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# Factors influencing the precipitation time of phenytoin in the presence of DDMS, one of its prodrugs

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## Summary

During a study on the development of water-soluble prodrugs of phenytoin, it was observed that precipitation times of aqueous solutions of these prodrugs were much longer than those times predicted from dilute solution kinetics of the prodrug and the intrinsic solubility of the parent drug. Increases in precipitation times were monitored by a well controlled study. Various factors such as (a) a change in the intrinsic solubility of phenytoin in the presence of its prodrug, and (b) a change in the rate of hydrolysis of the prodrug in the presence of higher concentrations thereof could account for the observed increases in precipitation times. Kinetic studies were performed to determine the extent of involvement of the initial prodrug concentration on the rate of hydrolysis. In order to determine whether the solubility of phenytoin was influenced by the presence of its prodrug, phase solubility studies were conducted. A reduction of 50% in the rate of hydrolysis was observed at higher prodrug concentrations, which could account for significant increases in the observed precipitation times at therapeutic levels. Phenytoin was found to be solubilised by its prodrug over the total concentration range studied. At therapeutic levels the solubility of phenytoin was increased 45-fold which also attributed to the observed increase in precipitation times.

## Introduction

It is well known that one of the major applications for the use of prodrugs is to improve the solubility of poorly water-soluble drugs (Bundgaard and Johansen, 1980; Varia, 1984a) to allow for parenteral intravenous formulations of the parent drug (Boucher et al., 1989). However, a complicating factor in more concentrated aqueous solutions of poorly water-soluble drugs, is the limited extent to which degradation may occur before the solution becomes saturated with respect to the relatively insoluble parent drug, with the resulting formation of a precipitate which obviously will have an effect on the shelf-life of such a product.

The shelf-lives of formulations of prodrug with high concentrations can be further reduced by the low solubility of the parent drug which is one of the major degradation products (Anderson et al., 1985). One such example is methylpred-

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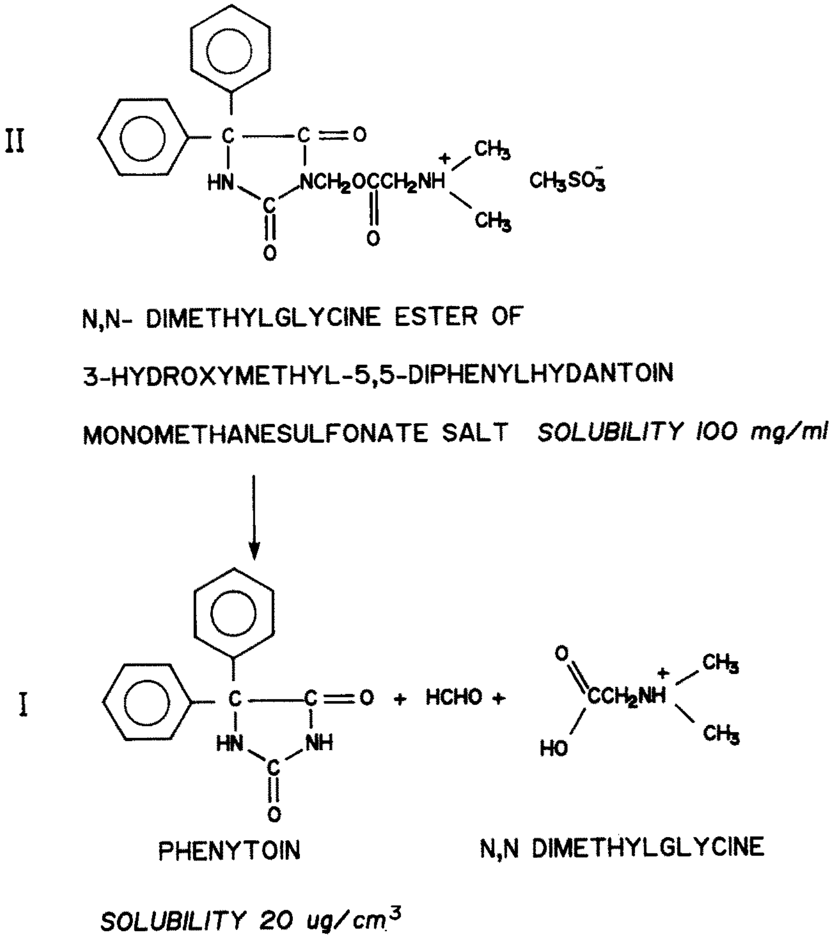


