greater than it would be from the same application placed on normal skin. Given the variable but potentially high, permeability through eschar and the violent systemic toxicity (14), phenol should not be used for burn-wound antiseptics.

Another factor is that the chemical burn effected by the highest phenol concentration (6% w/v) in a preceding study (7) and the thermal burns effected here at temperatures >80° are of comparable permeability. This suggests that the chemical and thermal treatments cause the same type of destructive alteration of the stratum corneum, albeit by vastly different mechanisms, resulting in a functional impairment of the same order. We regard this as strong evidence that the stratum corneum proteins are involved and denatured by extreme treatments of either kind. It is hard to envision a means whereby these different treatments could produce like effects in purely lipid domains in the stratum corneum. By either procedure the stratum corneum loses some or all of the ability to differentiate permeating species on the basis of polarity, depending on the intensity of the burn.

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Low-Melting Phenytoin Prodrugs as Alternative Oral Delivery Modes for Phenytoin: A Model for Other High-Melting Sparingly Water-Soluble Drugs

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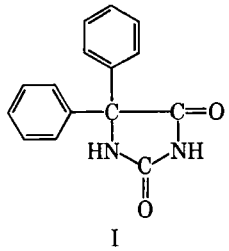
Abstract □ Phenytoin is a high-melting, weakly acidic, and sparingly water-soluble drug. Because of these physicochemical properties, phenytoin is subject to erratic bioavailability in a variety of dosage forms both in its acidic as well as sodium salt forms. A homologous series of 3-acyloxymethyl derivatives of phenytoin (acetyl through decanoyl) were synthesized and various physicochemical properties measured. The prodrugs were more readily soluble in various metabolizable glycerol esters such as tributyrin, trioctanoin, and triolein than phenytoin. The solubility of the prodrugs in the various organic vehicles studied was closely correlated to the melting point of the prodrug: the lower the melting point the greater the solubility. The cleavage rates of the prodrugs in plasma and tissue homogenates followed a parabolic relationship with chain length. The prodrug, 3-pentanoyloxymethyl-5,5-diphenylhydantoin when administered in tributyrin gave superior oral phenytoin bioavailability in rats when compared with sodium phenytoin administered as an aqueous solution.

Keyphrases □ Phenytoin—low-melting prodrugs, alternative oral delivery modes, model for high-melting sparingly water-soluble drugs □ Prodrugs—use in alternative oral delivery modes, model for high-melting sparingly water-soluble drugs, phenytoin

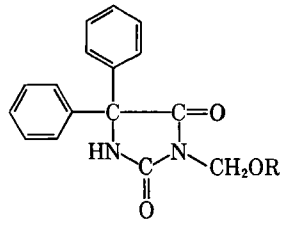
Phenytoin (I), a high-melting (293°) weakly acidic (1, 2) drug is sparingly soluble in water (2). Because of its physicochemical properties phenytoin is subject to erratic bioavailability in a variety of dosage forms both in the acidic as well as the sodium salt forms (3–6).

Since the problems associated with the release from the various dosage forms can be attributed to both the limited aqueous solubility and the weakly acidic nature of the phenytoin, it is likely that dissolution plays an important



I

R	
H-	II
CH_3CO-	III
C_2H_5CO-	IV
C_3H_7CO-	V
C_4H_9CO-	VI
tert-C_4H_9CO-	VII



II–XII

R	
$C_5H_{11}CO$	VIII
$C_6H_{13}CO$	IX
$C_7H_{15}CO$	X
$C_8H_{17}CO$	XI
$C_9H_{19}CO$	XII

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Table I—Melting Points and Elemental Analysis [a] for Various Esters of 3-Hydroxymethyl-5,5-diphenylhydantoin

Compound	mp, °	Molecular Weight, C	Calculated			Found		
			C	H	N	C	H	N
III	158–159	324.3	66.67	4.94	8.64	66.80	4.98	8.68
IV	172–174	338.4	67.47	5.33	8.28	67.90	5.38	8.30
V	134–135	352.4	68.18	5.68	7.95	68.23	5.77	8.00
VI	89–92	366.4	68.85	6.01	7.65	69.20	6.08	7.56
VII	134–135	366.4	68.85	6.01	7.65	69.31	6.20	7.58
VIII	107–108	380.4	69.47	6.32	7.37	69.68	6.39	7.33
IX	87–88	394.5	70.05	6.60	7.11	70.08	6.63	6.98
X	67.5–68.0	408.5	70.59	6.86	6.86	70.40	6.93	6.76
XI	78.5–80.0	422.5	71.09	7.11	6.64	70.93	7.28	6.54
XII	56–57	436.6	71.56	7.34	6.42	71.40	7.38	6.20

