# Aqueous Solubility and Dissolution Rate Does Not Adequately Predict in Vivo Performance: A Probe Utilizing Some *N*-Acyloxymethyl Phenytoin Prodrugs

VALENTINO J. STELLA,* SUWALDI MARTODIHARDJO,† AND VENKATRAMANA M. RAO

Contribution from *Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, Kansas 66047.*

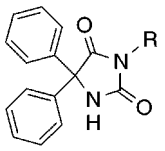
Received December 21, 1998. Final revised manuscript received May 19, 1999.
Accepted for publication May 26, 1999.

**Abstract** □ Some physicochemical properties of *N*-acyloxyalkyl prodrugs of phenytoin were reported previously.[1,2] It was shown that despite their lower aqueous solubilities relative to phenytoin, these lower-melting prodrugs with apparently disrupted crystalline structures gave either comparable or enhanced in vitro solubility and dissolution rate in simulated intestinal media made up of bile salts and lecithin (SIBLM).[2] The current objective was to compare the in vivo behavior of two of these prodrugs to phenytoin in dogs and attempt to correlate the in vitro behavior to their in vivo behavior. The oral bioavailability of phenytoin after administration of phenytoin (**1**) and the selected prodrugs, 3-pentanoyloxymethyl 5,5-diphenylhydantoin (**2**) and 3-octanoyloxymethyl 5,5-diphenylhydantoin (**3**), in fed and fasted beagle dogs were compared to intravenously administered phenytoin. Phenytoin and its prodrugs showed improvement in fed-state phenytoin bioavailability relative to the fasted state indicating that food enhanced the delivery of phenytoin from phenytoin and its prodrugs. The increased bioavailability in the fed state may be due to stimulation of bile release by food and, for the prodrugs, possible catalysis of their dissolution by lipases.[3] In both, fasted and fed states, prodrugs **2** and **3** gave higher AUC values of phenytoin than the parent compound. The enhanced bioavailability of phenytoin after oral administration were more obvious in fed dogs. Although enhanced, AUC values of phenytoin from the prodrugs relative to phenytoin were not statistically different (at 95% confidence level) in fasted state, but were different in fed state. Although the aqueous solubilities and dissolution of both prodrugs were lower than phenytoin, dissolution of **2** and **3** was equivalent and greater, respectively, relative to phenytoin in SIBLM. As expected, the in vivo behavior correlated better with the in vitro SIBLM dissolution behavior. These results indicate that aqueous solubility per se does not adequately predict in vivo behavior.

## Introduction

Phenytoin has a high melting point and poor aqueous and lipid solubility resulting in erratic and sometimes incomplete oral availability. The probable cause of this high melting point is strong intermolecular hydrogen bonding between the hydrogen atom on the $N_3$ of one molecule and a carbonyl oxygen of a neighboring molecule in the crystal packing.

*N*-Acyloxyalkyl prodrugs of phenytoin were synthesized to lower the melting point and alter the physicochemical properties.[1] Properties such as melting points, solubilities, dissolution rates, and partition coefficient were reported previously.[2] Of all the prodrugs studied, two prodrugs **2** and **3** (Figure 1) showed the most interesting physicochemical properties compared to phenytoin (**1**).[2] It was shown that the solubility and dissolution rate of the prodrugs in a simulated bile−lecithin mixture (SIBLM) was significantly enhanced relative to phenytoin even though their aqueous properties were significantly inferior to phenytoin (Table 1). These properties could not be correlated with the respective values in water, suggesting that water solubility could be a poor predictor of dissolution and bioavailability in vivo. It was therefore hypothesized that this increased solubility and dissolution rate in SIBLM should translate to a significant improvement in bioavailability of the prodrugs over the parent compound, phenytoin. Presented here are the results of an in vivo oral bioavailability study in dogs in both the fasted and fed state.



| compound | R |
|---|---|
| **1** | H |
| **2** | $CH_2OCOC_4H_9$ |
| **3** | $CH_2OCOC_7H_{15}$ |

**Figure 1**—The structure of phenytoin (**1**) and selected prodrugs (**2**, **3**).

## Experimental Section

Prodrugs **2** and **3** used in this study were prepared by procedures described earlier.[1] All other chemicals were of analytical grade.