Scheme 1. The degradation reaction of the prodrug(II) showing the formation of phenytoin(I), formaldehyde and *N*,*N*-dimethylglycine.

nisolone. The aqueous solubility of methylprednisolone is 0.09 mg $cm^{-3}$ (Amin and Bryan, 1973). Only 0.1% hydrolysis in a prodrug formulation containing the equivalent of 100 mg $cm^{-3}$ of methylprednisolone might lead to a solution supersaturated in methylprednisolone with possible precipitation. It is thus important for successful formulations of prodrugs of poorly water-soluble drugs to be able to solubilize the insoluble degradation prodrugs. It was found, for example, that the 21-hemiesters of methylprednisoline self-associate in water to form micelles (Anderson et al., 1985). The presence of micelles in these systems stabilized the ester toward hydrolysis and caused solubilization of free methylprednisolone with resultant precipitation times of such solutions. These increased precipitation times obviously may result in increased shelf-lives for such formulations.

In a study on the development of water-soluble prodrugs of the poorly water-soluble drug phenytoin, it was observed that precipitation times of aqueous solutions of these prodrugs were much longer than those times predicted from dilute solution kinetics of the prodrug and the intrinsic solubility of the parent compound (Varia et al., 1984b). Using first-order kinetics, a theoretical precipitation time of only 4 min was calculated for aqueous solutions of the prodrug at the therapeutic concentration, namely 50 mg $cm^{-3}$ (sodium phenytoin equivalents). An observed precipitation time of 12.95 h was recorded, showing a nearly 200-fold increase in precipitation time. Thus, the shelf-life of such formulations was unexpectedly markedly increased. The same phenomenon was reported for prodrugs of the poorly water-soluble drug methylprednisolone (Anderson et al., 1985).

Changed solubility and kinetics were reasoned to be probably the two factors mainly responsible for the observed increase in precipitation times of aqueous solutions of the prodrug of phenytoin.

A possible decrease in the rate of hydrolysis of the prodrug, with a resultant increase of the precipitation times of aqueous prodrug solutions, was investigated. On the other hand, an increase in solubility of phenytoin in the presence of its prodrug could also result in increased precipitation times of aqueous prodrug solutions.

The objective of the study, therefore, was to establish the degree of increase in precipitation times and to investigate the factors responsible for the increase in observed precipitation times. Hence, the factors involved could be used to formulate aqueous solutions of prodrugs of poorly water-soluble drugs with prolonged shelf-life properties. Further, it was decided to determine whether and to what extent the solubility of phenytoin was influenced by the presence of its prodrug, as well as to investigate the influence of initial prodrug concentrations on the rate of hydrolysis of the prodrug. With this purpose in mind, phenytoin (**I**) (Scheme 1) and one of its prodrugs, 3-(*N*,*N*-dimethylglycyloxymethyl)-5,5-diphenylhydantoin methane sulphonate (DDMS) (**II**), were chosen as model compounds.

## Materials and Methods

### *Materials*

Unless otherwise mentioned, all reagents and solvents used were analytical grade. The analytical method developed by Muller and Stella (1987) was used. The water used in the precipitation time study was deionized ($< 0.2\ \Omega^{-1}$ conductance) and distilled from an all-glass still. All glassware used in these studies was thoroughly rinsed with deionized water and dried.

### *Determination of the precipitation time profile as a function of the initial prodrug concentration*

To confirm the increase in observed precipitation times of aqueous solutions of prodrug seen by Varia et al. (1984b), an experiment was carried out to determine the precipitation time as a function of the following prodrug concentrations (0.5, 1.0, 2.5, 5.0, 10.0, 20.0, 40.0 and 50.0 mg $\mathrm{cm}^{-3}$), all expressed as sodium phenytoin equivalents. The various prodrug solutions were prepared using double-distilled particle-free water (Barnstead Nanopure Apparatus). Each solution was filtered (13 mm, 0.45 $\mu$m Metricel$^{R}$ membrane filter, Gelman Sciences Inc., Ann Arbor, MI) into 1 cm quartz cells after saturation of each filter. Each cell was fitted with a small stirring bar preventing accumulation of precipitates on the bottom of the cells, escaping detection. A precipitation time was taken as that time it took each sample from constitution with water, until the first absorbance (Perkin Elmer 555 Spectrophotometer, P.E. Corp., Norwalk, CT) was recorded at 350 nm.

