Increased Shelf-Life of Fosphenytoin: Solubilization of a Degradant, Phenytoin, through Complexation with $(SBE)_{7m}$-β-CD

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Abstract □ Fosphenytoin, a water-soluble prodrug of phenytoin, degrades primarily to phenytoin at pH values <8 during long term storage; phenytoin readily precipitates when formed from fosphenytoin due to its limited aqueous solubility. The objective of this study was to develop stable formulations of fosphenytoin in the pH range of 7.4–8.0 by inhibiting the phenytoin precipitation through complexation with a parenterally safe cyclodextrin, $(SBE)_{7m}$-β-CD. Phase solubility studies at 25 °C revealed that phenytoin could be effectively solubilized by $(SBE)_{7m}$-β-CD both in the presence and absence of 80.6 mg/mL fosphenytoin (as its dihydrate). The binding constants for the phenytoin/cyclodextrin complex were found to be 1073 and 792 M^{-1} at pH 7.4 and pH 8.0, respectively. Because of the competitive inclusion between fosphenytoin and phenytoin with $(SBE)_{7m}$-β-CD, the extent of solubilization of phenytoin was lower, as expected, in the presence of fosphenytoin than in the absence of fosphenytoin, even though the binding constants for the fosphenytoin/cyclodextrin complex were relatively small (41–45 M^{-1}). Initial rates were used to follow the production of phenytoin from fosphenytoin. Zero-order kinetics were observed under all conditions investigated. Phenytoin production rates were followed at 25, 37, and 50 °C in the presence of 0.03 or 0.06 M $(SBE)_{7m}$-β-CD. It was projected from the solubility of phenytoin and the kinetic information that fosphenytoin shelf lives as high as nine years at 25 °C and pH 7.4 in the presence of 60 mM of $(SBE)_{7m}$-β-CD might be possible while longer shelf lives might be possible at pH 8.

Introduction

Fosphenytoin (Figure 1; 3-(hydroxymethyl)-5,5-diphenylhydantoin, phosphate ester, disodium salt) is a parenterally useful prodrug form of phenytoin recently approved by the FDA. Phenytoin is a sparingly water-soluble (20−25 μg/mL), weakly acidic (pK_a 8.3) drug.[1] The advantages of fosphenytoin over sodium phenytoin[2] have been recently documented.[1] Fosphenytoin has also been shown to be useful after intramuscular administration[3] and to avoid second peak phenomena after intravenous injection.[4]

Although the maximum stability of fosphenytoin appears to be around pH values of 7.5−8.0, the pH of the commercially available fosphenytoin injection is adjusted to values greater than 8.5. The principle chemical degradation products of fosphenytoin around physiological pH are phenytoin, formaldehyde, and inorganic phosphate[5,6] as well as some other minor products. On the other hand, at pH values greater than 8, various ring-opened degradants, such as 5,5-diphenyl-glycinamide, 5,5-diphenyl-4-imidazolidinone, and hydantoic acid species, are claimed.[7] These degradants are more water soluble than phenytoin. Therefore, to avoid phenytoin precipitation during the long-term storage, the pH of the commercial product of fosphenytoin is adjusted to these higher values despite greater intrinsic stability around pH range 8.0. However, at the higher pH values refrigeration storage is required. To develop a stable fosphenytoin injection around physiological pH with a shelf life of at least two years at 25 °C, it would be necessary to solubilize the poorly soluble degradant, phenytoin, to prevent possible precipitation from solution during long-term storage.

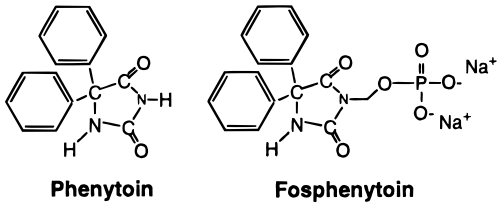

Figure 1—Chemical structures of phenytoin and fosphenytoin.