**Enzymatic Hydrolysis of Prodrugs**—The conversion rates of the ester prodrugs to the parent compound, phenytoin, were studied in dog plasma. The plasma was obtained by centrifuging fresh whole blood from a male beagle dog. Sodium ethylenediamine tetraacetate (Na EDTA) was added as an anticoagulant. Centrifugation was carried out in a Dynec I centrifuge (Beckon and Dickinson) for 10 min at 2000 rpm. A stock solution of each prodrug having a concentration of ~2 mg/mL phenytoin equivalent was prepared in acetonitrile. The plasma was equilibrated in a water bath at 37 °C for at least 10 min before the addition of an aliquot of the stock solution. Twenty microliters aliquot of stock solution was added to 2 mL of plasma. All the kinetic studies were followed to completion by monitoring the appearance of phenytoin. At appropriate time intervals 100 $\mu$L samples were withdrawn and added to 250 $\mu$L of acetonitrile which was then vortexed for 10−15 s. The mixture was then centrifuged at 2000 rpm for 5−10 min, and the supernatant was collected and analyzed by HPLC. No attempt was made to correct for pH drift in plasma samples. Conversion studies of these prodrugs in other animal species and tissues were reported earlier.[1,3]

* To whom correspondence should be addressed. Phone: (785) 864-3755. Fax: (785) 864−5736. E-mail: stella@hbc.ukans.edu.
† Current Address: Faculty of Pharmacy, Gadjahmada University, Sekiputara, Yogyakarta, Indonesia.


10.1021/js980489i CCC: $18.00
Published on Web 07/09/1999

**Table 1—Properties of Phenytoin (1) and Its Prodrugs (2 and 3) in Water and SIBLM[a]**

| compd no. | water solubility ($M \times 10^5$) | SIBLM solubility ($M \times 10^4$) | solubility ratio (SIBLM/water) | dissolution rate[b] in phosphate buffer ($\times 10^{-11}$ mol/cm$^2$/s) | dissolution rate[b] in SIBLM ($\times 10^{-11}$ mol/cm$^2$/s) | ratio of dissolution rates |
|---|---|---|---|---|---|---|
| **1** | 8.0 | 5.5 | 6.9 | 10.1 | 28.7 | 2.8 |
| **2** | 2.1 | 4.3 | 20.5 | 1.9 | 28.4 | 14.9 |
| **3** | 0.03 | 5.4 | 1800 | 0.04[c] | 55.9 | 1379 |

[a] Data reproduced from previously reported work from our laboratory.[2] [b] All the dissolution rate experiments were conducted at a rotation speed of 200 rpm. [c] The dissolution rates were estimated using the Levich equation.

**Intravenous Administration**—Four adult male beagle dogs (11−12.8 kg) were used in an iv administration study. The dogs were fasted overnight prior to administration of the drug, but they were allowed water ad libitum during the study. Each dog received a 5.5 and 10 mg/kg phenytoin dose as sodium phenytoin (Dilantin, Parke-Davis), and a two-week washout period was allowed between doses. The drug was injected into the femoral vein over a period of 2−3 min. After dosing, serial venous blood samples of 1.5−2 mL were taken at appropriate time intervals from the alternate femoral vein. The blood samples were then placed into 2 mL Vacutiners (Becton-Dickinson, Ruthford, NJ) containing 3 mg of ethylenediaminetetraacetic acid as the anticoagulant. The samples were shaken and centrifuged for 5 min at 2000 rpm. Two hundred microliters of the separated plasma sample was added to 500 $\mu$L of acetonitrile and vortexed for 10−15 s and centrifuged at 2000 rpm for 5−10 min, and the supernatant was collected and analyzed by HPLC.

**Oral Administration**—A dog model was chosen to study the oral bioavailability of phenytoin, **2** and **3**. The same four adult male beagle dogs used for the iv study were used for a 4 × 6 random crossover study. A two-week washout period was allowed between dosing.

The dogs were fasted overnight prior to drug administration, but were allowed water ad libitum during the study. The prodrugs and phenytoin used in this study were administered without any excipients in hard gelatin capsules which were placed in the back of the mouth cavity. To help ensure particle size homogeneity, the compounds were passed through a 100-mesh sieve and collected on a 200-mesh sieve resulting in a particle size distribution range of 149 to 74 $\mu$m.

