Table V—Effect of pH and Recovery Time on Time of Death of Goldfish Treated with Edetate Disodium and Exposed to 0.1 m*M* Secobarbital Sodium

	pH 6.4			pH 7.4			pH 8.4		
	Mean Time ± *SD*, min	*n*[a]	Significance	Mean Time ± *SD*, min	*n*	Significance	Mean Time ± *SD*, min	*n*	Significance
Treatment[b]	18.58 ± 3.54	5	NS[c]	18.74 ± 0.98	7	$p < 0.05$	39.11 ± 5.93	3	$p < 0.05$
Control[d]	19.76 ± 1.95	5		21.88 ± 2.87	10		51.77 ± 5.05	4	
Treatment[e]	14.88 ± 0.99	10	NS	20.21 ± 3.74	10	NS	52.29 ± 9.70	10	NS
Control[f]	13.49 ± 2.51	10		23.89 ± 5.80	10		62.30 ± 16.93	10	
Treatment[g]	18.73 ± 5.92	10	NS	23.03 ± 1.79	10	$p < 0.05$	58.83 ± 17.31	10	$p < 0.05$
Control[h]	15.80 ± 3.51	5		32.27 ± 8.07	10		97.84 ± 22.19	10	

[a] *n* = number of fish. [b] 24-hr treatment, zero recovery. [c] Not significant ($p > 0.05$). [d] 24-hr blank, zero recovery. [e] 24-hr treatment, 30-min recovery. [f] 24-hr blank, 30-min recovery. [g] 24-hr treatment, 24-hr recovery. [h] 24-hr blank, 24-hr recovery.

The predicted least-squares equations are, respectively:

$$1/t = 0.0413f_u + 0.0170 \quad (r = 0.9660) \quad \text{(Eq. 1}a\text{)}$$

and:

$$1/t = 0.0443f_u + 0.0093 \quad (r = 0.9906) \quad \text{(Eq. 1}b\text{)}$$

According to the Levy–Gucinski model (10) concerning the absorption of the ionized and unionized forms of drug in goldfish, a plot of reciprocal time of response ($1/t$) as a function of the fraction of drug unionized should be linear with a slope equal to $K_b(K_u - K_i)$ and an intercept equal to K_bK_i.

$$1/t = K_bK_i + K_b(K_u - K_i)f_u \quad \text{(Eq. 2)}$$

where K_b is a constant equal to the quotient of the secobarbital concentration to which the fish were exposed divided by the amount of barbiturate in the fish at death; K_i and K_u are the first-order rate constants for the ionized and unionized drug forms, respectively. Upon inspection of the data, two discrepancies appear. The controls fit the model reasonably well while the treated animals do so to a lesser degree. In both cases, however, curvature of a form representing an inverted exponential cannot be ruled out. The intercepts of both plots are also not significantly different ($p > 0.05$) from zero. Whether these discrepancies represent a breakdown of the model or assumptions of the model as specified by Levy and Gucinski or simply a large amount of statistical variation cannot be discerned at this time. However, due to these discrepancies, the analysis as performed earlier (5), using the ratio of slope to intercept to evaluate the ratios of K_u:K_i was not performed. Regardless of the model that characterizes the absorption of secobarbital sodium under these experimental conditions, it appears from Table V that edetate disodium changes membrane permeability to the ionized form of the drug and that the effect can be present 24 hr after theoretical exposure to the chelating agent.

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Effect of Various Vehicles and Vehicle Volumes on Oral Absorption of Triamterene in Rats

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Abstract □ The oral bioavailability of triamterene in rats was investigated after its administration as a suspension in lipid and aqueous vehicles in addition to a lactic acid solution. Triamterene is poorly soluble in both aqueous and lipid vehicles. A 1-ml oral dose volume showed that lipid vehicles may provide some enhancement of oral availability compared with aqueous suspensions. However, when the vehicle volume was reduced to a realistic dosage form volume for the rat, peanut oil and aqueous suspensions were indistinguishable from each other with respect to peak height, peak time, and overall bioavailability. For a given vehicle small vehicle volumes resulted in a better relative oral availability than did large vehicle volumes.