[a] Department of Medicinal Chemistry, University of Kansas.

role in the erratic *in vivo* behavior of phenytoin (3). In the case of phenytoin, strong intermolecular hydrogen bonding in the crystal lattice between the hydrogen atom on N(3) and a carbonyl oxygen of a neighboring phenytoin molecule is the probable cause of its inferior stability characteristics (7). This problem might be overcome by disrupting this hydrogen bonding in a bioreversible fashion, thereby increasing the lipid solubility of phenytoin, allowing incorporation in a dosage form such as a soft gelatin capsule or microencapsulation. In the present study, 3-hydroxymethyl-5,5-diphenylhydantoin (II) and various straight chain acyl (III–VI, VIII–XII) as well as the pivaloyl derivative of II (VII) were prepared and various physicochemical properties measured. Of particular interest was the increased solubility of compounds III–XII relative to phenytoin in cyclohexane and metabolizable lipid vehicles as well as the relationship between the structures of these prodrugs, their melting points, and lipid solubility. The ultimate objective was to see if the bioavailability of phenytoin, as a high-melting, sparingly water-soluble model compound, could be improved by the synthesis of low-melting prodrugs that could be incorporated into metabolizable vehicles suitable for formulation in soft gelatin capsules or microencapsulation.

EXPERIMENTAL

Apparatus—Ultraviolet spectral measurements[1] were performed using 1-cm cells with caps. Melting points were measured on a capillary melting point apparatus[2] and were uncorrected. A high-performance liquid chromatograph (HPLC) with an injection system[3], was used throughout the study. A gas chromatograph[4] was used for plasma and blood phenytoin analysis.

Materials and Reagents—The solvents used as a mobile phase were HPLC grade. All other chemicals were of analytical or reagent grade. 3-Hydroxy-5,5-diphenylhydantoin (II) was prepared as follows: a mixture of 45 g of phenytoin, 2.43 g of potassium carbonate, and 1620 ml of water was stirred while 180 ml of formalin was added. The stirring was continued at room temperature for 24 hr, the solution was filtered, and the solid was washed with a 3% formalin solution and then air dried for 3 days. Various esters of II were prepared by adding 10% excess of the corresponding acid chloride, dropwise with stirring, to 10 g of II dissolved in 40–50 ml of dry pyridine. For the synthesis of the 3-pentanoyloxymethyl derivative, the corresponding acid anhydride was used. The mixture was stirred until qualitative TLC showed the reaction to be complete. The pyridine solution was then poured into slightly acidic ice water with stirring. After neutralizing (or slightly acidifying) by the addition of hydrochloric acid, the solution was stirred for several hours. The acetyl and propionyl derivatives precipitated and were recrystallized from alcohol–ether. Other compounds did not solidify, but settled out as yellow oils which were purified by the following method. The water layer was removed by aspiration, and the oil was dissolved in ~150 ml of anhydrous ethyl ether (ethyl acetate was used for the butanoyl derivative). The organic layer was washed twice with 50 ml of 2% sulfuric acid, twice with 50 ml of 5% sodium carbonate, and twice with 50 ml of water. The organic layer was then dried over anhydrous magnesium sulfate for several hours. The mixture was filtered and the solvent was removed at reduced pressure to give solid material which was recrystallized from anhydrous ethyl ether. The melting point and elemental analysis of each compound are shown in Table I.

Solubilities—The solubilities of the various esters in cyclohexane were determined by placing 2–5 times excess ester and 2 ml of cyclohexane in a screw-capped vial containing a glass bead. The air was replaced by nitrogen and the vials were sealed. The mixtures were shaken for several days in a constant-temperature water bath at 25°. The mixture was filtered, an aliquot was diluted with an appropriate amount of cyclohexane, and the absorbance at 265 nm was measured. The concentration of the ester in the saturated solutions were calculated from the measured absorbances by reference to standard curves.

The solubilities in various oils were determined by suspending the compounds in oils and rotating the vials in a water bath for up to 1 month at 25°. The viscous-solutions were centrifuged for 5 min, and then the supernatant was diluted with an appropriate amount of tetrahydrofuran. The diluted solution (20 μl) was injected on an HPLC. The separation was carried out on a 25 cm × 4.6 mm (i.d.) prepacked normal-phase column[5] with use of a tetrahydrofuran–heptane (20–80 by volume) mobile