In the case of the dogs in the fed state, the capsules were given 30 min after feeding the dogs. The food used consisted of 250 g of dry dog food, 5 g of canned-dog food, and 12 mL of water. Once again, the dogs were allowed water ad libitum during the study. After dosing, the same procedures as described under the iv administration section were followed.

**HPLC Analysis of Phenytoin**—Reverse phase chromatography was used for the quantitative analysis of phenytoin and its prodrugs. A 15 cm long CPS hypersil column (i.d. 4.6 mm, particle size 5 $\mu$m) was used. The mobile phase consisted of acetonitrile: phosphate buffer (0.025 M, pH 6.0)/(25:75 v/v), and the samples were detected at 214 nm by Spectroflow 757, Kratos Analytical. The standard reference curve was obtained by spiking blank plasma with phenytoin and then treating the samples as for the plasma samples. Phenytoin concentration in plasma samples obtained from the bioavailability studies were calculated from the peak area by reference to the standard curve.

**Statistical Analysis**—Statistical comparison of AUC values obtained after oral administration of phenytoin and its prodrugs in both fed and fasted states was performed by analysis of variance method. A posthoc Bonferroni/Dunn test was conducted using STATVIEW 2.0 (Abacus Concepts, Inc., CA) to determine which of the AUC values were significantly different from each other ($p < 0.0033$).

## Results and Discussion

**Enzymatic Hydrolysis of 2 and 3 to Phenytoin**—The enzymatic hydrolysis of the phenytoin prodrugs (**2** and **3**) to phenytoin in dog plasma exhibited pseudo-first-order kinetics. Both the prodrugs completely hydrolyzed to phenytoin presumably by the action of plasma esterases. The hydrolysis of the prodrugs to the parent compound is a two-step reaction. The first step, which is rate-limiting, involves the cleavage of the ester group resulting in the formation of an *N*-hydroxymethyl phenytoin. The second step involving the dehydroxymethylation of *N*-hydroxymethyl phenytoin to phenytoin has been shown to be rapid (half-life < 2 s)[4] at pH 7.4 and 37 °C. The apparent first-order rate constants for compounds **2** and **3** were found to be $7.5 \times 10^{-2}$ min$^{-1}$ ($t_{1/2}$ = 9.2 min) and $0.9 \times 10^{-2}$ min$^{-1}$ ($t_{1/2}$ = 74.4 min), respectively. The half-lives of these prodrugs were adequate to ensure that phenytoin would be quantitatively produced from these prodrugs in vivo, and that the enzymatic conversion was probably not a limiting factor.

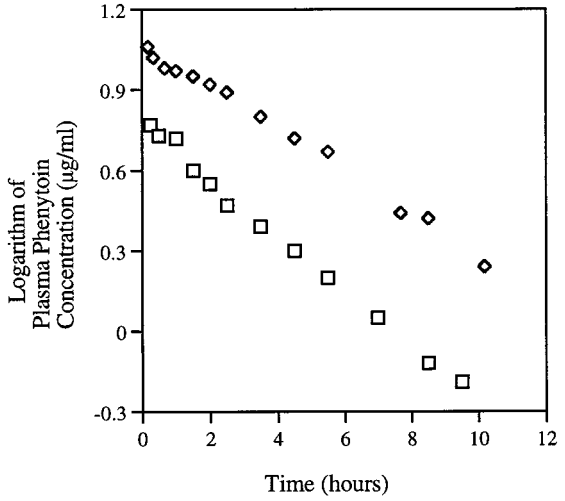



**Figure 2**—Plots of logarithm of plasma phenytoin concentrations versus time obtained after intravenous administration of 5 mg/kg (□) and 10 mg/kg (◇) of sodium phenytoin to dog no. 4.

Following oral administration, the conversion of the prodrugs to phenytoin could occur in presystemic tissues such as the intestinal lumen, the brush border, the enterocytes, blood, liver, etc.[5] It has also been shown that prodrugs **2** and **3** undergo lipolytic cleavage by pancreatic lipases.[3] Moreover, intact prodrugs were not detected following oral administration of the prodrugs, indicating that the enzymatic conversion is not a limiting factor in the absorption process after oral administration of these prodrugs.