Keyphrases □ Triamterene—poor solubility in lipid and aqueous vehicles □ Vehicle volume—small *versus* large vehicle volumes in oral availability in rats □ Oral bioavailability—parameters of triamterene administered as suspensions in lipid and aqueous vehicles and lactic acid solution

The rate and extent of absorption of orally administered drugs are influenced by factors within the GI environment, such as the solubility and extent of drug ionization, gastric emptying, intestinal motility, and stimulation of bile flow. The relative contribution of each factor to oral availability is often difficult to distinguish. The vehicle into which a

Table I—Mean Plasma Concentration (Nanograms per Milliliter) of Triamterene in Rats [a] following an Oral Dose of 10 mg/kg in a 1-ml Vehicle Volume

Hours	Lactic Acid Solution	Aqueous Suspension	Peanut Oil Suspension	Oleic Acid Suspension	Triolein Suspension
0.5	196 (28)[b]	257 (82)	178 (29)	65 (8)	141 (56)
1.0	236 (29)	267 (106)	185 (11)	166 (60)	164 (53)
1.5	350 (38)	174 (49)	338 (50)	152 (23)	220 (2)
2.0	368 (52)	179 (54)	282 (52)	224 (61)	189 (50)
2.5	371 (43)	123 (27)	294 (41)	162 (36)	130 (17)
3.0	448 (50)	114 (33)	231 (52)	144 (16)	102 (11)
4.0	404 (87)	99 (28)	206 (39)	129 (13)	132 (24)
5.0	351 (107)	61 (17)	202 (31)	138 (41)	140 (33)
6.0	168 (62)	62 (14)	194 (31)	111 (24)	116 (30)
12.0	127 (43)	51 (6)	104 (24)	202 (62)	69 (13)
24.0	40 (2)	37 (15)	40 (1)	201 (50)	59 (14)

[a] Mean of four rats. [b] Numbers in parentheses are the standard errors of the means.

drug is incorporated and the vehicle volume administered may affect all of these factors in addition to any interactions the vehicle may have with the drug itself.

BACKGROUND

A traditional problem in oral drug delivery has been the relatively low bioavailability exhibited by many poorly water-soluble drugs. Considerable research has centered on the possible enhancement of the oral bioavailability of such drugs by their incorporation into various lipid vehicles. It is unclear whether lipid vehicles may affect oral bioavailability through some biochemical and/or physiological effects, whether solubilization of the drug is the mechanism, or a combination of these factors is operative.

Crounse (1) demonstrated an increase in griseofulvin bioavailability when administered with a high fat diet to humans. Griseofulvin bioavailability in rats also was enhanced when administered in various corn oil vehicles (2, 3). Indoxole bioavailability was increased in both humans (4) and rats (5) when administered in lipid vehicles. Sulfisoxazole (6) and dicumarol (7) are other examples of drugs whose bioavailability is enhanced in lipid vehicles.

Grisafe and Hayton (8) concluded that triglycerides had the ability to enhance the oral absorption of griseofulvin due to the enhanced dissolution and not directly to the lipid-induced increases in absorption. Solubilization of poorly water-soluble drugs as a method of improving oral bioavailability was confirmed by other investigators (9–11).

Yamahira *et al.* (12–14) recently demonstrated that the volume of vehicle in which the drug is administered can influence the results obtained in oral bioavailability studies. It was concluded that many oral bioavailability studies, particularly those with rats, used unrealistically large vehicle volumes. Yamahira *et al.* (13) developed a reproducible method of administering very small vehicle volumes (2–20 μl) to rats to eliminate the physiological effects caused by large vehicle volumes.

In the present study, the effects of various vehicles and vehicle volumes were correlated to the oral absorption of the poorly soluble, potassium-sparing diuretic, triamterene, in rats.

EXPERIMENTAL

Materials—Pure triamterene powder[1] was used to prepare all drug suspensions and solutions. Five drug vehicles were studied initially: water, peanut oil[2], triolein[3], lactic acid[4], and oleic acid[5]. All solvents for chromatography were high-performance liquid chromatographic (HPLC) grade[6], and other reagents were analytical grade[6].