Cyclodextrins (CDs) have been reported to be effective for increasing the aqueous solubility, stability, and bioavailability of drugs.[8−10] In addition to natural CDs (α-, β-, and γ-CDs), various types of modified CDs have been developed to improve on the physical, chemical, and safety properties of the natural CDs. A sulfobutyl ether derivative with and average degree of substitution of seven, sodium salt, termed $(SBE)_{7m}$-β-CD or Captisol (Figure 2) is an anionically charged cyclodextrin with greater solubility in water than the parent material, β-cyclodextrin. Recently it was reported that $(SBE)_{7m}$-β-CD could increase aqueous solubility of various neutral and charged drugs and has been shown to have greater safety after parenteral administration.[11−14]

The objective of this work, therefore, was to examine the possibility of developing a stable formulation of fosphenytoin at or near physiological pH, 7.4 or 8.0, by using $(SBE)_{7m}$-β-CD to solubilize phenytoin produced from the degradation of fosphenytoin. The concept is illustrated in Scheme 1. Phase solubility analysis was used to determine the amount of $(SBE)_{7m}$-β-CD necessary to solubilize phenytoin in the presence of fosphenytoin. Initial rate, accelerated temperature studies, as well as studies at 25 °C were then used to project shelf lives under a variety of conditions.

Experimental Section

Materials—Fosphenytoin, isolated as its dihydrate, was synthesized according to the method developed by Varia et al.[15] The final material, as a 80.6 mg/mL aqueous solution contained about

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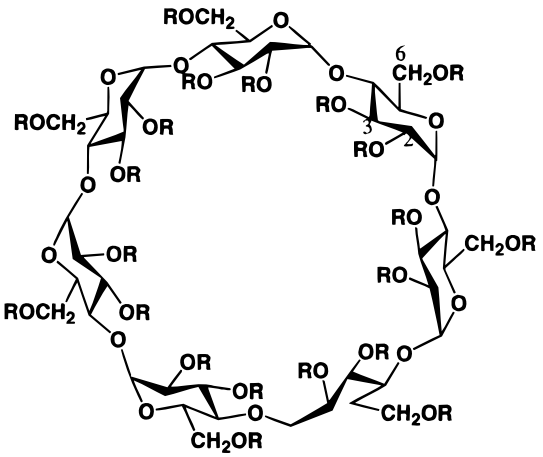
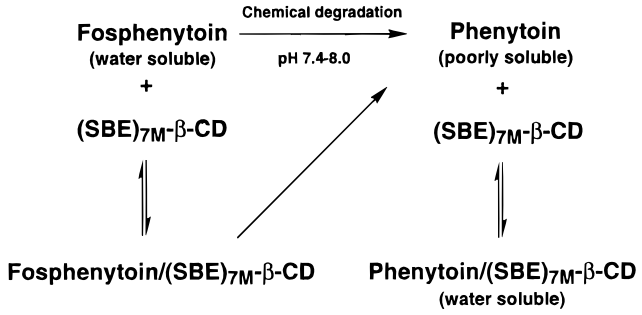


Figure 2—Chemical structure of $(SBE)_{7m}$-β-CD.



Scheme 1

20 μg/mL of phenytoin as an impurity. The synthesis and characterization procedures for $(SBE)_{7m}$-β-CD have been described elsewhere.[16,17] HPLC grade methanol was obtained from Fisher Scientific (Pittsburgh, PA). Tris(hydroxymethyl)aminomethane HCl (Trizma hydrochloride, Sigma Chemical Co., St. Louis, MO) and tris(hydroxymethyl)aminomethane (Trizma base, Sigma Chemical Co.) were used for preparation of Tris buffer solutions. All other chemicals were reagent grade. All glassware was washed with purified water and 70% (w/v) ethanol, followed by drying at 90 °C for at least 24 h before use. Double distilled water was used throughout.

Phenytoin Analysis—Reversed-phase HPLC analysis of phenytoin was carried out using a Shimadzu 6A-HPLC pump (Shimadzu Corp., Kyoto, Japan), a Shimadzu SPD-6A UV detector (Shimadzu Corp.), a Shimadzu CR601 integrator (Shimadzu Corp.), and a Rheodyne injector (Rheodyne, Berkeley, CA) fitted with a 20 μL loop. A reversed phase column (150 × 4 mm, Phenyl Hypersil, 5 μm particle size) was used for the analysis at 50 °C, and phenytoin was quantitated at UV 254 nm. The mobile phase consisted of 35% (v/v) methanol and 65% (v/v) of aqueous potassium phosphate monobasic solution (25 mM) adjusted to pH 3.8 with phosphoric acid. When the flow rate was 1.1 mL/min, the retention times of fosphenytoin and phenytoin were 4 and 11 min, respectively.

