Chem. Pharm. Bull.
34(8)3408—3414(1986)

Dissolution and Bioavailability of Phenytoin in Phenytoin–Polyvinylpyrrolidone–Sodium Deoxycholate Coprecipitate

Shigeru Yakou,*[a,1)] Sachiko Yamazaki,[a] Takashi Sonobe,[b]
Tsuneji Nagai,[c] and Masayasu Sugihara[a]

Pharmaceutical Department, Tokyo Women's Medical College,[a] 10 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan, Product Development Laboratories, Yamanouchi Pharmaceutical Co., Ltd.,[b] 180 Ozumi, Yaizu-shi, Shizuoka 425, Japan and Faculty of Pharmaceutical Sciences, Hoshi University,[c] 2–4–41 Ebara, Shinagawa-ku, Tokyo 142, Japan

(Received January 21, 1986)

The coprecipitates of phenytoin (PHT) with combinations of carriers such as sodium deoxycholate and polyvinylpyrrolidone (DC-Na–PVP), sodium deoxycholate and polyethylene glycol (DC-Na–PEG), and sodium deoxycholate and hydroxypropylcellulose (DC-Na–HPC) were prepared. The dissolution characteristics of various coprecipitates were determined by the use of the JPX dissolution test apparatus in a pH 6.8 test medium. All of the coprecipitates prepared with combined carriers significantly enhanced the dissolution rate of PHT. Among them, the combination of PVP–DC-Na (1:1) as a carrier for the coprecipitate resulted in the fastest dissolution of PHT, but the dissolution rate of coprecipitate containing polyethylene glycol 4000 (PEG 4000), or hydroxypropylcellulose (HPC) was similar to that in the absence of the polymer. The dissolution rate of PHT coprecipitates with PEG 4000 and DC-Na, or HPC and DC-Na was slightly enhanced in the medium containing 0.1% polysorbate 80. Unexpectedly, the PHT–DC-Na coprecipitate containing PVP showed a depressed dissolution rate in the same medium. A two-way cross-over study was carried out for a coprecipitate of PHT, DC-Na and PVP prepared in a ratio of 1:1:1 (w/w) and the physical mixture of these ingredients in six rabbits. The area under the blood concentration–time curve of PHT following the administration of the coprecipitate was about 1.63 times that of the physical mixture in rabbits. It is suggested that PVP–DC-Na is a useful combination of carriers for PHT coprecipitates, considerably improving the dissolution and bioavailability of poorly water-soluble PHT.

Keywords——coprecipitate; sodium deoxycholate; phenytoin; dissolution; bioavailability; polyvinylpyrrolidone; polyethylene glycol; hydroxypropylcellulose

It was reported that the bioavailability of a poorly water-soluble drug is controlled by its solubility and dissolution rate in the gastrointestinal tract.[2)] A coprecipitate of such a drug with a water-soluble material such as polyvinylpyrrolidone (PVP)[3)] or a bile acid[4)] shows enhanced dissolution rate and bioavailability of the drug. Phenytoin (PHT) is practically insoluble in water, and its absorption varies significantly from brand to brand as well as from dosage form to dosage form.[5)] The authors reported that a PHT formulation prepared as an amorphous powder by coprecipitating PHT with sodium deoxycholate (DC-Na) showed remarkably improved dissolution of PHT *in vitro*.[6)] Conventional coprecipitating methods generally use a single carrier. We are aware of only one study on a combination carrier, which reported that the combination of 40% polyethylene glycol 6000 (PEG 6000) and 60% dextrose as the carrier for a coprecipitate yielded the most rapid dissolution of tolbutamide.[7)] No work has been done on the dissolution rate of a drug from coprecipitates with a combination of a bile acid and a water-soluble polymer.

The purpose of the present investigation was to evaluate the dissolution characteristics and bioavailability of PHT in the coprecipitates prepared with various combinations of DC-Na and a water-soluble polymer, as carriers.