The suspensions used initially were at concentrations of 4.0 mg/ml. Ten-milliliter aliquots were transferred to 15-ml screw-capped tubes and shaken for 30 min on a mixer[7] with a modified shaker head. Five drops of surfactant[8] were added to the aqueous suspensions. For the solution vehicle, triamterene was dissolved in an 8% lactic acid solution. In subsequent studies, peanut oil and aqueous suspensions were prepared as described at a concentration of 45 mg/ml. The range of solubilities of triamterene in all vehicles (other than the lactic acid solutions) was 10^{-4}–10^{-5} *M*.

Table II—Mean Peak Plasma Concentration, Mean Time of Peak Concentration, and Mean *AUC* in Rats [a] following an Oral Dose of 10 mg/kg of Triamterene in a 1-ml Vehicle Volume

Vehicle	Mean Peak Plasma Concentration, ng/ml	Mean Time of Peak Concentration, hr	Mean *AUC*, 0–24 hr, ng hr/ml
Lactic acid solution	510 (55)	3.75 (0.48)	4184 (915)
Aqueous suspension	286 (104)	0.62 (0.12)	1647 (288)
Peanut oil suspension	348 (44)	2.50 (0.61)	3219 (43)
Oleic acid suspension	266 (86)	2.50 (0.54)	4744 (842)
Triolein suspension	249 (42)	2.62 (0.83)	2214 (294)

[a] Means calculated from four individual experiments in four different rats in a balanced incomplete block design.

Animal Studies—Initial studies evaluated five vehicles in a balanced incomplete block design. Ten rats were each randomly assigned to receive two of the formulations, and each formulation was tested in four rats. A 1-week washout period was allowed before a rat was used again.

Male rats[9], 250–300 g, were fasted for 12 hr prior to dosing with 10 mg of triamterene/kg, suspended or dissolved in the various vehicles. Immediately prior to dosing, suspensions were removed from the shaker and the appropriate dose was drawn into a tuberculin syringe[10]. The volume was adjusted to 1 ml with the requisite vehicle, and the syringe was shaken again.

Lightly ether-anesthetized animals were dosed with a 76-mm intubation needle[11] attached to the tuberculin syringe. Blood samples were taken by tail clipping while the animals were restrained in plexiglass cages[11]. Blood samples were obtained every 0.5 hr for 3 hr; then every hour until 6 hr, and then at 12 and 24 hr. In later studies, a 9-hr sample was added.

Whole blood (~350-μl samples) was collected in heparinized caraway capillary tubes[12], blown into 1.5-ml microcentrifuge tubes[13], and spun for 3 min[14]. Plasma aliquots (100 μl) were placed in 4-ml polypropylene tubes[15] with fitted caps. Plasma samples were frozen until analysis.

Later studies compared peanut oil and aqueous suspensions administered in a 20-μl volume in a complete crossover study in four rats. The washout period was 1 week. To administer the 20-μl volume, the procedure of Yamahira *et al.* (13) was adopted with some modifications. The suspensions were prepared at concentrations of 45 mg/ml so that each rat received 0.9 mg in the 20-μl volume. The dosing system consisted of 19-gauge flexible tubing with a luer-lock end[16] sleeved with polyethylene tubing for rigidity.

A 50-μl syringe[16] was used to draw the dose, and the tubing was calibrated to double check the volume. Each dose was followed by a small volume of air injected through the tubing to ensure that no material re-

[1] Smith Kline and French, Philadelphia, Pa.
[2] Planters, Standard Brands, New York, N.Y.
[3] Seventy-five percent practical grade, Sigma Chemicals, St. Louis, Mo.
[4] Eighty-five percent laboratory grade, Fisher Scientific Co., Fair Lawn, N.J.
[5] Purified, Fisher Scientific Co., Fair Lawn, N.J.
[6] Fisher Scientific Co., Fair Lawn, N.J.
[7] Vortex Genie, Scientific Industries, Bohemia, N.Y.
[8] Tween 85, ICI America, Wilmington, Del.
[9] Sprague-Dawley, Madison, Wis.
[10] Monoject, Sherwood Medical Industries, Deland, Fla.
[11] Perfektum, Popper and Sons, New Hyde Park, N.Y.
[12] Dade Division, American Hospital Supply, Miami, Fla.
[13] Centaur Sciences, Stamford, Conn.
[14] Eppendorf microcentrifuge, Brinkmann Instruments, Westbury, N.Y.
[15] Elkay Products, Shrewsbury, Mass.
[16] Hamilton Co., Reno, Nev.

