Bioavailability of Griseofulvin from Tablets in Humans and the Correlation with its Dissolution Rate

NOBUO AOYAGI ˣ, HIROYASU OGATA, NAHOKO KANIWA, MASANOBU KOIBUCHI †, TOSHIO SHIBAZAKI, and AKIRA EJIMA

Received July 31, 1981, from the *Division of Drugs, National Institute of Hygienic Sciences, 18-1, Kamiyoga 1-chome, Setagaya-ku, Tokyo 158, Japan.* †Deceased. Accepted for publication December 30, 1981.

Abstract □ Dissolution rates of 10 commercial microsize griseofulvin tablets and one ultramicrosize griseofulvin tablet were preliminarily determined in 18 liters of pH 7.2 phosphate buffer and in 900 ml of 40% dimethylformamide as test media. Addition of dimethylformamide affected the dissolution behavior of the formulations. The products, three microsize and one ultramicrosize, were selected for further studies on the bioavailability in humans and dissolution. Significant differences among the formulations were found in serum levels, C_{max}, and $AUC_{47.5\ hr}$, but not in AUC_{∞} and t_{max}. The maximum difference of C_{max} was ~40%. The ultramicrosize product showed lower C_{max} and serum levels at earlier sampling times than two microsize products. The dissolution rates determined under sink and nonsink conditions without pretreatment significantly correlated with the serum level at 1 hr but not with the other *in vivo* parameters. Only the dissolution rate determined by the sink method with pretreatment with a small quantity of water (1.0 ml) and plastic beads significantly correlated with serum levels at 3 and 5 hr, C_{max}, and $AUC_{47.5\ hr}$.

Keyphrases □ Bioavailability—griseofulvin from tablets in humans, correlation with dissolution rate □ Dissolution, rates—correlation with bioavailability of griseofulvin from tablets in humans □ Griseofulvin—bioavailability from tablets in humans, correlation with dissolution rate

The absorption of a poorly water soluble drug is considered to be dissolution rate limited. Griseofulvin used as an antifungal agent is a practically insoluble compound. The *in vivo* availability is enhanced by increasing the dissolution rate by means of reduction of particle size of the crystals (1–6). A good correlation between the bioavailability and dissolution rate was found for griseofulvin tablets (7, 8). However, fine particles may not necessarily produce the expected dissolution rate and bioavailability due to their aggregation and agglomeration (4, 9). A microsize griseofulvin powder has been widely used in commercial tablets, and now a new formulation, an ultramicrosize griseofulvin tablet, can be obtained, which has been formulated with the drug dispersed in polyethylene glycol 6000 (10–12) and has been shown to have better bioavailability than microsize products (11, 12). However, recently lower absorption of the drug from an ultramicrosize than from a microsize formulation was shown (13).

The present investigation was undertaken to study the dissolution rate and bioavailability in humans for commercial microsize griseofulvin tablets and an ultramicrosize griseofulvin tablet, and to clarify the relation between the *in vitro* and *in vivo* findings.

EXPERIMENTAL

Formulation—Ten commercial microsize griseofulvin tablets available in Japan and one ultramicrosize griseofulvin tablet[1] were used for the preliminary dissolution test. Each tablet contained 125 mg of griseofulvin. Based on preliminary dissolution data, four formulations, including an ultramicrosize formulation, were selected to provide a broad range of dissolution rates with the expectation that those formulations would show a wide variation in their bioavailabilities.

Table I—t_{50} for Griseofulvin Tablets [a]

Tablet	Method	
	Beaker[b]	Paddle[c]
1 (A)	13.8	8.3
2	25.4	24.7
3	102.6	9.1
4	80.3	10.6
5 (B)	8.1	11.0
6	73.9	37.0
7	85.0	6.0
8 (D)	211.0	38.8
9 (C)	107.8	9.0
10	86.8	—
11	66.0	29.5

[a] Time (t_{50}) in minutes. [b] 18 liters of pH 7.2 phosphate buffer. [c] 40% Dimethylformamide (900 ml).

Solubility—The solubility of griseofulvin in water [pH 7.2 sodium phosphate buffer (0.01 *M*) and 40% dimethylformamide] was determined at 37° spectrophotometrically after filtration of the equilibrated solution of griseofulvin through a 1.0-μm membrane filter.

Disintegration Time—Disintegration times of the griseofulvin formulations were determined with six tablets in pH 7.2 sodium phosphate buffer (0.01 *M*) according to Japanese Pharmacopeia IX specifications (30 strokes/min, 37°). The time when there were no particles of tablets or only a trace amount of soft residue on the screen was selected as the disintegration time.