Experimental

Materials——PHT, JP X, and DC-Na were purchased from Fujinaga Seiyaku Co., Ltd. (Lot 37157), and Kanto Chemical Co., Tokyo, respectively. PVP K-15, K-30 and K-90 (molecular weights of 10000, 40000 and 360000, respectively) were obtained from Tokyo Kasei Industrial Co., Tokyo. Polyethylene glycol 4000 (PEG 4000) and hydroxypropylcellulose (HPC) were of JP X grade. All other chemicals were of reagent grade, and were used as received.

Preparation of Dosage Forms——Flow charts for the preparation of dosage forms are shown in Fig. 1.

a) Simple Blending Method: PHT crystals were passed through a 100 mesh sieve and the residue on a 200 mesh sieve was collected. The sieved PHT crystals were blended with DC-Na and PVP uniformly in a blender to make a physical mixture.

b) Coprecipitation Method: Coprecipitate of PVP, DC-Na and PHT was prepared from the physical mixture of specified proportions of the three components by a coprecipitation method. The mixture was dissolved in ethyl alcohol at 50 °C on a steam bath. The solvent was removed *in vacuo* using a rotary evaporator at 40 °C. The residue was dried *in vacuo* at about 40 °C for 48 h and sieved with 100—200 mesh sieves. The formulations of coprecipitates prepared are shown in Table I.

Powder X-Ray Diffraction Study——Powder X-ray diffractometry was carried out with a Rigaku Denki Ru 200 diffractometer by using monochromated Cu-K_α radiation.

Infrared (IR) Absorption Spectrometry——The absorption spectra in the region from 1900 to 1600 cm^{-1} were obtained by the KBr-tablet method using a Shimadzu IR-435 double-beam IR spectrometer.

Dissolution Study——The dissolution of PHT was tested in JP X disintegration test medium No. 2 (pH 6.8) at an agitation speed of 100 rpm at 37 °C. Samples tested were 200 mg of PHT crystals and coprecipitate preparations equivalent to 200 mg of PHT. After a sample was added to the medium, 5 ml of the test medium was removed at

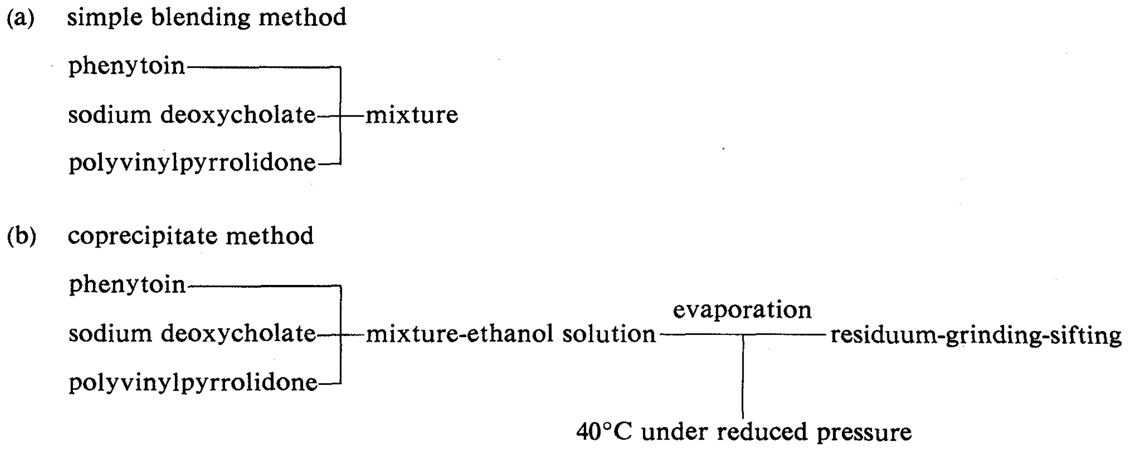

Fig. 1. Preparation of Phenytoin Powder, and Sodium Deoxycholate and Polyvinylpyrrolidone Coprecipitate

TABLE I. Formulations of PHT Coprecipitates

Material	Coprecipitate		
	P-I	P-II	P-III
PHT	1	1	1
DC-Na	1	1	1
PVP K-15	1	—	—
PEG 4000	—	1	—
HPC	—	—	1

appropriate time intervals through a membrane filter (pore size; 0.22 μm), and immediately replaced with an equal volume of fresh test medium. One ml of sample solution from the coprecipitate containing PVP was diluted to 5 ml with JP X disintegration test medium No. 2 (pH 6.8) prior to assay, though the other sample solutions were directly subjected to assay. The absorbance of sample solutions other than those containing PVP was measured by a previously reported method.[8] For sample solutions containing PVP, the assay was performed by an high performance liquid chromatography (HPLC) method.[9]

The test was done in triplicate for each test sample.

