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Dissolution Behaviors and Gastrointestinal Absorption of Phenytoin in Phenytoin-Polyvinylpyrrolidone Coprecipitate[1]

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Phenytoin-polyvinylpyrrolidone (PVP) coprecipitate was prepared. The X-ray diffraction spectra indicated that phenytoin in the coprecipitate did not exhibit its crystalline property. Comparative studies were made on the *in vitro* dissolution and the *in vivo* absorption of the coprecipitate and phenytoin alone. The dissolution rate of phenytoin was markedly increased in the phenytoin-PVP coprecipitate in the pharmacopoeial disintegration media at pH 1.2 and 7.5. The concentration of phenytoin released from the coprecipitate reached supersaturation within a few minutes in dissolution studies. The solution remained supersaturated for a long period. The dissolution rate of phenytoin in the coprecipitate was greater when the ratio of drug to PVP was smaller and when PVP of smaller molecular weight was used for the preparation of the coprecipitate. *In vivo* absorption studies of each preparation was carried out in five subjects by measuring the urinary excretion rate of free and conjugated forms of a main metabolite, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin. Excretion rate and cumulative amount of the metabolite excreted following the oral administration of the coprecipitate were greater than those of phenytoin alone. The plasma levels of phenytoin following the administration of the coprecipitate were almost twice as high as those of the phenytoin alone, in rabbits. It was indicated that the drug was rapidly and almost completely absorbed following oral administration of the coprecipitate.

Keywords——bioavailability; phenytoin; polyvinylpyrrolidone; coprecipitate; dissolution; gastrointestinal absorption; dosage forms; anticonvulsant; urinary excretion rates; blood levels

For poorly water-soluble drugs, the rate-limiting step in the absorption process is usually dissolution in the biological fluids of the gastrointestinal tract.[3] Different products of such drugs (*e.g.*, different dosage forms or different brands or lots of the same dosage form) may have a potential of therapeutic inequivalence due to differences in bioavailability even though these products meet existing official and compendial standard.[4]

Phenytoin is the drug of choice for treatment of the most type of epileptic seizures except petit mal. It has been pointed out to be a drug exhibiting large differences in bioavailability following oral administration to patients,[5] because of its poor water-solubility. It has often been difficult in phenytoin therapy to keep the effective therapeutic blood level (10—20 μg/ml).[6] It is generally accepted that effective therapy requires monitoring of plasma

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phenytoin concentrations.⁷⁾ Modification of the dissolution characteristics of phenytoin has been attempted to gain a good bioavailability. Yamamoto *et al.*⁸⁾ were successful in improving the dissolution characteristics of phenytoin by vibrational ball milling of the mixture of phenytoin and crystalline cellulose, and obtained a better bioavailability with the ground mixture in man than with phenytoin powder.

The authors investigated the modification of the dissolution characteristics of phenytoin by coprecipitating⁹⁾ phenytoin with polyvinylpyrrolidone (PVP). Gastrointestinal absorption of phenytoin in phenytoin-PVP coprecipitate was also evaluated in human subjects and rabbits.

Experimental

Materials——Phenytoin (J.P.IX) was obtained from Dainippon Pharmaceutical Co., Osaka (Aleviatin, lot HL435HN). The mean particle size of a phenytoin sample, as measured by optical microscope, was 47.1 μm (Green diameter). 5-(*p*-Hydroxyphenyl)-5-phenylhydantoin and 5-(*p*-methylphenyl)-5-phenylhydantoin were obtained from Aldrich Chemical Co., Milwaukee, Wis. Phenyltrimethylammonium hydroxide was a 20—25% solution in methanol (Tokyo Kasei Industrial Co., Tokyo). PVP K-15, K-30 and K-90 (respective average molecular weights of 10000, 40000, and 360000) were obtained from Daiichi Pure Chemicals Co., Tokyo. All other chemicals were of reagent grade.

Preparation of the Coprecipitate——Phenytoin-PVP coprecipitate was prepared as follows; After dissolving both phenytoin and PVP in a suitable weight ratio, in ethyl alcohol, the solvent was removed *in vacuo* using rotary evaporator at 40°. Then, the preparation was dried *in vacuo* at about 60° for twenty hours. A physical mixture was prepared by blending phenytoin and PVP in a mortar with a spatula.