Dissolution Rate—The dissolution rate of the drug from each dosage form was determined at 37° in pH 7.2 sodium phosphate buffer (0.01 *M*) unless otherwise specified. Hydrochloric acid solution (pH 1.2) and 40% dimethylformamide were also used as solvents. The amount of the drug dissolved was monitored spectrophotometrically by passing the solution through a glass filter stick (porosity G-3) to a flow cell and was expressed as a percentage of the labeled amount. An average dissolution rate was obtained after three dissolution runs. The dissolution rate was represented as t_5, t_{30}, and t_{50}, which indicate, respectively, the time required for 5, 30, and 50% of the drug to be dissolved. Polysorbate 80[2] and diastase (Japanese Pharmacopeia IX grade) were used to investigate their effects on the dissolution.

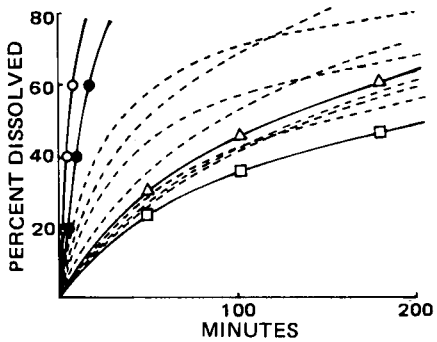

Figure 1—*Dissolution curves of griseofulvin tablets with the beaker method at pH 7.2. Key (●) Tablet A; (○) Tablet B; (△) Tablet C; (□) Tablet D; (- - -) dissolution curves of the other tablets.*

[1] Dorsey Laboratories, Division of Sandoz Inc.

[2] Tween 80, Wako Pure Chemical Industries Ltd., Osaka, Japan.

0022-3549/82/01000-1165$01.00/0

Table II—Dissolution Rates of Griseofulvin from Four Different Tablets with Sink Methods

In Vitro Test		t_{30}, min				t_{50}, min			
Method	Condition	A	B	C	D	A	B	C	D
Beaker	—	8.7	4.8	32.8	63.3	14.1	6.5	80.6	157.5
	0.1% Polysorbate 80	9.1	4.8	27.4	44.3	13.6	6.6	70.2	105.3
	0.014% Diastase	8.0	4.8	34.0	31.5	14.5	6.3	76.0	71.7
	848 rpm	6.5	4.1	28.7	48.0	9.5	5.6	65.3	119.0
	pH 1.2	10.0	3.0	31.5	85.0	—	—	—	—
	pH 1.2, 0.1% Polysorbate 80	7.5	3.5	16.0	30.0	—	—	—	—
Basket	—	6.5	5.0	26.0	21.5	9.0	7.0	75.0	57.0
Method I	—	3.1	1.7	8.3	2.7	6.1	2.5	26.7	4.6
Method II	—	1.8	1.9	6.6	3.3	2.7	3.2	17.3	6.4

Sink Method—*Nonpretreatment Method*—The beaker method consisted of agitating the solution with a three-bladed screw-type impeller (5.0-cm i.d., stirring rate: 512 rpm) in the middle of the solvent (18 liters) in a 20-liter flat-bottom beaker (29.0-cm i.d.).

The basket method consisted of placing a tablet in a cylindrical basket (1.7-cm i.d. × 2.3 cm) of 80-mesh stainless steel cloth. This basket was placed in a basket (Apparatus 1) as used in USP XX. The basket was held ~10 cm below the surface of the solvent and rotated at 400 rpm, ~7 cm from the wall of the beaker. The dissolution medium was agitated with a three-bladed impeller as described for the 18-liter beaker method.

With the paddle method (USP XX), 900 ml of 40% dimethylformamide was used as a solvent and was stirred at 120 rpm.

Pretreatment Method—Method I: A tablet was put into a 100-ml round bottle containing 1.0 ml of water and was gently shaken for 1 min. After standing for 5 min, 20 g of plastic beads (8-mm i.d.)[3] was added to the bottle. The bottle was fixed at an angle of 5° and was rotated at 3.8 rpm in a water bath (37°) for 15 min. The contents then were poured into 18 liters of the solvent with 100 ml of water for washing through a sieve to remove the plastic beads. Then the dissolution rate was determined according to the 18-liter beaker method procedure.

Method II: A tablet was gently shaken in 20 ml of water contained in a 50-ml round bottle for 5 min, and then 27 g of the plastic beads used in Method I was added. The subsequent procedure was the same as method I.

