Oral Absorption of Griseofulvin in Dogs: Increased Absorption *via* Solid Dispersion in Polyethylene Glycol 6000

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Abstract □ Four different dosage forms of griseofulvin were administered orally to dogs: (*a*) griseofulvin in the solution of polyethylene glycol (PEG) 400; (*b*) griseofulvin dispersed in PEG 6000 (1:9 w/w) prepared by the fusion method and administered in capsule form; (*c*) a commercial tablet of micronized griseofulvin; and (*d*) a commercial capsule of micronized griseofulvin. The drug can be followed in the blood for 8–12 hr. after a 250- or 500-mg. dose. However, the blood data can lead to a false conclusion as to the degree and duration of the absorption process. This is due to fast metabolism ($t_{1/2}$ = 40–50 min.), to absorption being a dissolution rate-limited process, and finally to an assay that is insufficient to follow the total time course of the drug in the body. In contrast, the urinary excretion data for 6-demethylgriseofulvin (6-DMG) yield convincing evidence for prolonged absorption of griseofulvin for over 30 hr. for the commercial preparations. By comparison of the percent 6-DMG excreted to that obtained after i.v. administration, absorption was found to be complete for the solution form, 88% for the PEG dispersion, 45% for the commercial capsule, and 33% for the commercial tablet.

Keyphrases □ Griseofulvin dosage forms, oral—absorption, dogs □ Polyethylene glycol 6000 effect—griseofulvin absorption □ Dissolution rates—griseofulvin dosage forms □ Absorption, dissolution rates—correlation □ Urinary excretion—griseofulvin metabolites

Sekiguchi and Obi (1) were the first to apply the principle of solid dispersions utilizing a water-soluble carrier as a matrix for a poorly soluble drug to increase the rate of dissolution and oral absorption. They proposed the formation of a eutectic mixture of a poorly water-soluble drug with a physiologically inert, readily soluble carrier. Goldberg *et al.* (2) later suggested the formation of solid solutions (mixed crystals) rather than eutectic mixtures to obtain faster dissolution and absorption rates. Recently, Chiou (3) proposed, from the theoretical standpoint, that a poorly soluble or insoluble drug can achieve the fastest rates of dissolution and absorption when dispersed in a glass solution of a water-soluble carrier. Upon exposure to aqueous fluids, the active drug will be released in a state of fine particles (eutectic mixture) or single molecule (solid or glass solution). The enhancement of *in vitro* dissolution rates has been shown with solid dispersions containing chloramphenicol (4, 5), griseofulvin (Gris) (6, 7), and reserpine (8). However, the *in vivo* investigation of such systems has been limited. Only sulfathiazole (1), chloramphenicol (4), and reserpine (9) have been studied. One major and commonly used approach to enhance oral absorption is micronization. Yet, no study has been reported to compare the absorption of a drug in micronized form and in a solid dispersion form. Therefore, the clinical and practical value of the solid dispersion approach has not been fully established. The main objective of this communication is to compare quantitatively the absorption characteristics of a water-insoluble antibiotic, Gris, in dogs. The absorption properties of these systems in man will be reported in a future article.

In another communication (10), the authors reported that the dissolution rate of Gris was increased considerably when dispersed in the carriers of polyethylene glycol (PEG) 4000, 6000, and 20,000; citric acid; pentaerythritol; and pentaerythrityl tetraacetate. The results obtained after i.v. studies of Gris and its metabolite, 6-demethylgriseofulvin (6-DMG), in the same dogs have also been previously reported (11). The PEG 6000 was selected as a model carrier to test in dogs.

EXPERIMENTAL

Dosage Forms—Four different dosage forms were used for oral studies: 250 mg. of Gris dissolved in 50 ml. of PEG 400; 250 mg. of Gris dispersed in 2250 mg. of PEG 6000 (250 mg. 10% Gris–PEG 6000) by the melting method (10) and packed loosely into five gelatin capsules (size 00); a commercial tablet containing 500 mg. of micronized Gris; and a commercial capsule containing 250 mg. of micronized Gris.