Plasma Level of PHT in Rabbits——White male rabbits (2.7—3.3 kg) which had been fasted for 48 h, but allowed free access to water, were orally administered P-I physical mixture or coprecipitate equivalent to 100 mg of PHT with 40 ml of water. Blood samples were taken from the rabbits at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 24 h after the administration with heparinized syringes. Doses were administered by the cross-over arrangement after an interval of one week. The plasma samples were assayed for PHT by an enzyme immunoassay method.[10]

Results and Discussion

The X-Ray Diffraction Patterns and IR Spectroscopy

The X-ray diffraction patterns of P-I, P-II and P-III coprecipitates and P-I physical mixture are shown in Fig. 2.

In P-I and P-II coprecipitates, the characteristic peaks attributed to PHT crystal were absent and only a halo was observed in the X-ray diffraction patterns. The X-ray peaks characteristic of PHT were observed in P-III coprecipitate and in the physical mixtures. It was reported that PHT loses its crystal structure upon coprecipitation with PVP or DC-Na when the weight ratio of the polymer to PHT exceeds three or five, respectively.[6] In this study, even though the ratio of polymer to drug was less than the above values, P-I and P-II showed no X-ray diffraction peaks. These results suggest that combined carriers such as DC-Na–PVP and DC-Na–PEG interact more strongly with PHT than a single-component carrier during and after the solvent removal process and synergetically inhibit or retard the crystallization of the drug.

Figure 3 shows the IR spectra of PHT coprecipitates and PHT crystals. Peaks at 1773, 1740 and 1719 cm^{-1} were assigned to carbonyl $\nu_{C=O}$ bands characteristic of PHT (spectrum D). In the IR spectrum of P-I coprecipitate (A), the characteristic bands at 1740 and 1719 cm^{-1} had disappeared and two new bands at 1726 and 1661 cm^{-1} were found. For

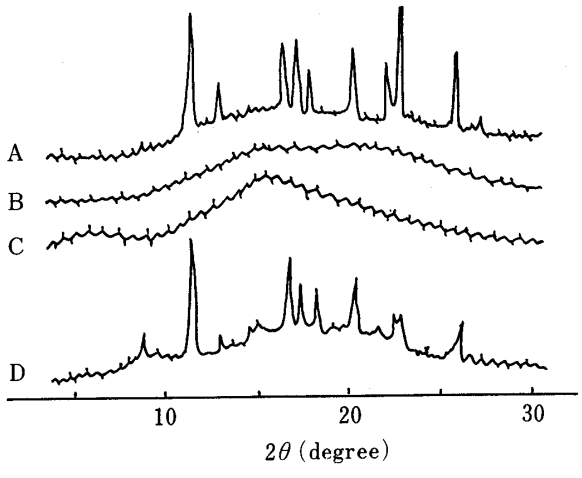

Fig. 2. X-Ray Diffraction Spectra of PHT Coprecipitates and the Physical Mixture

A, P-I physical mixture; B, P-I coprecipitate; C, P-II coprecipitate; D, P-III coprecipitate.

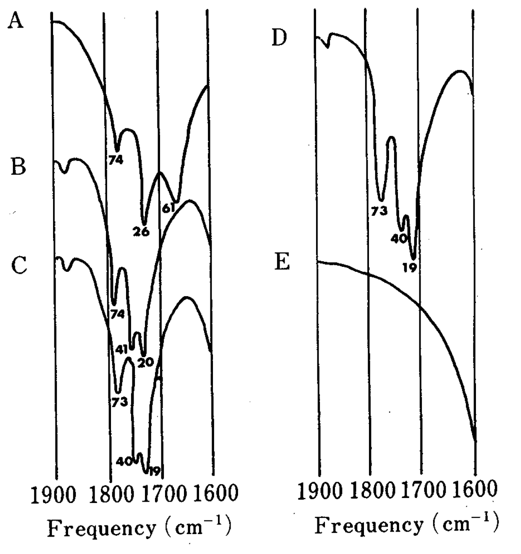

Fig. 3. IR Spectra of PHT Coprecipitates and PHT Crystals

A, P-I coprecipitate; B, P-II coprecipitate; C, P-III coprecipitate; D, PHT crystals; E, DC-Na.