Dissolution Rate Studies——Dissolution rates of phenytoin from the preparations in 1 l of J.P.IX disintegration medium No. 1 (pH 1.2) or No. 2 (pH 7.5) were measured at 37.0±0.1° in a constant-temperature water bath (Taiyo, Thermounit, HM Type). The beaker had a 1 l capacity and 105 mm in diameter. A stainless steel three-bladed propeller (40 mm in diameter and about 2 cm^2 in area of each blade) was immersed into the beaker at a depth of 30 mm from the bottom, and was rotated at 60 rpm. The amount of the preparation used was 200 mg of the phenytoin equivalent. Each preparation was transferred directly into the dissolution medium. A suitable aliquot was removed at the specified time with syringe, then filtered quickly through a membrane filter (Toyo, TM-4, pore size of 0.2 μm) and analyzed for drug by GC method.⁸⁾ The same volume of fresh medium was added into the beaker.

X-Ray Diffraction Patterns——X-ray powder diffraction patterns were obtained with a Rigaku Denki D-9C X-Ray Diffractometer.

Urinary Excretion of the Metabolite of Phenytoin——Phenytoin (250 mg) or the coprecipitate (weight ratio of phenytoin: PVP K-15=1: 3, 1000 mg) was orally administered to five normal male subjects. They were 22—24 years old, and average body weight was 58 kg (range 51—64 kg). Preparations were administered to each subject with 200 ml of water at approximately 9 a.m. following an overnight fast. Crossover design was used. No food or beverage was taken for 4 hr postadministration. Urine was collected at hourly intervals for the first 9 hr and at a convenient time intervals up to 120 hr after administration. A minimum of 2 weeks was allowed for between experiments. The volume and pH of each urine were recorded, and a portion of the urine was stored in the refrigerator until analyzed. The amount of 5-(*p*-hydroxyphenyl)-5-phenylhydantoin and its glucuronide conjugate, the main metabolite in human,¹⁰⁾ in urine was assayed after acid hydrolysis by GC method⁸⁾ using 5-(*p*-methylphenyl)-5-phenylhydantoin as an internal standard.

Plasma Level of Phenytoin in Rabbits——White male rabbits, 2.5—3.3 kg, were used in this study following stomach-emptying-time-controlling treatments.¹¹⁾ Rabbits were fed a special soft diet (Nihon Clea Co., Tokyo) for one week and received a gastric lavage with saline prior to the administration of the preparations. Phenytoin (30 mg/kg) or coprecipitate (weight ratio of phenytoin: PVP K-15=1: 3, 120 mg/kg) in capsules (J.P. No. 2) was orally administered with about 50 g of special soft diet, and water was allowed *ad libitum.*

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7) *a*) A.J. Wilensky and J.A. Lowden, *Neurology*, **23**, 318 (1973); *b*) H. Kutt and F. McDowell, *J. Am. Med. Assoc.*, **203**, 167 (1968); *c*) F.B. Gibberd, J.F. Dunne, A.J. Handley, and B.L. Hazlemans, *Brit. Med. J.*, **1970 1**, 147.

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9) *a*) H. Sekikawa, M. Nakano, and T. Arita, *Yakugaku Zasshi*, **98**, 62 (1978); *b*) A.P. Simonelli, S.C. Mehta, and W.I. Higuchi, *J. Pharm. Sci.*, **58**, 538 (1969); *c*) E.I. Stupak, H.A. Rosenberg and T.R. Bates, *J. Pharmacokin. Biopharm.*, **2**, 511 (1974); *d*) E.I. Stupak and T.R. Bates, *J. Pharm. Sci.*, **62**, 1806 (1973).

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11) T. Maeda, H. Takenaka, Y. Yamahira, and T. Noguchi, *J. Pharm. Sci.*, **66**, 69 (1977).

Blood samples were taken from the rabbits at 0, 2, 4, 6, 8, 10, and 24 hr postadministration by the heparinized syringe. The blood samples were centrifuged (3500 rpm, 20 min), and the plasma was stored in the refrigerator until assayed. Rabbits were prevented from the coprophagy by wearing the muzzles during the night.[11] The concentration of phenytoin in the plasma samples was assayed by the GC method.[8]

Results and Discussion

The X-Ray Diffraction Patterns

The X-ray diffraction patterns of phenytoin, phenytoin-PVP coprecipitate and the physical mixture are shown in Fig. 1. PVP is an amorphous powder having no crystalline structure.[9a] By coprecipitation with PVP, sharp diffraction peaks attributed to phenytoin crystal disappeared, and only the halo was observed in the X-ray diffraction pattern. Sharp diffraction peaks still remained in the simple physical mixture.