Protocol in Dog Studies—Male, mongrel, conditioned, unanesthetized dogs weighing 19–22 kg. were used throughout the studies. Dogs were fasted with water *ad libitum* for 16 to 18 hr. prior to experiments. The Gris in the solution form was administered through a stomach tube followed by 30 ml. of 50% aqueous PEG 400 solution to rinse the syringe and the stomach tube. The solid dosage forms, mixed with a small amount of ground meat, were swallowed quickly by the dogs. One hundred fifty milliliters of lukewarm tap water was then given through the stomach tube. Dogs were observed for at least 2 hr. to make sure that there was no vomiting of the drug. Food was withdrawn for 8 hr. after administration, while water was freely available.

Blood samples (5 ml.) were drawn at 0, 1, 2, 3, 5, 8, and occasionally up to 12 hr. after drug administration from a cephalic vein with a 22-gauge disposable needle attached to a 6-ml. syringe. For the solution dosage form, additional samples were taken at 15 and 30 min. Urine samples were taken at 0, 2, 5, 8, 30, and 48 hr. through a urethral catheter. After the initial withdrawal of urine, at least 20 ml. of saline was used to wash the bladder. Both the urine and the washing were combined together for the assay. Occasionally, only blood or urine samples were taken.

Table I—Plasma Data (mcg./ml.) after Oral Administration of Various Dosage Forms of Gris to Dogs

Dosage Forms	Expts.	Time 15 min.	30 min.	1 hr.	2 hr.	3 hr.	5 hr.	8 hr.	Area, min. mcg./ml.
250 mg. *in solution*	F-5	1.00	0.92	2.12	1.23	0.55	0.17	0.00	280
	G-13	2.52	2.08	2.46	1.63	0.95	0.32	0.08	434
	H-3	1.56	3.43	3.25	2.20	1.44	0.71	0.21	647
	K-1	2.19	2.25	2.73	2.34	1.82	0.82	0.26	658
	Av.	1.82±	2.17±	2.64±	1.85±	1.19	0.51	0.14±	505±
	± *SEM*	0.34	0.51	0.24	0.26	0.28	0.15	0.06	91
250 mg. dispersed in PEG 6000 (capsule)	H-2			0.35	1.33	1.50	0.66	0.22	345
	H-5			0.94	1.44	1.28	0.58	0.19	367
	H-6			0.34	0.59	0.77	0.32	0.13	185
	G-2			1.20	1.71	2.87	2.16	0.80	830
	G-19			0.62	1.08	1.17	0.95	0.39	445
	K-2			0.12	0.40	0.65	1.27	0.61	335
	K-19			0.08	0.28	0.70	0.56	0.53	217
	Av.			0.55±	0.98±	1.24±	0.97±	0.41±	389±
	± *SEM*			0.18	0.21	0.34	0.27	0.09	81
500 mg. micronized (tablet)	H-1			0.10	1.60	1.97	1.01	0.40	466
	H-4			0.14	0.25	0.31	0.34	0.10	112
	H-14			0.19	0.38	0.59	0.31	0.12	145
	G-1			0.88	1.27	1.73	1.04	0.34	471
	G-4			0.33	0.50	0.53	0.18	0.04	129
	G-14			0.05	0.12	0.11	0.13	0.06	46
	G-15			0.41	0.48	0.53	0.20	0.05	137
	K-15			0.17	0.31	0.36	0.29	0.10	115
	Av.			0.28±	0.61±	0.77±	0.44±	0.15±	203±
	± *SEM*			0.10	0.19	0.24	0.13	0.05	57.4
250 mg. micronized (capsule)	D-2			0.20	0.24	0.21	0.12	0.06	69
	D-6			0.41	0.22	0.25	0.17	0.14	112
	F-12			0.10	0.32	0.36	0.07	0.00	68
	G-12			0.13	0.26	0.54	0.26	0.07	118
	H-12			0.11	0.34	0.23	0.10	0.03	67
	H-13			0.18	0.35	0.43	0.22	0.07	107
	H-15			0.19	0.30	0.37	0.17	0.06	95
	Av.			0.19±	0.29±	0.34±	0.16±	0.06±	91±
	± *SEM*			0.04	0.02	0.04	0.02	0.02	6.7

Samples of urine and plasma obtained after separation from red cells by centrifugation were stored at 4° until required for analysis. The spectrophotofluorometric assay of Gris in the plasma (12) and the UV assay of 6-DMG in the urine (13) were conducted as previously described. An interval of at least 1 week separated each experiment.