coprecipitates P-II (B) and P-III (C), smaller changes than those in A were observed, though slight deviations to higher frequency were seen. It was reported that an interaction between PHT and a carbonyl group causes the stretching band at 1715 cm^{-1} of PHT to move to a higher frequency range.[11] The evidence described above suggests that a molecular complex was formed between PHT and the DC-Na–PVP carrier, while weak hydrogen bonding was formed between PHT and DC-Na–PEG or CD-Na–HPC.

Dissolution Studies

Figure 4 shows the dissolution of PHT from P-I, P-II and P-III coprecipitates. The dissolution of PHT–DC-Na (1 : 1) coprecipitate is also shown for comparison. P-I coprecipitate gave a drug concentration of 278 μg/ml within 5 min; this is 9.3 times higher than the solubility of PHT crystals (30.2 μg/ml at 37 °C). The combination of DC-Na–PVP as the carrier of the P-I coprecipitate yielded the most rapid dissolution of PHT. However, from 5 min after the start of dissolution, the solution concentration gradually declined, which indicates that PHT recrystallized in the bulk solution. Such characteristic dissolution behavior has also been observed in the dissolution of polymorphs or anhydrous drugs. The greater dissolution rate of P-I coprecipitate is compatible with the amorphous form demonstrated by the X-ray diffraction pattern, and the components probably formed a molecular complex as indicated by IR spectrometry. It was reported that a phenytoin–PVP coprecipitate improved the dissolution characteristics of PHT at a PHT-to-PVP ratio of 1 : 3, and the maximum concentration reached in the dissolution was about 2.5×10^{-4} M (=63.1 μg/ml).[12] In this study, however, a maximum concentration of 278 μg/ml, which is 4.4 times that reported previously, was reached at a PHT–DC-Na–PVP ratio of 1 : 1 : 1. Sekikawa *et al.* reported that addition of PVP inhibited or retarded the crystallization of sulfamethizole in ethanol solution, and consequently the solid drug coprecipitated with PVP without crystallization.[13] The inhibitory effect might be enhanced by adding DC-Na to PVP or PEG solution. Saito reported that nonionic polymers and ionic surfactants formed complexes and their aqueous solutions showed very different physical properties from those of the individual solutions.[14] On the other hand, P-II and P-III coprecipitates showed equivalent dissolution behavior to PHT–DC-Na (1 : 1) coprecipitate. If the drug interacted strongly in P-II coprecipitate and was completely dispersed in the matrix, forming amorphous drug, the dissolution should have

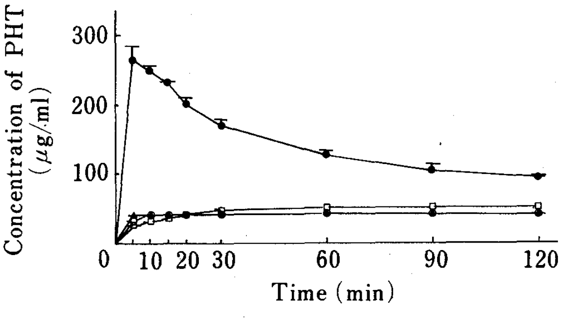

Fig. 4. Dissolution of PHT from Various Coprecipitates in 500 ml of JP X Disintegration Test Medium No. 2 (pH 6.8) at 37 °C

Each point denotes the mean of three determinations ± S.E.

●, P-I coprecipitate; ▲, P-II coprecipitate; □, P-III coprecipitate; ○, PHT–DC-Na (1 : 1) coprecipitate.

