Absorption Characteristics of Solid Dispersed and Micronized Griseofulvin in Man

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Abstract □ Griseofulvin dispersed in polyethylene glycol 6000, prepared by the melting or solvent method, was found to be completely and rapidly absorbed after oral administration to two human subjects. The absorption from the commercially available, micronized griseofulvin was irregular and incomplete (and the average was only 45% of the dose absorbed). In addition, the absorption process from the commercial product was found to continue for up to 3 days after administration.

Keyphrases □ Griseofulvin, solid dispersion—absorption kinetics, man □ Absorption kinetics, oral—griseofulvin solid dispersion, man

Although application of solid dispersion systems to increase rates of dissolution and oral absorption of poorly water-soluble or insoluble drugs was proposed in 1961 (1), its potential and practical application in clinical therapeutics was only recently demonstrated in this laboratory in dogs (2). The drug tested was griseofulvin, which is a water-insoluble and neutral antibiotic. The dispersion of griseofulvin in a solid matrix of polyethylene glycol 6000 was found to give rise to a much higher and more constant absorption than that of the micronized products. This paper reports on the verification of these results in man. Not only does this finding have potential importance to griseofulvin therapy, it also may lead to a new mechanism for the formulation of other poorly soluble or insoluble drugs.

EXPERIMENTAL

Preparation of Dosage Forms—The parenteral solution of griseofulvin, 25 mg./ml. in polyethylene glycol 300, was prepared by a method similar to that described by Rowland *et al.* (3). Dosage forms for the oral administration included micronized griseofulvin in tablet form[1] and griseofulvin dispersed in polyethylene glycol 6000 as described later. Griseofulvin–polyethylene glycol 6000 (1:9 w/w) solid dispersions, prepared by both fusion and ethanol solvent methods, were described previously (4). The 80–200-mesh powders were collected to prepare two final dosage forms: capsule and tablet. Each capsule, size 00, contained 500 mg. mixture, which was equivalent to 50 mg. of griseofulvin. Nondisintegrating tablets, containing 500 mg. of the mixture, were prepared by direct tableting of the powder using an IR pellet-making machine[2]. Griseofulvin–polyethylene glycol 6000 (2:8 w/w) mixture was prepared by the ethanol method (4) and was administered in a size 00 gelatin capsule containing 625 mg. of the mixture (80–200-mesh powders).

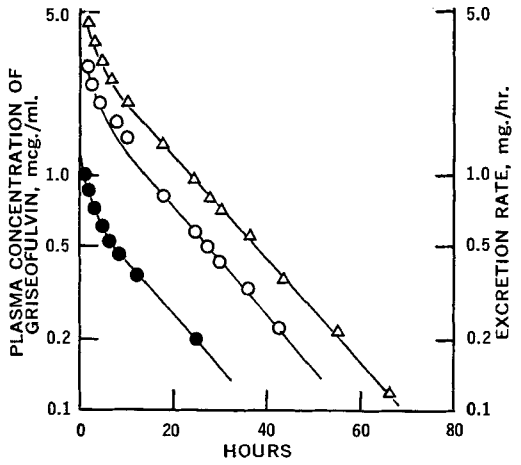

Figure 1—*Plasma griseofulvin levels and 6-demethylgriseofulvin urinary excretion-rate data after intravenous administration of 108 mg. griseofulvin to Subject A. Key:* ●, *plasma griseofulvin levels;* O, *free 6-demethylgriseofulvin; and* △, *total 6-demethylgriseofulvin.*

Procedures for Intravenous Studies—Griseofulvin, 108 mg., was administered through the cephalic vein to a 68-kg. (150-lb.) male subject (Subject A). The method of administration was the same as that described by Rowland *et al.* (3). To prevent the possible precipitation of griseofulvin in the vein and possible hemolysis, the parenteral solution was slowly injected over a 4-min. period, using a Harvard infusion pump[3], and diluted into rapidly flowing saline drip (15 ml./min.) before entering the vein.