Nonsink Method—A 900 ml volume of the solvent was used in each experiment. The following procedures were used:

1. Rotating basket method (USP XX): The basket was rotated at 120 rpm.
2. Paddle method (USP XX): The stirring rate was 120 rpm.
3. Beaker method: A three-bladed screw-type impeller (5.0-cm i.d.) used as a stirring device was rotated at 2.5 cm from the bottom of the beaker which was used for the paddle method at 120 rpm.

Bioavailability—Twelve healthy male volunteers who participated in a Latin square crossover study were randomly assigned to one of four groups of equal size. The subjects ranged in age from 22 to 51 years (22, 22, 22, 22, 23, 24, 30, 32, 37, 37, 50, and 51; mean 31), in height from 160 to 180 cm (mean 170), and in weight from 53 to 69 kg (mean 60). Before the studies the participants were given a clinical examination to ensure they were healthy. All of the subjects were prohibited from taking medicines and alcoholic beverges from 3 days before the drug administration to the end of the test. Each subject took a test tablet orally with 200 ml of water at 9:00 am after fasting overnight. No foods or liquids were allowed until 4 hr after ingestion of the tablet. Blood samples (5 ml) were obtained at 1, 3, 5, 8, 23.5, 33, and 47.5 hr after administration of a tablet and the serum samples were kept frozen at −15° until assayed. The experiments were repeated every 2 weeks according to the dosage schedule. The following parameters were statistically subjected to ANOVA, and the differences among the treatments were examined by Tukey's test:

1. Serum levels at each sampling time.
2. Peak serum level (C_{max}).
3. Time to reach peak serum level (t_{max}).
4. Area under serum concentration–time curves from zero to the time t (AUC_t) calculated by the trapezoidal rule

The AUC_∞ was calculated by the method of Wagner (14).

Dose–Bioavailability Relation—A single tablet and one-half tablet of Formulation B, corresponding to 125 and 62.5 mg of griseofulvin, respectively, were given orally to three subjects according to a crossover design. The sampling times were the same as described in the bioavailability study.

Assay—The serum griseofulvin concentration was determined by the GLC method described previously (15). To a 0.5-ml aliquot of serum were added 0.5 ml of saturated sodium chloride solution and 5 ml of ether. After shaking for 10 min, a 4-ml aliquot of the ether phase was taken and evaporated to dryness *in vacuo*. The residue was dissolved with 0.4 ml of benzene containing 1.1 μg of clothiapine as internal standard, and 5 μl of the solution was taken for the GLC assay. GLC conditions: column, glass column (3-mm i.d. × 70 cm) packed with 5% OV-17 on 60–80 mesh Chromosorb W; injection temperature, 260°; detector temperature, 260°.

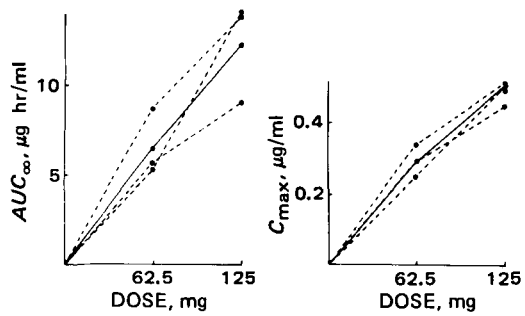

Figure 2—*Relations of griseofulvin dose with* AUC_∞ *and peak concentration after oral administration of the drug. Key: (- - -) responses of the individual subjects; (—) the average response.*

[3] Sartorius-Membranfilter GmbH.

RESULTS

Dissolution Rate—The solubilities of griseofulvin at 37° in water, pH 7.2 buffer, and 40% dimethylformamide were 31.8, 32.2, and 482.1 μg/ml, respectively; therefore, the preliminary dissolution tests were carried out with 18 liters of the aqueous medium (18-liter beaker method) and 900 ml of 40% dimethylformamide (paddle method) in order to get a sink condition. Figure 1 shows the dissolution profiles with the 18-liter beaker method. Relatively large differences were observed among the microsize griseofulvin formulations. The ultramicrosize formulation (A) showed rapid dissolution. Table I lists t_{50} in 18 liters of aqueous solvent and in 40% dimethylformamide. Addition of the organic solvent to aqueous medium altered the dissolution behavior of griseofulvin; however, the use of a partially alcoholic medium was described for the dissolution test of water insoluble drugs (16). On the basis of the *in vitro* data, four formulations (A, B, C, D), including an ultramicrosize formulation, were selected for further investigations concerning their dissolution rates and bioavailabilities.

