ground mixture in JP VIII disintegration medium No. 1 (pH 1.2) at 37° is shown in Fig. 2. These plots show the concentration attained in solution for each preparation containing 100 mg of free acid or its equivalent. Since the drug solubility in this medium at 37° was 25.3 μg/ml, 100 mg of the drug in 1 liter of the dissolution medium corresponded to about four times its solubility. The ground mixture exhibited a faster dissolution rate than the fine powder and yielded a solution approximately 3.3 times as concentrated as a solution of the fine powder at 180 min. However, the dissolution rate of the sodium salt powder was as fast as that of the ground mixture.

Since the medium was acidic, the recrystallization of free acid took place immediately after the dissolution process and supersaturation did not occur. In the ground mixture, however, supersaturation, about twice the solubility, was observed. Although the faster dissolution rate and the phenomenon of supersaturation in the ground mixture may be due partly to deaggregation and the increased surface area, the amorphous nature of the drug may play a significant role.

Figure 3 shows the dissolution curves of three preparations in JP VIII disintegration medium No. 2 (pH 7.4) at 37°. The dissolution profile of the sodium salt powder in this medium differed significantly from that in the acidic medium Following the fast dissolution, an

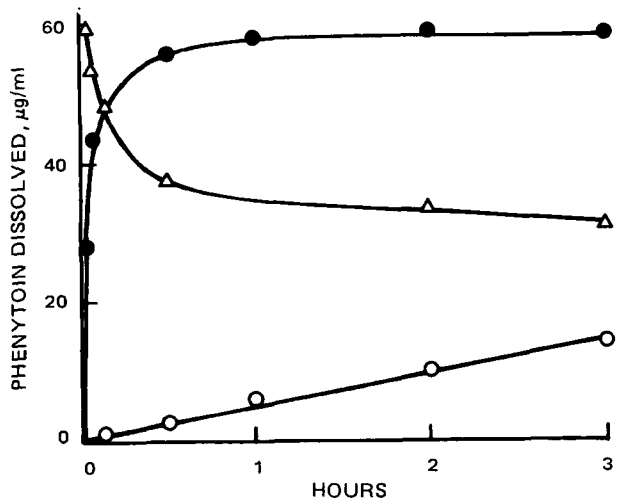

Figure 3—*Dissolution profiles of phenytoin from three preparations in 1 liter of JP VIII disintegration medium No. 2 (pH 7.4) at 37°. Each data point represents the mean of three determinations. Key: see Fig. 2.*

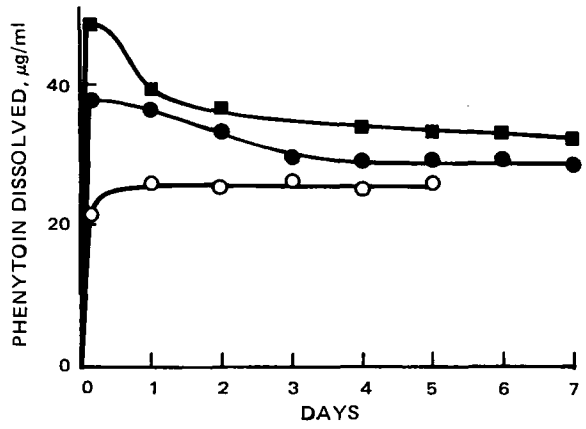

Figure 4—*Solution profiles of phenytoin in 50 ml of JP VIII disintegration medium No. 1 at 37°. Each data point represents the mean of six determinations. Key: ■, 150 mg of the ground mixture; ●, 50 mg of the ground mixture; and ○, a simple blend of 5 mg of the fine powder and 45 mg of amorphous cellulose.*

apparent decline was observed in the amount of drug dissolved. Since the pH of this medium was 7.4 and the pKa value of the drug is 8.3 (15), the slow recrystallization of free acid followed the initial rapid dissolution of the salt.

Dispersions of drugs in macromolecules such as polyethylene glycol and povidone have been employed in enhancing the dissolution and availability of drugs. Chiou and Riegelman (2) reported that the drug was molecularly and/or colloidally dispersed in the polyethylene glycol–drug solid dispersion system. Stupak *et al.* (3) suggested that reserpine in a coprecipitate with povidone had high thermodynamic activity. The exact physical nature of the ground mixture has not been determined, but drug molecules in the ground mixture probably are dispersed on the surface of cellulose and present in an amorphous state. Its energy level is expected to be higher than the original crystal.

When the solution profile of the ground mixture was followed for a longer period, the amount of drug in solution after the initial supersaturation decreased (Fig. 4). This finding may be attributed to conversion of amorphous phenytoin to a crystalline form. Moreover, with the ground mixture, the greater the amount added, the higher was the supersaturation level achieved. Even in the presence of amorphous cellulose, supersaturation was not observed when the stable fine powder was added.

