

Improved dissolution and bioavailability of phenytoin by sulfobutylether- β -cyclodextrin ((SBE) $_{7m}$ - β -CD) and hydroxypropyl- β -cyclodextrin (HP- β -CD) complexation

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Abstract

The inclusion complexation of phenytoin with charged and neutral water-soluble cyclodextrins (CDs), (SBE) $_{7m}$ - β -CD and HP- β -CD, was studied in order to improve the low aqueous solubility and incomplete oral bioavailability of phenytoin. Effects of CDs on the aqueous solubility of phenytoin were determined by phase-solubility method at pH 7.4 and 11.0. Solubility of phenytoin increased as a function of CD concentration, showing A_L type diagrams for both (SBE) $_{7m}$ - β -CD and HP- β -CD which indicate a formation of 1:1-complexes. Solid inclusion complexes of phenytoin with (SBE) $_{7m}$ - β -CD and HP- β -CD were prepared by freeze-drying. Dissolution rate of phenytoin was increased with inclusion complexes as well as with phenytoin/HP- β -CD physical mixture in vitro. Also the freeze-drying of phenytoin tended to enhance the dissolution of phenytoin in vitro. However, plain phenytoin (300.0 mg) pharmacokinetics after oral administration as a crystal form and as a freeze-dried form were comparable in dogs. CD-based formulations of phenytoin increased peak plasma concentration of phenytoin about 1.6-fold and bioavailability (AUC_{0–24 h}) of phenytoin about 2-fold compared to plain phenytoin. Oral pharmacokinetics were not statistically different among various CD formulations. This study indicates that increased bioavailability of phenytoin in the presence of CDs was due to an increased extent of drug dissolution. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Phenytoin; Cyclodextrins; Solubility; Dissolution; Bioavailability; Oral administration

1. Introduction

Phenytoin (weak acid, pK_a = 8.3) is a widely used anticonvulsant for the treatment of grand mal epileptic seizures. It has been pointed out to be a drug exhibiting slow rate of absorption (Jung

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et al., 1980) and large differences in bioavailability following oral administration to patients (Suzuki et al., 1970; Pentikäinen et al., 1975; Rambeck et al., 1977). These are probably due to the slow and incomplete dissolution of phenytoin due to its poor aqueous solubility. The poor aqueous solubility of phenytoin has been overcome by prodrugs (Varia and Stella, 1984a,b; Scriba and Lambert, 1997) and complexation of phenytoin with α -, β - and γ -cyclodextrin (Hsyu et al., 1984; Menard et al., 1988) and with β -cyclodextrin-epichlorohydrin polymer (Uekama et al., 1985). Phenytoin prodrugs have been developed for both oral and parenteral administration, and the phosphate ester of 3-hydroxymethylphenytoin is currently, as a parenteral dosage form, in clinical use in the US. The phenytoin prodrugs developed for oral administration have increased the oral bioavailability of phenytoin in animals (Varia and Stella, 1984a; Scriba and Lambert, 1997). In case of CD-complexation, epichlorohydrin polymer of β -CD has only been reported to increase the oral bioavailability of phenytoin in animals (Uekama et al., 1985).

Stella and Rajewski have concluded that the primary use of CDs in oral formulations is to increase bioavailability through increased rate and extent of drug dissolution (Rajewski and Stella, 1996; Stella and Rajewski, 1997). There are numerous reports showing that the aqueous solubility and dissolution rate of various compounds are significantly increased in vitro by cyclodextrin complexation (Uekama et al., 1985; Loftsson et al., 1991; Brewster et al., 1992a; Esclusa-Díaz et al., 1996; Ventura et al., 1997). In contrast, significantly less number of papers have been published to report the effect of CDs, especially water-soluble CD-derivatives, on oral absorption of various drugs in vivo. The reported studies have shown that water-soluble CD-derivatives are able to increase the oral bioavailability of various drugs (Betlach et al., 1993; Järvinen et al., 1995; Panini et al., 1995; Puglisi et al., 1995; Brewster et al., 1997).

In the present study, we evaluated if water-soluble CDs are useful additives also in oral formulations prepared from sparingly soluble drugs which form inclusion complexes on low extent. Modified

water-soluble CDs, HP- β -CD and (SBE) $_{7m}$ - β -CD, were used in the present study since they have been suggested to be the most suitable CDs for pharmaceutical applications (Rajewski and Stella, 1996; Irie and Uekama, 1997; Thompson, 1997).