Table II lists the dissolution rates (t_{30} and t_{50}) of these formulations determined under the sink condition. With the 18-liter beaker method

Table III—Dissolution Rate of Griseofulvin from Tablets with Nonsink Methods [a]

Method	Polysorbate 80	t_5, min A	B	C	D
Rotating basket	0	6.4	5.0	21.0	24.0
	0.1%	2.7	3.0	15.0	18.5
Paddle	0	4.5	4.7	9.9	18.6
	0.1%	4.2	4.0	9.0	11.0
Beaker	0	3.4	3.6	6.5	14.8
	0.1%	3.0	2.8	4.6	8.2

[a] At pH 7.2.

Table IV—Serum Levels, C_{max}, t_{max}, and AUC After Oral Administration of 125-mg Griseofulvin Tablets

In Vivo Parameter	Time, hr	Formulation[a] A	B	C	D	ANOVA[b]	Tukey's[c] Test
Serum levels, μg/ml	1.0	0.250 ± 0.058	0.331 ± 0.048	0.154 ± 0.025	0.126 ± 0.023	$p < 0.01$	B>A>C>D
	3.0	0.446 ± 0.065	0.593 ± 0.052	0.340 ± 0.041	0.462 ± 0.074	$p < 0.01$	B>D>A>C
	5.0	0.408 ± 0.036	0.576 ± 0.045	0.365 ± 0.038	0.486 ± 0.063	$p < 0.01$	B>D>A>C
	8.0	0.326 ± 0.035	0.462 ± 0.039	0.320 ± 0.035	0.439 ± 0.041	$p < 0.01$	B>D>A>C
	23.5	0.234 ± 0.021	0.199 ± 0.022	0.192 ± 0.019	0.243 ± 0.025	$p < 0.01$	D>A>B>C
	33.0	0.152 ± 0.018	0.109 ± 0.015	0.146 ± 0.020	0.133 ± 0.024	$p < 0.05$	A>C>D>B
	47.5	0.071 ± 0.011	0.046 ± 0.006	0.072 ± 0.010	0.062 ± 0.011	$p < 0.05$	C>A>D>B
C_{max}, μg/ml		0.502 ± 0.049	0.660 ± 0.046	0.395 ± 0.036	0.546 ± 0.070	$p < 0.01$	B>D>A>C
t_{max}, hr		5.3 ± 1.7	3.6 ± 0.3	6.0 ± 1.7	7.9 ± 2.1	NS	
$AUC_{47.5}$, μg hr/ml		10.57 ± 0.86	11.53 ± 0.76	9.46 ± 0.73	11.47 ± 0.67	$p < 0.01$	B>D>A>C
AUC_∞ μg hr/ml		11.83 ± 0.95	12.30 ± 0.86	11.27 ± 0.91	12.76 ± 0.81	NS	

[a] The figures indicate means ± standard errors. [b] NS: not significant. [c] Formulations underlined by a common line did not differ significantly; $p < 0.05$.

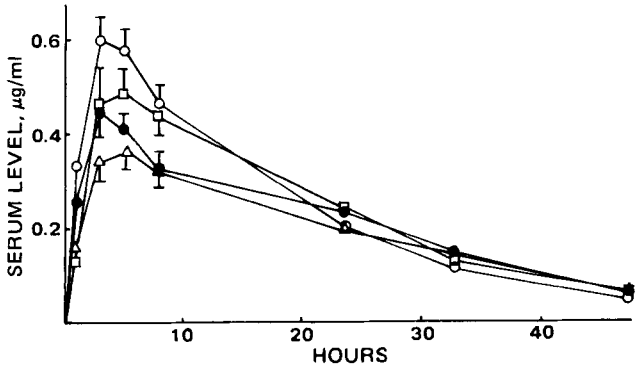

Figure 3—*Mean serum griseofulvin concentration after oral administration of 125-mg griseofulvin tablets to humans. Key: (●) Tablet A; (○) Tablet B; (△) Tablet C; (□) Tablet D. The vertical lines indicate standard errors.*

at either pH 7.2 or 1.2 without additives, the drug rapidly dissolved from Formulations A and B due to their rapid disintegration into fine particles. It slowly dissolved, however, from Formulations C and D due to the large particles resulting from disintegration. Polysorbate 80 and diastase, which was used to investigate the digestive action on the starch widely employed in tablets as the disintegrant or excipient, enhanced the dissolution from Formulation D, and in the presence of diastase its dissolution rate was faster than that from Formulation C. This can be attributed to a wetting action of the surfactant and a digestive one of the diastase. The dissolution rates were not enhanced by an increase of agitation intensity, but the dissolution from Formulation D was specifically facilitated with the basket method in which its deaggregation into fine particles seemed to be promoted due to being rubbed against the sieve wall of the basket as it was rotated. This suggests that deaggregation, especially for Formulation D, must be more accelerated by mechanical forces than by the flow of the dissolution medium. This was further ascertained by the pretreatment methods in which the dissolution of the drug, especially from Formulation D, was greatly enhanced. This is probably due to the strong deaggregation effects of the plastic beads.