Blood samples (5 ml.) were drawn from the opposite arm at 0, 0.5, 1, 2, 3, 4, 5, 8, 12, 24, and 28 hr. Blood samples collected in heparinized test tubes were centrifuged, and the plasma was stored at 4° before assayed. Food and drugs that interfere with the fluorescent assay of griseofulvin in the plasma (especially salicylates) were avoided.

Procedures for Oral Studies—Micronized griseofulvin tablets (500 mg.) and griseofulvin dispersed in polyethylene glycol 6000 (250 mg.) were administered to two normal subjects[4], on empty stomachs, with approximately 200 ml. of water. No food was eaten for at least 2 hr. postadministration. A minimum of 1 week separated each experiment. Both subjects received four studies on the micronized griseofulvin, while Subject A received five studies and Subject B received three studies on the dispersed griseofulvin. The numerical number for each experiment listed in Tables I and II indicates the relative order of each absorption study.

Seven studies were conducted on the 10% griseofulvin dispersion. Among them, the capsule form was used in six studies and the tablet form (nondisintegrating) was used only in one study. The dispersed griseofulvin was all prepared by the melting method, with only one exception (Experiment A-13 in Table II). The 20% griseofulvin dispersion prepared by the solvent method and administered in the capsule form was studied only once (Experiment B-7 in Table II). Urine samples were usually collected at 4, 8, 12, 24, 48, and 72 hr. and occasionally at 2, 6, 36, 60, 84, 96, and up to 102 hr. The volume of urine was recorded, and an aliquot was stored in a plastic container at 4° prior to assay. The urine pH was also measured by a pH meter[5].

Assay of Plasma and Urine Samples—The spectrophotofluorometric assay of griseofulvin in the plasma (3) and UV spectrophotometric assay (5) for the two main metabolites, 6-demethylgriseofulvin and 6-demethylgriseofulvin glucuronide, were previously reported. Duplicate assay was done only on a selective basis.

RESULTS AND DISCUSSION

Intravenous Data—The pharmacokinetic study of griseofulvin in man after intravenous administration was first reported by Rowland

[1] Grifulvin V, 500 mg., Product No. 21470, McNeil Laboratories Inc.
[2] Carver Laboratory Press, model B, Fred S. Carver Inc., Summit, N. J.
[3] Multispeed transmission, mold model 600, Dover, Mass.
[4] Subject A: male, 30 yr., 68 kg. (150 lb.); Subject B: female, 30 yr., 45.3 kg. (100 lb.).
[5] Corning, model 7, Matheson Scientific, Inc.

Table I—Cumulative Total 6-Demethylgriseofulvin Urinary Excretion Data[a] after Oral Administration to Humans of 500-mg. Griseofulvin[b] Tablet

Experiment	Hours 4	8	12	24	48	72	96	192
A-2	—	—	—	—	—	153	—	—
A-5	19	37.8	53.0	85.0	134.7	150.7	—	—
A-7	13.2	27.0	43.7	85.9	139.9	158.4	—	—
A-8	—	17.4	24.8	49.7	72.6	79.1	—	—
B-1	17.8	31.0	43.2	76.8	103.1	124.5	—	—
B-4	17.3	30.5	50.9	92.9	128.8	154.9	173.2	175.2
B-5	25.0	48.8	64.2	88.7	119.9	132.3	135.2	—
B-6	—	46.5	74.2	115.2	151.2	163.2	166.3	—
Average ± *SEM*	18.5 ± 1.9	34.1 ± 4.1	50.6 ± 6.0	84.9 ± 7.4	121.5 ± 9.9	139.5 ± 9.8	158.2 ± 11.7	175.2

[a] Milligrams of total 6-demethylgriseofulvin. [b] Grifulvin.

et al. (3) from this laboratory. The data obtained on Subject A in this study show a biexponential decay of the plasma concentration of griseofulvin, which corresponds to a two-compartment open model with a half-life for the slower disposition phase of 14 hr. (Fig. 1).