Chemical Stability Studies—The chemical stability of fosphenytoin was investigated in 0.02 M tris buffer solutions at pH values of 7.4 and 8.0. Fosphenytoin concentration (as its dihydrate) was 80.6 mg/mL. This is equivalent to 75 mg/mL anhydrous fosphenytoin and on a mole basis, equivalent to 50 mg/mL sodium phenytoin. At pH 7.4, reactions were run in the presence of 0 and 60 mM $(SBE)_{7m}$-β-CD, while at pH 8.0, reactions were run in the presence of 0, 30, and 60 mM $(SBE)_{7m}$-β-CD. The solutions were filtered through a 0.2 μm membrane filter (Disposal Sterile Syringe Filter, cellulose acetate membrane, 25 mm, Corning Glass Works, NY) before filling into 1 mL glass ampules (prescored funnel top ampule, Fisher Scientific, Pittsburgh, PA) to remove fine particulate matter and for sterility purposes. The ampules were stored in a temperature-controlled water bath at 25 °C or ovens at 37, 50, and 60 °C and periodically removed and analyzed for phenytoin content. Sampling times were adjusted according to expected reactivities at differing temperatures. The concentration of phenytoin in ampules versus time was quantitated to determine the initial rates of phenytoin production. In all cases, phenytoin production followed apparent zero-order kinetics with linear correlation coefficients of >0.99. Over the time range studied, the loss of fosphenytoin was negligible. Another earlier eluting peak was also quantitated and compared to phenytoin production, results not presented here. At pH 8.0, this peak had a HPLC peak area comparable to that of phenytoin while at pH 7.4 phenytoin was the major degradant peak observed. All results are presented as the average of duplicate runs.

Phase Solubility Studies—Excess phenytoin solid was added to 1 mL of Tris buffer solutions in the presence (80.6 mg/mL) or absence of fosphenytoin dihydrate as a function of various amounts of $(SBE)_{7m}$-β-CD (0.00−0.08 M). After sonication and mixing by a vortex mixer, the phenytoin-suspended solutions were placed in a shaking, temperature-controlled water bath for at least 5 days at 25 °C. After equilibration, checked by periodic sampling, the suspensions were filtered through a membrane filter (Acrodisc, PVDF 0.2 μm, Gelman). The filtrate was isolated and diluted with HPLC mobile phase, and the concentration of phenytoin was determined by HPLC. This work was performed in duplicate.

Results and Discussion

Phenytoin Solubility in the Presence of Fosphenytoin—To predict the time when phenytoin could precipitate from fosphenytoin samples, phenytoin solubility was measured in the absence and presence of fosphenytoin at 25 °C. The fosphenytoin concentration of 80.6 mg/mL (75 mg/mL anhydrous fosphenytoin) was the same as the commercial product. The solubility of phenytoin was 18.1 μg/mL in the absence of fosphenytoin, and 49.8 μg/mL in the presence of fosphenytoin at a pH 7.4. At pH 8.0, the solubility of phenytoin was 27.5 μg/mL in the absence of fosphenytoin, and 61.9 μg/mL in the presence of fosphenytoin. The slightly higher solubilities at pH 8.0 relate well to the pK_a value of 8.06−8.33 for phenytoin.[18] The solubility of phenytoin is elevated in the presence of fosphenytoin probably through micellar solubilization or complex formation.[19,20] The possibility that fosphenytoin may form associative species was not addressed in this paper.

Phase Solubility Studies—Phenytoin was found to interact with β-CD.[21] Figure 3 shows the phase solubility diagrams for phenytoin with $(SBE)_{7m}$-β-CD at 25 °C in the presence or absence of 80.6 mg/mL of fosphenytoin in 0.02 M Tris buffer solution at pH values 7.4 (Figure 3a) and 8.0 (Figure 3b), respectively. All phase solubility diagrams are A_L-type, according to the classification of Higuchi et al.,[22] suggesting 1:1 phenytoin /$(SBE)_{7m}$-β-CD complex formation at both pH values. No evidence in this or other studies supported the presence of higher order complexes although A_L-type diagrams only confirm that the interaction is first order with respect to ligand. Since fosphenytoin can compete with phenytoin for $(SBE)_{7m}$-β-CD binding, the solubility enhancement in the presence of fosphenytoin, as expected, was lower than that in the absence of fosphenytoin.