***In Vivo* Absorption Studies**—The major metabolite of phenytoin in humans is the *p*-hydroxylated derivative (14). It is excreted in the urine mainly as a conjugate with glucuronic acid. Glazko *et al.* (16) reported that 76% of the dose was accounted for by a urinary metabolite over 5 days following intravenous administration of 250 mg of the sodium salt. The mean recovery of the metabolite over 96 hr was 64% when 0.5 g of the drug was orally administered to 12 subjects (17).

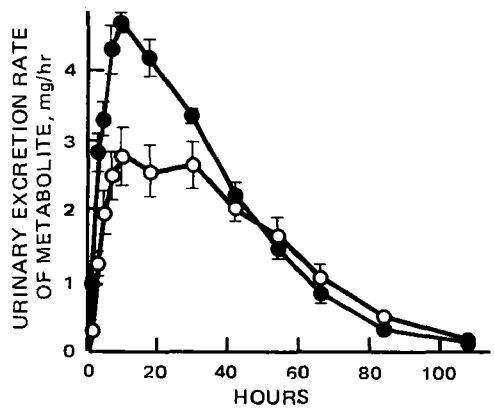

Figure 5—*Urinary excretion patterns of total 5-(p-hydroxyphenyl)-5-phenylhydantoin after oral administration of 250 mg of the fine powder (○) and 2500 mg of the ground mixture (●) to five volunteers (mean ± SEM).*

Table I—Urinary Excretion of Total *p*-Hydroxylated Phenytoin Compared by the Paired *t*-Test

Time Interval, hr	Urinary Excretion			Significance Level	
	Ground Mixture	Fine Powder	Sodium Salt Powder	Ground Mixture *versus* Fine Powder	Ground Mixture *versus* Sodium Salt Powder
	Excretion Rate[a], mg/hr				
0–2	0.98 ± 0.18	0.30 ± 0.10	1.33 ± 0.46	$p < 0.025$	N.S.[b]
2–4	2.85 ± 0.29	1.27 ± 0.17	2.08 ± 0.36	$p < 0.025$	N.S.
4–6	3.35 ± 0.24	1.98 ± 0.32	2.50 ± 0.49	$p < 0.005$	N.S.
6–8	4.32 ± 0.35	2.51 ± 0.35	2.91 ± 0.45	$p < 0.005$	N.S.
8–12	4.72 ± 0.15	2.79 ± 0.42	3.21 ± 0.66	$p < 0.005$	N.S.
12–24	4.21 ± 0.26	2.57 ± 0.38	2.71 ± 0.54	$p < 0.025$	N.S.
24–48	2.81 ± 0.16	2.37 ± 0.28	1.90 ± 0.36	N.S.	$p < 0.05$
48–72	1.19 ± 0.16	1.35 ± 0.24	0.65 ± 0.12	N.S.	$p < 0.05$
	Cumulative Amount Excreted[a], mg				
0–24	92.82 ± 4.15	53.73 ± 7.09	62.92 ± 11.07	$p < 0.005$	N.S.
0–48	160.36 ± 3.33	110.07 ± 13.51	108.19 ± 19.11	$p < 0.025$	$p < 0.05$
0–120	200.05 ± 6.68	162.76 ± 21.37	128.71 ± 22.05	N.S.	$p < 0.05$

[a] Mean ± *SEM*. [b] Not significant.

The mean urinary excretion rates of the metabolite are shown in Figs. 5 and 6. Figure 5 shows the mean urinary excretion rates after oral administration of the fine powder and the ground mixture. Excretion rates during the first 20 hr differed distinctly between the two preparations. The maximum mean excretion rate occurred in the 8–10-hr period following administration of the ground mixture. With the fine powder, however, a prolonged plateau region was observed during 10–30 hr postadministration. The intersubject variations of excretion rates were considerably smaller when the ground mixture was administered.

Figure 6 shows the mean excretion rates of the metabolite after oral administration of the sodium salt powder and the ground mixture. Their initial excretion rates did not differ significantly. However, remarkable intersubject variations in the excretion rates were observed upon the administration of the sodium salt powder. These excretion patterns were well correlated with the *in vitro* dissolution behavior of each preparation. The rapid dissolution of the ground mixture and the sodium salt powder resulted in the initially fast appearance of the metabolite in urine, and the supersaturation attained after the administration of the ground mixture resulted in the apparent high level in the maximum excretion rate.