The cells were kept at a constant temperature of 25 °C by means of a temperature regulator fitted to the spectrophotometer.

### *Solubility study*

Phase-solubility experiments (Higuchi and Connors, 1965), were conducted to determine whether the solubility of phenytoin was influenced by the presence of its prodrug. Phenytoin well in excess of its aqueous solubility (10 mg $\mathrm{cm}^{-3}$) was added to varied concentrations (0.5, 1.0, 2.5, 5.0, 10.0, 20.0, 40.0 and 50.0 mg $\mathrm{cm}^{-3}$) of prodrug in water. These solutions were spun in a rotating water bath at $25.0 \pm 0.1$ °C. Assuming pseudo-equilibrium conditions because of the instability of the prodrug in solution, the solutions were filtered after only 24 h. An aliquot of each filtrate was separated and analyzed using the method as described.

The prodrug was synthesized by the method reported by Varia et al. (1984a) while the purity was determined with differential scanning calorimetry (DSC, Perkin Elmer Corp., Norwalk,

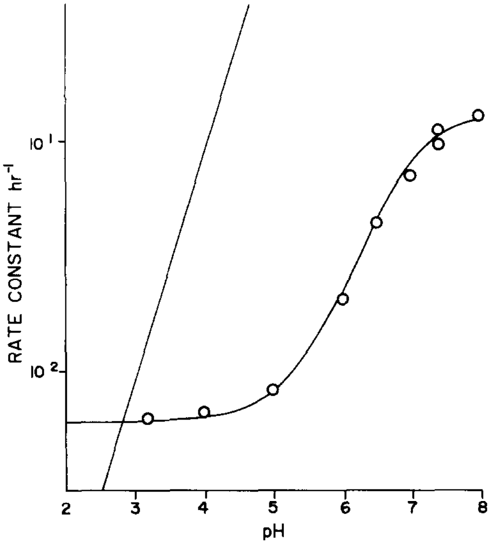


Fig. 1. The pH-rate profile of the prodrug (o——o) as well as of *N*-hydroxymethylphenytoin (Varia et al., 1984b).

CT) and HPLC. The amount of phenytoin contamination present in the prodrug was determined by HPLC (Altex Model 110A pump and a Waters Associates Model 450 Variable Wavelength Detector).

*Kinetic study*

All kinetic studies were carried out at a constant temperature maintained by a circulating water bath (Forma Scientific 2095 Bath and Circulator, Marietta, OH). The kinetics of the hydrolysis of the prodrug as a function of the initial prodrug concentration were studied by the initial rate method.

The rate of formation of phenytoin at 25 ± 0.1 °C and water as solvent was followed without controlling the pH and the ionic strength. Since the pH values of solutions of prodrug in water were in the plateau region of maximum stability, according to the pH-rate profile (Varia et al., 1984b) (Fig. 1), and dropped even further during hydrolysis (Table 1) due to the formation of *N*,*N*-dimethylglycine and to exclude possible buffer catalysis, the pH was not controlled.

Addition of salts of prodrug in water can alter the salt form of the prodrug, changing its characteristics. Addition of salts can also change the characteristics of associative or micellar species in solution and therefore may influence the kinetics of such species. The ionic strength was thus not controlled during this study.

TABLE 1

*The acidity of prodrug solutions ($N = 3$) in water as a function of concentration*

| Initial prodrug concentration (mg/cm$^3$) | pH | Mean $N \pm \%$ coefficient of variation |
|---|---|---|
| 0.5 | 4.70; 4.50; 4.96 | 4.72 ± 4.87 |
| 1.0 | 4.30; 4.29; 4.73 | 4.45 ± 5.39 |
| 2.5 | 4.20; 4.10; 4.33 | 4.21 ± 2.72 |
| 5.0 | 3.70; 3.75; 3.80 | 4.04 ± 0.99 |
| 10.0 | 3.70; 3.75; 3.80 | 3.75 ± 1.06 |
| 20.0 | 3.44; 3.41; 3.47 | 3.44 ± 0.87 |
| 40.0 | 3.15; 3.15; 3.22 | 3.17 ± 1.26 |
| 50.0 | 2.90; 2.84; 2.89 | 2.87 ± 1.05 |

Aliquots (20 μl or less when concentrated) of the various prodrug solutions in water were taken at certain intervals, separated and analyzed using the methods as described.