This phenomena is illustrated in Scheme 2. The binding constant for the phenytoin/$(SBE)_{7m}$-β-CD complex, K_1, can be calculated by the slope and intercept of the data from Figure 3 (absence of fosphenytoin) according to eq 1.[22]

$$K_1 = \text{slope}/\text{intercept}/(1 - \text{slope}) \qquad (1)$$

K_2, the binding constant for the fosphenytoin/$(SBE)_{7m}$-β-CD complex, can be calculated according from eqs 2 and

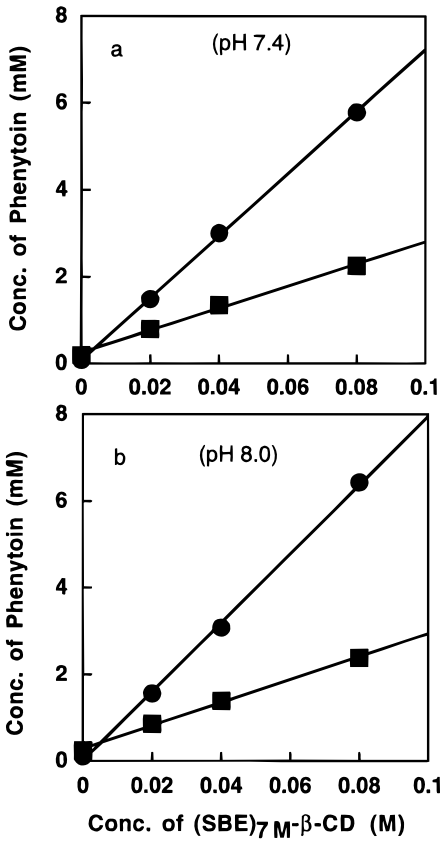
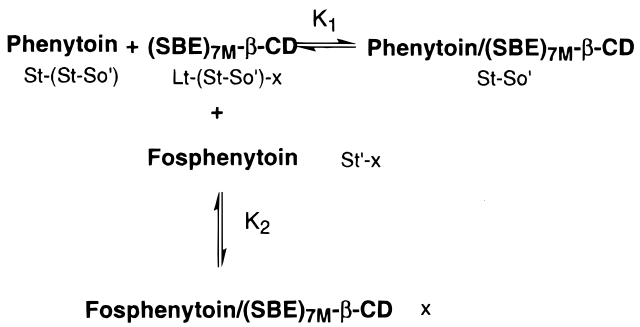


Figure 3—Phase solubility diagram for phenytoin in the presence of increasing $(SBE)_{7m}$-β-CD concentration pH 7.4 and pH 8.0 in the absence (●) or presence (■) of 80.6 mg/mL fosphenytoin (as its dihydrate).



St = Total phenytoin concentration in the presence of fosphenytoin and $(SBE)_{7M}$-β-CD
So' = Phenytoin solubility in the presence of fosphenytoin
St' = Total fosphenytoin concentration
Lt = Total $(SBE)_{7M}$-β-CD concentration
x = Concentration of fosphenytoin/$(SBE)_{7M}$-β-CD complex
K_1 = Binding constant for the phenytoin/$(SBE)_{7M}$-β-CD complex
K_2 = Binding constant for the fosphenytoin/$(SBE)_{7M}$-β-CD complex

Scheme 2

3 as follows:

$$K_1 = (St - So')/(St - (St - So'))/(Lt - (St - So') - x) \quad (2)$$

$$K_2 = x/(St' - x)/(Lt - (St - So') - x) \quad (3)$$

where the various terms are defined in Scheme 2. Since K_1 is easily calculated from the phase solubility diagram in the absence of fosphenytoin and the other terms in eq 2 are either known or are determined experimentally, x can be calculated for variations in Lt. Using the calculated values of x and substituting into eq 3 allows one to estimate K_2 for each Lt concentration. Some assumptions are made in performing this calculation. These include that So′ is constant and the same in the presence and absence of CD, tris buffer components do not interact with the CD, only 1:1 complexes are formed, and that the CDs do not disrupt any associative species.