2. Materials and methods

2.1. Materials

Phenytoin (phenytoin sodium) was purchased from Research Biochemicals International (Natick, USA). Sulfobutylether β -cyclodextrin ((SBE) $_{7m}$ - β -CD); CaptisolTM; average degree of sulfobutyl substitution was seven, average MW = 2160 g/mol) was kindly supplied by CyDex (Kansas City, USA). Hydroxypropyl- β -cyclodextrin (HP- β -CD; Encapsin[®]; MW = 1383 g/mol) was obtained from Janssen Biotech N.V (Belgium). Phenacetin was purchased from Tamro (Finland). All other materials and solvents used were of analytical reagent grade and used as received.

2.2. Apparatus

High performance liquid chromatography (HPLC) system contained a Beckman System Gold programmable Solvent Module 116, Beckman Detector Module 166 with variable wavelength UV detector (set at 203 nm), System Gold data module (Beckman Instruments, San Ramon, USA), a marathon autosampler equipped with column thermostat (Spark Holland, Emmen, The Netherlands) and a Rheodyne injection valve with a 20 μ l loop. Kromasil C8 reversed-phase column (15 cm \times 4.6 mm i.d., 5 μ m) (Higgins Analytical, CA, USA) was used for the separations in in vivo and phase-solubility studies and Supelcosil LC-8-DB reversed-phase column (15 cm \times 4.6 mm i.d., 5 μ m) (Supelco, Bellefonte, USA) in dissolution studies. The chromatographic conditions were as follows: injection volume, 20 μ l; column temperature, 40°C; flow rate, isocratic at 1.0 ml/min. The mobile phase used consisted of 45% (v/v) monobasic potassium phosphate buffer (0.02 M, pH 5.0) in methanol. Bond Elut C18 solid phase

extraction cartridges were obtained from Analytichem International (Harbor City, USA). The readings of pH were carried out on an Orion model SA520 pH-meter (Boston, USA) equipped with a combination pH electrode.

2.3. Phase-solubility studies

Solubility measurements were carried out according to Higuchi and Connors (1965). An excess of phenytoin was added to pH 7.4 phosphate buffer solution (0.16 M, $\mu = 0.5$) and pH 11.0 NaOH solution (0.05 M). Buffer solutions contained various concentrations of HP- β -CD or (SBE) $_{7m}$ - β -CD (3.6–72.3 mM). The suspensions were shaken at room temperature for 72 h in order to reach an equilibrium. The pH of the suspensions was monitored during the equilibration and held constant by adding HCl or NaOH if necessary. After equilibration the suspensions were filtered through 0.45 μ m membrane filter. A portion of the sample was diluted with the buffer used in the solubility study and analyzed chromatographically at 203 nm.

2.4. Preparation of dosage forms

Solid-complexes were prepared by dissolving phenytoin in 0.05 M NaOH solution at pH 11.0 containing 72.3 mM (SBE) $_{7m}$ - β -CD or HP- β -CD. The solutions were then freeze-dried. The contents

of phenytoin in the freeze dried products were determined by HPLC. The pH value of 11.0 was chosen since at lower pH values the amount of CDs needed to dissolve phenytoin was too large for oral administration due to smaller intrinsic solubility of phenytoin at lower pH. The freeze-dried product was then placed either in two (phenytoin/HP- β -CD) or three (phenytoin/(SBE) $_{7m}$ - β -CD) hard gelatin capsules (No. 000). The physical mixture was made by mixing phenytoin and cyclodextrin that were freeze-dried (from 0.05 M NaOH solution, pH 11.0) separately. The physical mixture was placed in two hard gelatin capsules (No. 000). Freeze-dried phenytoin was freeze-dried from 0.05 M NaOH solution at pH 11.0 and placed into a hard gelatin capsule (No. 000). A crystalline phenytoin was administered in a hard gelatin capsule (No. 000).