## Results and Discussion

*Altered precipitation time*

From the results shown in Fig. 2 a significant difference was found between the theoretical and observed precipitation times for different concentrations of the prodrug. The theoretical precipita-

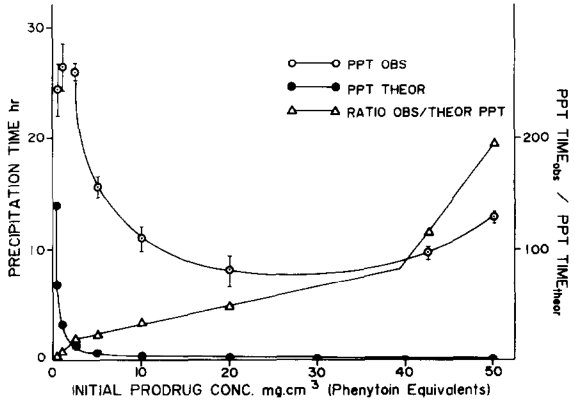


Fig. 2. The observed (o——o) and the theoretical (●——●) precipitation time (hours) found and calculated, respectively, as a function of the initial precipitation time (mg cm$^{-3}$).

tion time for the prodrug at the therapeutic concentration (50.0 mg cm$^{-3}$ phenytoin equivalents), for example, was found to increase from 0.067 to 12.95 h. This is a 194-fold increase in the observed precipitation time from the theoretical precipitation time.

Another interesting feature of the observed precipitation time curve is the unexpected initial increase in precipitation time at prodrug concentrations of 0.5 and 1.0 mg cm$^{-3}$. This increase is followed by a relatively sharp drop in the curve at the prodrug concentration range from 2.5–20.0 mg cm$^{-3}$, while the curve shows an increase in precipitation times at prodrug concentrations higher than 20.0 mg cm$^{-3}$. This apparently abnormal behaviour of aqueous prodrug solutions with respect to their precipitation times can possibly be attributed to the formation of various associative species of the prodrug, the formation of which is concentration dependent.

Another significant curve is obtained when the ratio of the experimental and theoretical precipitation times is plotted as a function of the initial prodrug concentration. This curve shows at least two and probably three linear regions. These linear regions, spanning the following prodrug concentrations from 0 to 2.5; 2.5 to 30.0–40.0 and from 30.0–40.0 to 50.0 mg cm$^{-3}$, can be an indication of the existence of at least two and possibly three associated prodrug species present in solution. A third linear region may be doubtful, since just two values were available to obtain the linear line at high prodrug concentrations.

Changes taking place in both the solubilization capacity of the prodrug solutions and the rate of prodrug degradation occurring at the same time, are responsible for the observed precipitation time curve.

### *Kinetics*

The curve obtained (Fig. 3) where the rate of phenytoin formation ($\mu$g cm$^{-3}$ min$^{-1}$) was plotted as a function of the initial prodrug concentration ($\mu$g cm$^{-3}$) in phenytoin equivalents, shows three distinct regions in the concentration range studied. The slope of the linear region at low prodrug concentrations (0–5.0 mg cm$^{-3}$), being an indication of the rate of prodrug hydrolysis, compares excellently with the rate of hydrolysis obtained by Varia et al. (1984a), which is an indication of the accuracy of the values obtained. Extrapolation of this line to higher prodrug concentration, gives a line which represents the rate of hydrolysis at higher prodrug concentrations, should the concentration of the prodrug have no influence on the rate of hydrolysis. The rate constant obtained from the slope of this line is $3 \times 10^{-3}$ min$^{-1}$.