The volume of water used in the pretreatment affected the dissolution, especially from the ultramicrosize formulation (A). It formed a pastelike agglomerate and showed slower dissolution when a small quantity of water (1.0 ml) was used (Method I) than when 20 ml of water was employed. In the latter case the formulation rapidly disintegrated into fine particles.

Table V—Power Analysis with $\alpha = 0.05$ and $\beta = 0.2$

Parameter	Time, hr	Subjects for 20% difference	Minimum Detectable Difference, %
Serum level	1	76	53
	3	28	30
	5	24	28
	8	20	26
	23.5	20	25
	33	44	39
	47.5	60	47
C_{max}		20	24
t_{max}		216	90
$AUC_{47.5}$		12	17
AUC_∞		16	21

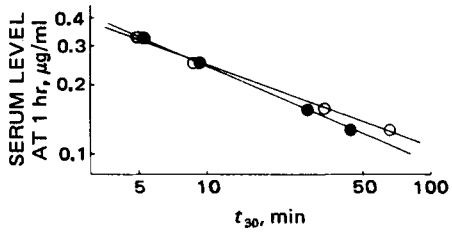

Figure 4—*Log–log plots of serum level of griseofulvin at 1 hr against t_{30} determined by the beaker method at pH 7.2 without an additive (○) and in the presence of polysorbate 80 (●).*

The initial dissolution rates (t_5) determined under the nonsink condition are shown in Table III. The results were similar to those determined with nonpretreatment methods under the sink condition, which suggests that by using the initial dissolution rates, the dissolution under the sink condition can be predicted.

Disintegration Time—The mean disintegration times of Formulations A, B, C, and D were 9.3, 12.5, 0.4, and 2.4 min, respectively. Contrary to the disintegration findings, the slow dissolution of the drug from Formulations C and D led to the conclusion that the resultant particulate state after disintegration is more important for the dissolution of griseofulvin than the disintegration time.

Bioavailability—The relations of griseofulvin dose with AUC_∞ and C_{max} are shown in Fig. 2. The nearly linear relationships of dose–AUC_∞ ($r = 0.829$) and dose–C_{max} ($r = 0.944$) indicate that linear pharmacokinetics can be applied to the serum level of griseofulvin within the dose ranges studied.

Figure 3 shows the mean serum concentration–time curves of griseofulvin in humans after oral administration of four formulations. Table IV lists the mean values of each parameter for these formulations. The rank order of serum level at 1 hr was B>A>C>D, but the serum levels during 3–8 hr, C_{max} and $AUC_{47.5}$, were B>D>A>C. The lowest peak

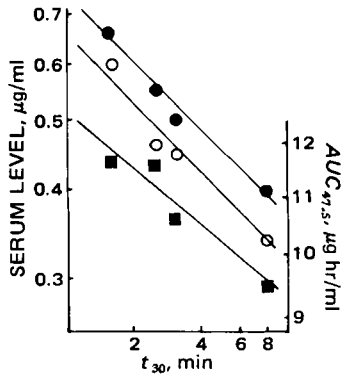

Figure 5—*Log–log plots of serum level at 3 hr (○), C_{max} (●), and $AUC_{47.5}$ (■) against t_{30} determined by Method I.*

Table VI—Correlation Coefficients Between *In Vivo* Parameters (X) and t_{30} (Y) Determined by Sink Methods