In the measurement with differential scanning calorimeter, endothermic peak accompanied by the melting of phenytoin crystal (295°) disappeared in phenytoin-PVP coprecipitates. Phenytoin might be present without its crystalline structure in PVP matrix. This phenomenon has been attributed to the inhibitory effect of PVP on the crystallization of the drug during the removing process of the solvent from the solution.[12] Well-defined coprecipitates[9a] were formed in 1:1, 1:2, 1:3, and 1:5 phenytoin-to-PVP ratio coprecipitates.

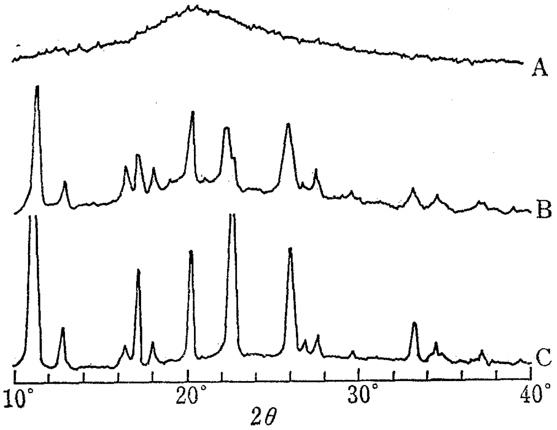

Fig. 1. Comparison of X-Ray Diffraction Spectra of Three Preparations

Key: A, phenytoin: PVP K-15=1:3 coprecipitate; B, phenytoin: PVP K-15=1:3 physical mixture; C, phenytoin alone.

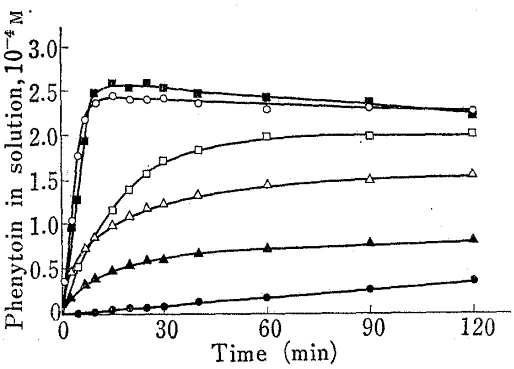

Fig. 2. Dissolution Profiles of Phenytoin from Six Test Preparations in Disintegration Medium No. 1 (J.P. IX) at 37°

Key: ■, phenytoin: PVP K-15=1:5 coprecipitate;
○, 1:3 coprecipitate;
□, 1:2 coprecipitate;
△, 1:1 coprecipitate;
▲, 1:3 physical mixture;
●, phenytoin alone.
Each point represents the mean of three determinations.

Dissolution Studies

The dissolution behaviors of phenytoin alone, coprecipitates and the physical mixture in J.P.IX disintegration medium No. 1 (pH 1.2) at 37° is shown in Fig. 2.

The coprecipitates exhibited faster dissolution rates than phenytoin alone or the physical mixture. The dissolution rate of phenytoin in the coprecipitate was greater when the ratio of drug to PVP was smaller. Though the solubility of phenytoin in this medium was 1.00 $\times 10^{-4}$ M, its concentration following the dissolution of the coprecipitates exceeded this value, indicating supersaturation. The concentrations of phenytoin following the dissolution of the 1:3 or 1:5 coprecipitates were almost 2.3 times as much as phenytoin solubility. After the

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[12] H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **26**, 118 (1978).

concentration reached the peak, it decreased gradually, indicating recrystallization, but the supersaturation continued for a long period. Phenytoin in the physical mixture dissolved faster than phenytoin alone. PVP in the medium from the physical mixture might lower the surface tension of the medium, resulting in wetting of the hydrophobic phenytoin crystalline surface.

Figure 3 shows the dissolution curve of phenytoin in coprecipitates with PVP of different molecular weight in 1: 3 weight ratio of phenytoin-PVP in the medium No. 1.