***In Vitro* Dissolution Rate Studies**—Dissolution rate studies of 125 mg. of Gris in three solid dosage forms were run in 18 l. of simulated intestinal fluid (14) at 36.7 ± 0.05° in an apparatus previously described (10). For dissolution studies, dispersed Gris was filled in two gelatin capsules (size 00), an equivalent amount of powder from the commercial capsule was refilled in a size 1 gelatin capsule, and a single mass was cut from the commercial tablet. Dissolution was studied using the USP disintegration apparatus (Scientific Glass Apparatus Co., Bloomfield, N. J.). However, a single cylindrical covered basket, diameter 2.8 cm. and height 5.6 cm., made up of an 8-mesh stainless steel screen, was used instead of the conventional basket-rack assembly, because Gris–PEG preparation was found to stick to the plastic wall in the standard basket.

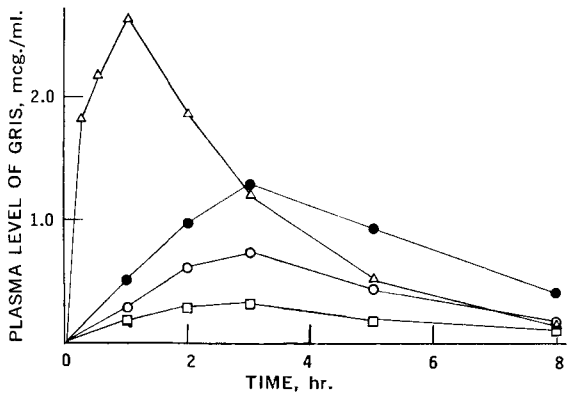

Figure 1—*Mean plasma levels of Gris after oral administration of various dosage forms to dogs. Key: △, 250 mg. in solution; ●, 250 mg. dispersed in PEG 6000; ○, commercial tablet of 500 mg. micronized Gris; and □, commercial capsule of 250 mg. micronized Gris.*

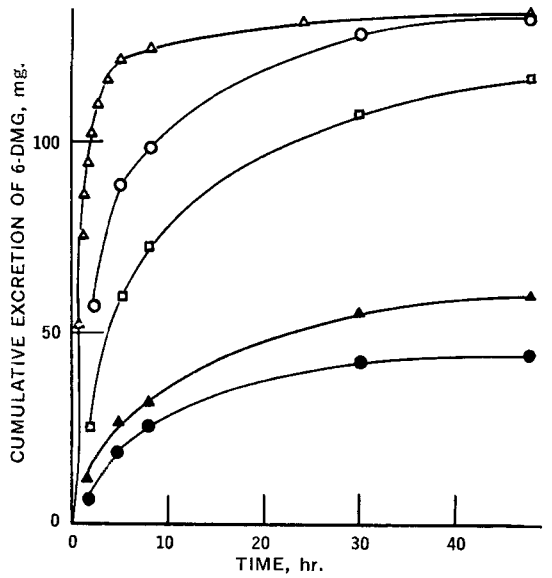

Figure 2—*Average cumulative excretion of 6-DMG after oral and i.v. doses of Gris. Key: △, i.v. Gris; ○, Gris in solution; □, Gris dispersed in PEG 6000; ▲, commercial capsule of micronized Gris; and ●, commercial tablet of micronized Gris. (All data corrected for 250-mg. dose.)*

RESULTS AND DISCUSSION

Plasma Levels of Gris after Oral Administration—The plasma concentration data after oral administrations of four different dosage forms of Gris are shown in Table I and their average values are plotted in Fig. 1.

Although Gris has long been used for antifungal therapy in dogs (15), its oral absorption has not thus far been reported. The recommended dose of 5 mg./lb./day in dogs is the same as that used in man. The results reported from this laboratory (11, 16) indicated that the metabolic rate of Gris in dogs may be 20–30 times faster than that in man. Therefore, it is not surprising that very low blood levels of Gris were obtained from 250 mg. of commercial capsule (Table I) administered to dogs weighing 45 lb. (approximately 5 mg./lb.) as compared with that obtained from man (12). The average peak level was found to be about 0.3 mcg./ml., and the concentration after 8 hr. of administration was almost negligible. Furthermore, even the blood level from the solution dosage form was very low after 8 hr. of administration. It has been reported that the minimal plasma concentration of Gris required for the effective therapy in man is about 1 mcg./ml. (17). Hence, it is highly doubtful that the presently recommended dose in dogs is adequate. Further study of this aspect should be pursued.