In Vitro Test		$X - Y^{-1}$					log (X) − log (Y)				
		Serum Level					Serum Level				
Method	Condition	1 hr	3 hr	5 hr	C_{max}	$AUC_{47.5}$	1 hr	3 hr	5 hr	C_{max}	$AUC_{47.5}$
Beaker	—	0.995[a]	0.809	0.655	0.727	0.430	−0.998[a]	−0.608	−0.399	−0.508	−0.229
	Polysorbate 80	0.990[a]	0.820	0.679	0.471	0.441	−0.999[a]	−0.650	−0.453	−0.554	−0.276
	Diastase	0.990[a]	0.840	0.680	0.763	0.489	−0.975[b]	−0.771	−0.564	−0.689	−0.460
	848 rpm	0.998[a]	0.792	0.617	0.708	0.420	−0.995[a]	−0.624	−0.403	−0.526	−0.259
	pH 1.2	0.942	0.848	0.765	0.782	0.482	−0.991[a]	−0.611	−0.442	−0.514	−0.217
	pH 1.2 Polysorbate 80	0.976[b]	0.813	0.696	0.736	0.423	−0.992[a]	−0.613	−0.442	−0.516	−0.220
Basket	—	0.978	0.796	0.598	0.716	0.466	−0.951	−0.769	−0.545	−0.690	−0.483
Method I	—	0.719	0.998[a]	0.965[b]	0.997[a]	0.896	−0.559	−0.982[b]	−0.917	−0.987[b]	−0.953[b]
Method II	—	0.814	0.742	0.513	0.686	0.570	−0.742	−0.824	−0.601	−0.780	−0.697

[a] $p < 0.01$. [b] $p < 0.05$.

Table VII—Correlation Coefficients Between *In Vivo* Parameters (X) and t_5 (Y) Determined by Nonsink Methods

In Vitro Test		$X - Y^{-1}$					log (X) − log (Y)				
		Serum Level					Serum Level				
Method	Additive	1 hr	3 hr	5 hr	C_{max}	$AUC_{47.5}$	1 hr	3 hr	5 hr	C_{max}	$AUC_{47.5}$
Rotating basket	none	0.986[a]	0.758	0.554	0.670	0.402	−0.954[a]	−0.627	−0.387	−0.527	−0.260
	Polysorbate 80	0.895	0.591	0.329	0.498	0.380	−0.947	−0.591	−0.325	−0.494	−0.269
Paddle	none	0.912	0.503	0.245	0.394	0.120	−0.939	−0.387	−0.135	−0.274	0.002
	Polysorbate 80	0.954[a]	0.641	0.402	0.544	0.282	−0.974[a]	−0.584	−0.335	−0.484	−0.235
Beaker	none	0.892	0.428	0.170	0.313	0.220	−0.907	−0.287	−0.044	−0.169	0.118
	Polysorbate 80	0.937	0.492	0.262	0.378	0.553	−0.934	−0.345	−0.119	−0.229	0.068

[a] $p < 0.05$.

concentration (Formulation C) was only 60% of the highest one (Formulation B). Significant differences were found among the formulations; however, there were no significant differences in AUC_∞, which suggests that the four formulations were equivalent in the extent of bioavailability.

The mean peak times did not show significant differences, though the maximum difference (3.6–7.9 hr) was relatively large. This can be attributed to the large variations in the parameter which will be due in some degree to a few peak times of 23.5 hr, which occurred with all formulations except B. It may have been artificially caused by the long interval of the sampling time from 8 to 23.5 hr. The power analysis was employed to estimate the minimum detectable difference between the formulations which would be statistically significant ($\alpha = 0.05$, $\beta = 0.2$) or the number of subjects required for a 20% difference to be significant (Table V). The results of this analysis indicate considerably low detectability of t_{max} compared with the other parameters; only 90% of the minimum difference could be detected in this study, and >200 subjects would have been required for a 20% difference to be significant. The parameters of $AUC_{47.5}$ and AUC_∞ provided better detectabilities, which must be due to the small variabilities in the parameters.

The ultramicrosize formulation (A) did not show good bioavailability, which is coincident with previous results (13), though absorption of the drug from the formulation was reported to be approximately twice that from microsize formulations (11, 12).

Correlation Between Dissolution Rate and Bioavailability—The correlation coefficients between the *in vivo* and *in vitro* parameters (t_{30} and t_5 determined by sink and nonsink methods, respectively) are shown in Tables VI and VII. The t_{30} determined by sink methods without pretreatment correlated significantly with the serum level at 1 hr in normal–reciprocal and log–log regressions but not with the other *in vivo* parameters. Similar relations were found between t_5 determined by nonsink methods and the *in vivo* parameters. The t_{30} determined by Method I with pretreatment with 1.0 ml of water was significantly correlated with serum levels at 3–5 hr and C_{max} in normal–reciprocal regression and even with $AUC_{47.5}$ in log–log regression. Those determined by Method II using 20 ml of water, however, did not correlate significantly with any of the *in vivo* parameters. Figures 4 and 5 illustrate the log–log regression lines that were significantly correlated between *in vivo* and *in vitro* findings.