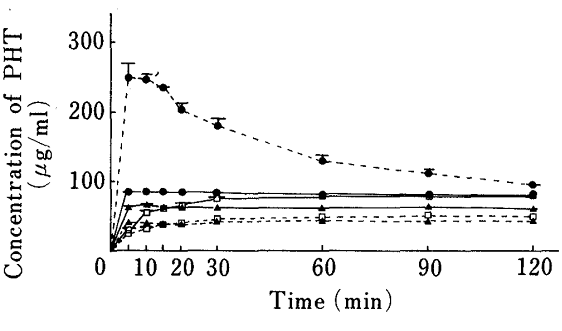

Fig. 5. Comparison of Dissolution of PHT from Three Coprecipitates in 500 ml of JP X Disintegration Test Medium No. 2 (pH 6.8) in the Presence and Absence of 0.1% Polysorbate 80 at 37 °C

Each point denotes the mean of three determinations ± S.E.

Presence of 0.1% polysorbate 80: —●—, P-I coprecipitate; —▲—, P-II coprecipitate; —□—, P-III coprecipitate; absence of 0.1% polysorbate 80: ---●---, P-I coprecipitate; ---▲---, P-II coprecipitate; ---□---, P-III coprecipitate.

been improved as much as in the case of P-I coprecipitate. However, the solubility was lower than that of P-I coprecipitate, even though PHT was amorphous in P-II coprecipitate as demonstrated by the X-ray diffraction pattern. The lower dissolution rate of P-III was due to the presence of crystalline PHT, whose existence was demonstrated by the X-ray diffraction pattern shown in Fig. 2.

The proposed dissolution mechanism for a coprecipitate consists of three processes: 1) the coprecipitate interacts with water in its vicinity,[12] 2) finely dispersed drug in the matrix is released, and 3) solubilized drug is supersaturated in the diffusion layer.[15] The dissolution mechanism of P-I coprecipitate is postulated to involve the release of amorphous PHT in step 2) because a molecular complex of PHT and PVP–DC-Na is formed in the matrix. Figure 5 shows the dissolution of PHT from P-I, P-II and P-III coprecipitates in a test medium containing 0.1% polysorbate 80. P-II and P-III coprecipitates increased their dissolution rates when the wettability was improved. However, the dissolution of P-I was significantly depressed by the incorporation of polysorbate 80 in the test medium. Hydrophilic binders such as PVP can improve the wettability of a drug. Despite improved wettability, however, dissolution of P-I was depressed in the medium containing the surfactant. This paradoxical result is considered to be related to the physical characteristics of the polymer used. Heng and Wan reported that PVP retarded drug dissolution, and that polysorbate 80 also depressed the dissolution of sulfanilamide–PVP granules.[16] It seems likely that a protective layer was formed on the surface of P-I particles, probably due to an interaction of PVP with polysorbate 80.

Figure 6 shows the dissolution rates of PHT from PHT crystals, P-I physical mixture, and P-I, P-II and P-III coprecipitates in toluene or methanol. When toluene, a nonpolar solvent, was used as the test medium instead of JP X No. 2 solution, the amount of PHT dissolved from each coprecipitate was only 4—10%. The apparent dissolution rates of PHT were in the following order: P-I < P-III < P-II. Wettability of the polymer may be one of the factors that influence the dissolution rate of the drug in toluene. The dissolution rate of PHT crystals in toluene was similar to that of P-I physical mixture. On the other hand, no difference was found in the dissolution of coprecipitates in methanol. Kigasawa *et al.* reported that PHT dissolved rapidly from a ground mixture of PHT and gelatin in a nonpolar solution (toluene).[17] They suggested the existence of hydrogen bonding between the additive and the drug. We speculate that the coprecipitate, which consists of DC-Na, polymer species and PHT, forms strong hydrogen bonding in a nonpolar solvent (toluene), whereas the hydrogen

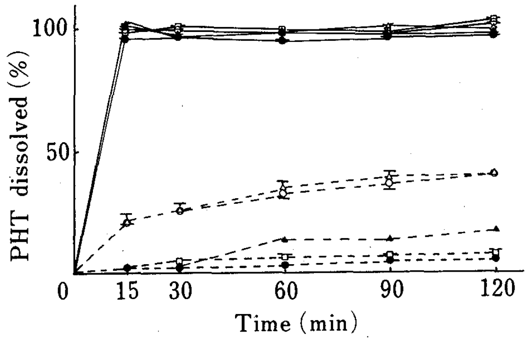

Fig. 6. Dissolution of PHT from Preparations in Toluene (----) or in Methanol (——) at 20 °C

Each point denotes the mean of three determinations ± S.E.