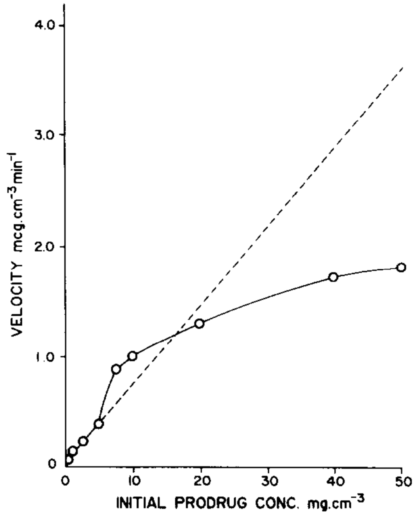
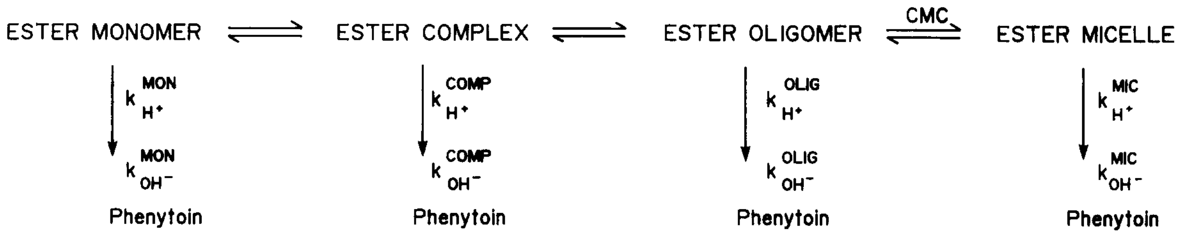


Fig. 3. The rate of hydrolysis of the prodrug in water at 25 °C ($\mu$g cm$^{-3}$ min$^{-1}$) as a function of the initial prodrug concentration (mg cm$^{-3}$).

The second region observed was within the concentration range 5.0–18.0 mg cm$^{-3}$, where the rate of hydrolysis was higher than the rate represented by the extrapolated line. This apparent increase in rate of hydrolysis over the small concentration range observed can be attributed to either a change in pH or the ionic strength which was not controlled as was previously described.

Since the pH values of the various prodrug solutions (Table 1) were in the plateau area of maximum stability for the prodrug (Fig. 1), a small change in pH thus should not have a major influence on the $k_{(\mathrm{obs})}$. The pH values of the various aqueous prodrug solutions dropped even further as is shown by Table 1, during the degradation reaction toward the plateau of maximum stability at pH 4 to 2. Thus, the probability that



Scheme 2. A model to rationalize the kinetic data.

pH plays a major role in causing an alteration in $k_{(obs)}$ seems small.

The ionic strength is an important factor to consider as the prodrug may self-associate in water. The ionic strength for a 0.5 mg $cm^{-3}$ prodrug solution is 0.00198 M while that for the 50 mg $cm^{-3}$ prodrug solution is 0.2006 M. One should expect a decrease in the rate of hydrolysis of the prodrug at higher ionic strengths, because the formation of associative species will be enhanced in aqueous solutions with higher ionic strength. In such species the ester bond may be less available for hydrolysis with a resultant decrease in rate of hydrolysis.

In an effort to verify the validity of this hypothesis, a hydrolysis experiment was performed in which the ionic strength and the pH were controlled. The rates of hydrolysis of prodrug solutions of three different concentrations (5.0, 10.0 and 50.0 mg $cm^{-3}$) were determined at constant ionic strength (0.5 M with KCl) and at a constant pH of 2.5.

At a constant ionic strength an increase in the rate of hydrolysis was observed, compared to the rate of hydrolysis observed without addition of KCl. This result is unexpected, but proves that the decrease in hydrolysis rate found at higher prodrug concentrations, if the ionic strength was not regulated, was not due to the increase in ionic strength from 0.00198 M for 0.5 mg $cm^{-3}$ to 0.2006 M for the 50 mg $cm^{-3}$ prodrug concentration, but may explain the apparent increase in the rate of hydrolysis over the 5.0 to 18.0 mg $cm^{-3}$ concentration range.

Another factor which may cause an increase in the rate of hydrolysis in the 5.0–18.0 mg $cm^{-3}$ concentration range, is the possibility of self-association of the prodrug in aqueous media. It may be possible that because of a certain molecular arrangement at these concentrations, the position of the ester bond will be such that attack of $H^+$ or $OH^-$ or of water molecules may be facilitated.