Table 1—Binding Constants for Phenytoin and Fosphenytoin at 25 °C with $(SBE)_{7m}$-β-CD

	binding constant (M^{-1})	
	pH 7.4	pH 8.0
phenytoin/$(SBE)_{7m}$-β-CD (K_1)	1073	792
fosphenytoin/$(SBE)_{7m}$-β-CD (K_2)	45	41

Table 2—Phenytoin Production Rates in Different Formulations and at Various Temperatures of Fosphenytoin

		rate (μg/mL/day)		
pH	temp °C	0 mM CD	30 mM CD	60 mM CD
7.4	25	0.160	–	0.133
7.4	37	–	–	0.993
7.4	50	–	–	21.37
7.4	60	111.8	–	–
8.0	25	0.083	0.088	0.075
8.0	37	0.634	0.600	0.562
8.0	50	–	14.43	13.82
8.0	60	67.20	–	–

The estimated values of K_1 and K_2 at pH values 7.4 and 8.0 are listed in Table 1. The K_1 value at pH 8.0 was found to be smaller than at pH 7.4. An explanation for this observation is that a fraction of phenytoin at pH 8.0 is in its anionic form[18] (see earlier discussion), and anionically charged drugs interact weakly with $(SBE)_{7m}$-β-CD.[12] K_2 was found to be much smaller than K_1 at both pH levels, consistent with the dianionic nature of fosphenytoin at both pH values. Earlier work from this laboratory[12] showed weaker interaction of anionically charged drugs with $(SBE)_{7m}$-β-CD presumably due to Coulombic repulsion.

Phenytoin Production at pH Values 7.4 and 8.0—On the basis of solubility analysis, and initial projection of phenytoin production from a preliminary study at 60 °C (results included in Table 2) in the absence of $(SBE)_{7m}$-β-CD, 60 mM $(SBE)_{7m}$-β-CD was chosen as the desired CD concentration at pH 7.4 while 30 mM and 60 mM concentrations where chosen for pH 8.0. In hindsight, lower levels may have been possible but initial stability data obtained at 60 °C overestimated phenytoin production rates at lower temperatures.

Figures 4 shows typical plots of initial phenytoin production profiles versus time at 37 °C. At all temperature conditions investigated, phenytoin production followed similar pseudo zero-order kinetics; phenytoin is produced linearly at all temperatures and CD concentrations and at both pH values. Since the concentration of fosphenytoin (80.6 mg/mL as its dihydrate, 180 mM) is higher than that of $(SBE)_{7m}$-β-CD (0, 30 or 60 mM) and because the binding of fosphenytoin to $(SBE)_{7m}$-β-CD is weak (see Table 1), $(SBE)_{7m}$-β-CD appeared to only minimally influence the phenytoin production rate; there was a trend to greater stability with increasing $(SBE)_{7m}$-β-CD concentration, suggesting that fosphenytoin was more chemically stable at the complex compared to its free form. Apparent phenytoin production rates under all conditions investigated are summarized in Table 2.

Figure 5 shows Arrhenius plots for phenytoin production rate from fosphenytoin. The apparent energy of activation,

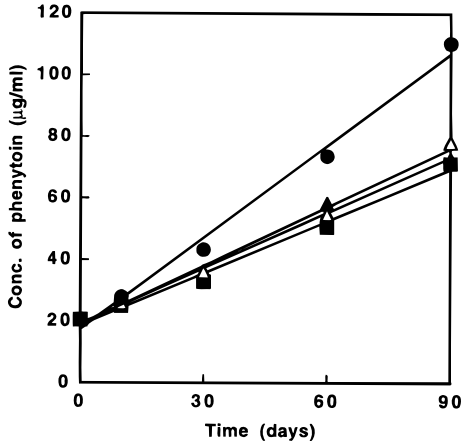


Figure 4—Production of phenytoin from the degradation of fosphenytoin at 37 °C in 0.02 M Tris buffer solution. Key: (●), pH 7.4/60 mM $(SBE)_{7m}$-β-CD; (△), pH 8.0/without $(SBE)_{7m}$-β-CD; (▲), pH 8.0/30 mM $(SBE)_{7m}$-β-CD; (■), pH 8.0/60 mM $(SBE)_{7m}$-β-CD.