2.5. Dissolution studies

The dissolution studies were performed at pH 1.2 (simulated gastric fluid without pepsin) and 7.4 (phosphate buffer) solutions using USP 23 apparatus 2 (rotating paddle method) at 37°C. Powdered samples containing always equivalent of 10.0 or 100.0 mg of phenytoin sodium were gently spread on the surface of the dissolution medium which was stirred at 50 rpm. The solution was sampled (5 ml) at appropriate time intervals and the samples were filtered rapidly through a

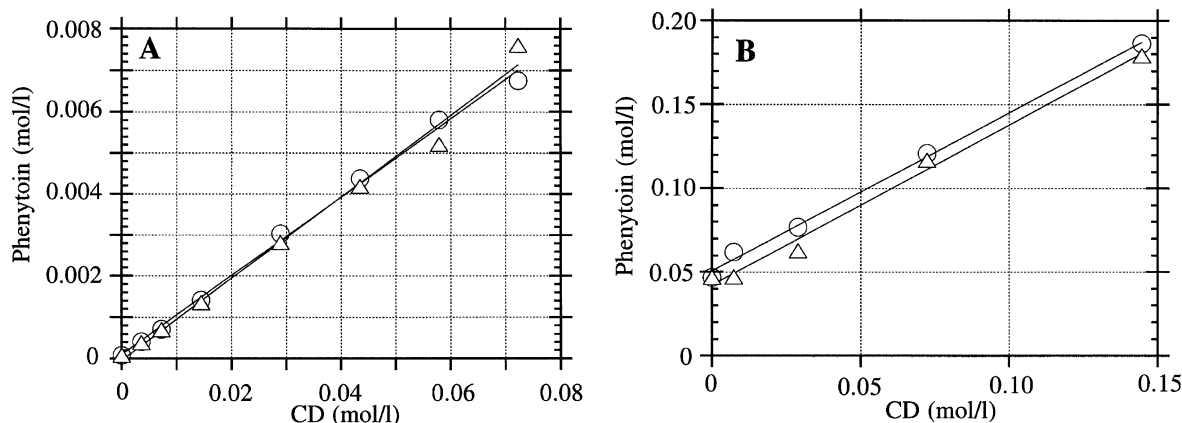


Fig. 1. Phase-solubility diagrams for phenytoin in the presence of (SBE) $_{7m}$ - β -CD (Δ) and HP- β -CD (\circ) in: (A) 0.16 M phosphate buffer at pH 7.4, and (B) in 0.05 M NaOH buffer at pH 11.0.

Table 1
Dissolution data for different phenytoin formulations

Time (min)	Formulation	Concentration ($\mu\text{g/ml}$)			
		pH 7.4		pH 1.2	
		Middle	Bottom	Middle	Bottom
1	Crys. PH	35.6 \pm 1.1****	38.4 \pm 0.5****	17.8 \pm 2.0*	16.8 \pm 1.1*
	Lyophilized PH	43.1 \pm 0.4** ****	40.7 \pm 0.9****		
	Physical mixture	51.3 \pm 0.2** ****	49.3 \pm 0.9** ****		
	PH/HP- β -CD	72.3 \pm 0.8** ***	53.3 \pm 0.8**	37.3 \pm 0.7*	37.3 \pm 0.5*
	PH/SBE- β -CD	50.4 \pm 0.9** ****	48.6 \pm 1.3** ****		
3	Crys. PH	39.2 \pm 0.0****	40.0 \pm 2.6****	27.7 \pm 0.8*	18.8 \pm 2.3*
	Lyophilized PH	48.9 \pm 0.7** ****	44.3 \pm 1.0****		
	Physical mixture	56.4 \pm 0.3** ****	54.8 \pm 0.0**		
	PH/HP- β -CD	74.9 \pm 3.9** ***	55.9 \pm 1.5**	44.6 \pm 0.4*	44.1 \pm 0.8*
	PH/SBE- β -CD	52.6 \pm 0.6** ****	51.6 \pm 1.1**		
5	Crys. PH	42.3 \pm 0.8****	38.9 \pm 2.7****	30.4 \pm 1.8*	22.4 \pm 1.8*
	Lyophilized PH	50.5 \pm 0.2** ****	48.3 \pm 0.1** ****		
	Physical mixture	58.3 \pm 0.3** ****	56.9 \pm 0.1**		
	PH/HP- β -CD	70.9 \pm 3.2** ***	58.2 \pm 1.2**	48.2 \pm 0.4*	45.4 \pm 1.2*
	PH/SBE- β -CD	55.6 \pm 0.6** ****	54.5 \pm 1.5**		
8	Crys. PH	44.7 \pm 0.6****	40.6 \pm 1.8****	30.9 \pm 0.3*	24.8 \pm 2.0*
	Lyophilized PH	50.9 \pm 0.4** ****	47.6 \pm 0.1** ****		
	Physical mixture	59.8 \pm 0.1** ***	57.3 \pm 0.7**		
	PH/HP- β -CD	68.3 \pm 1.5** ***	57.2 \pm 1.0**	48.4 \pm 0.5*	48.0 \pm 0.1*
	PH/SBE- β -CD	54.9 \pm 0.4** ****	53.8 \pm 0.9**		
1440	Crys. PH	49.8 \pm 0.7****	49.8 \pm 0.4	38.4 \pm 0.2*	38.0 \pm 0.5*
	Lyophilized PH	47.8 \pm 0.3****	47.2 \pm 0.4****		
	Physical mixture	52.8 \pm 0.6** ****	51.9 \pm 0.0		
	PH/HP- β -CD	62.2 \pm 0.6** ***	53.7 \pm 0.4	49.0 \pm 0.3*	48.8 \pm 0.2*
	PH/SBE- β -CD	56.6 \pm 0.5**	55.6 \pm 0.2**		