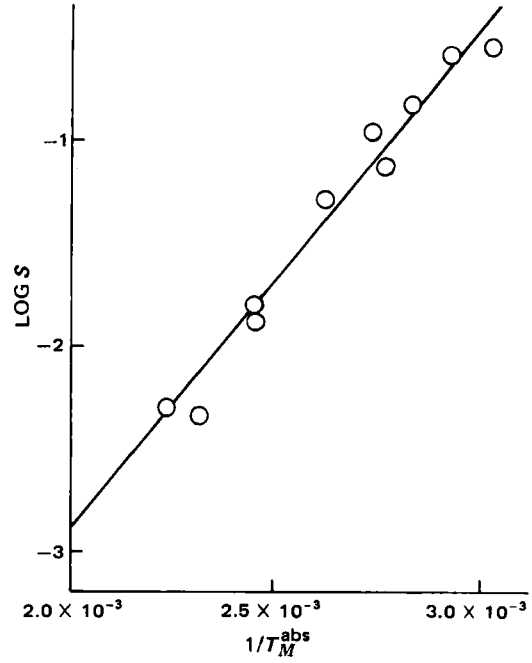


Figure 1—*Plot of the logarithm of the solubility (log S, S in units of moles/liter) of various 3-acyloxymethyl-5,5-diphenylhydantoins in ethyl oleate against the recipricol of the melting points in absolute degrees (T_M^{abs}) of the compounds. Solid line is given by the equation log S = 2404/T_M^{abs} − 7.694 (r = 0.9796).*

[1] Cary Instruments, Model 219.
[2] Uni-Melt, Thomas-Hoover.
[3] Altex Model 110A, with a Rheodyne model 7125 injector system and an Altex Model 153 detector.
[4] Varian Model 2100.
[5] Economy Column LiChrosorb Si-60-10, Chrompack.

Table II—Solubilities of Various Esters of 3-Hydroxymethyl-5,5-diphenylhydantoin at 25°

Compound	Solubilities, mg/ml					Phenytoin Equivalents
	Cyclohexane	Ethyloleate	Triolein	Trioctanoin	Tributyrin	
III	0.036	1.5	0.99	3.6	15.8	0.78
IV	0.068	1.7	0.82	3.5	15.1	0.75
V	0.11	4.6	2.4	8.2	34.4	0.72
VI	5.5	40.8	17.1	65.7	270	0.69
VII	0.44	9.5	4.9	15.5	63.0	0.69
VIII	1.9	19.9	9.5	34.2	134	0.66
IX	3.9	29.4	11.3	43.2	143	0.64
X	61.3	105	38.2	144	284	0.62
XI	20.3	54.5	20.5	75.0	196	0.60
XII	306[a]	123	81.9	224	485	0.58
Phenytoin (I)	0.039	0.36	0.28	0.92	3.9	1.00

[a] Estimated from dissolved amount.

phase at a flow rate of 2.0 ml/min. The column effluent was monitored at 254 nm at 0.08 absorbance unit full scale. The concentrations of saturated solutions were calculated from the peak height of standard solution of each compound dissolved in tetrahydrofuran.

Stabilities—The compounds with the shortest and the longest carbon chain, 3-acetyloxymethyl- and 3-decanoyloxymethyl-5,5-diphenylhydantoin, were chosen as examples for the stability studies. A solution of each ester in each solvent studied (except cyclohexane) was prepared and placed into ampules, each of which contained 200 μl of solution. The ampules were sealed under nitrogen and kept at room temperature, 40°, and 60°. After appropriate intervals, the ampules were opened and the concentrations of the prodrugs were measured by the same HPLC method as used in the solubility study.

Kinetics in Human Plasma—The stock solution of each prodrug in acetonitrile (~2 mg/ml phenytoin equivalents) was added to the human plasma[6] which was kept in a water bath at 37° so that the final concentration of phenytoin formed was 20 μg/ml. At appropriate times a 100-μl sample was removed and the concentration of phenytoin formed by hydrolysis of the prodrugs with longer carbon chains (pentanoyl to decanoyl) was measured by GLC (8). The sample was added to 100 μl of 10% *meta*-phosphoric acid to quench any enzymatic reaction, and then 500 μl of cyclohexane was added. This mixture was vortexed for 1 min and centrifuged for 5 min. The cyclohexane layer was removed by aspiration and 100 μl of the aqueous layer was analyzed as previously described (8).