DISCUSSION

The *in vivo* and *in vitro* findings for griseofulvin formulations suggest the complex dissolution behavior of the drug from its dosage forms in the GI tract in humans. The serum levels 1 hr after administration of the formulation correlated well with the dissolution rates determined under sink and nonsink conditions without pretreatment, which leads to the conclusion that initial absorption is mainly controlled by relatively simple dissolution behavior as shown artificially in the dissolution tests without pretreatment. However, the serum levels during 3–5 hr and C_{max} did not correlate well with these dissolution rates, which is probably due to the unexpectedly low values for Formulation A and high values for D for the *in vivo* parameters. It may be considered that for a drug having as low solubility in water or biological fluids as griseofulvin, the *in vivo* disintegration and dissolution must be affected more by physiological factors in the GI tract than those of a drug having high solubility, because the former drug must stay in the GI tract longer. The *in vitro* pretreatment, which decreases the sizes of aggregates or particles available from dissolution with plastic beads, markedly increased the dissolution, especially from Formulation D. The resulting dissolution rates highly correlated with the serum levels at 3 and 5 hr, C_{max}, and $AUC_{47.5}$. These findings suggest a strong deaggregation action on the aggregates and/or particles while the drug having low solubility stays in the GI tract.

A previous report on sugar-coated tablets of chloramphenicol also suggested the violent destructive force on the formulations *in vivo* (17). Therefore, the absorption of a drug having low solubility from its dosage forms seems to be correlated more with the dissolution rates determined under the conditions of vigorous agitation and destructive intensities than under mild conditions, though the absorption of a drug having high solubility such as aspirin may be correlated more with the dissolution rates determined under the latter conditions (18, 19).

Formulation A showed rapid dissolution under sink and nonsink conditions without pretreatment, which is probably due to the original ultramicrosize particulate state of the drug. But the rapid dissolution did not contribute to the *in vivo* absorption. Formulation A formed a pastelike agglomerate when treated with a small quantity of water (1.0 ml). Such an agglomerate may be also produced in the GI tract after rapid gastric emptying and rapid absorption of water coadministered with the formulation and may be responsible for slower dissolution and the resulting lower absorption of the drug.

REFERENCES

(1) R. M. Atkinson, C. Bedford, K. J. Child, and E. G. Tomich, *Nature (London)*, **193,** 588 (1962).

(2) P. Kabasakalian, M. Katz, B. Rosenkrantz, and E. Townley, *J. Pharm. Sci.*, **59,** 595 (1970).

(3) M. Kraml, J. Dubac, and D. Beall, *Can. J. Biochem. Physiol.*, **40,** 1449 (1962).

(4) R. M. Atkinson, C. Bedford, K. J. Child, and E. G. Tomich, *Antibiot. Chemother.*, **12,** 232 (1962).

(5) M. Kraml, J. Dubuc, and D. Dvornik, *Arch. Dermatol.*, **87**, 179 (1963).
(6) J. R. Marvel, D. A. Schlichting, D. Denton, E. J. Levy, and M. M. Cahn, *J. Invest. Dermatol.*, **42**, 197 (1964).
(7) B. Katchen and S. Symchowicz, *J. Pharm. Sci.*, **56**, 1108 (1967).
(8) S. Symchowicz and B. Katchen, *ibid.*, **57**, 1383 (1968).
(9) S. Lin, J. Menig, and L. Lachman, *ibid.*, **57**, 2143 (1968).
(10) W. L. Chiou and S. Riegelman, *ibid.*, **60**, 1376 (1971).
(11) W. E. Barrett, *Curr. Ther. Res.*, **18**, 501 (1975).
(12) *Ibid.*, **18**, 491 (1975).
(13) A. B. Straughn, M. C. Meyer, G. Raghow, and K. Rotenberg, *J. Pharmacokinet. Biopharm.*, **8**, 347 (1980).
(14) J. G. Wagner, "Fundamentals of Clinical Pharmacokinetics," Drug Intelligence Publications, Hamilton, Ill., 1975, p. 344.
(15) H. J. Schwarz, B. A. Waldman, and V. Madrid, *J. Pharm. Sci.*, **65**, 370 (1976).
(16) "USP Pharmacopeial Forum," **3**, 22–25 (1977).
(17) H. Ogata, T. Shibazaki, T. Inoue, and A. Ejima, *J. Pharm. Sci.*, **68**, 712 (1979).
(18) G. Levy, *ibid.*, **50**, 388 (1961).
(19) *Ibid.*, **52**, 1039 (1963).