Samples were taken either from the bottom or the middle of the container (rotating paddle method; supersaturated solution) (mean \pm S.E.M., $n = 3$).

* Significantly different from the value for corresponding preparation at pH 7.4.

** Significantly different from the value of crystalline phenytoin (crys. PH) at pH 7.4 (sampling from the same location).

*** Significantly different from the value for corresponding formulation when samples were taken from the bottom of the vessel.

**** Significantly different from the value for corresponding PH/HP- β -CD ($P < 0.05$, by Fisher's P.L.S.D. test).

membrane filter (pore size 0.22 μm). Samples were withdrawn from a conventional position (a zone midway between the surface of dissolution medium and the top of the rotating blade, about 10 cm from the bottom of the vessel) and from the bottom of the vessel (about 2 cm from the bottom of the vessel). A correction was applied for the cumulative dilution caused by replacement of the samples by equal volumes of the original medium. Samples were analysed, directly or diluted when needed, chromatographically at

203 nm as described above. All measurements were made in triplicate.

2.6. In vivo absorption studies

2.6.1. Oral dosing

A total of four male beagle dogs (weighing 10.5–12.3 kg) were used as experimental animals in this study. The dogs were fasted overnight prior to oral administration of the drug. During all experiments water was allowed ad libitum.

Solid meals were given at 8 h from dosing. In order to eliminate the cumulative effect of phenytoin time interval of 1–3 weeks was used between separate doses. The test powder, equivalent to 300 mg of phenytoin sodium, packed in hard gelatin capsules was administrated orally with 20 ml of water. Dose of 300 mg was chosen to make sure the detectability of phenytoin in plasma by HPLC-UV method.

Blood samples of 3.5 ml were withdrawn from cephalic saphenous or jugular vein just prior (blank plasma) and 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, and 24.0 h after administration of the drug. Blood samples were centrifuged for 15 min at 3000 rpm. After centrifugation the plasma was withdrawn and stored at -20°C until analyzed.

2.6.2. HPLC assay method

To 1.2 ml of plasma 50 μl of methanol containing phenacetin (internal standard) was added. Phenytoin and internal standard were extracted from plasma using solid phase extraction cartridges; methanol was used as an eluent in the process. After extraction the samples were evaporated to dryness and the residues were dissolved in

250 μl of mobile phase (45% 0.02 M phosphate buffer; pH 5.0 in methanol) and 20 μl was injected into an HPLC. The results were calculated from peak-area ratios.

Standard curves were prepared for each dog by spiking each dogs blank plasma with a known amount of phenytoin. Standard curves prepared ranged from 0.21 to 41.67 $\mu\text{g/ml}$ (five points). All standard curves showed good linearity ($r^2 \geq 0.997$) which made one-point calibration feasible. Every day prior to analysis two spiked blank plasma samples were prepared (for each dog separately). One concentration was near the lowest sample concentration and the other was close to the highest sample concentration. These daily prepared spiked plasma samples were used to calculate the concentration of phenytoin in plasma samples. The lower limit of quantitation of phenytoin was 10 ng/ml in plasma.