**Intravenous Administration of Sodium Phenytoin**—Figure 2 is a representative plot of plasma phenytoin concentration versus time curve obtained after intravenous administration of sodium phenytoin (doses 5.5 and 10 mg/kg) to a dog. Phenytoin followed an apparent two-compartment model with a rapid but short distribution phase allowing the overall kinetics to be effectively modeled as a one-compartment model with saturable metabolism since the clearance and the elimination is dose-dependent.[6−8] These findings were in agreement with previously reported studies showing that phenytoin exhibited dose-dependent kinetics in dogs.[6,9] The possible cause for the dose-dependency may be due to the capacity-limited, saturable enzymatic conversion of phenytoin to aromatic hydroxylated metabolites.[10] Such a capacity-limited elimination

**Table 2—Pharmacokinetic Properties of Phenytoin after Intravenous Administration of Two Different Doses of Sodium Phenytoin to Four Beagle Dogs**

| dog | dose[a] (mg/kg) | half-life (h) | AUC (mg·h/mL) | $K_m$ ($\mu$g/mL) | $V_m$ ($\mu$g/mL/h) | $V_d$ (L/kg) |
|---|---|---|---|---|---|---|
| 1 | 5.5 | 3.0 | 24.3 | 8.17 | 2.13 | 1.03 |
| | 10 | 3.3 | 61.5 | 8.32 | 1.44 | 0.88 |
| 2 | 5.5 | 2.2 | 17.7 | 5.33 | 2.39 | 1.03 |
| | 10 | 3.0 | 52.3 | 5.72 | 1.14 | 1.09 |
| 3 | 5.5 | 2.0 | 16.8 | 5.09 | 2.35 | 1.33 |
| | 10 | 2.7 | 57.4 | 5.49 | 1.16 | 0.84 |
| 4 | 5.5 | 1.9 | 15.6 | 7.33 | 3.08 | 1.38 |
| | 10 | 2.7 | 54.8 | 7.83 | 1.44 | 1.05 |

[a] Phenytoin dose equivalent.

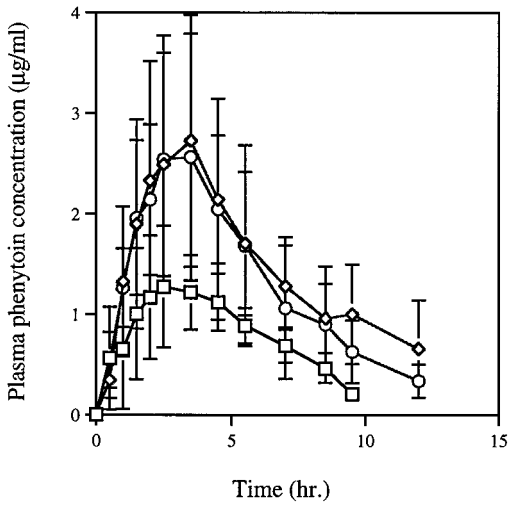



**Figure 3**—Mean plasma phenytoin concentrations in fasted dogs ($n = 4$) after oral administration of **1** (□), **2** (◇), and **3** (○) at a dose of 10 mg/kg phenytoin dose equivalent. The bars represent standard errors of the mean.

process can be described by the Michaelis Menten equation.

$$\frac{dC}{dt} = -\frac{V_m C}{K_m + C} \quad (1)$$

$V_m$, theoretical maximum velocity of the capacity-limited process and $K_m$, Michaelis−Menten constant were calculated using a nonlinear, least-squares iteration of eq 1 as reported previously by Varia et al.[11] The apparent volume of distribution ($V_d$) was determined as the ratio of dose administered and $C_0$, obtained by extrapolating the elimination phase of the plot of the logarithm of plasma concentration versus time neglecting the short distribution phase (see Figure 2). The area under the plasma concentration versus time curves $[AUC]^{0\rightarrow\infty}$ were calculated using the trapezoidal rule and the apparent half-lives obtained from the linear, terminal slopes and are given in Table 2 along with apparent $K_m$ and $V_m$ values for each dog. The values obtained for both $K_m$ and $V_m$ were comparable to that obtained by Varia et al.[11]

**Oral Administration of Phenytoin**—The oral administration of **1**−**3** to the dogs in fasted and fed states was carried out in a 4 × 6 crossover study design. Figures 3 and 4 show plots of the mean plasma concentration versus time following the oral administration of 10 mg/kg phenytoin equivalent dose of **1**−**3** to the four dogs in both the fasted and the fed states, respectively. The AUCs were calculated using the trapezoidal rule. The apparent elimination half-lives of phenytoin and phenytoin from its prodrugs after oral administration were calculated using the linear, terminal slopes of the logarithm of plasma