The excretion rate of a drug is usually expected to be directly proportional to its concentration in the blood. In some cases, the excretion rate of a metabolite can reflect the blood level of its precursor (18, 19). The urinary appearance rate of hydroxylated phenytoin is expected to be controlled by its formation rate. Figure 7 shows the mean blood levels of the drug and the corresponding urinary excretion rates of the metabolite in two subjects after oral administration of the fine powder and the ground mixture. These results indicated that the drug in the ground mixture was more efficiently absorbed from the GI tract than the fine powder. Urinary excretion patterns showed that the excretion of the metabolite took many hours to reach a maximum value and was not directly proportional to the plasma levels of the drug.

Dill *et al.* (20) reported that, in a normal subject receiving a single intravenous dose of phenytoin sodium, the maximum plasma level of the metabolite occurred about 8 hr after administration and that a peak excretion rate was observed 6–8 hr after dosing, indicating a direct relationship between the plasma level of the metabolite and its urinary excretion rate. Glazko *et al.* (16) reported that the delayed appearance of the metabolite in plasma and urine could be caused by many different factors such as binding of the drug to protein, enterohepatic recirculation, and rate-limited hydroxylation or conjugation. Although the urinary excretion rate of the metabolite was not proportional to levels of the intact drug in the blood, it may be used to predict relative blood levels and relative absorption rates of the drug from different preparations if an appropriate experimental design is used.

From the *in vitro* dissolution behavior of the ground mixture and the fine powder and from the blood levels of the drug and urinary excretion rates of the metabolite following oral administration of these preparations, the following prediction may be made. After oral administration of the ground mixture, phenytoin dissolves rapidly to form a supersaturated solution in GI fluids. Subsequently, rapid absorption of the drug takes place. After oral administration of the fine powder, however, the drug dissolves slowly and the dissolution rate tends to be dependent on physiological conditions of individuals, resulting in great intersubject variations in absorption rates.

Table I summarizes the excretion data and the results of the paired *t*-test for the excretion rate and the cumulative amount excreted. Statistical analysis showed that there were significant differences,

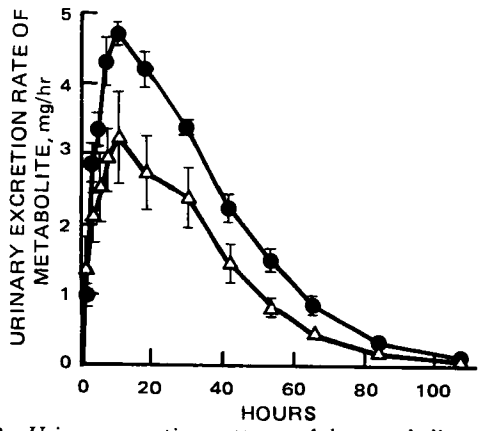

Figure 6—*Urinary excretion patterns of the metabolite after oral administration of 272 mg of the sodium salt powder (△) and 2500 mg of the ground mixture (●) to five volunteers (mean ± SEM).*

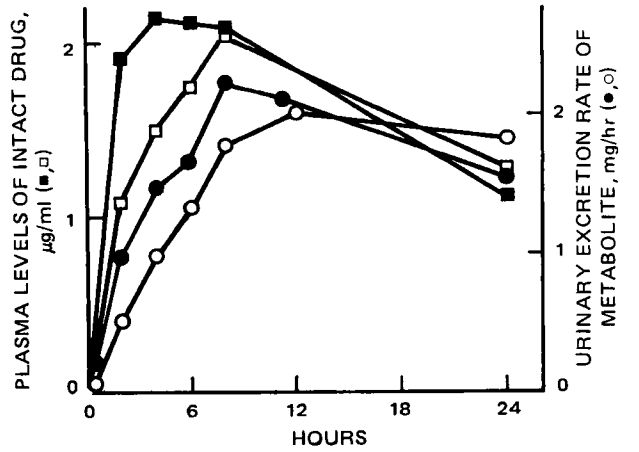

Figure 7—*Comparison of plasma levels (squares) of phenytoin with urinary excretion rates (circles) of the metabolite after oral administration of 250 mg of the fine powder (open symbols) and 2500 mg of the ground mixture (solid symbols) to two volunteers.*

at least at the 97.5% level of confidence, during the first 24 hr post-administration between the excretion rates of the metabolite following administration of the fine powder and of the ground mixture. There were significant differences among their cumulative amounts excreted during the initial time periods. The comparison of the sodium salt powder with the ground mixture, however, revealed no statistical differences in excretion rates and cumulative amounts excreted in a 0–24-hr period.

The present investigation showed that the improvement in the dissolution behavior of phenytoin due to vibrational ball milling with microcrystalline cellulose affected significantly the absorption characteristics of a drug whose absorption was dissolution rate limited. It is of interest to explore the vibrational ball milling of other poorly water-soluble drugs with microcrystalline cellulose.

REFERENCES

(1) S. A. Kaplan, in "Dosage Form Design and Bioavailability," J. Swarbrick, Ed., Lea & Febiger, Philadelphia, Pa., 1973, p. 20.