Phenytoin concentration after dissolving each coprecipitate, was higher than phenytoin alone, and reached supersaturation. The dissolution rate of coprecipitate with PVP of lower molecular weight was greater, *i.e.*, K-15>K-30>K-90. This tendency was similar to the case in sulfisoxazole-PVP coprecipitates.[9a)]

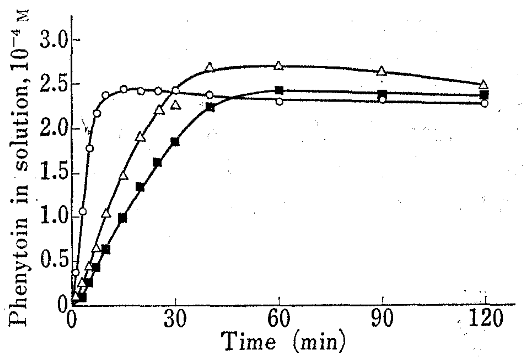

Fig. 3. Dissolution Profiles of Phenytoin from 1: 3 Phenytoin-PVP Coprecipitates Prepared with PVP of Different Molecular Weight, in Disintegration Medium No. 1 (J.P. IX) at 37°

Key: ○, K-15 (mol. wt. 10000);
△, K-30 (mol. wt. 40000);
■, K-90 (mol. wt. 360000).
Each point represents the mean of three determinations.

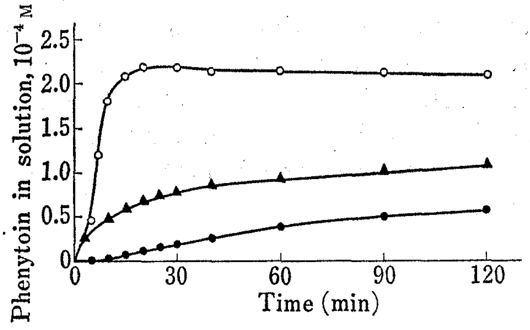

Fig. 4. Dissolution Profiles of Phenytoin from Three Test Preparations in Disintegration Medium No. 2 (J.P. IX) at 37°

Key: ○, phenytoin: PVP K-15=1: 3 coprecipitate,
▲, 1: 3 physical mixture,
●, phenytoin alone.
Each point represents the mean of three determinations.

Figure 4 shows the dissolution curves of three preparations in J.P.IX disintegration medium No. 2 (pH 7.5) at 37°.

The dissolution profile was similar to that in the medium No. 1. Since the pK_a value is 8.3,[13)] a small part of phenytoin molecule is considered to be ionized in this medium.[14)] Dissolution rate of phenytoin alone in the medium No. 2 was higher than that in the medium No. 1. Phenytoin in the solution following the dissolution of the coprecipitate exhibited supersaturation in the same way as in the medium No. 1.

In Vivo Absorption Studies

Phenytoin in the phenytoin-PVP coprecipitate was expected to have a good bioavailability, because of its large dissolution rate in both acidic and neutral media. Phenytoin-PVP coprecipitate and phenytoin alone were orally administered to human subjects or rabbits to evaluate their absorption characteristics. The selection of the ratio of phenytoin-to-PVP in the coprecipitates was based on both high dissolution rate and larger drug to PVP ratio, because a large quantity of the macromolecular additives might interfere with absorption of the drug.[15)] 1: 3 Phenytoin-to-PVP K-15 coprecipitate was used in the absorption studies.

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13) S.P. Agarwal and M.I. Blake, *J. Pharm. Sci.*, **57**, 1434 (1968).
14) P.A. Schwartz, C.T. Rhodes, and J.W. Cooper, *J. Pharm. Sci.*, **66**, 994 (1977).
15) H. Sekikawa, K. Ito. T. Arita, R. Hori, and M. Nakano, submitted for publication.