Bioavailability of Griseofulvin from Tablets in Beagle Dogs and Correlation with Dissolution Rate and Bioavailability in Humans

NOBUO AOYAGI *x, HIROYASU OGATA *, NAHOKO KANIWA *, MASANOBU KOIBUCHI *†, TOSHIO SHIBAZAKI *, AKIRA EJIMA *, NORIYASU TAMAKI ‡, HIDETAKA KAMIMURA §, YOSHIO KATOUGI ‡, and YUKIO OMI §

Received July 31, 1981, from the **Division of Drugs, National Institute of Hygienic Sciences, 18-1, Kamiyoga 1-chome, Setagaya-ku, Tokyo 158, Japan;* the ‡*Yaizu Plant, Yamanouchi Pharmaceutical Co. Ltd., Ozumi-180, Yaizu-shi, Shizuoka-ken 425, Japan;* and the §*Institute of Research and Development, Yamanouchi Pharmaceutical Co. Ltd., 1-8, Azusawa 1-chome, Itabashi-ku, Tokyo 174, Japan.*
†Deceased. Accepted for publication December 30, 1981.

Abstract □ The bioavailability of four griseofulvin tablets in beagle dogs, including an ultramicrosize tablet used previously in a human bioavailability study, was investigated on the basis of the plasma 6-demethylgriseofulvin concentration. The relations with the *in vivo* findings in humans and the *in vitro* dissolution rates also were examined. Contrary to the lower bioavailability of the ultramicrosize formulation in humans, it provided the best bioavailability in beagles. The microsize griseofulvin formulations showed similar *in vivo* results to those in humans. Poor correlation of *in vivo* parameters between humans and beagles was attributed to the discrepancy of the availability of the ultramicrosize formulation between the two species. The dissolution rates determined by the pretreatment method using plastic beads were correlated more with the *in vivo* findings than those determined by the other methods. Beagles were a useful animal model for bioavailability studies of certain griseofulvin formulations but not ultramicrosize ones.

Keyphrases □ Bioavailability—griseofulvin from tablets in beagle dogs, correlation with dissolution rate and bioavailability in humans □ Dissolution rates—bioavailability of griseofulvin from tablets in beagle dogs, bioavailability in humans □ Griseofulvin—bioavailability from tablets in beagle dogs, dissolution rate and bioavailability in humans

The bioavailabilities for four lots of griseofulvin tablets in humans have been reported previously, and the relations with *in vitro* dissolution rates have been discussed (1).

Beagle dogs are often used as an animal model for bioavailability studies, but their suitability has not been clarified sufficiently. A good relation of penicillin bioavailability between humans and dogs was reported (2). Previous studies on bioavailability of diazepam formulations in humans and beagles revealed no good relations between the results from both species. The discrepancy was considered to be due to the differences of physiological states of the GI tract, especially of gastric emptying rate and GI transition time (3).

In the present study the bioavailability of griseofulvin from tablets in beagles was studied, and the relations with *in vivo* results in humans and *in vitro* dissolution rates were investigated.

EXPERIMENTAL

Formulations—Four lots of tablets containing 125 mg of griseofulvin employed in the human bioavailability study (1) were used. One formu-

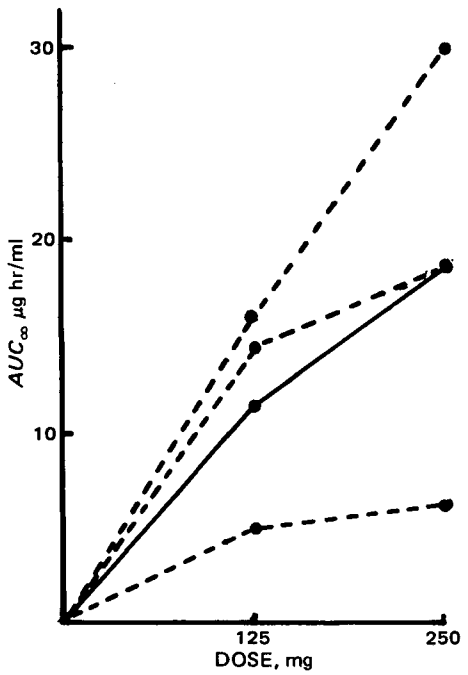

Figure 1—*Relation between griseofulvin dose and* AUC_∞ *of 6-demethylgriseofulvin. Key: (---) responses of the individual dogs; (—) average response.*

0022-3549/82/01000-1169$01.00/0