2.6.3. Data analysis

Areas under the concentration versus time curves for 0–24 h ($\text{AUC}_{0-24\text{ h}}$) were calculated by using the linear trapezoidal method. In four of 20 cases the plasma concentration of phenytoin at 24 h was less than the lower quantitation limit (i.e. 10 ng/ml). In these cases the concentrations at 24 h were assumed to be zero. Mean residence times (MRT) were calculated from $\text{MRT} = \text{AUMC}_{0-24\text{ h}} / \text{AUC}_{0-24\text{ h}}$ where, AUMC is the area under the (time \times phenytoin concentration) versus time curve. Although the truncated AUC and AUMC values were used, the relative cut-off error due to this procedure is small because the concentrations of phenytoin in dog plasma were very small compared with peak drug concentrations. The phenytoin maximum concentrations in plasma (C_{max}) and t_{max} were determined from the actual data points.

A one-factor analysis of variance (ANOVA for repeated measurements (in vivo) and ANOVA factorial (in vitro)) was used to test the statistical significance of differences between groups. Significance in the differences in the means was tested using Fisher's protected least significance difference (P.L.S.D.) at 95% confidence.

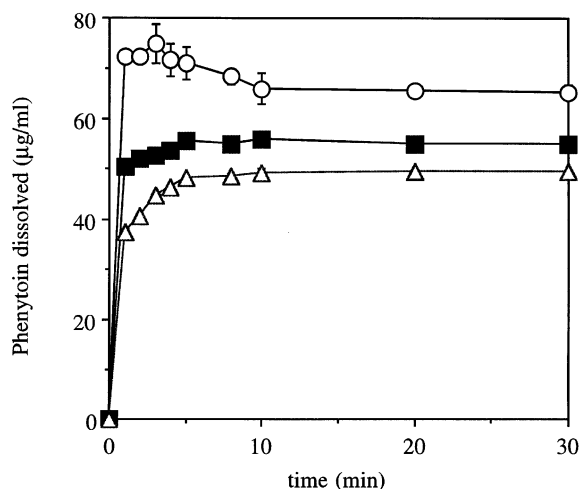


Fig. 2. Dissolution profiles of phenytoin/HP- β -CD (○) and phenytoin/(SBE) $_{7m}$ - β -CD (■) at pH 7.4 and phenytoin/HP- β -CD (△) at pH 1.2 (saturated medium). Mean \pm S.E.M. are shown ($n = 3$). All samples were withdrawn from the middle of the vessel.