Peaks of plasma level of Gris from three solid formulations were all reached at about 3 hr. after administration as found in man (12), cats (18), and rats (19). The absorption from the solution form was much faster, as expected. The peak plasma levels after administration of the Gris–PEG solution were in the range of 15–30 min. in Dogs G and H.

The absorption from the commercially available micronized preparations appears to be quite incomplete. The average peak levels from these preparations are about 25 to 29% of that from Gris dispersed in PEG 6000 on the basis of equal amount of Gris administered.

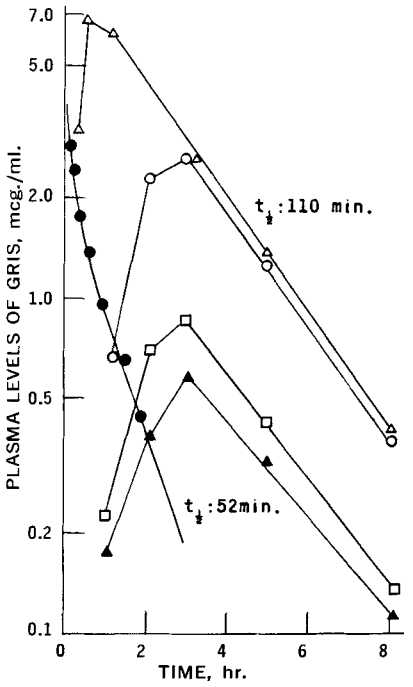

Figure 3—*Plasma concentration of Gris after administration of various dosage forms to Dog H (oral doses all corrected to 50 mg. Gris). Key: △, Gris in solution (H-3); ○, Gris dispersed in PEG 6000 (H-6); □, commercial capsule of micronized Gris (H-13); ▲, commercial tablet of micronized Gris (H-14); and ●, 50 mg. Gris i.v. (H-9).*

Table II—Cumulative 6-DMG Urinary Excretion Data (mg. of 6-DMG) after Oral Administration of Various Dosage Forms of Gris to Dogs

Dosage Forms	Expts.	Time 2 hr.	5 hr.	8 hr.	30 hr.	48 hr.
250 mg. in solution	F-5	54.0	82.2	90.7	114.3	128.3
	G-13	59.6	89.6	97.2	122.4	130.4
	H-3	55.0	91.6	103.0	—	132.8
	K-5	—	—	—	—	—
	Av. ± *SEM*	56.2 ± 1.72	87.8 ± 2.8	97 ± 3.5	118 ± 4.0	130.5 ± 1.3
250 mg. dispersed in PEG 6000 (capsule)	F-6	16.3	54.7	69.0	97.1	109.8
	F-9	28.8	63.5	81.7	103.1	113.3
	G-2	17.0	53.6	71.3	108.0	119.0
	G-19	19.7	49.6	65.4	108.6	123.8
	H-2	15.9	44.8	56.2	88.3	96.3
	H-6	27.4	71.7	81.4	117.2	124.2
	H-5	46.5	72.7	83.4	117.0	125.0
	Av. ± *SEM*	24.5 ± 4.2	58.7 ± 4.1	72.6 ± 3.8	105.6 ± 3.9	115.9 ± 3.9
500 mg. micronized (tablet)	H-1	11.8	64.2	80.8	103.3	106.4
	H-4	10.0	29.4	39.2	72.5	75.8
	H-14	9.0	30.9	40.2	63.5	67.1
	H-8	—	—	37.4	68.1	71.0
	G-1	14.3	49.9	66.1	—	—
	G-4	14.4	32.6	37.6	62.1	75.0
	G-8	—	—	46.3	89.5	98.2
	G-14	6.8	20.0	26.3	52.1	63.0
	G-15	17.8	46.9	61.3	119.8	136.8
	F-8	—	—	66.5	122.5	138.7
	F-14	—	—	—	—	85.6
	K-15	—	—	—	—	37.8
	Av. ± *SEM*	12.0 ± 1.4	39.1 ± 5.7	50.2 ± 5.5	83.7 ± 8.7	87 ± 9.3
250 mg. micronized (capsule)	F-2	5.2	20.6	24.3	72.2	75.8
	G-12	6.0	25.1	30.6	60.4	72.4
	H-12	10.3	21.1	24.6	36.3	37.0
	H-13	15.7	38.9	45.5	59.6	68.9
	H-15	7.8	20.8	25.8	40.0	43.5
	Av. ± *SEM*	9.0 ± 1.9	25.3 ± 3.5	30.2 ± 4.0	53.7 ± 6.7	59.5 ± 8.0