The excretion rate of 6-demethylgriseofulvin and total 6-demethylgriseofulvin (summation of 6-demethylgriseofulvin and its glucuronide) peaked during the 1st hr., after which time it was found proportional to the blood level of griseofulvin except at 15 min. These data are shown in Fig. 1. (The initial point at 15 min. is not shown.) The urinary excretion rate of weak acids like 6-demethylgriseofulvin (pKa = 4.5, *Reference 6*) may depend upon the pH of the urine. A higher urinary pH will favor excretion because the renal reabsorption will be minimized by the ionization of the molecule. The urinary pH was found to be within the range of 5.3–6.9, which may play a possible role in the urinary excretion rate in various samples.

It is usually expected that the excretion rate of a compound is proportional to its concentration in the blood. However, in some circumstances the excretion rate of a metabolite can reflect the blood level of its precursor. Such a situation is seen in Fig. 1, where the excretion rates of 6-demethylgriseofulvin, free and total, have the identical slope as that obtained from the blood level of griseofulvin data. One must assume that the 6-demethylgriseofulvin excretion rate is several orders of magnitude faster than the formation rate; therefore, the appearance of 6-demethylgriseofulvin in the urine is rate limited by the formation-rate constant of 6-demethylgriseofulvin. This is in marked contrast to the experiments done in dogs (7) where the excretion data were triexponential, with a slowest phase showing a half-life ranging from 3 to 5 hr., while the griseofulvin disposition half-life was normally less than 1 hr. Unfortunately, it was not feasible to administer 6-demethylgriseofulvin intravenously to man to confirm this contention.

The recovery of 6-demethylgriseofulvin in 72 hr. was 42.5%, and that of the 6-demethylgriseofulvin glucuronide was 22.8%. The total 6-demethylgriseofulvin excretion exceeded five half-lives. Further, when one considers the α-phase, it is inclusive of better than 99% of the infinite excretion values. Therefore, the total recovery from these two known metabolites in this subject is 65.3% of the dose. No intact griseofulvin was detected. The excretion of the intact griseofulvin was reported to be negligible in man (8, 9) and in other animals (8–14). The metabolites were shown to be excreted through the bile after intravenous administration of radioactive griseofulvin-^{14}C to rats and rabbits (14) but not dogs (15). Only about 42% of the radioactivity was recovered in the urine of rats and 77% in rabbits. In dogs, about 60% of 6-demethylgriseofulvin and its glucuronide was recovered from the intravenous dose (7). Hence, fecal excretion and, conceivably, biliary excretion may also be present in man.

Oral Data—The cumulative excretion of total 6-demethylgriseofulvin after oral adminstration of micronized griseofulvin and dispersed griseofulvin in polyethylene glycol 6000 is shown in Tables I and II. The average cumulative excretion of 6-demethylgriseofulvin and total 6-demethylgriseofulvin is shown in Figs. 2 and 3.

The amount of 6-demethylgriseofulvin and total 6-demethylgriseofulvin after oral administration of griseofulvin–polyethylene glycol dispersion was remarkably constant within each subject. In Subject A, 65% of the administered dose was excreted in these experiments, which is identical to the percent excreted after intravenous administration. Therefore, it appears that the amount of metabolites excreted can serve as a basis of evaluating the availability of griseofulvin from oral dosage forms. Almost complete

Table II—Cumulative Total 6-Demethylgriseofulvin Urinary Excretion Data[a] after Oral Administration to Humans of 250 mg. Griseofulvin–Polyethylene Glycol 6000 Solid Dispersion in Capsule or Tablets