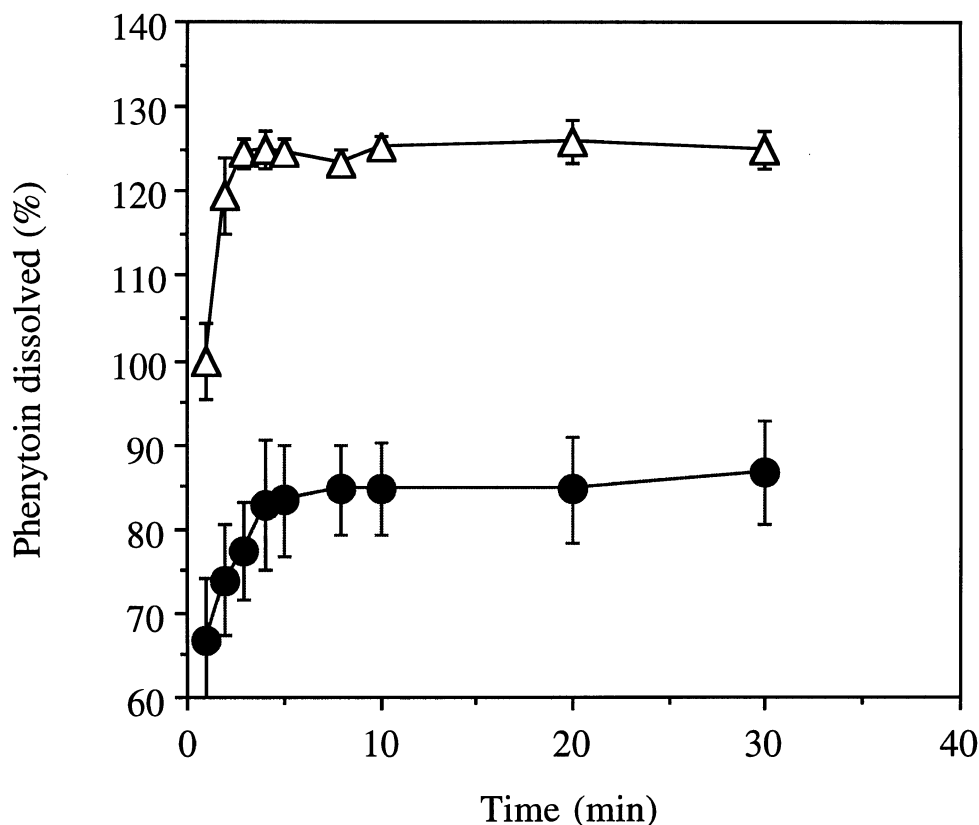


Fig. 3. Dissolution profiles of phenytoin/HP- β -CD (Δ) and a crystalline phenytoin (\bullet) at pH 7.4 (an amount equivalent to 10 mg of phenytoin was used. Mean \pm S.E.M. are shown ($n = 3$).

3. Results

3.1. Phase solubility study

The aqueous solubility of phenytoin increased linearly as a function of CDs ((SBE) $_{7m}$ - β -CD and HP- β -CD). The solubility curve was classified as type A_L (Higuchi and Connors, 1965) which indicates the formation of 1:1-complexes at pH 11.0 and 7.4 and CD concentration range used (Fig. 1a and 1b). Brewster and co-workers have reported formation of 1:2-complexes, besides formation of 1:1-complexes, between phenytoin and HP- β -CD, but pH of solution was not informed (Brewster et al., 1992b). The stability constants for 1:1-complexes ($K_{1:1}$) were calculated using equation 1:

$$K_{1:1} = \text{Slope}/S_o(1 - \text{Slope}) \quad (1)$$

where $K_{1:1}$ is the stability constant for the complex and S_o is the solubility of the drug in the absence of CD. $K_{1:1}$ values for the phenytoin/HP- β -CD and phenytoin/(SBE) $_{7m}$ - β -CD-complexes were determined to be 1215 and 1267 M⁻¹ at pH 7.4, and 352 and 476 M⁻¹ at pH 11.0, respectively. The intrinsic solubility (S_o) of phenytoin at pH 7.4 was 23.84 μ g/ml (0.0869 mM), which is in good agreement with the literature value (Schwartz et al., 1977). S_o value at pH 11.0 was determined to be 12.86 mg/ml (46.9 mM).

3.2. Dissolution study

3.2.1. Effect of CDs on phenytoin dissolution

Table 1 shows concentration of phenytoin in dissolution mediums (pH 1.2 and 7.4) as a function of time when powdered preparations contain-

ing 100 mg of phenytoin sodium were spread on the surface of the dissolution medium. A 100% dissolution was not reached at the end of experiment due to saturated solutions.

All CD formulations (solid complexes and physical mixture) enhanced phenytoin dissolution in the tested dissolution mediums compared to a crystalline phenytoin. Phenytoin was dissolved better with and without CD at pH 7.4 than at pH 1.2. The dissolution curve of phenytoin/HP- β -CD-complex showed a descending portion before reaching a plateau at pH 7.4, but this phenomenon was not observed at pH 1.2 (Fig. 2).

When powdered preparations containing 10 mg of phenytoin sodium were spread on the surface of the dissolution medium and samples were withdrawn from a conventional position, all the CD-formulations had released 117–125% of phenytoin after 5 min, while 84% of phenytoin was released from a freeze-dried phenytoin (Fig. 3).

3.2.2. Effect of sampling position on phenytoin dissolution

Samples were withdrawn either from a conventional position (i.e. according to USP requirements from the zone midway between the surface of the dissolution medium and the top of the rotating blade) or from the bottom of the vessel in order to clarify the effect of sampling position on dissolution profile.

Sampling position affected significantly only dissolution profile of phenytoin/HP- β -CD-complex (Table 1). Phenytoin concentrations in samples withdrawn from the bottom of the vessel were significantly lower than in the samples withdrawn from the middle of the vessel. Dissolution profiles were comparable among various CD formulations at pH 7.4, when samples were withdrawn from the bottom of the vessel (Table 1).