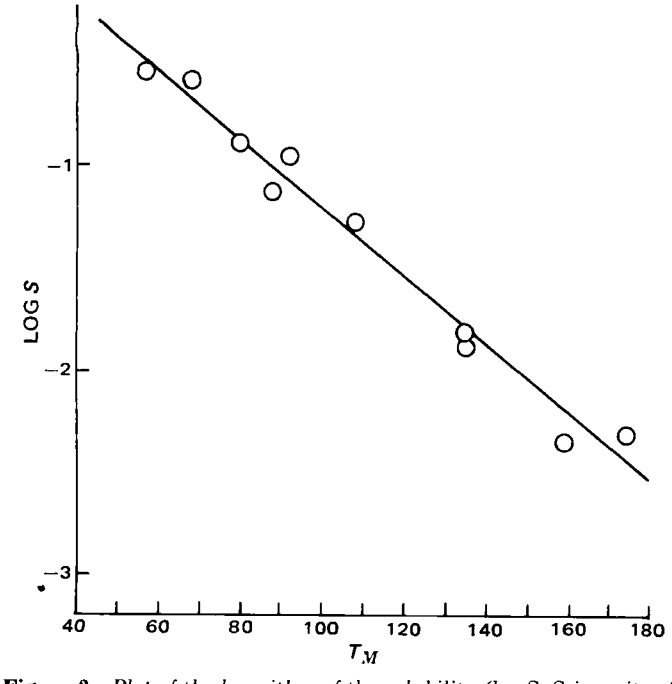


Figure 2—*Plot of the logarithm of the solubility (log* S, S *in units of moles/liter) of various 3-acyloxymethyl-5,5-diphenylhydantoins in ethyl oleate against their melting points* (T_M) *in degrees C. Solid line is given by the equation* log S = −0.0167 T_M + 0.4606 (r = 0.988).

[6] Community Blood Center of Greater Kansas City.

The concentration of phenytoin produced by the hydrolysis of prodrugs with shorter carbon chains (acetyl through to butanoyl) was determined by HPLC. The plasma samples were added to 250 μl of acetonitrile, vortexed for 5–10 sec, and then centrifuged. The supernatant was directly injected into the HPLC and was eluted with the mixture of acetonitrile and water, acidified to pH 2.5 with *meta*-phosphoric acid, at flow rate 1.3 ml/min on a 25 cm × 4.6 mm (i.d.) prepacked reverse-phase column[7]. The detector sensitivity setting was 0.005 absorbance unit full scale at 254 nm. The concentration of phenytoin was calculated from the peak height by reference to a standard curve.

The rate constants were obtained from the plots of log $(C_\infty - C_t)$ *versus* time, where C_∞ and C_t are the concentrations of phenytoin at infinity and at time t, respectively, by using the least-squares method. In all cases, the prodrugs quantitatively reverted to phenytoin and followed pseudo first-order kinetics.

Kinetics in Rat Plasma—Plasma taken from male rats were kept frozen until used. A 300-μl volume of plasma was used for each kinetic experiment. A 50-μl sample was removed at appropriate times, and the enzymatic reaction quenched by the addition of 125 μl of acetonitrile. The concentrations of phenytoin in the supernatant were measured by the HPLC method used in the kinetics in human plasma. To obtain good

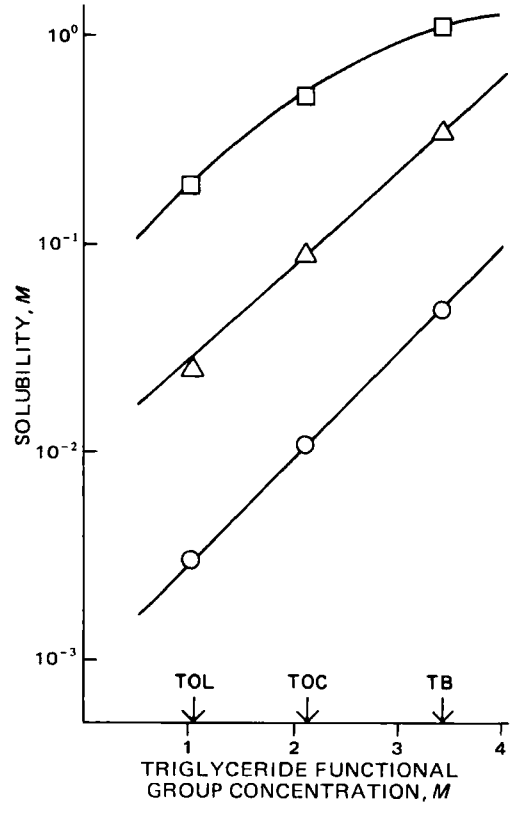


Figure 3—*Plot of log* S *for III (○), VII (△), and XII (□) versus triglyceride functional group concentration for the three solvents, tributyrin (TB), trioctanion (TOC), and triolein (TOL).*

[7] Economy Column LiChrosorb 10RP 18, Chrompack.