Table III—Plasma Concentration of Triamterene following an Oral Dose of 0.9 mg to Rats in a 20-μl Vehicle Volume in a Complete Crossover Study

Hours	Rat 1, ng/ml	Rat 2, ng/ml	Rat 3, ng/ml	Rat 4, ng/ml
		Peanut Oil Suspension		
0.5	96	201	95	138
1.0	202	248	152	154
1.5	236	222	190	134
2.0	281	276	289	148
2.5	284	277	281	110
3.0	178	212	188	127
4.0	124	148	164	136
5.0	162	99	168	108
6.0	90	81	116	161
9.0	76	54	72	75
12.0	76	68	52	60
24.0	77	45	65	39
		Aqueous Suspension		
0.5	213	160	216	167
1.0	147	252	314	182
1.5	201	142	292	233
2.0	223	222	308	213
2.5	149	222	244	191
3.0	234	179	208	180
4.0	200	194	118	228
5.0	150	86	90	122
6.0	136	218	80	84
9.0	110	92	180	70
12.0	72	96	52	68
24.0	51	99	94	48

mained on the inside. This dosing system was checked with the actual suspensions used and was found to provide reproducible doses within ±10%.

Analytical Procedure—The analytical procedure was a modification of the method of Sved *et al.* (15). Plasma samples were thawed, 0.2 ml of perchloric acid was added, and the sample was mixed. Methylisobutylketone[17] (0.8-ml), which had been saturated with 1 *M* $HClO_4$, was then added, and the sample was mixed again. Sample tubes were then capped and shaken for 20 min, samples were centrifuged for 10 min, and the methylisobutylketone layer was removed and refrigerated in glass vials. Standards were prepared by adding appropriate concentrations of triamterene to 100 μl of blank plasma and extracted in the same manner. This extraction procedure provided ~90% recovery when compared to standards prepared directly in methylisobutylketone in a plasma concentration range of 10–850 ng/ml.

HPLC[18] was used to analyze the extracted plasma samples. Fifty-microliter injections were made onto the column[19], and the flow rate was 2 ml/min. No attempts were made to quantitate metabolites. The system operated at 1000 psi at a fluorometer setting of 335-nm excitation and 470-nm emission. The mobile phase consisted of methylene chloride–hexane–methanol–perchloric acid (55:35:10:0.1). Concentrations were quantitated by comparing peak height to the standards developed for each set of samples.

RESULTS

In the first series of experiments, 10 mg of triamterene/kg was administered to rats in 1 ml of the following vehicles: solution in 8% lactic acid, aqueous suspension, oleic acid suspension, triolein suspension, and peanut oil suspension. Ten rats were randomly assigned to a balanced incomplete block design in which each rat received two formulations in trials separated by 1 week. Each formulation was administered four times to four different rats.

Table I shows the mean plasma concentrations with associated standard errors for each formulation in the four rats at each sampling time. Table II shows the mean peak concentration, mean time of peak concentration, and mean area under the plasma concentration–time curve (0–24 hr) computed by trapezoidal integration from the four individual experiments with each formulation[20].

[17] Mallinckrodt, Paris, Ky.

[18] The chromatographic system consisted of a 6000 A pump and U6K universal injector (Waters Associates, Milford, Mass.) coupled to an FS 970 fluorometer (Schoeffel Instrument Corp., Westwood, N.J.).

[19] Lichrosorb Si-60-7 (250 × 4.6 mm), Chrompak, Whittier, Calif.