The decreased precipitation time is probably because in this concentration range, phenytoin solubilization is independent of prodrug concentration (Fig. 4). Therefore, since the rate of phenytoin formation is dependent on the initial prodrug concentration (Fig. 3), a sharp decrease in precipitation time is observed.

The third region to be distinguished in Fig. 3 is over the prodrug concentration range of 20–50.0 mg $cm^{-3}$. In this region the rate of hydrolysis is slower than expected. As the concentration of prodrug increases the difference between $k_{(obs)}$ and the expected rate of hydrolysis increases. At the 50.0 mg $cm^{-3}$ prodrug concentration a $k_{(obs)}$ of 1.80 $\mu g\ cm^{-3}\ min^{-1}$ was found, while a $k_{(obs)}$ of 3.61 $\mu g\ cm^{-3}\ min^{-1}$ was expected. A 50%

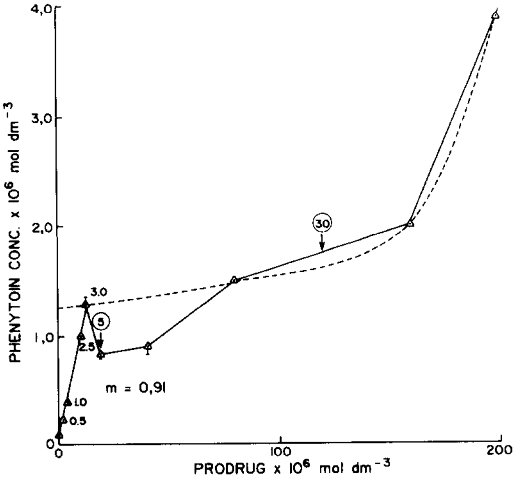


Fig. 4. The solubility of phenytoin (mol $dm^{-3}$) as a function of the initial prodrug concentration (mol $dm^{-3}$).

reduction in rate of hydrolysis was recorded, resulting in a slower production of insoluble phenytoin which probably significantly contributes to the increase in precipitation time.

### *Kinetic model*

All the different species may undergo specific acid- and specific base-catalyzed hydrolysis where $k_{\text{mon}}^{+}$ and $k_{\text{mon}}^{-}$ (Scheme 2) represent the second-order rate constants for acid- and base-catalyzed hydrolysis of monomers, and $k_{\text{comp}}^{+}$ and $k_{\text{comp}}^{-}$ the corresponding rate constants for hydrolysis of the ester in the complex form. The same assumptions can be made for the corresponding rate constants for hydrolysis of the prodrug ester in the associative and micellar species.

It will be extremely difficult to develop an equation for the absolute hydrolysis rates in relation to total prodrug concentration $C_T$ as the various associative species and their rate constants for hydrolysis are constantly changing. The rate constants for neutral catalysis in the various species have been ignored in the model, hence oversimplifying it. While these issues are of interest, they did not fall in the scope of the present study.

In accordance with predictions based on electrostatic data, $OH^-$-catalyzed reactions occurring in the Stern layer of micelles (assuming that micelles are involved) are generally accelerated by cationic micelles and inhibited by anionic micelles and vice versa for the hydrogen ion catalyzed reactions (Cordes, 1973; Fendler and Fendler, 1975). The ester linkage in the prodrug compound, being located quite far from the charged substituent and nearer to the center of the molecule, may undergo hydrolysis in the interior of the micelle rather than in the Stern layer. Thus, both acid- and base-catalyzed hydrolysis may be retarded in micelles.

It is probable that, structurally, phenytoin ester micelles are quite different from the classical spherical micelles formed by highly flexible surfactants and even for typical surfactants, the classical 'oil-drop' micelle model is no longer considered adequate (Shinoda, 1978; Mukerjee, 1979). The magnitude of enhancement or inhibition of acid- and base-catalyzed hydrolysis rates in such micelles may be highly sensitive to the location and average orientation of the reactive bond in the micelle as well as the accessibility of this region to hydrophilic species of varying size and charge.