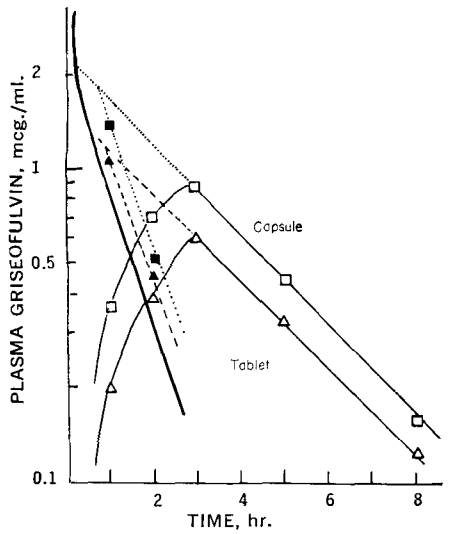

Figure 4—*Replot of the data shown in Fig. 3 on 500 mg. Gris administered to Dog H (see Fig. 3 for details). Extrapolation difference curves (solid circles and triangles) indicate the faster of the two rate processes.*

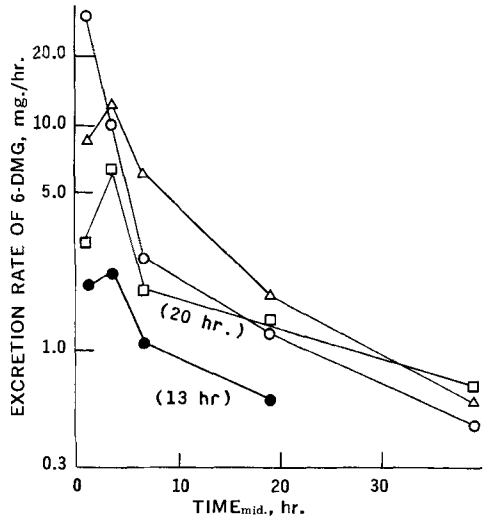

Figure 6—*6-DMG excretion rate plots after oral administration of various dosage forms to Dog G (all data corrected to 500-mg. dose). Key: ○, Gris in solution (G-13); △, Gris dispersed in PEG 6000 (G-2); □, commercial capsule of micronized Gris (G-12); and ●, commercial tablet of micronized Gris (G-14).*

The solution form of Gris might be presumed to be more completely absorbed and could be used as a standard for comparison of the dosage forms. By comparison with the area under the plasma concentration–time curve in 8 hr. from the solution form, the availability is 77% for Gris dispersed in PEG 6000, 26% for the commercial tablet, and 18% for the commercial capsule. There is, however, a fallacy in this method of comparison, since it was reported in a previous communication (11) that the elimination characteristics of Gris after i.v. administration in some dogs followed dose-dependent kinetics. Therefore, it seems invalid to compare the availability on the basis of the blood area. However, as reported in the previous communication (11), the total urinary excretion of 6-DMG, its major metabolite, was found to be almost constant for every dog studied and to be independent of doses in dogs exhibiting dose-dependent kinetics of Gris. Therefore, it was concluded that the total 6-DMG excretion in the urine can be used to evaluate the extent of drug absorption.

The absorption of micronized Gris preparation in man has been shown in this laboratory to continue for more than 30 or 40 hr.