Experiment	Formulation	Hours 4	8	12	24	48	72
A-1	10% Griseofulvin–polyethylene glycol 6000	—	—	—	—	—	315.6
A-3	10% Griseofulvin–polyethylene glycol 6000	59.8	112.8	150.6	233.0	292.4	316.6
A-6	10% Griseofulvin–polyethylene glycol 6000	56.8	100.6	139.2	218.0	277.8	310.8
A-10	10% Griseofulvin–polyethylene glycol 6000[b]	50.0	93.4	125.6	200.0	284.8	312.8
A-13	10% Griseofulvin–polyethylene glycol 6000[c]	47.0	88.0	112.0	191.6	285.0	315.2
B-2	10% Griseofulvin–polyethylene glycol 6000	66.4	128.4	167.8	230.4	305.4	324.2
B-3	10% Griseofulvin–polyethylene glycol 6000	38.0	105.2	129.8	225.2	305.6	334.8
B-7	20% Griseofulvin–polyethylene glycol 6000[c]	62.0	110.6	150.6	228.6	303.4	322.0
Average ± *SEM*		54.3 ± 3.7	105.6 ± 5.1	139.4 ± 7.0	218.1 ± 6.1	293.6 ± 4.3	319.0 ± 2.7

[a] All values, milligrams of total 6-demethylgriseofulvin, corrected to an equivalent excretion as if 500-mg. dose administered. [b] Administered in tablet form, while administered in capsule form in all other experiments. [c] Prepared by the ethanol solvent method, while others were prepared by direct fusion method.

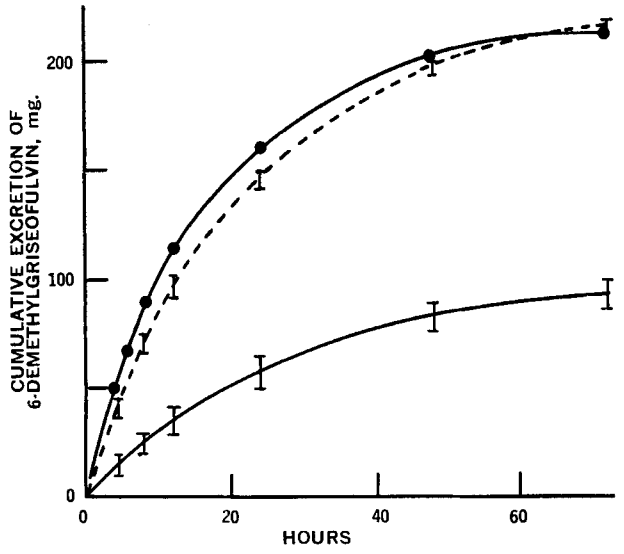

Figure 2—*Cumulative free 6-demethylgriseofulvin urinary excretion data after intravenous and oral administration of griseofulvin to Subjects A and B (intravenous data only for Subject A; others are mean data). Key: ●, intravenous griseofulvin to Subject A; - - -, griseofulvin dispersed in polyethylene glycol 6000; and ——, micronized griseofulvin (all data corrected for 500 mg. griseofulvin).*

absorption was found in all five trials of the dispersed griseofulvin and only 43% from four studies of micronized griseofulvin in Subject A. The cumulative excretion of 6-demethylgriseofulvin from intravenous and oral administration (Figs. 2 and 3) indicates fast and complete absorption from the dispersed griseofulvin in these subjects. The incomplete and rather irregular absorption from the micronized griseofulvin also confirms the findings by