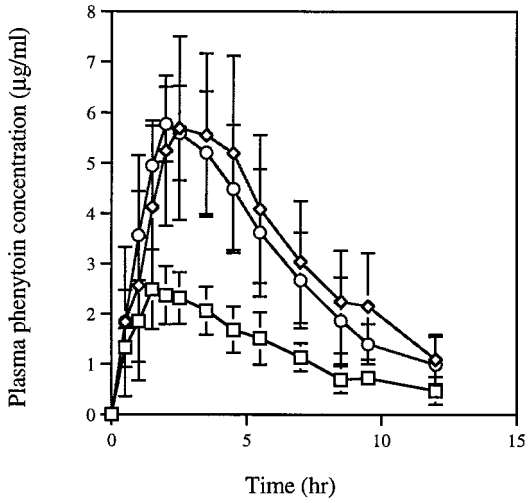



**Figure 4**—Mean plasma phenytoin concentrations in fed dogs ($n = 4$) after oral administration of **1** (□), **2** (◇), and **3** (○) at a dose of 10 mg/kg phenytoin dose equivalent. The bars represent standard errors of the mean.

**Table 3—Apparent Phenytoin Pharmacokinetic Parameters after Oral Administration of Phenytoin (1) and Its Prodrugs 2 and 3 to Fasted and Fed Dogs[a] ($n = 4$)**

| state | compd | $AUC^{0\rightarrow\infty}$ ($\mu$g·h/mL) | apparent elimination half-life (h) | $t_{max}$ (h) |
|---|---|---|---|---|
| fasted | **1** | 8.8 (1.9) | 2.5 (0.7) | 2.9 (0.7) |
| | **2** | 20.4 (6.1) | 3.1 (0.4) | 2.8 (0.8) |
| | **3** | 17.3 (7.2) | 2.9 (0.4) | 2.9 (0.8) |
| fed | **1** | 17.1 (4.2) | 2.9 (0.4) | 2.1 (0.8) |
| | **2** | 44.8 (11.4) | 3.3 (0.4) | 3.1 (1.0) |
| | **3** | 40.9 (10.7) | 2.9 (0.3) | 2.4 (0.4) |

[a] The values shown are the mean values with their standard deviations in parentheses.

phenytoin concentration versus time assuming a simple first-order elimination model. These pharmacokinetic parameters are summarized in Table 3. The in vivo regeneration of phenytoin from its prodrugs appeared to be rapid as intact prodrugs were not detected in the plasma. On the basis of the in vitro half-life of **3** in dog plasma (74 min), one would expect to observe this prodrug with phenytoin in plasma samples. The absence of prodrug in the plasma samples perhaps suggested that the regeneration of phenytoin from **3** was also occurring by the lipase-catalyzed hydrolysis in the lumen or conversion in the brush border, enterocyctes, or liver.[1,3] For example, the half-life for the conversion of **2** and **3** to **1** in rat intestine homogenates was been reported to be less than 2 min.[1]

A two-way ANOVA indicated that both the prodrugs and food had an overall significant effect on phenytoin AUC values. To determine which of the treatments significantly differed from each other, a posthoc Bonferroni/Dunn test was conducted (95% confidence interval, number of comparisons =15, $p < 0.0033$). A portion of the results which are useful for this discussion are presented in the Table 4. In the fasted state, the phenytoin AUC values for phenytoin and its prodrugs were not statistically significant from each other at the 95% confidence level. Qualitative differences were seen, however. The phenyotin AUC values for the dogs in the fed state were significantly different with **2** and **3**, providing higher levels compared to phenytoin per se.