[20] Although the oleic acid suspension resulted in the largest *AUC*, this result is biased by the 12- and 24-hr time points in which plasma concentrations began to increase again. This observation is currently not explained and is being reevaluated.

Table IV—Mean Peak Plasma Concentration, Mean Time of Peak Concentration, and Mean *AUC* in Rats[a] following an Oral Dose of 0.9 mg of Triamterene in a 20-μl Vehicle Volume

Vehicle	Mean Peak Plasma Concentration, ng/ml	Mean Time of Peak Plasma Concentration, hr	Mean *AUC*, ng hr/ml
Aqueous suspension	258 (19)	1.62 (0.47)	2560 (169)
Peanut oil suspension	251 (32)	2.00 (0.35)	2162 (103)

[a] Means calculated from four individual experiments in four different rats in a complete crossover study; none of the means in any column are significantly different ($\alpha = 0.05$)..

The data of Tables I and II show a trend with peanut oil suspensions toward higher plasma triamterene levels and an overall increase in the availability of triamterene when compared to the aqueous suspensions. These findings led to a further investigation of peanut oil as a potential vehicle for enhancing the oral availability of triamterene. A second series of experiments, in a complete crossover study, was conducted in which the peanut oil suspension was compared to aqueous suspensions in four rats, also at a dose of 10 mg/kg in a 1-ml volume. The specific results of this study are not shown here; however, it confirmed the potential of peanut oil as a vehicle to enhance the oral availability of triamterene.

The third series of experiments was conducted to evaluate the oral availability of triamterene using aqueous and peanut oil suspensions in a realistic dosage form vehicle volume. In this study, 20 μl of peanut oil or aqueous suspensions of triamterene containing 45 mg of drug/ml were administered to four rats in a complete crossover design. Each rat received 0.9 mg of triamterene in a 20-μl dose volume, which represents a realistic dosage form volume when scaled to the size of the rat (13). Table III shows the individual plasma triamterene levels measured in the four rats with both aqueous and peanut oil suspensions. Figure 1 shows a plot of the mean plasma level at each time point for both the aqueous and peanut oil suspensions, and Table IV shows the mean peak concentrations, time of peak concentration, and mean *AUC* (0–24 hr).

DISCUSSION

In the initial study with the 1-ml vehicle volume, the three lipid vehicles exhibited a trend toward a later peak time and maintained higher plasma levels for a longer time when compared to aqueous suspensions. With all formulations tested, a rather large intersubject variability was noted. This finding was consistent with what other investigators observed following triamterene administration (16). Such variability coupled with the small number of trials (four) performed with each vehicle made it difficult to evaluate statistical differences among the vehicles even though the trends were clear. Additionally, any differences among the lipid vehicles with respect to triamterene availability cannot be explained on the basis of drug solubility in the vehicles. Even with oleic acid, which was the suspension vehicle in which triamterene was most soluble, <1% of the administered drug was in solution.

The lactic acid solution clearly provided the highest plasma triamterene levels of the vehicles evaluated with a 1-ml dosing volume. As previously noted, the oleic acid vehicle resulted in the largest *AUC*, al-

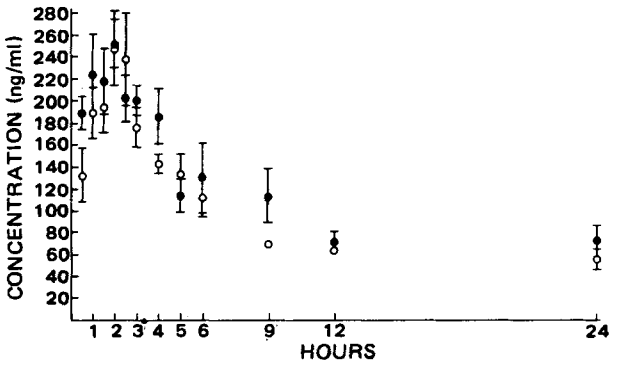

Figure 1—*Mean plasma levels of triamterene in rats following oral administration of 0.9 mg in a 20-μl vehicle volume in a complete crossover study. Key:* ○, *peanut oil suspension; and* ●, *aqueous suspension. Bars represent standard error of the mean.*

though this result was biased by the 12- and 24-hr time points. Oleic acid was not investigated further in this study, although Noguchi *et al.* (17) concluded that oleic acid may be a useful vehicle to sustain the release of poorly water-soluble drugs, thus, prolonging their effects.