●, P-I coprecipitate; ▲, P-II coprecipitate; □, P-III coprecipitate; ○, P-I physical mixture; △, PHT crystals.

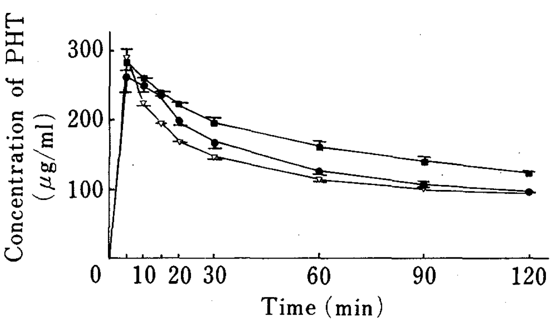

Fig. 7. Dissolution of PHT from PHT–DC-Na–PVP (1 : 1 : 1) Coprecipitate Prepared with PVP of Various Molecular Weights in 500 ml of JP X Disintegration Test Medium No. 2 (pH 6.8) at 37 °C

●, PVP K-15; ■, PVP K-30; ▽, PVP K-90.

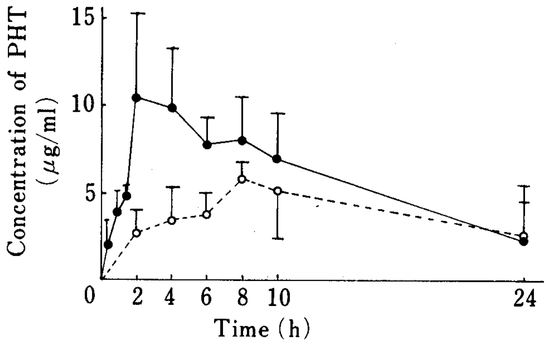

Fig. 8. Mean Plasma Levels of PHT Following the Oral Administration of 300 mg of PHT–DC-Na–PVP (1 : 1 : 1) Coprecipitate (●) and Physical Mixture (○) in Rabbits

Each point represents the mean of six determinations ± S.D.

TABLE II. Mean Plasma Levels of PHT and AUC Compared by the Paired *t*-Test

Time (h)	Plasma level[a] (μg/ml)		Significance of difference[b] between physical mixture and coprecipitate	
	PHT–DC-Na–PVP physical mixture[c]	PHT–DC-Na–PVP coprecipitate[d]		
0.5		2.11 ± 1.48		
1		3.88 ± 1.26		
1.5		4.71 ± 0.35		
2	2.63 ± 1.29	10.4 ± 4.99	$t = 3.551$	$0.01 < p < 0.05$
4	3.39 ± 2.07	9.89 ± 3.40	$t = 3.247$	$0.01 < p < 0.05$
6	3.72 ± 1.32	7.79 ± 1.57	$t = 4.181$	$0.001 < p < 0.01$
8	5.79 ± 1.05	8.07 ± 2.45	$t = 3.049$	$0.01 < p < 0.05$
10	5.11 ± 2.75	7.06 ± 2.55	$t = 1.435$	N.S.
24	2.65 ± 1.99	2.38 ± 3.16	$t = -2.553$	N.S.
AUC (h · μg/ml)	89.08 ± 36.5	144.4 ± 42.3	$t = 4.296$	$0.001 < p < 0.01$

a) Mean ± S.D. *b*) t (5, 0.001) = 6.859; t (5, 0.01) = 4.032; t (5, 0.05) = 2.571. *c*) Dose: 100 mg/body. *d*) Dose: 100 mg/body. AUC: area under the blood concentration–time curve. N.S.: not significant.

bonding is easily broken in a polar solvent (methanol).