Table III—Half-lives for the Conversion of Various Phenytoin Prodrugs to Phenytoin at 37° in Human Plasma

Compound	$t_{1/2}$, min	k, min^{-1}
III	6.7	0.104
IV	2.3	0.306
V	1.6	0.437
VI	1.9	0.361
VII	75.6	0.00918
VIII	2.6	0.266
IX	4.7	0.148
X	12.6	0.0555
XI	14.8	0.0470
XII	33.2	0.0209

separation of the phenytoin peak from an interfering peak in rat plasma, 35% acetonitrile was used in the mobile phase instead of 40%, and the flow rate was 1.5 ml/min.

Kinetics in Rat Intestine Homogenates—A male rat (Sprague-Dawley) was sacrificed and a part of the intestine removed. After being sliced on a glass plate kept on ice, the intestine was placed in a beaker with cold Sorensen's isotonic buffer. The volume of buffer was adjusted so that the ratio of the weight of the intestine to the buffer was 1:4. The mixture was homogenized while cooling with ice, then centrifuged for 10 min at 2500 rpm, and the supernatant removed and kept cold (0°).

The kinetic studies were carried out by adding 20 μl of acetonitrile solution of the prodrug (2 mg phenytoin equivalent/ml) to 2 ml of diluted homogenate (×500) kept in a water bath (37°) for 10 min before the experiment. One hundred-microliter samples were removed at the appropriate times. The assay for phenytoin was the HPLC method used in the kinetics in human plasma except for the flow rate of mobile phase, which was 1.5 ml/min in this study.

***In Vivo* Experiment**—Adult, male Sprague-Dawley rats (225–300 g) were used in the crossover study. Six rats were randomly divided into two groups. Both groups of rats were fasted overnight as well as during the sampling time but water was allowed *ad libitum*.

Each rat was given a 100-μl sample of either sodium phenytoin in water or 3-pentanoyloxymethyl-5,5-diphenylhydantoin (VI) dissolved in tributyrin *via* gastric intubation. Approximately 30 mg/kg of phenytoin equivalents were given to each rat.

Blood sampling after drug administration was done *via* a tail clip. Two hundred microliter samples of whole blood were withdrawn at 1, 2, 4, 6, and 26 hr postdose and used for analysis. After a 2-week washout period both groups of rats received the alternate dosage form. The blood samples were analyzed for phenytoin as previously described (8).

RESULTS AND DISCUSSION

The solubilities of prodrugs III–XII in the various organic solvents are shown in Table II. For the solubility of 3-decanoyloxymethyl-5,5-diphenylhydantoin (XII) in cyclohexane only a rough estimate was made. This compound, in cyclohexane, displayed liquid crystal-like behavior, making a true solubility determination difficult. For all the prodrugs, crystals isolated from the excess solids used in the cyclohexane solubility determinations were checked for possible variations in melting behavior. In all cases the melting behavior of the excess solids was identical to the starting crystals.

There was no quantitative relationship, as expected, between the solubilities of the various esters and the length of the ester alkyl chain, but there was an obvious relationship between the melting points and solubility. Figure 1 is a plot of the logarithm of the solubility of the various esters in ethyl oleate against the reciprocal of the melting points in absolute degrees. Similar plots with correlation coefficients between 0.956 and 0.984 were seen with the other solvents.

Valvani and Yalkowsky (9) have also suggested that plots of the logarithms of solubility (as mole fraction) to the melting points may be linear for a series of structurally related molecules. Reasonable linearity of plots of the logarithm of molar solubility for our series of molecules was observed. Figure 2 shows such a plot for the esters in ethyl oleate. Neither of the plots (Figs. 1 and 2) are meant to imply anything other than the fact that crystal lattice energy differences, as indicated by melting point behavior, appear to influence the solubility of the esters in the organic solvents studied.

The low melting point of the 3-pentanoyloxymethyl derivative, VI, relative to the higher and lower homologues, V and VIII, should be noted. This unusually low melting behavior is reflected in its superior solubility in the various solvents when compared to compounds V and VIII. This

Table IV—Half-lives[a] for the Conversion of Various Phenytoin Prodrugs to Phenytoin in Different Lots of Rat Plasma at 37°

Compound	Lot I	Lot II	Lot III	Lot IV	Ratio of Rate Constant[b]
III				1.89	0.342
IV				0.85	0.753
V	1.04				0.889
VI	0.93	1.18	0.84	0.64	1.00
VII					0.442[c]
VIII		0.98			1.20
IX	0.69	0.79			1.49
X	0.52	0.71			1.67
XI			0.49		1.71
XII			0.55		1.52

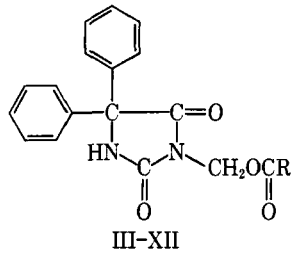
[a] In minutes. [b] VI was taken as 1.0. [c] 10% rat plasma.

may represent a particularly disrupted member in the series that does not interact well with neighboring molecules in its crystal lattice.