The ratio of $[AUC]^{0\rightarrow\infty}$ after oral dosing to $[AUC]^{0\rightarrow\infty}$ after iv dosing gives an "apparent" absolute bioavailability because the absorption rate and subsequent plasma levels of phenytoin due to the nonlinearities in phenytoin clearance. This can affect bioavailability estimates.[11] Therefore, a correction to the "apparent" absolute bioavailability was

**Table 4—Multiple Comparison of AUCs after Oral Administration of Phenytoin (1) and Its Prodrugs 2 and 3 to Fasted and Fed Dogs[a] Using Posthoc Bonferroni/Dunn Test**

| comparison between treatments | significance[b] (95% confidence, $p < 0.0033$)[c] |
|---|---|
| **1** (fasted), **1** (fed) | NS |
| **2** (fasted), **2** (fed) | S |
| **3** (fasted), **3** (fed) | S |
| **1** (fasted), **2** (fasted) | NS |
| **1** (fasted), **3** (fasted) | NS |
| **1** (fed), **2** (fed) | S |
| **1** (fed), **3** (fed) | S |

[a] The values shown are the mean values with their standard deviations in parentheses ($n = 4$). [b] S means significantly different and NS means significantly different. [c] A total of 15 comparisons were conducted at a 95% confidence level making. $p < 0.05/15 = 0.0033$.

needed to obtain a more accurate estimate of the absolute bioavailability. One method of calculating bioavailabilities of drugs possessing dose-dependent elimination due to enzyme saturation was to assume a one-compartment model with a constant (dose-independent) volume of distribution and a capacity-limited pathway of elimination.[11−13] Assuming a rapid conversion of prodrugs to phenytoin, the rate of change of phenytoin concentration in the body after administration of phenytoin or its prodrugs may be written as

$$\frac{dC}{dt} = \frac{k_a F D_{iv} \exp(-k_a t)}{V_d} - \frac{V_m C}{(K_m + C)} \qquad (2)$$

where $k_a$ is the apparent first-order absorption constant, $F$ is the fraction of the total administered dose that is absorbed, $D_{iv}$ is the equivalent iv dose. The true or corrected absolute bioavailability is given as

$$F = \frac{\left(\int_0^\infty \frac{V_m C}{K_m + C}\, dt\right)}{\left(\frac{D_{iv}}{V_d}\right)} \qquad (3)$$

The specific $V_m$ and $K_m$ values for each dog were obtained from the iv data.

The numerator of the above equation was evaluated by applying the trapezoidal rule on $V_m C/(K_m + C)$ versus time curve between time limits $t = 0$ to $t =$ last time point. The contribution of the integral from the last time point to infinity is assumed to be negligible as the concentration at the last time point is small.

Apparent relative bioavailabilities of phenytoin after oral administration of **2** and **3** were calculated as

$$F_{app,rel} = \frac{[AUC]_{prodrug}^{0\to\infty}}{[AUC]_{phenytoin}^{0\to\infty}} \qquad (4)$$

where the AUC are the mean values.

Phenytoin apparent absolute bioavailability, corrected absolute bioavailability and apparent relative bioavailability after oral administration of phenytoin and **2** and **3** are given in Table 5. In the fasted state, the apparent relative bioavailability of prodrugs **2** and **3** was 2.3 and 2 times, respectively, compared to phenytoin. In the fed state, the apparent relative bioavailability of prodrugs **2** and **3** compared to phenytoin were 2.6 and 2.4. The corrected absolute bioavailabilities in the fed state were found to be 84.2 (±16.5)% and 77.5 (± 22.1)%, respectively. These values appear to be close to quantitative suggesting that

**Table 5—Calculated Percent Bioavailabilities of Phenytoin after Oral Administration of Phenytoin (1) and Its Prodrugs 2 and 3 to Beagle Dogs[a] ($n = 4$)**

| state | compd | apparent absolute % bioavailability[b] | apparent relative % bioavailability[c] | corrected absolute % bioavailability[d] |
|---|---|---|---|---|
| fasted | **1** | 15.5 (3.3) | 100 | 21.0 (6.9) |
| | **2** | 36.5 (11.9) | 232 | 44.2 (16.2) |
| | **3** | 30.7 (13.5) | 197 | 40.7 (19.8) |
| fed | **1** | 30.4 (4.2) | 100 | 37.8 (9.3) |
| | **2** | 79.0 (11.4) | 262 | 84.2 (16.5) |
| | **3** | 73.0 (22.4) | 239 | 77.5 (22.1) |

[a] The values shown are mean values with standard deviations in the parentheses. [b] Apparent absolute bioavailability was calculated as $[AUC]^{0\to\infty,oral}/[AUC]^{0\to\infty,iv}$. [c] Equation 4. [d] Equation 3.

when administered in the fed state, **2** and **3** perhaps overcome the dissolution limitations observed with phenytoin.