Figure 7 shows the dissolution rate of PHT from P-I coprecipitates with PVP of various molecular weights. The initial dissolution was higher than that of PHT crystals; the solution immediately became supersaturated, and the dissolution gradually declined. No significant difference in dissolution was found among the coprecipitates prepared with PVP of various molecular weights, although the dissolution rate of the drug in a coprecipitate with lower-molecular-weight PVP was reported to be greater than that in the case of higher-molecular-weight PVP.[12] This may be because of unfavorable physical properties such as poor dispersability, wetting, and clumping in aqueous solution in the case of the latter coprecipitate. However, in the present study no significant difference was found in the dissolution characteristics of the coprecipitates. This is probably because DC-Na improved the unfavorable properties of higher-molecular PVPs.

In Vivo Absorption Studies

Figure 8 shows the mean plasma levels of PHT following the oral administration of P-I coprecipitate and the physical mixture in rabbits. At 2 h after administration, P-I coprecipitate gave the maximal plasma level of 10.4 μg/ml, which was 1.8 times in the case of the physical mixture.

This initial increase in drug absorption might be due to the high dissolution rate of P-I coprecipitate, *i.e.*, 9.3 times that of P-I physical mixture. The plasma level of PHT following administration of the P-I coprecipitate was significantly higher than that of P-I physical mixture up to 8 h (Table II). The AUC of the P-I coprecipitate up to 10 h following the oral administration was 1.62 times that of the physical mixture.

The P-I coprecipitate, using the mixture of PVP and DC-Na instead of PVP or DC-Na alone, showed excellent drug dissolution characteristics and bioavailability in rabbits. It is suggested that a molecular interaction between PHT and the CD-Na–PVP combined carrier exists. It is concluded that the use of a combined carrier consisting of DC-Na and PVP in a ratio of 1 to 1 (w/w) greatly improves the dissolution characteristics and bioavailability of PHT, an extremely poorly water-soluble drug.

References and Notes

1) Present address: *Pharmaceutical Department, Tokyo Women's Medical College Daini Hospital, 2–1–10 Nishiogu, Arakawa-ku, Tokyo 116, Japan.*
2) D. E. Wurster and P. W. Taylor, *J. Pharm. Sci.*, **54**, 169 (1965).
3) H. Sekikawa, T. Naganuma, J. Fujiwara, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **27**, 31 (1979).
4) R. G. Stoll, T. R. Bates, K. A. Nieforth, and J. Swarbrick, *J. Pharm. Sci.*, **58**, 1457 (1969).
5) A. P. Meliken, A. B. Straughn, G. W. A. Slywka, P. L. Whyatt, and M. C. Meyer, *J. Pharmacok. Biopharm.*, **5**, 133 (1977).
6) S. Yakou, S. Yamazaki, T. Sonobe, and M. Sugihara, *Yakuzaigaku*, **46**, 140 (1986).
7) M. J. Miralles, J. W. Mc-Ginty, and A. Martin, *J. Pharm. Sci.*, **71**, 302 (1982).
8) S. Yakou, Y. Yajima, T. Sonobe, M. Sugihara, and Y. Fukuyama, *Chem. Pharm. Bull.*, **30**, 319 (1982).
9) A. Kuchiki, K. Sasaki, A. Inoue, and I. Sugimoto, *Yakuzaigaku*, **44**, 31 (1984).
10) S. Kurooka, N. Sunahara, and M. Hashimoto, *Proc. Symp. Chem. Physiol. Pathol.*, **16**, 33 (1976).
11) M. Tsuruoka, T. Hashimoto, H. Seo, S. Ichimasa, O. Ueno, T. Fujinaga, M. Otagiri, and K. Uekama, *Yakugaku Zasshi*, **101**, 360 (1981).
12) H. Sekikawa, J. Fujiwara, T. Naganuma, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **26**, 3303 (1978).
13) H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **27**, 1223 (1979).
14) S. Saito, *Yukagaku*, **12**, 133 (1963).
15) W. L. Ciou and S. Riegelman, *J. Pharm. Sci.*, **60**, 1281 (1971).
16) P. W. S. Heng and L. S. C. Wan, *J. Pharm. Sci.*, **74**, 269 (1985).
17) K. Kigasawa, K. Maruyama, M. Tanaka, K. Watanabe, and O. Koyama, *Yakugaku Zasshi*, **101**, 733 (1981).