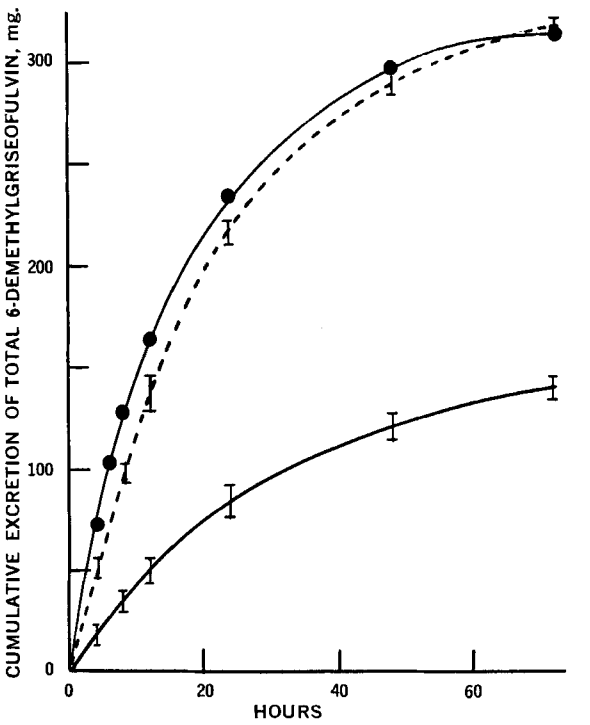

Figure 3—*Cumulative total 6-demethylgriseofulvin urinary excretion data after intravenous and oral administration of griseofulvin to Subjects A and B (intravenous data only for Subject A; others are mean data). Key: ●, intravenous griseofulvin to Subject A; - - -, griseofulvin dispersed in polyethylene glycol 6000; and ——, micronized griseofulvin (all data corrected for 500 mg. griseofulvin).*

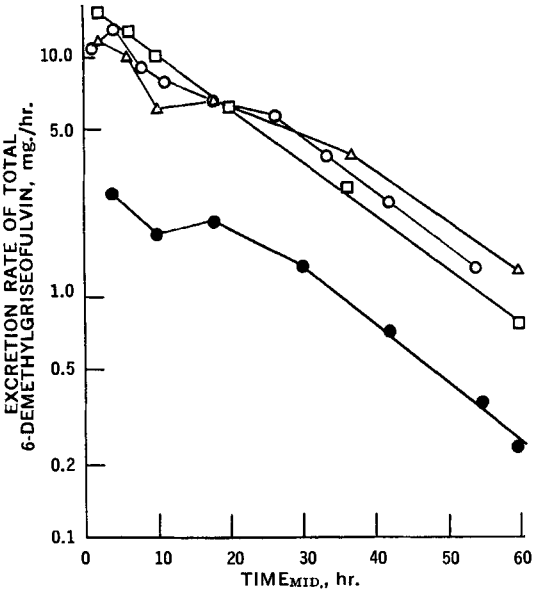

Figure 4—*Plots of urinary excretion rate of total 6-demethylgriseofulvin after oral administration of different dosage forms of griseofulvin to Subject A (all data corrected for 500 mg. griseofulvin). Key: △, 10% griseofulvin–polyethylene glycol 6000 tablet (A-10, melt method); ○, 10% griseofulvin–polyethylene glycol 6000 capsule (A-13, solvent method); □, 10% griseofulvin–polyethylene glycol 6000 capsule (A-3, melt method); and ●, commercial tablet of micronized griseofulvin (A-8).*

Rowland *et al.* (3) that somewhat less than 50% of the micronized drug is absorbed orally in man.

The semilog plots of the excretion rate of total 6-demethylgriseofulvin reveal interesting results (Figs. 4 and 5). For the fused mixture of griseofulvin–polyethylene glycol 6000 administered to Subject A in capsule forms, all the points from 2 to 60 hr. fall on the straight line, with the half-life exactly the same as that obtained from the intravenous study. This indicates that griseofulvin was probably completely absorbed in 2 hr. or less. The same excretion pattern from this dosage form also occurred in Subject B. Although the intravenous study was not carried out in this subject to obtain the disposition half-life and fraction of metabolites excreted, it is believed that the half-life, 13 hr., obtained from the dispersed griseofulvin study reflects the slower disposition half-life of griseofulvin. Furthermore, the total urinary metabolite recovery from three trials (B-2, B-3, and B-7) is very constant. It is, therefore, believed that the absorption from the dispersed system was also fast and complete in this subject.

The absorption of the dispersed griseofulvin in dogs was not as fast and complete as in man. This may be due to the following two reasons. First, the dose given to dogs was about threefold higher than in man on the basis of weight. Since griseofulvin is water insoluble and, therefore, requires a high amount of GI fluids to dissolve 250 mg. of the dose before being absorbed, the absorption of such a high dose in dogs may be partly rate limited by the intrinsic absorption process. Second, it is possible that absorption also may be related to the motility of the GI tract. Since the dogs remained almost stationary during the first few hours postadministration, the expected lower motility of the gut may, therefore, affect the absorption rate.