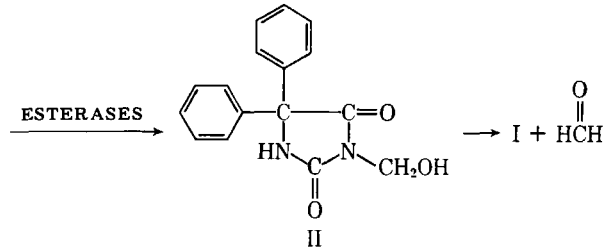
The relative solubilities of any particular prodrug in tributyrin, trioctanoin, and triolein follow a predictable trend. The greater solubilities in tributyrin than in trioctanoin and triolein were probably due to the greater polarity of this solvent because of the higher molar concentration of the polar triglyceride functional group. For example, if the molar concentration of the triglyceride functionality is calculated from the solvent density and molecular weights of the three solvents, it can be seen in Fig. 3 that a plot of the logarithm of the solubility for compounds III, VIII, and XII in the three solvents against the molar triglyceride functional group concentration is reasonably linear. This suggested that the increased solubility of the prodrugs in going from tributyrin to triolein was largely due to specific interactions between the prodrugs and the triglyceride functional group of the solvents. In fact, if it is assumed that the triglyceride functionality acts as a single-ester function, because of steric and entropic considerations, the predicted solubility of the prodrugs in ethyl oleate can be estimated within a factor of 2–3, and the intercepts in Fig. 3 predict the solubilities in cyclohexane well within an order of magnitude.

The chemical stability of 3-acetyloxymethyl and 3-decanoyloxymethyl derivatives stored in ethyl oleate at room temperature (~25°) and at 40° and 60° was determined after 1, 3, and 5 months. No loss of the prodrugs was observed. The stabilities of these two esters in tributyrin, trioctanoin, and triolein were also evaluated after storage at 60° for 3 months. No measurable degradation was observed. Though acyl exchange reactions between the esters and solvent might have been anticipated, no such reactions could be confirmed.

Enzymatic cleavage of compounds III–XII was expected to occur *via* the following scheme (Scheme I).



III–XII



II

Scheme I

It has been shown in this laboratory[8] and by others (10) that II readily dehydroxymethylates to phenytoin at pH 7.4 and 37° with a $t_{1/2}$ of <2 sec. Therefore, phenytoin production from III–XII probably occurred *via* initial cleavage of the ester bond followed by a very rapid dehydroxymethylation step to give phenytoin without any accumulation of II. In

[8] S. Varia and V. J. Stella, unpublished results.

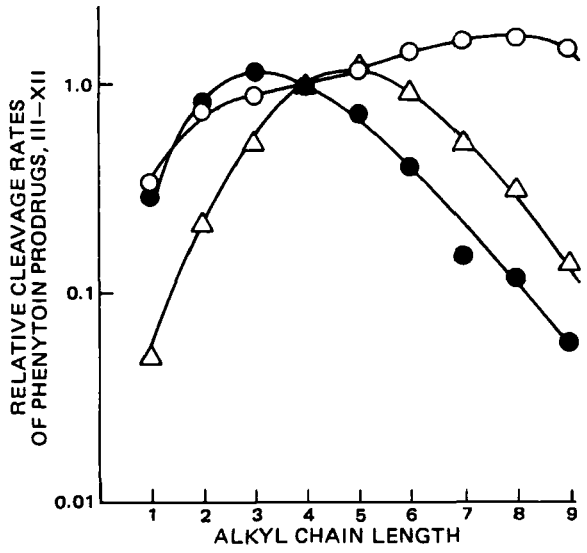


Figure 4—*Ratio of the rate constants for the cleavage of compounds III–VI, VII–XII to phenytoin in human (●) and rat (○) plasma and rat intestinal homogenates (△) at 37° to the 3-pentanoyloxymethyl derivative, VI, against alkyl chain length of the acyl function.*

all the studies with compounds III–XII quantitative cleavage to phenytoin was observed.

The rate constants and/or half-lives for the conversion of all the prodrugs to phenytoins in human and rat plasma and rat intestinal homogenates at 37° are shown in Tables III–V. In the case of rat plasma, various lots of rat plasma were studied with the cleavage rates of the prodrugs being compared with the 3-pentanoyloxymethyl derivative in each lot. The profiles for the relative cleavage rates for the prodrugs in all three tissues to the alkyl chain length are shown in Fig. 4. A parabolic relationship can be seen for each tissue, with the optimal chain length varying with the tissue and animal species.