3.3. In vivo absorption study

All the tested preparations were well-tolerated by the dogs i.e. no obvious side-effects were observed. The mean values of pharmacokinetic parameters for all preparations are summarized in Table 2. Plasma concentrations versus time profiles of phenytoin are shown in Fig. 4.

Oral pharmacokinetics (C_{\max} , t_{\max} , $AUC_{0-24\text{ h}}$) were comparable after administration of phenytoin as a crystalline form and as a lyophilized form. Compared to administration of plain phenytoin, administration of inclusion complexes and the physical mixture increased C_{\max} and $AUC_{0-24\text{ h}}$ values of phenytoin. As an example, the ratio of mean $AUC_{0-24\text{ h}}$ between phenytoin/(SBE) $_{7m}$ - β -CD and a crystalline phenytoin was 2.13. T_{\max} and MRT values of phenytoin were not affected by CD co-administration. Oral pharmacokinetics of phenytoin were not statistically different among various CD preparations.

Table 2

Mean values (mean \pm S.E.M.) of pharmacokinetic parameters for phenytoin (PH) in plasma after oral administration (300 mg) in various formulations to beagle dogs

Treatment	C_{\max} ($\mu\text{g/ml}$)	$AUC_{0-24\text{ h}}$ ($\mu\text{gh/ml}$)	t_{\max} (h)	MRT (h)
Crystal PH	$4.22 \pm 0.56^{***}$	$34.90 \pm 4.06^{***}$	3.0 ± 0.6	6.05 ± 0.61
Lyophilized PH	$4.29 \pm 0.49^{***}$	$35.72 \pm 3.65^{***}$	3.5 ± 0.5	5.63 ± 0.19
Physical mixture	6.92 ± 1.30	68.88 ± 12.31	3.5 ± 0.5	6.22 ± 0.27
PH/HP- β -CD	7.06 ± 0.85	70.33 ± 11.01	3.0 ± 0.6	6.16 ± 0.26
PH/(SBE) $_{7m}$ - β -CD	6.87 ± 0.78	74.22 ± 8.60	4.0 ± 0.0	6.05 ± 0.13

* Significantly different from the value for the capsules containing PH/HP- β -CD.

** Significantly different from the value for the capsules containing PH/(SBE) $_{7m}$ - β -CD.

*** Significantly different from the value for the capsules containing physical mixture ($P < 0.05$ by ANOVA, Fisher's P.L.S.D. test).

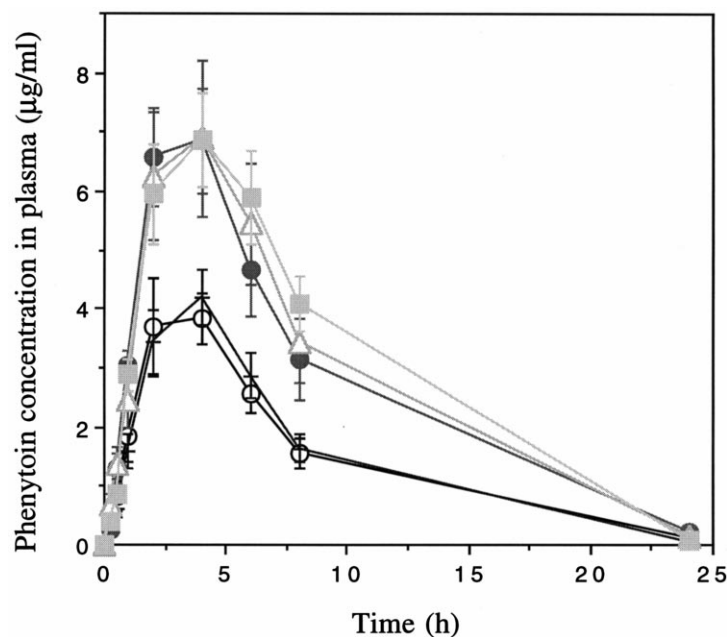


Fig. 4. Plasma levels (mean \pm S.E.M., $n = 4$) of phenytoin following the oral administration of different phenytoin preparations (equivalent to 300 mg phenytoin) in dogs. (■), PH/(SBE)_{7m}-β-CD; (●), PH/HP-β-CD; (△), physical mixture; (+), lyophilized phenytoin; (○) untreated phenytoin.