Analysis of the excretion rate from the micronized preparation shows slow and prolonged absorption. Absorption appeared to continue for 30–40 hr. in Subject A (Fig. 4) and 40–84 hr. in Subject B (Fig. 5), as indicated by the similar slope of the excretion rate after these times with that from the intravenous or dispersed griseofulvin dose. The urinary assay is accurate enough to confirm these data (optical density ranging from 0.3 to 0.7). The absorption process was also found to continue for 40 hr. in dogs, as noted previously (2). It is believed that this was the first instance where absorption was found to continue for more than 3 days for any drug.

An interesting comparison of the data on the dispersed and micronized griseofulvin can be made when the relative availability

Table III—Ratio of Cumulative Total 6-Demethylgriseofulvin Urinary Excretion between Dispersed Griseofulvin and Micronized Griseofulvin after Oral Administration

Griseofulvin	Hours					
	4	8	12	24	48	72
Micronized	1.0	1.0	1.0	1.0	1.0	1.0
Dispersed	2.9	3.1	2.8	2.6	2.4	2.3

is compared for these two different dosage forms, using cumulative excretion of metabolites at different times. As noted in Table III, the relative availability of the dispersed griseofulvin compared to the micronized griseofulvin is about threefold during the first 8 hr. and decreases to 2.3-fold by 72 hr. owing to the prolonged absorption of the micronized form. Symchowicz and Katchen (16) gave three griseofulvin preparations with different dissolution rates to 18 normal subjects for 7 days (500 mg./day). If one utilizes the area under the plasma concentration–time curve reported by these workers to evaluate the relative drug availability, the availability changes with time as shown in Table IV. The availability of Preparation 6 with the slowest dissolution rate was assumed as a standard at all the times. The better availability from Preparations 2 and 6 with faster dissolution rates is quite impressive in the first 8 hr.; however, they become much less significant if one compares the data through to 173 hr.

The complete and fast absorption of the 250-mg. dose of griseofulvin dispersed in polyethylene glycol 6000 is quite striking considering the volume of water required to dissolve this amount of drug. One might ask: Should not the solid dispersion precipitate free griseofulvin and lead to results much like those obtained from the micronized preparation? Chiou and Riegelman (4) pointed out that the solid dispersion can be classified into three groups, namely, eutectic mixture, solid solution, and glass solution, since the fused mixture probably belongs to a combination type. Even if these systems are predominantly solid solutions, the limited amount of the available GI fluids would cause precipitation before