The accuracy of $F$ depends on the accuracy of the estimates of $K_m$ and $V_m$. In this study the $K_m$ and $V_m$ values were determined by nonlinear curve fitting of limited iv data (only two doses). A wider range of drug dosage would enable one to determine the Michaelis−Menten constants with more accuracy. The purpose for presenting these "corrected" values was simply to point out that the apparent absolute bioavailabilties based on AUC comparisons alone can lead to undersestimates of the true bioavailability values due to the nonlinear elimination behavior of phenytoin. Note, as pointed earlier, the $V_m$, $K_m$, and $V_d$ values obtained here are within the range of values reported for phenytoin in dogs in an earlier study.[11]

**Correlation between in Vitro Dissolution Studies and in Vivo Bioavailability**—The larger AUC values in the fed state were found to be significantly different from those in fasted state from **2** and **3**. In the fasted state, the AUC values for phenytoin and its prodrugs were not statistically significant from each other at the 95% confidence level. However, the AUC values in the fed state were significantly different.

On the basis of solubility and dissolution characteristics in water alone, **2** and especially **3** were expected to give a lower bioavailability relative to the parent compound.[2] A portion of the results published previously are reproduced in Table 1 for the present discussion. It was obvious from the bioavailability studies that the in vitro dissolution studies in water do not predict the in vivo results. If the dissolution and solubility characteristics in SIBLM were considered, the prodrugs were expected to give higher or equivalent bioavailabilities with respect to the parent compound, phenytoin. In the fed state, the contents of gastrointestinal tract (GIT) will be influenced by the byproducts of food digestion as well as an increased level of bile acids, lecithin, and the lipase/colipase complex. The ratio of dissolution rate of all the compounds in SIBLM to that in water indicates the probable sensitivity of these compounds to changes in the GIT contents. On the basis of the ratio of the dissolution rates in SIBLM to those in water, the bioavailability of phenytoin from **2** and **3** were expected to be much more sensitive to changes in the GIT content than phenytoin itself. This was consistent with the in vivo observation that the bioavailabilities of phenytoin from **2** and **3** were qualitatively superior to phenytoin in the fasted state, and that the differences were quantitatively superior in the fed state animals. When administered in fed state, the prodrugs appeared to have overcome dissolution rate limitations as the corrected absolute bioavailabilities were close to 100%.

The reasons for the altered bioavailability of orally administered drugs in the fed state have been described earlier.[14,15] The most plausible explanation for the effect of food on the bioavailability of phenytoin from phenytoin and phenytoin from its two prodrugs was that the dissolution rates of the drugs may be increased due to the food-induced stimulation of bile flow.[14,16]

This enhanced dissolution rate in the presence of food may be the reason for the improved bioavailability observed after oral administration of several lipophilic drugs such as danazol,[17] itracanazole,[18] phytonadione,[19] 5-methoxypsoralen.[20] The importance of physiologically relevant dissolution media in predicting the effect of food on the oral bioavailability of poorly soluble drugs has been emphasized in a recent review.[21] From the present study, it was clear that the inferior aqueous solubilities of **2** and **3** do not have as great an influence on their in vivo behavior, while their relative behavior in the presence of SIBLM reasonably predicted their in vivo behavior.

## Conclusions

Despite possessing poor aqueous solubilities, prodrugs **2** and **3** showed superior qualitative bioavailability of phenytoin relative to phenytoin in the fasted state and a significant enhancement in the fed state. Physicochemical properties such as aqueous dissolution rate or aqueous solubility did not correlate with the in vivo performance in this homologous prodrug series. The in vitro dissolution rates correlated better with the in vivo results when SIBLM was used as the dissolution medium.