4. Discussion

4.1. Phase solubility

The phase-solubility study at pH 7.4 showed almost complete complexation of phenytoin in aqueous solutions containing CDs (98.8 and 98.7% complexation of phenytoin for (SBE)_{7m}-β-CD and HP-β-CD, respectively). At pH 11.0 a lower degree of complexation was observed (59.2 and 56.6% of the phenytoin was in a complexed form with (SBE)_{7m}-β-CD and HP-β-CD, respectively). The phenytoin solutions were prepared at pH 11.0 for freeze-drying process for practical reasons, i.e. more reasonable amount of CD was required for formulating phenytoin solutions at pH 11.0 than at 7.4. This was due to much higher intrinsic solubility of phenytoin (weak acid, $pK_a = 8.3$) at pH 11.0. This combined approach of pH-adjustment and CD-complexation has been described to be an useful method for ionizable drugs to reach the desired solubility enhancement (Tinwalla et al., 1993; Johnson et al., 1994).

Phenytoin ($pK_a = 8.3$) is mostly as an anionic form at pH 11.0 and adverse electrostatic repulsions might be observed in complexation between anionic phenytoin and anionic (SBE)_{7m}-β-CD at pH 11.0. However, the binding constant between anionic phenytoin and anionic (SBE)_{7m}-β-CD (476 M^{-1}) was similar to that observed for neutral HP-β-CD (352 M^{-1}). This result that anionic drug has similar binding constant between anionic and neutral CD is in good agreement with earlier reported results (Okimoto et al., 1996).

4.2. Dissolution

In vitro results clearly show that CD complexation increases extent of phenytoin dissolution. Concentrations of dissolved phenytoin in the presence and absence of CDs were higher at pH 7.4 than at pH 1.2 due to higher intrinsic solubility of phenytoin at pH 7.4 than at 1.2. Differences in intrinsic solubility may explain why dissolution curve of phenytoin/HP-β-CD-complex showed a descending portion before reaching a plateau at

pH 7.4, but increased as a function of time at pH 1.2. Dissolution profiles comparable to phenytoin/HP- β -CD-complex dissolution profile at pH 7.4 have been earlier reported for fenofibrate/HP- β -CD-complexes (Palmieri et al., 1997) and phenytoin/HP- β -CD-epichlorohydrin-polymer-complexes (Uekama et al., 1985). Palmieri and coworkers explained that a descending portion before reaching a plateau may be due to an initial carrier effect.

Pedersen (1997) suggested that correlation between results from in vitro dissolution study and oral bioavailability study with CD based formulations may depend on the method used to prepare a drug/CD inclusion complex. The present study shows that in some cases sampling position may affect in vitro dissolution profiles. Samples withdrawn from a conventional position suggested that phenytoin/HP- β -CD-complex enhances phenytoin dissolution more than the other CD formulations. In the present study, samples withdrawn from the bottom of the vessel in dissolution study predicted better the effects of CD formulations on oral bioavailability of phenytoin.

4.3. Absorption study

Although the coadministered CDs doubled the absorption of phenytoin, the inter-animal variation in C_{\max} and AUC values was not decreased with CDs. This could be due to the low degree of complexation between phenytoin and CDs. In vitro results predicted that extent of phenytoin dissolution rather than dissolution rate is increased with CDs (Fig. 2). In vivo results confirmed that CD coadministration increases C_{\max} and AUC values of oral phenytoin but does not affect t_{\max} values (Table 2). Comparable findings were discovered by Uekama and co-workers (Uekama et al., 1985) when β -CD-epichlorohydrin polymer was used in complexing phenytoin. Lyophilization of phenytoin tended to increase aqueous solubility of phenytoin in vitro but oral pharmacokinetics after administration of a crystalline and a lyophilized phenytoin were comparable.

In conclusion, the water-soluble CD-derivatives, anionic (SBE) $_{7m}$ - β -CD and neutral HP- β -

CD, have similar binding values with anionic phenytoin followed with similar solubility enhancement. These CDs are useful additives in improving oral absorption of drugs whose oral absorption is limited due to their low aqueous solubility in GI-tract even though drug does not form inclusion complexes effectively.

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