In rat plasma all the prodrugs readily cleaved to phenytoin with half-lives of <2 min. Cleavage in human plasma was considerably slower, al-

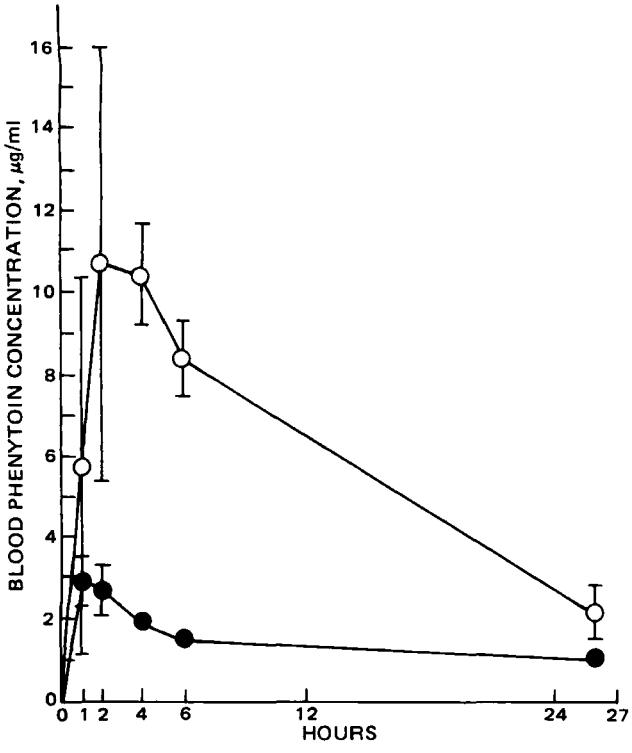


Figure 5—*Mean ± SD phenytoin whole blood concentrations in rats after oral administration of a 30-mg/kg phenytoin equivalent dose of 3-pentanoyloxymethyl-5,5-diphenylhydantoin in tributyrin (○) compared with sodium phenytoin in water (●).*

Table V—Half-lives and Rate Constants for the Conversion of Various Phenytoin Prodrugs to Phenytoin at 37° in Rat Intestine Homogenates

Compound	$t_{1/2}$, min	k, min^{-1}
III	16.4	0.0429
IV	3.78	0.184
V	1.56	0.444
VI	0.82	0.853
VII	46.7	0.0149
VIII	0.66	1.04
IX	0.87	0.796
X	1.58	0.440
XI	2.58	0.268
XII	5.86	0.118

though the 3-pentanoyloxymethyl derivative, VI, had a half-life of only 1.9 min in the human plasma used in the present study. In each tissue the cleavage rate of the 3-pivaloyloxymethyl derivative, VII, was very slow compared with the other compounds. This was presumably due to steric hindrance by the *tert*-butyl group to cleavage.

The kinetics in rat plasma diluted (to 4–20%) with isotonic Sorensen's buffer were also examined. Compounds XI and XII cleaved with half-lives of about 0.5 min in 4% plasma, while compound VI cleaved with a half-life of 3.4 min. Qualitatively, the logarithm of the rate constant *versus* alkyl chain plot did not change with the maximum cleavage still occurring with the 3-nonoyloxymethyl derivative, XI.

The cleavage rates in rat intestinal homogenate were quite rapid when the homogenate supernatant was isolated from a 2500-rpm, 10-min centrifugation of the initial homogenate. Homogenate supernatant samples prepared by ultracentrifugation at 7000×*g* for 2 hr resulted in a drop in apparent esterase activity towards the prodrugs, suggesting that both the soluble as well as microsomal-bound esterases were responsible for the observed cleavage of the esters.

Based on the melting point observations, solubilities, as well as cleavage rates, it seemed that 3-pentanoyloxymethyl-5,5-diphenylhydantoin or VI might be a viable prodrug of phenytoin. Its cleavage produces, apart from phenytoin, pentanoic or valeric acid and formaldehyde in concentrations that should not be toxic. Incorporation of this prodrug into a vehicle suitable for oral administration would depend on the dose of drug to be administered, the acceptability of the vehicle, and a reliable mechanism for drug release from the vehicle.

Studies on lipid-soluble drug release from metabolizable vehicles have suggested the following mechanism for this process. After intraluminal lipolysis of the oils by pancreatic lipases, the lipolytic products are dispersed in bile salt-mixed micelles. Calcium ions along with the fatty acids form a liquid crystal-like phase which may include monoglycerides (11). Lipid drugs are presumed to be released from the vehicle by this lipolysis. The drug along with the fatty acids and monoglycerides then become available for absorption (12).