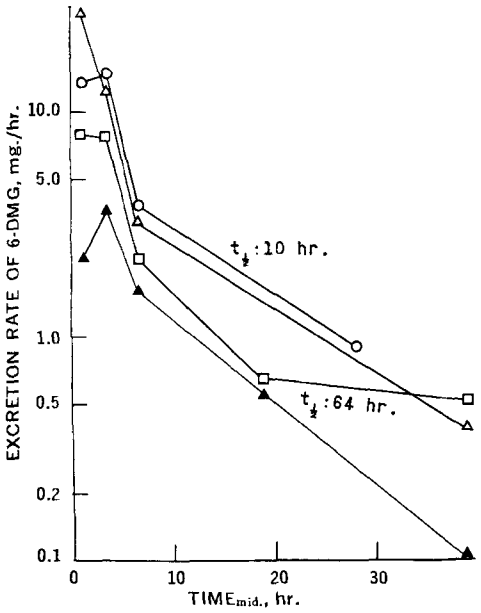

Figure 5—*6-DMG excretion rate plots after oral administration of various dosage forms to Dog H (see Fig. 3 for details). The half-life of 6-DMG excretion from i.v. dose to Dog H is 4.8 hr.*

(12). However, after the first 10 hr., the rate of absorption is much reduced. This may also take place in dogs; the drug concentration might fall below the level of spectrophotofluorometric assay sensitivity after 8 or 12 hr. postadministration, even though the drug is continuing to be absorbed. The authors, therefore, may not be able to follow the drug long enough in the blood to detect the total absorption process. This will be discussed further.

Urinary Excretion of 6-DMG after Oral Administration—Two urinary metabolites, 6-DMG and 6-DMG glucuronide, were previously identified in this laboratory after an i.v. dose of Gris to dogs (16). The excretion of 6-DMG glucuronide was found to contribute only insignificantly to the metabolic process either after i.v. or oral administration of Gris (11).

The excretion of 6-DMG after administration of four different dosage forms is shown in Table II. The average cumulative data for 6-DMG from i.v. (11) and oral doses are shown in Fig. 2. The percent of the total excretion of 6-DMG in 48 hr. from four dogs was surprisingly constant with an average of 55.1%, which is virtually identical to that obtained from i.v. dose, 56.4% (11), and indicates complete absorption from Gris in solution form. Using the amount of metabolite excretion in 48 hr. after the i.v. doses, the metabolite recovery is 88% from the Gris dispersed in PEG 6000, 45% from the commercial capsule, and 33% from the commercial tablet. Therefore, it is evident that the insoluble Gris dispersed in a water-soluble matrix of PEG 6000 does indeed result in a faster and more complete absorption than micronized products. Of additional importance is the fact that the absorption appears to be more consistent from the PEG dispersion.

There appear to be many potential physical and chemical advantages of a solid dispersion prepared with water-soluble carriers. The carriers will obviously be chosen on their ability to dissolve the required amounts of the drug in the solid dispersion. As such, it may show an increased tendency to produce supersaturated solution, fast dissolution rate, and good wetting and dispersion on exposure to the aqueous fluids. Although the micronization of insoluble drugs can increase the specific surface area and thereby increase the dissolution rate, this potential advantage may be easily lost due to the aggregation or agglomeration during the formulation or processing, which may not be overcome by adequate wetting in the biological fluids during the absorption process. It appears that the physicochemical advantages intrinsic in the solid dispersion form markedly influence the biological availability of the Gris in dogs. It is hoped that the approach of solid dispersion can also be applied to other insoluble drugs.

Long Absorption Time of Gris in Dogs—An interesting absorption phenomenon was frequently observed in dogs. Typical plasma concentration curves of Gris after administration of different dosage forms to a dog are shown as semilog plots in Fig. 3. One

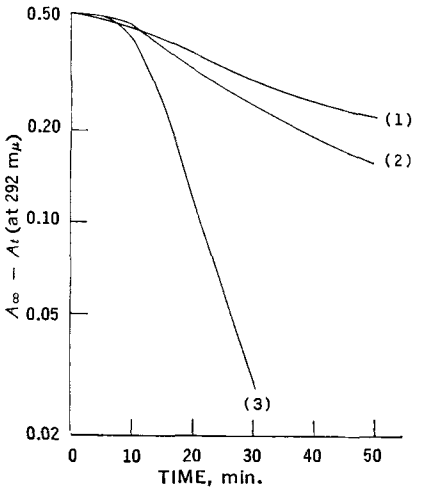

Figure 7—*Gris dissolution rate data (amount remaining to be dissolved) from 125 mg. in 18 l. of simulated intestinal fluid at 36.7°. Key:* (1), *commercial capsule;* (2), *commercial tablet; and* (3), *capsule of Gris dispersed in PEG 6000.*

certainly would wonder why four different preparations with different dissolution rates will have the same postpeak disappearance curve with a half-life of about 2 hr. (even up to 12 hr. postadministration). This would usually be defined as the elimination half-life of the drug.