In the last series of this study, the oral availability of triamterene was evaluated from peanut oil and aqueous suspensions in which the dosing volume was reduced to 20 μl. Peanut oil was selected for comparison with the aqueous vehicle based on results from the initial study. In that study, the peanut oil vehicle provided a similar peak plasma level as the aqueous suspension, although peak levels occurred somewhat later. The decline from peak levels was slower for peanut oil than for the aqueous suspension, resulting in a larger overall *AUC* for peanut oil suspensions. Finally, the intersubject variability in the initial study was smallest with the peanut oil suspensions. It was thus concluded that peanut oil might be a promising vehicle for formulating triamterene and improving its oral availability.

The results (Tables III and IV and Fig. 1) of the two-way crossover study, comparing peanut oil and aqueous suspensions of triamterene, did not confirm the initial optimism regarding peanut oil as a vehicle when administered in realistic dosage form vehicle volumes. A weighted unpaired *t*-test revealed no significant differences between the aqueous and peanut oil vehicles with respect to peak plasma concentration, peak time, or *AUC* ($\alpha = 0.05$). These results suggest that any enhanced availability in the peanut oil vehicle, which was suggested by the initial study, may have been due to physiological effects on the GI tract caused by the relatively large vehicle volume used. Such effects appeared to be eliminated when the dosage form vehicle volumes were used.

A further aspect of these studies is the comparison of the doses used in both the large and small volume experiments. In the 1-ml administered volume study, each rat received ~2.5 mg of triamterene; in the 20-μl volume study, the administered dose was ~0.9 mg. The *t*-test revealed that neither peak height nor peak time was significantly different between these two studies ($\alpha = 0.5$). However, with the aqueous suspension, the *AUC* for the 20-μl dose volumes was greater ($p < 0.05$) than with the 1-ml volume. With the peanut oil suspensions, the *AUC* for the 20-μl dose volume was significantly less than with the 1-ml volume ($p < 0.001$) but, in absolute terms, was reduced by one-third compared with the dosage reduction of a factor of ~3. Clearly, the larger dose volumes for both peanut oil and aqueous suspensions adversely affected the oral availability of triamterene. The precise mechanism of this effect is unexplained, although it is probably due to some alteration of physiological processes within the GI tract caused by the large vehicle volumes.

The results indicated that the methodology used to evaluate the effects of various vehicles on the GI absorption of drugs must be carefully considered. The results of *in situ* perfusion studies and those employing large vehicle volumes may not be directly applicable to an actual dosage form. With triamterene, a drug poorly soluble in both aqueous and lipid vehicles, a large volume of lipid vehicle may provide some enhancement of oral availability when compared to aqueous vehicles. At least with peanut oil, however, when the vehicle volume is reduced to a realistic dosage form volume, the potential advantage is lost. Furthermore, small vehicle volumes result in better relative oral availability for triamterene than do large vehicle volumes. Such a finding might be considered with regard to the administration of triamterene in conjunction with some foods.

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Compression Properties of Granulations Made with Binders Containing Different Moisture Contents

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Abstract □ The role of the granulation moisture content on compression properties of granules made with selected binders was studied. The results suggested that, at lower pressures, higher moisture-containing granules were slightly more compressible than lower moisture-containing granules. However, at higher pressures, the reverse was true because of the water lubrication effect. At lower moisture levels, the crushing strength of the tablets was dependent on the binder; at higher moisture levels, binder differences became less significant.

Keyphrases □ Compression—effect of moisture content on granulations made with various binders □ Granulations—effect of moisture content on compression properties, various binders □ Binders—various, effect of moisture content on compression properties of granulations

The compression behavior of four pharmaceutical powders of widely different particle-size distribution and shape was reported previously (1). It was shown that the Heckel (2) and Cooper–Eaton (3) equations can be used

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