(2) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **58**, 1505(1969).

(3) E. I. Stupak, H. A. Rosenberg, and T. R. Bates, *J. Pharmacokinet. Biopharm.*, **2**, 511(1974).

(4) A. Ampolsuk, J. V. Mauro, A. A. Nyhuis, N. Shah, and C. I. Jarowski, *J. Pharm. Sci.*, **63**, 117(1974).

(5) S. Miyazaki, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **23**, 552(1975).

(6) K. Yamamoto, M. Nakano, T. Arita, and Y. Nakai, *J. Pharmacokinet. Biopharm.*, **2**, 487(1974).

(7) K. Arnold, N. Gerber, and G. Levy, *Can. J. Pharm. Sci.*, **5**, 89(1970).

(8) K. S. Albert, E. Sakmar, M. R. Hallmark, D. J. Weidler, and J. G. Wagner, *Clin. Pharmacol. Ther.*, **16**, 727(1974).

(9) L. Lund, *Eur. J. Clin. Pharmacol.*, **7**, 119(1974).

(10) A. J. Glazko and T. Chang, in "Antiepileptic Drugs," D. M. Woodbury, J. K. Penry, and R. P. Schmidt, Eds., Raven, New York, N.Y., 1972, p. 127.

(11) Y. Saitoh, K. Nishihara, F. Nakagawa, and T. Suzuki, *J. Pharm. Sci.*, **62**, 206(1973).

(12) A. J. Wilensky and J. A. Lowden, *Neurology*, **23**, 318(1973).

(13) H. J. Kupferberg, *Clin. Chim. Acta*, **29**, 283(1970).

(14) T. C. Butler, *J. Pharmacol. Exp. Ther.*, **119**, 1(1957).

(15) S. P. Agarwal and M. I. Blake, *J. Pharm. Sci.*, **57**, 1434(1968).

(16) A. J. Glazko, T. Chang, J. Baukema, W. A. Dill, J. R. Goulet, and R. A. Buchanan, *Clin. Pharmacol. Ther.*, **10**, 498(1969).

(17) A. J. Glazko and T. Chang, in "Antiepileptic Drugs," D. M. Woodbury, J. K. Penry, and R. P. Schmidt, Eds., Raven, New York, N.Y., 1972, p. 130.

(18) "Guidelines for Biopharmaceutical Studies in Man," APhA Academy of Pharmaceutical Sciences, Washington, D.C., 1972.

(19) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60**, 1376(1971).

(20) W. A. Dill, J. Baukema, T. Chang, and A. J. Glazko, *Proc. Soc. Exp. Biol. Med.*, **137**, 674(1971).

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Solubility of Nonelectrolytes in Polar Solvents IV: Nonpolar Drugs in Mixed Solvents

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Abstract □ The molecular and group surface area approach to solubility is shown to be applicable to mixed aqueous solvent systems. An equation is derived which is consistent with the exponential increase in the aqueous solubility of nonpolar drugs that frequently accompanies the addition of a cosolvent. This equation predicts that: (*a*) the ability of a drug to be solubilized by a cosolvent is proportional to its hydrophobic surface area per molecule, and (*b*) the ability of a cosolvent to solubilize any drug is inversely proportional to its interfacial tension against a reference liquid hydrocarbon. These predictions are experimentally verified with solubility studies of several alkyl *p*-aminobenzoates in propylene glycol–water mixtures and of hexyl *p*-aminobenzoate in mixtures of water with ethanol, methanol, ethylene glycol, propylene glycol, glycerin, and formamide.

Keyphrases □ Solubility—nonelectrolytes in mixed aqueous solvent systems, molecular and group surface area approach □ Nonelectrolytes—solubility in mixed aqueous solvent systems □ Polar solvents, mixed—solubility of nonelectrolytes, molecular and group surface area approach □ Cosolvent systems, polar—solubility of nonelectrolytes, molecular and group surface area approach □ Alkyl *p*-aminobenzoates—solubility in propylene glycol–water mixtures □ Hexyl *p*-aminobenzoate—solubility in mixed polar solvent systems

Cosolvents are routinely used to increase the solubility of drugs in an aqueous medium. In general, the selection of a mixed solvent system is performed in a hit-and-miss fashion. There are few if any useful guidelines for assessing the relative solubilizing efficiency of the available liquids. Dielectric constant and solubility parameter correlations are of only limited utility, especially for drugs having very low aqueous solubilities. Yet it is precisely for these poorly soluble drugs that solubilization is most important.

A survey of the pharmaceutical literature (1–10) revealed that there is an exponential increase in aqueous solubility for many nonpolar drugs as the cosolvent is added. This increase was observed for many chemical