The elimination half-life ($t_{1/2}$ = 52 min.) in this dog after i.v. dose was found to be dose-independent (Fig. 1 in *Reference 11*). Therefore, it indicates that the postpeak curve is primarily due to the slower process, the absorption process, which continued for at least 8 hr. Further evidence for this contention is seen in Fig. 4 in which some of the data from the previous figure have been redrawn. The linear portions of the postpeak curves for the capsule and tablet experiments have been extrapolated back to zero time, and the method of extrapolation difference has been used to estimate the rate constant for the faster of the two competing processes which primarily contribute to the rising portion of the blood curves. The extrapolation difference values led to the dashed lines representing the contribution from this first-order rate process. These lines show essentially the same slope as found after i.v. administration of Gris (shown as the heavy solid line). This interpretation would require the definition of the postpeak curve as indicative of the apparent absorption rate of the drug with a half-life of approximately 2 hr. Figure 5 includes plots of the 6-DMG excretion rate for the same experiments. The slopes of these curves during the same time interval are compatible with the previous interpretation of the blood data. This unusual pattern of absorption is similar to that of the oral administration of spironolactone (a drug of similar insolubility to Gris) to man (21) and was left unexplained by Levy (22).

The prolonged slow absorption of Gris can be shown by review of the urinary excretion rate data for the metabolite of Gris which are found in Table II and Figs. 5 and 6. If the absorption process stops at 8 hr., the excretion rate should be the same as that of the slow phase of excretion after i.v. dose of Gris ($t_{1/2}$ = 3–4.8 hr. in the two dogs shown). However, it is clear from Figs. 5 and 6 that the apparent excretion rate is much slower. Indeed, the half-life of the processes contributing to the postpeak curves 8 or more hr. after administration of the drug ranges from 10 to 20 hr. The authors interpret this to mean that the absorption process is the rate-limiting step and continues for more than 30 hr. This finding is in agreement with the report of Gris absorption in man from this laboratory (12).

The urinary excretion method described in this communication can serve as a convenient means of screening dosage form effects on a drug which is dissolution rate limited on the absorption. Thus, even though the blood data are of limited value due to slow absorption followed by rapid metabolism, the urinary excretion of the metabolite continues long after the drug is undetectable in the blood.

Correlation between the Absorption and the Dissolution Rate—Dissolution rates of Gris in three solid dosage forms in the 18 l. of simulated intestinal fluid are shown in Fig. 7. An interesting correlation appears to exist between the *in vitro* dissolution rate data and the *in vivo* data discussed; namely, the cumulative urinary excretion of 6-DMG in 48 hr. was found to correlate linearly with the logarithm of percent of Gris dissolved in 25 min. in the simulated intestinal fluid. This is shown in Fig. 8. It should be noted that similar correlation between the area under the blood concentration–time curve with the specific surface area of Gris powder (23) and the dissolution rates (24, 25) of Gris dosage forms in the simulated intestinal fluid have been reported in the past. The amount of data available to include in this plot is very minimal; it merely serves once again to point out *in vivo–in vitro* correlations can be established.

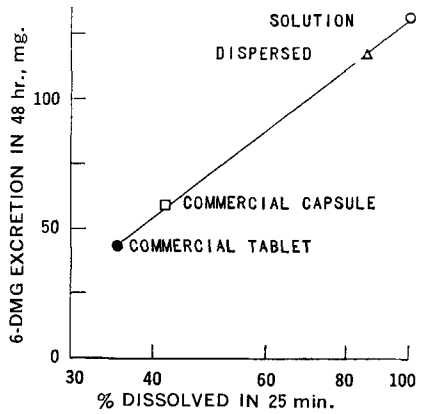

Figure 8—*Correlation between dissolution rate and total 6-DMG excretion in 48 hours.*