The four vehicles chosen in the present study represented examples of short- (tributyrin), medium- (trioctanoin), and long-chain triglycerides (triolein), while ethyl oleate represented a simple long-chain fatty acid ester. The interest in these vehicles as well as others being studied, results from a long-term goal to study the mechanism of drug release from metabolizable vehicles. Long-chain triglycerides are readily attacked by the lipase–colipase–bile acid–calcium system to produce various liquid crystal and mixed micellar phases (11). The short- and medium-chain triglycerides are also cleaved (13, 14), but it is anticipated that they would tend to form a simple two-phase system of oil droplets and a true solution phase.

As an initial screen of whether the prodrug–lipid vehicle concept might

Table VI—Phenytoin Whole Blood Concentration [a] in Rats After Oral Administration of VI [b] in Tributyrin Compared with Sodium Phenytoin [b] in Aqueous Solution

Time, hr	Phenytoin Blood Concentrations	
	Sodium Phenytoin, μg/ml	VI in Tributyrin, μg/ml
1	2.91 ± 0.67	5.75 ± 4.60
2	2.69 ± 0.60	10.66 ± 5.38
4	1.93 ± 0.24	10.43 ± 1.22
6	1.52 ± 0.04	8.42 ± 0.92
26	1.03 ± 0.26	2.17 ● 0.68
$[AUC]_0^{26}$ in μg hr/ml	39.1	162.1

[a] Mean ± *SD*. [b] 30 mg/kg phenytoin equivalents.

represent a viable drug delivery mode, plasma phenytoin levels from 3-pentanoyloxymethyl-5,5-diphenylhydantoin in tributyrin, administered orally to rats at a 30 mg/kg phenytoin equivalent dose were compared with phenytoin from an aqueous solution of sodium phenytoin. Figure 5 is a plot of the mean blood levels for the two dosage forms. The superiority of the lipid vehicle–prodrug combination is obvious. Table VI summarizes the mean (and standard deviations) phenytoin blood levels at each sample time and the AUCs up to 26 hr. Presumably, the poor bioavailability of phenytoin from the sodium phenytoin solution was due to the slow redissolution of phenytoin precipitated when the sodium phenytoin was exposed to stomach acid.

In summary, the lipid solubility of high-melting, sparingly water- and lipid-soluble drugs can be altered by transient molecular modifications. Such modification may act to disrupt the major intermolecular interactions in the crystal lattice responsible for the undesired physical properties. For these poorly lipid and water soluble drugs, improved oral delivery can be effected by the synthesis of low-melting lipoidal prodrugs, which can then be incorporated into metabolizable vehicles. *In vivo* parent drug release from such a vehicle–prodrug combination is speculated to be initial lipolysis of the vehicle giving rise to prodrug release, followed by prodrug absorption and cleavage.

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Computation of In-house Quality Control Limits for Pharmaceutical Dosage Forms Based on Product Variability

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Abstract □ A method for establishing sampling plans for in-house limits that fix both the producer's and consumer's risks is presented for pharmaceutical systems in which both between-batch and within-batch variations are present. Such plans can always be constructed and require more or less sample assays depending on the variability of the process. The computations involve a numerical approximation to the bivariate normal distribution.

Keyphrases □ Product variability—pharmaceutical dosage forms, quality control limits □ Pharmaceutical dosage forms—quality control limits, product variability □ Quality control limits—pharmaceutical dosage forms, product variability

A recent article by Boudreau and Harrison (1) described a method for establishing "House Guides" that achieve "a high degree of assurance at a minimum of cost." These guides were set up in an effort to establish reasonable in-house limits, tighter than official specifications, which would give a high level of assurance that the finished product would not be out of specifications set by the NDA, FDA, official compendia, or company policy. According to Boudreau and Harrison (1), the FDA has recommended that a risk of releasing an out-of-specification product should be ≤5% based on the in-house guidelines. The establishment of in-house specifications is important because of problems that can arise when the assay of a batch of material is close to, but within, the official specifications. In these cases, the true mean potency has a good chance of being outside the official limits. Boudreau and Harrison in developing their formula, EVAL, were prompted by the difficulty of computing house limits using a single formula that would satisfy the 5% criterion and would, at the same time, consistently pass good batches which have a relatively large variation. They recommended the use of three formulas based on the relative amount of variation. It is possible to establish such in-house limits (hereafter referred to as IHLs) for any product based on its variability. If the batch-to-batch variability is so great that many batches truly fall outside the official limits, no plan will consistently pass these batches. In these situations, it is the responsibility of the manufacturer to improve the process so as to reduce the variability.

However, once the sources of variability have been identified, plans can be established with known properties. In the present case, the plans should accept out-of-specification material 5% of the time, at most. Another important criterion is that the plan should pass good material with a known probability, *e.g.*, 90% of the time.

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