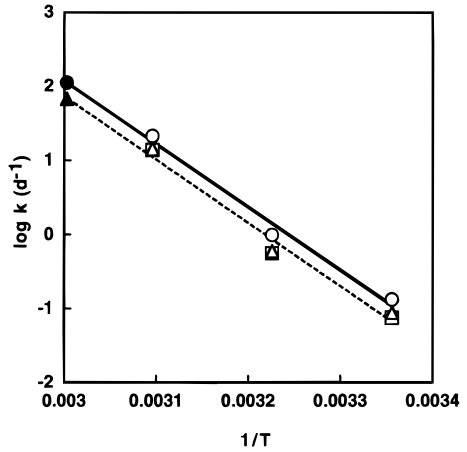


Figure 5—Arrhenius plots for phenytoin production rates from fosphenytoin degradation. Key: (○), pH 7.4/60 mM $(SBE)_{7m}$-β-CD; (△), pH 8.0/30 mM $(SBE)_{7m}$-β-CD; (□), pH 8.0/60 mM $(SBE)_{7m}$-β-CD; (●), pH 7.4/without $(SBE)_{7m}$-β-CD; (▲), pH 8.0/without $(SBE)_{7m}$-β-CD; —, regression line for pH 7.4; ----, regression line for pH 8.0.

E_a, values were found to be 38.9 kcal/mol for pH 7.4 and 39.5 kcal/mol for pH 8.0. These values are higher than those reported previously; 30.8 kcal/mol, and are also higher than E_a values reported from most other drug degradation studies (10−30 kcal/mol).[23] Possible explanations for the difference may include the effect of temperature on the pH of Tris buffer solutions. It was found that the pH of the Tris buffer solution used here dropped to pH 6.77 at 50 °C, even though the pH is adjusted at 7.40 at 25 °C. Consequently, the change of phenytoin production rate can attribute not only to the direct effect of temperature on the kinetics but also the effect of temperature on pH. The role that self-association of fosphenytoin may have on the kinetics may be an additional cause. Also, increased temperature would lower the association of fosphenytoin with $(SBE)_{7m}$-β-CD, and although there did not seem to be a large stabilizing effect of $(SBE)_{7m}$-β-CD, this effect would be superimposed on other contributions. Since our principle goal was to study the effect of temperature on the stability of some prototype formulations, buffer pH values were not adjusted at each temperature, and no attempt was made to correct for self-association and pH shifts, etc.

Table 3 lists projected shelf lives of fosphenytoin at 25 °C which can be calculated from the rate data in Table 2 and various limiting conditions listed in Table 3. Two different shelf life criteria were considered: time to exceed

Table 3—Projected Shelf Lives at 25 °C of Fosphenytoin Based on Phenytoin Production Rates and Solubility in the Presence and Absence of $(SBE)_{7m}$-β-CD

		solubility criteria		stability criteria	
pH	$(SBE)_{7m}$-β-CD concentration (nM)	phenytoin concn (μg/mL)	shelf life[a] (years)	phenytoin concn (μg/mL)	shelf life[b] (years)
7.4	0	49.8	0.9	–	–
7.4	60	450.8	9.3	230	4.7
8.0	0	61.9	2.0	–	–
8.0	30	274.4	8.5	230	7.2
8.0	60	475.5	17.4	230	8.4

[a] Time to exceed phenytoin solubility at the stated pH and concentration of added $(SBE)_{7m}$-β-CD. [b] Time to exceed the concentration of phenytoin equivalent to 0.5% production of phenytoin from 80.8 mg/mL fosphenytoin (as its dihydrate).

phenytoin solubility in the presence and absence of $(SBE)_{7m}$-β-CD and 0.5% phenytoin production. Since 80.6 mg/mL of fosphenytoin dihydrate is equivalent to 50 mg/mL of sodium phenytoin or 46 mg/mL of phenytoin, 0.5% phenytoin production corresponds to the productions of 230 μg/mL phenytoin from 80.6 mg/mL fosphenytoin. When 60 mM $(SBE)_{7m}$-β-CD was used, phenytoin should not precipitate for over two-years at 25 °C at either pH value; the most apparent stable formulation, which is a combination of pH 8.0 and 60 mM of $(SBE)_{7m}$-β-CD concentration, suggested that phenytoin precipitation should not occur for at least 17 years if maintained at 25 °C. Using the 0.5% phenytoin production as the shelf life cutoff criteria, greater than two year shelf lives was also possible. Obviously, the amount of $(SBE)_{7m}$-β-CD could be adjusted to meet other phenytoin production criteria. These results clearly indicate that physically stable formulations of greater than two years at 25 °C of fosphenytoin in the pH range 7.4−8.0 should be possible.

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