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Synthesis of Some Glycidic Hydrazides and Amides as Potential Psychotropic Agents and Anticholinergic Agents

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Abstract □ A series of glycidic hydrazides and amides was prepared by hydrazinolysis or aminolysis of glycidic esters obtained *via* a modified Darzens condensation. The hydrazides thus obtained were subjected to suitable acylating or alkylating reagents to obtain *N*-substituted hydrazides. The results of a preliminary pharmacological evaluation are summarized. The synthesized compounds were tested for their ability to reverse reserpine hypothermia in mice. Compounds synthesized as potential anticholinergics were evaluated for their spasmolytic activity using isolated rabbit ileum.

Keyphrases □ Glycidic hydrazides, amides—synthesis □ Hydrazides, glycidic—synthesis □ Amides, glycidic—synthesis □ IR spectrophotometry—identity □ Pharmacological screening—glycidic hydrazides, amides

Appropriately substituted hydrazides and amides have been of interest to the medicinal chemist for various reasons. Monoamine oxidase-inhibitory hydrazides have proved to possess dynamic pharmacological properties (*i.e.*, antitubercular and/or antidepressant properties). Amides that are analogous to bioactive esters (*e.g.*, procaine *versus* procainamide) offer models for structure–activity analysis on the basis of the predicted greater metabolic stability of amides due to their greater resonance stabilization.

Since the epoxide group affects the physicochemical properties (*e.g.*, lipid–water partition coefficient) of a compound, this function might also influence pharmacologic properties. Hence, it was decided to prepare α,β-epoxy hydrazides and amides for pharmacologic evaluation and to provide a basis for the study of the effect of the epoxide moiety on bioactivity.

Literature reports and reviews (1–4) substantiate the utility and applications of the Darzens glycidic ester condensation. Consequently, this reaction was applied to the synthesis of α,β-epoxy esters which, when exposed to hydrazinolysis and/or aminolysis, yield potentially active hydrazides and amides.

α,β-Epoxy amides and hydrazides have been of interest to the authors and others (5) as potential therapeutic agents. In appropriately substituted glycidic hydrazides, the presence of the epoxide function may affect the distribution of compounds possessing monoamine oxidase-inhibiting pharmacophores. In addition, the epoxide function may affect the susceptibility of such compounds to metabolic degradation. Conceivably, the drug–receptor interaction would be influenced as well, depending upon the degree of hydrolysis of the hydrazide linkage. Zeller (6) and others (7) have postulated that certain substituents play an important function in the bioactivity of appropriately substituted hydrazine derivatives. Several basic structural features appear to be associated with optimal monoamine oxidase inhibitory activity. These can be summarized as follows: (*a*) there should be at least one alkyl substituent on the hydrazine moiety, and (*b*) *N*-1 alkylation and *N*-2 acylation yield compounds with increased activity and decreased toxicity. On the other hand, disubstitution of either hydrazine nitrogen leads to inactive compounds. The alkyl and aralkyl substituents contribute to electronic, steric, and hydrophobic factors involved in the inhibitor–enzyme interaction, whereas the acyl moiety has been implicated as affecting the distribution and should be of such a nature that it can be easily hydrolyzed (8). Accordingly, the choice of the acyl moiety presumably is important with regard to tissue selectivity and susceptibility to metabolic cleavage to yield the postulated active moiety.

Since this work involves the synthesis of selected α,β-epoxy hydrazides as potential psychotropic agents, it is fundamental to the study of the effect of the epoxide function on absorption, distribution, and metabolic fate of hydrazine derivatives.

Additionally, glycidic amides were prepared modeled after classical anticholinergic agents. Such compounds possessing the α,β-epoxy amide function, in addition to the potential ammonium group and appropriately positioned bulky, semirigid, and hydrophobic moieties, should exhibit anticholinergic spasmolytic activity; those without a potential ammonium function should be less active. Accordingly, it was decided to compare Compound X with the classic anticholinergic atropine as well as with the analogous amides: Compounds VII and VIII, which do not possess potential ammonium functions. The epoxide cycle should affect distribution as well as the receptor interaction; hence, α,β-epoxy amides were chosen for this study.

The compounds described herein were prepared by the application of the following reactions: Darzens