Urinary Excretion of the Metabolite in Human Subjects

Butler[10] reported that the major metabolites of phenytoin in humans were 5-(*p*-hydroxyphenyl)-5-phenylhydantoin and its glucuronic acid conjugate. Sulfate or unmetabolized phenytoin were not detectable in the urine sample. Urinary excretion of free and conjugated hydroxylated phenytoin in human subject, accounted for 76 per cent of the dose (range 65—81 per cent) over a period of five days following the intravenous administration of 250 mg of phenytoin sodium.[16] Smith *et al.*[17] reported that following oral administration of single dose of 250 mg phenytoin as tablets, recovery of the metabolite excreted in urine in 168 hours were 62.5 per cent (range 39.0—86.6 per cent). Peak of the plasma level of phenytoin was observed at 4 to 12 hours postadministration. On the other hand, maximum rate of the urinary excretion of the metabolite was observed at 24 to 48 hours.

The mean urinary excretion rates of the metabolite in five human subjects are shown in Fig. 5.

Excretion rates during the first 30 hours differed significantly between two preparations. Following the administration of the coprecipitate, the maximum value of mean urinary excretion rate of the metabolite appeared in the 8—12 hour period (among individuals, 6—12 hours). Excretion rate at this maximum corresponded to almost twice as great as the rate following the administration of phenytoin alone in this time period. With the phenytoin alone, however, clear peak was not observed in the plot of the mean excretion rate against time. Time of maximum excretion rates varied among the subjects (6—24 hours post-administration), resulting in prolonged plateau regions in the plot of the mean values. The intersubject variations of excretion rates were considerably smaller when the coprecipitate was administered. Yamamoto *et al.*[8] showed that the peak in the urinary excretion rates of metabolites appeared a few hours behind the peak plasma concentration of intact drug and that greater urinary excretion rates for the first 10 hours after administration of the fast-dissolving form of the drug than those of phenytoin alone were reflection of greater plasma

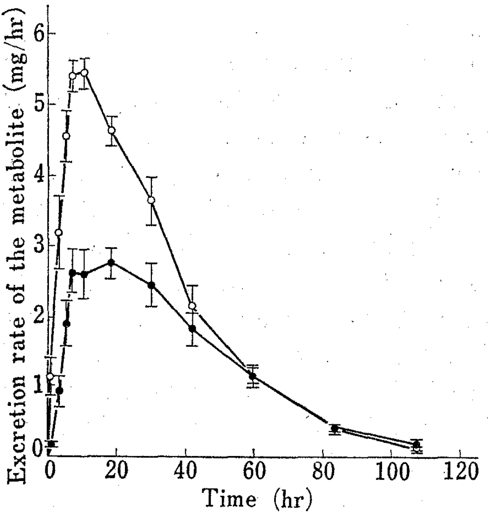

Fig. 5. Urinary Excretion Rate of the Metabolite following the Oral Administration of 250 mg Phenytoin (●) and 1000 mg Coprecipitate (○)

Each point represents the mean ±S.E.M. of five subjects.

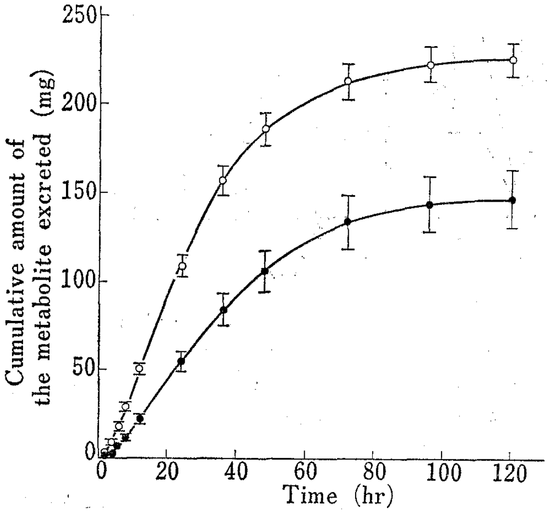

Fig. 6. Cumulative Urinary Excretion of the Metabolite following the Oral Administration of 250 mg Phenytoin (●) and 1000 mg Coprecipitate

Each point represents the mean ±S.E.M. of five subjects.

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[16] A.J. Glazko, T. Chang, J. Baukema, W.A. Dill, J.R. Goulet, and R.A. Buchanan, *Clin. Pharmacol. Ther.*, **10**, 498 (1969).

[17] T.C. Smith and A. Kinkel, *Clin. Pharmacol. Ther.*, **20**, 738 (1976).

level of the drug a few hours earlier. Thus much greater excretion rates of the metabolites for the first 30 hours after administration of the coprecipitate than those of phenytoin alone in the present studies may be reflection of greater absorption rates following administration of the coprecipitate than those of phenytoin alone.