## References and Notes


1. Yamaoka, Y.; Roberts, R. D.; Stella, V. J. Low-melting phenytoin prodrugs as alternative oral delivery modes for phenytoin: A model for other high-melting sparingly soluble drugs. *J. Pharm. Sci.* **1983**, *72*, 400−405.
2. Stella, V. J., Martodihardjo, S.; Terada, K.; Rao, V. M. Some relationships between the physical properties of various 3-acyloxymethyl prodrugs of phenytoin to structure: potential in vivo performance implications. *J. Pharm. Sci.* **1998**, *87*, 1235.
3. Alvarez, F.; Stella, V. J. Pancreatic lipase-catalyzed hydrolysis of esters of hydroxymethyl phenytoin dissolved in various metabolized vehicles, dispersed in micellar systems, and in aqueous suspensions. *Pharm. Res.* **1989**, *6*, 555−563.
4. Bundgaard, H., Johansen, M. Hydrolysis of N−(alpha-hydroxybenzyl)benzamide and other N−(alpha-hydroxyalkyl)amide derivatives: implications for the design of N-acyloxyalkyl-type prodrugs. *Int. J. Pharm.* **1984**, *22*, 45−56.
5. Krisch, K. In *The Enzyme*, 3rd ed.; Academic Press: New York, 1971; Vol. V, p 43.
6. Frey, H.; Loscher, W. Clinical pharmacokinetics in the dog: a reevaluation. *Am. J. Vet. Res.* **1980**, *41*, 1635.
7. Sanders, J. E.; Yeary, R. A. Serum concentrations of orally administered diphenylhydantoin in dogs. *J. Am. Vet. Med. Assoc.* **1978**, *172*, 153.
8. Arnold, K.; Gerber, N. Rate of decline of diphenylhydantoin in human plasma. *Clin. Pharmacol. Ther.* **1970**, *11*, 121.
9. Dayton, P. G.; Cucinell, S. A.; Weiss, M.; Perel, J. M. Dose-dependence of drug plasma level decline in dogs. *J. Pharmac. Exp. Ther.* **1967**, *158*, 305.
10. Atkinson, A. J.; MacGee, J.; Strong, J.; Garteiz, D.; Gaffney, T. E. Identification of 5-meta-hydroxyphenyl-5-phenylhydantoin as a metabolite of diphenylhydantoin. *Biochem. Pharmacol.* **1970**, *19*, 2483.
11. Varia, S. A.; Stella, V. J. Phenytoin prodrugs V: In vivo evaluation of some water-soluble phenytoin prodrugs in dogs. *J. Pharm. Sci.* **1984**, *73*, 1080−1087.
12. Jusko, W. J.; Koup, J. R.; Alvan, G. Nonlinear assessment of phenytoin bioavailability. *J. Pharmacokinet. Biopharm.* **1976**, *4*, 327.
13. Martis, L., Levy, R. Bioavailability calculations for drugs showing simultaneous first order and capacity limited elimination kinetics. *J. Pharmacokinet. Biopharm.* **1973**, *1*, 283.
14. Charman, W. N.; Porter, C. J. H.; Mithani, S.; Dressman, J. B. Physicochemical mechanisms for the effects of food on drug absorption: the role of lipids and pH. *J. Pharm. Sci.* **1997**, *86*, 269−282.
15. Welling, P. G. Influence of food and diet on gastrointestinal drug absorption: review. *J. Pharmacokinet. Biopharm.* **1977**, *5*, 291−334.
16. Hamaguchi, T.; Shinkuma, D.; Irie, T.; Yamanaka, Y.; Morita, Y.; Iwamoto, B.; Miyoshi, K.; Mizuno, N. Effect of high-fat meal on the bioavailability of phenytoin in a commercial powder with a large particle size. *Int. J. Clin. Pharm., Therapy Toxicol.* **1993**, *31*, 326−330.
17. Charman, W.; Rogge, M. C.; Boddy, A. W.; Berger, B. M. Effect of food and a monoglyceride emulsion formulation on danazol absorption. *J. Clin. Pharmacol.* **1993**, *33*, 381−386.
18. Van Peer, A.; Woestenborghs, R.; Heykants, J.; Gasparini, R.; Gauwenbergh, G. The effects of food and dose on the oral systemic availability of itraconazole in healthy subjects *Eur. J.. Clin. Pharmacol.* **1989**, *36*, 423−426.
19. Tadakazu, T.; Tsushima, Y.; Machida, Y.; Kayano, M.; Nagai, T. Evaluation of bioavailability upon oral administration of phytonadione preparations in beagle dogs. *Biol. Pharm. Bull.* **1993**, *16*, 319−321.
20. Ehrsson, H.; Wallin, I.; Ros, A. M.; Eksborg, S.; Berg, M. Food-induced increase in bioavailability of 5-methoxypsoralen. *Eur. J. Clin. Pharmacol.* **1994**, *46*, 375−377.
21. Dressman, J. B.; Amidon, G. L.; Reppas, C.; Shah, V. P. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm. Res.* **1998**, *15*, 11−22.


JS980489I