### *Solubility*

The results of this experiment (Fig. 4) show a definite increase in the solubility of phenytoin in the presence of increasing concentrations of prodrug over the entire prodrug concentration range studied. Phenytoin is solubilized even at the lower concentrations of the prodrug. From Fig. 4, two main regions of solubilization can be distinguished over the concentration range studied. The first of these regions shows an initial apparent linear relationship between the initial prodrug concentration present in solution and the concentration of phenytoin solubilized by the system. This linear region (0–3 mg $\text{cm}^{-3}$ concentration) is followed by a plateau region (3–10 mg $\text{cm}^{-3}$) where no dramatic increase in the concentration of phenytoin is experienced with increase in prodrug concentration. The 5.0 and 10.0 mg $\text{cm}^{-3}$ concentrations are indicated in circles in Fig. 4. The results obtained can probably be explained by complexation between phenytoin and its prodrug. The slope of the linear region ($m = 0.91$) suggests that 1 mol of phenytoin needs 9 mol of prodrug to be solubilised.

The plateau region suggests a region of maximum solubility of the complex formed and is followed by a region of increased phenytoin solubility with increase in prodrug concentration. The increase in solubility of phenytoin because of complexation is about 5-fold if the plateau region is considered to be the maximum solubility of the complex. The spike observed is probably because of supersaturation phenomena. The 5-fold increase in solubility observed is fairly consistent with literature where increases in solubility found with complexation mostly range from 5 to 10-fold. Whether this increase is due to simple complexation or solubilization of phenytoin by prodrug aggregates is difficult to say.

At prodrug concentrations higher than 10 mg $\text{cm}^{-3}$ processes other than complexation cause solubilization of phenytoin. At these prodrug concentrations molecular aggregates of prodrugs are probably formed which are able to include phenytoin, and which cause phenytoin to show a higher apparent solubility. At prodrug concentrations higher than around 30 mg $cm^{-3}$ the solubility of phenytoin increases dramatically. The cause for this dramatic increase is probably due to the formation of micelles or higher aggregates, which enable them to include more of the hydrophobic phenytoin molecules into the hydrophobic interior of the micelles.

Micelle or higher aggregate formation is often viewed as a process similar to phase separation. The solubilization of phenytoin in micelles or higher aggregates of the prodrug can be visualized as a partition phenomenon above the critical micelle concentration (CMC) (Attwood and Udeala, 1975) or phase change. The solubility of phenytoin in such micellar systems can be expressed by the following equation:

$$\text{Solubility} = C_s + K[C_s] \cdot [C_t\text{-CMC}]$$

where $C_s$ is the saturation solubility of phenytoin in water, $C_t$-CMC is the amount of prodrug present in micelles, and $K$ is a constant proportional to the partition coefficient of phenytoin from water into the micellar pseudophase. This equation predicts that the solubility of phenytoin should be linearly related to the total ester concentration above the CMC.

In Fig. 4 which represents the solubility of phenytoin vs the concentration of the prodrug no distinct CMC is evident, while the plots show no linear parts above the apparent CMC, indicating the probable existence of several associative species in solution. Each of these species probably has a varying capacity to solubilize phenytoin. The steep increase in apparent solubility toward the 50.0 mg $cm^{-3}$ prodrug concentration is an indication of the formation of higher aggregate species which probably have a higher capacity to solubilize phenytoin.

At the 50.0 mg $cm^{-3}$ prodrug concentration, the apparent solubility increase of phenytoin is about 45-fold, from 20 to 900 $\mu$g $cm^{-3}$. It is thus obvious that precipitation times for aqueous solutions of prodrugs will be increased due to solubilization of the insoluble entity.

## Conclusion

As was qualitatively observed by Varia et al. (1984a), the observed precipitation times were much higher (nearly 200-fold) compared to the theoretical precipitation times probably because of mainly two factors.

The first of the factors probably is a decrease in the rate of hydrolysis which causes less phenytoin to be formed per time unit, which may prevent precipitation.

The second factor is solubilization of phenytoin by the prodrug. If the solubility of phenytoin is increased by some mechanism in the presence of prodrug, precipitation will be prevented which will obviously increase the precipitation times of the prodrug solutions.

The results obtained confirm the observations made by Varia et al. (1984a) and Anderson et al. (1985), who both demonstrated increased observed precipitation times of hydrocortisone and phenytoin, respectively.