Figure 6 shows the mean cumulative amount of the metabolite excreted in urine during 120 hours following the administration of two preparations.

The recoveries of the metabolites excreted in urine for 120 hours following the administration of the coprecipitate and phenytoin alone were 84.3 per cent (range 72.8—88.0 per cent) and 54.7 per cent (range 42.1—77.9 per cent) as phenytoin equivalent, respectively. The intersubject variations of the cumulative amounts were smaller when the coprecipitate was administered. Extent of bioavailability of phenytoin in phenytoin-PVP coprecipitate was 1.54 times greater than that of phenytoin alone.

Yamamoto *et al.*[8] improved the dissolution characteristics of phenytoin by vibrational ball milling of the mixture of phenytoin and crystalline cellulose. They obtained higher excretion rate and larger extent of the cumulative amount of the metabolites excreted after administration of the ground mixture than those of the drug alone. The extent of the bioavailability of phenytoin in the ground mixture was 1.23 times greater than that of phenytoin alone. The bioavailability of phenytoin was improved further by the administration of the coprecipitate than that by the ground mixture. These excretion patterns may be considered to be reflection of the *in vitro* dissolution behavior of each preparation. High dissolution rate and supersaturation of phenytoin from the coprecipitate resulted in the large improvement of the rate and extent of the bioavailability of poorly water-soluble phenytoin.

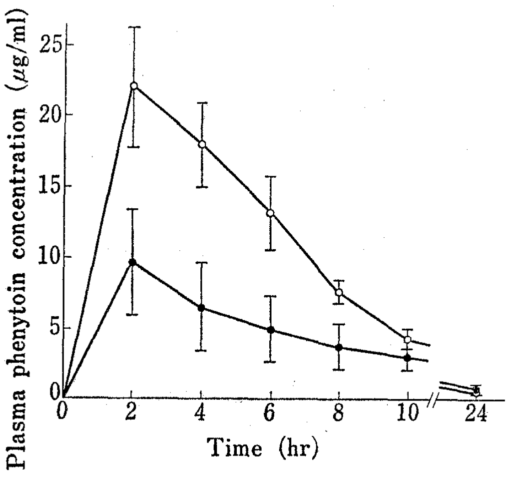

Fig. 7. Plasma Levels of Phenytoin following the Oral Administration of Phenytoin (●) and the Coprecipitate (○)

Each point represents the mean ±S.E.M. of three rabbits.

Plasma Level of Phenytoin in Rabbits

Figure 7 shows the mean plasma levels following the oral administration of two preparations in three rabbits.

Plasma level of phenytoin at 2 hours postadministration of the coprecipitate was almost twice as high as that of the phenytoin alone. Plasma level at 24 hour postadministration, was higher after administration of phenytoin alone than that of the coprecipitate. Poorly water-soluble phenytoin might dissolve slowly in the gastrointestinal tract and the absorption of the drug might continue for a long period. Excretion data in Fig. 6, however, indicate the incomplete absorption of phenytoin following the administration of phenytoin alone. Unabsorbed phenytoin might be recovered in feces. Bioavailability of phenytoin from phenytoin-PVP coprecipitate up to 10 hours postadministration, was 2.37 times as much as that from phenytoin alone.

From the *in vitro* dissolution behaviors of the coprecipitate and phenytoin alone, and from the plasma levels or urinary excretion data, the following consideration may be made. After oral administration of the coprecipitate, phenytoin dissolves rapidly in the gastrointestinal fluid. Supersaturated phenytoin in the fluid may be absorbed rapidly from the gastrointestinal tract. Following the administration of phenytoin alone, on the other hand, the drug dissolves slowly, and this dissolution rate of the phenytoin may be the rate-determining step in absorption process in individual subjects with a slightly different physiological conditions, resulting in large intersubject variations in absorption rates.

The present investigation showed that improvement of the dissolution rate of phenytoin by coprecipitating the drug with PVP resulted in increase in the rate and extent of the bioavailability of the drug with less variation. The method of increasing the dissolution characteristics of the poorly water-soluble drugs by coprecipitation with PVP may be widely applicable to efforts to improve the bioavailability of the drugs.

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