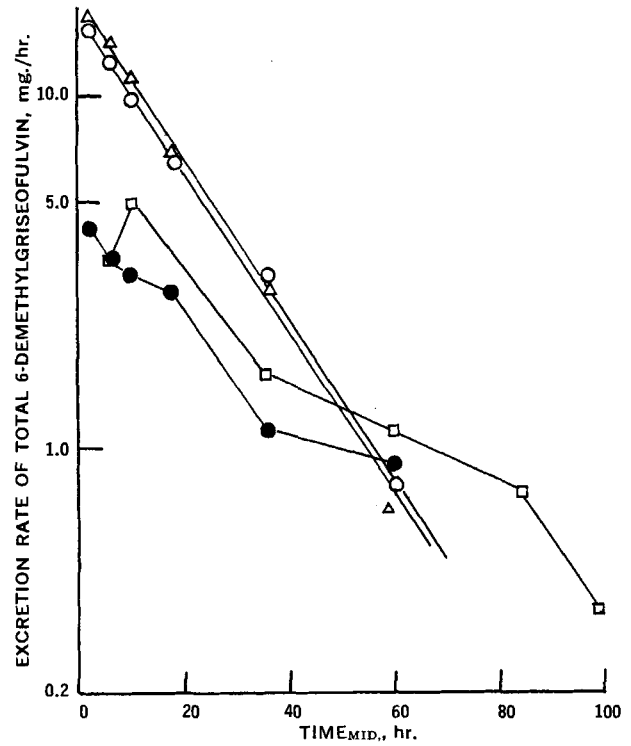

Figure 5—*Plots of urinary excretion rate of total 6-demethylgriseofulvin after oral administration of different dosage forms of griseofulvin to Subject B (all data corrected for 500 mg. griseofulvin). Key: △, 10% griseofulvin–polyethylene glycol 6000 capsule (B-2, melt method); ○, 20% griseofulvin–polyethylene glycol 6000 capsule (B-7, solvent method); □, commercial tablet of micronized griseofulvin (B-4), and ●, commercial tablet of micronized griseofulvin (B-1).*

Table IV—Comparative Availability after Repeated Doses of Griseofulvin in Different Dosage Forms[a]

Preparation	*In Vitro* Dissolution Data[b]	Comparative Areas		
		0–8 hr.	0–25 hr.	0–173 hr.
6	33	1.00	1.00	1.00
2	50	1.22	1.15	1.06
5	94	1.48	1.36	1.19

[a] Data calculated from *Reference 12.* [b] Percent dissolved in 30 min.

absorption. However, the precipitated griseofulvin might be in the colloidal or submicron range which will redissolve rapidly. The system might also form a supersaturated solution, as was found in the *in vitro* studies (4). Griseofulvin dispersed in polyethylene glycol 6000, prepared by the ethanol solvent method, not only showed visible and "colloidal" precipitate but also exhibited a much slower dissolution rate than the fused mixture (Fig. 2 in *Reference 4*). However, *in vivo* tests in man on these mixtures indicated that they were rapidly and completely absorbed (with the exception of A-10 and A-13 studies, which showed slower but complete absorption). Their excretion data are shown in Tables I and II and Figs. 4 and 5. The fusion method appears to give consistently rapid and efficient absorption from capsule form in Subject A. One can conclude, therefore, that fast-release solid solution is not absolutely required, but readily wetted and dispersed particles, colloidal or microfine, are essential for the complete and fast absorption of griseofulvin. In other words, fast and complete absorption of insoluble drugs should be obtained from fast-release solid dispersions: eutectic mixture, solid solution, or glassy solution. This was even noted when the dispersed griseofulvin was compressed into a hard tablet. It, nevertheless, was completely absorbed (Table II and Fig. 4).

Several authors have discussed how griseofulvin is absorbed in man and animals (3, 11, 17). The fast and complete absorption from the dispersed griseofulvin, with its maximum absorption rate in the first 2–3 hr., supports the idea that the upper small intestine is the major absorption site. It appears that there may be a limited time of sojourn through a limited region of the GI tract where conditions for optimum absorption exists. In spite of this, absorption continued for more than 20 hr. in one of the tests conducted on the dispersed griseofulvin preparation (Fig. 4, A-13). This could possibly be explained by a certain fraction of griseofulvin passing through the main absorption site without being absorbed, possibly due to a variation in motility such that a shorter time was available at the optimum absorption sites. Nevertheless, in this instance the drug was ultimately absorbed completely, probably due to the microfine size of the precipitated griseofulvin. In the case of the micronized preparation, the poorly wetted and agglomerated griseofulvin granules probably limit the surface available to the dissolution process; this, therefore, becomes rate limiting. The continuous absorption for more than 3 days might be rationalized by the supposition that the aggregated or agglomerated coarse particles are adsorbed to the intestinal invaginations where the particles slowly dissolve and are absorbed.

Since the percent of absorption from the dispersed griseofulvin is more than two times higher than the commercial micronized product, it is suggested that the present dose, 500 mg./day, can be reduced to 50%, *i.e.*, 250 mg./day, with a solid dispersion system. It is also believed that results similar to those from this study might be achieved with other insoluble drugs.