A reduction of 50% in the rate of hydrolysis was observed at higher prodrug concentrations, which accounts for a significant increase in the observed increase in precipitation time at the therapeutic concentration. The reduction in hydrolysis observed is probably due to the self-association of the prodrug molecules in aqueous media, and thus it can be postulated that the ester bonds are positioned in the associated species in such a way that hydrolysis is enhanced or reduced depending on the self-associative species formed at a given concentration.

The prodrug of phenytoin apparently shows a different self-association pattern over the concentration range studied. Here, we probably have a stepwise formation of dimers, trimers etc., to oligomers with each species showing a different rate of hydrolysis. This probably explains why at some concentrations (5.0–20 mg $cm^{-3}$) acceleration, and at other prodrug concentrations (20–50 mg $cm^{-3}$), stabilization of the rate of hydrolysis was observed.

Solubilization of phenytoin and the decreased rate of formation of phenytoin in solution are most probably the two main factors responsible for the increase in precipitation times observed. These two factors can probably account for at least 75% of the observed increase in precipitation times in aqueous prodrug solutions. Other factors like supersaturation and cosolvent effects probably account for the other 25%. The kinetic, precipitation time, and phenytoin solubility curves all suggest the possibility of the prodrug forming various aggregate species in aqueous solution.

## References

Amin, M.I. and Bryan, J.T., Kinetics and factors affecting the stability of methylprednisolone in aqueous formulation. *J. Pharm. Sci.*, 62 (1973) 1768–1771.

Anderson, B.D., Conradi, R.A., Knuth, K.E. and Nail, S.L. Strategies in the design of solution stable water soluble prodrugs. II. Properties of micellar prodrugs of methylprednisolone. *J. Pharm. Sci.*, 74 (1985) 375–381.

Attwood, D. and Udeala, O.K., Aggregation of antihistamines in aqueous solution. The effect of electrolyte on the micellar properties of some diphenylmethane derivatives. *J. Pharm. Pharmacol.*, 27 (1975) 754–759.

Boucher, A.B., Bombassaro, A.M., Rasmussen, S.N., Watridge, C.B., Achari, R. and Turlapaty, P., Phenytoin prodrug 3-phosphoryloxymethyl phenytoin (ACC-9653): pharmacokinetics in patients following intravenous and intramuscular administration. *J. Pharm. Sci.*, 78 (1989) 929–932.

Bundgaard, H. and Johansen, M., Prodrugs as drug delivery systems. VIII. Bioreversible derivatization of hydantoins by *N*-hydroxymethylation. *Int. J. Pharm.*, 5 (1980) 67–77.

Cordes, E.H., *American Chemical Society, Symposium on Reaction Kinetics in Micelles*, New York, 1972, Plenum, New York, pp. 157–172.

Fendler, J.H. and Fendler, E.J., *Catalysis in Micellar and Macromolecular Systems*. Academic Press, New York, 1975, pp. 545–559.

Higuchi, T. and Connors, K.A., Phase-solubility techniques. *Adv. Anal. Chem. Instrum.*, 4 (1965) 117–125.

Mukerjee, P., Solubilization in aqueous micellar systems, In Mittal, K.L., ed. *Solution Chemistry of surfactants*, Plenum, New York, 1979, pp. 153–165.

Muller, D.G. and Stella, V.J., An analytical method to determine small quantities of phenytoin in the presence of excess amounts of one of its prodrugs, the monomethane sulphonate salt of 3-(*N,N*-dimethylglycyloxymethyl)-5,5-diphenylhydantoin. *J. Pharm. Biomed. Anal.*, 5 (1987) 415–419.

Shinoda, K., *Principles of Solution and Solubility*, Dekker, New York, Ch. 9–10, pp. 157–199.

Varia, S.A., Schuller, S., Sloan, K.B. and Stella, V.J., Phenytoin prodrugs. III: Water soluble prodrugs for oral and for parenteral use. *J. Pharm. Sci.*, 73 (1984a) 1068–1073.

Varia, S.A., Schuller, S. and Stella, V.J., Phenytoin prodrugs. IV: Hydrolysis of various 3-(hydroxymethyl) phenytoin esters. *J. Pharm. Sci.*, 73 (1984b) 1074–1079.