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Hydrolysis of Benzothiadiazines

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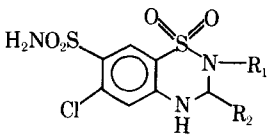
Abstract □ The hydrolysis of hydrochlorothiazide and two other hydrothiazides was studied as a function of pH. Reversible kinetics were observed for the hydrolytic reaction, and a bell-shaped pH–rate profile was obtained. The equilibrium constant, however, was relatively independent of hydrogen-ion concentration. The hydrolytic rate constants and the equilibrium constants for the overall reaction were evaluated. General catalysis was checked at several pH values, utilizing acetate and imidazole buffers, and no significant buffer catalysis was observed. The bell-shaped pH–rate profiles cannot be explained completely by the ionization of reactants, but they can be interpreted by postulating the presence of an imine intermediate that undergoes attack by water or hydroxide to form a carbinolamine which subsequently decomposes to products.

Keyphrases □ Benzothiadiazines—hydrolysis, mechanism, pH–rate profiles □ Hydrochlorothiazide, 3- and 2-ethyl analogs—hydrolysis, mechanism, pH–rate profiles □ Hydrolysis, rates and mechanism—benzothiadiazines

Benzothiadiazines form one of the most important classes of compounds used as diuretics. They have been divided into two main categories: "thiazides," which are 2*H*-1,2,4-benzothiadiazine-1,1-dioxides, and "hydrothiazides," which are 3,4-dihydro-[2*H*]-1,2,4-benzothiadiazine-1,1-dioxides. The former is represented by chlorothiazide, which is formed by condensing 5-chloro-2,4-disulfamylaniline (hereafter referred to as "disulfonamide") with formic acid; the latter is represented by hydrochlorothiazide, which is formed by condensing disulfonamide with formaldehyde (1).

Although these compounds form an important class of drugs, few publications concerning their routes and mechanisms of degradation have appeared. Yamana *et al.* (2) reported on the hydrolysis of chlorothiazide, and the stability of this compound was also studied by Charnicki *et al.* (3) and Baer *et al.* (4). Hydrothiazides, however, have not been studied in detail. Previous reports from this laboratory considered the analysis of hydrochlorothiazide (5) and presented the pH–rate profile for its hydrolysis (6). Yamana *et al.* (7) also published a similar report covering the pH–rate profile and reported on the hydrolysis in 1 *N* NaOH (8).

The study of the hydrolysis of hydrochlorothiazide was extended in this laboratory to explore the validity of the hypotheses that the reaction is reversible and that the extent of reaction is independent of pH. In addition, factors that influence the rate of reaction were investigated in order to postulate a possible mechanism for the hydrolysis. The present article is an extensive report on the hydrolysis of hydrochlorothiazide and its 3-ethyl (Su 9604) and 2-ethyl (Su 6835) analogs.



hydrochlorothiazide	$R_1 = R_2 = H$
N-ethyl hydrochlorothiazide (Su 6835)	$R_1 = C_2H_5$, $R_2 = H$
C-ethyl hydrochlorothiazide (Su 9604)	$R_1 = H$, $R_2 = C_2H_5$

EXPERIMENTAL

Materials—The purity of hydrochlorothiazide, m.p. 268°, was determined by phase-solubility analysis. All material used in these studies had a minimum assay of 99.4% by this method. The purity of 5-chloro-2,4-disulfamylaniline, m.p. 251–252°, was also determined by phase-solubility analysis. All material used had a minimum assay of 99.2% by this method. The following compounds were prepared in the research laboratories at CIBA and were previously reported (1, 9)[1]:

1. 6-Chloro-2-ethyl-3,4-dihydro-7-sulfamyl-2*H*-1,2,4-benzothiadiazine-1,1-dioxide [Su 6835], m.p. 190–191°.

Anal.—Calc. for $C_9H_{12}ClN_3O_4S_2$: C, 33.18; H, 3.71; N, 12.90. Found: C, 32.87; H, 3.70; N, 13.18.

2. 6-Chloro-3-ethyl-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide [Su 9604], m.p. 257°.

Anal.—Calc. for $C_9H_{12}ClN_3O_4S_2$: C, 33.18; H, 3.71; N, 12.90. Found: C, 33.06; H, 3.92; N, 13.15.

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