Dissolution and Bioavailability of Phenobarbital in Solid Dispersion with Phosphatidylcholine

Makiko Fujii,* Katsuhiko Harada, Keiko Kakinuma and Mitsuo Matsumoto
Showa College of Pharmaceutical Sciences, 3-3165 Higashimatsuyugawaraken, Machida-shi, Tokyo 194, Japan. Received November 2, 1990

The dissolution of phenobarbital (PB) from solid dispersion with phosphatidylcholine (PC) was studied. PB was present in an amorphous state in solid dispersion (PB-PC) if the mole fraction of PB was under 0.75. Thus, supersaturation was observed when an excess amount of PB-PC was dispersed in pH 1.2 and 6.8 media. The degree of supersaturation was largest when the mole fraction of PB was 0.25, although it was only 1.3-fold of the PB solubility in this case. Dissolution from PB-PC was rapid and complete in both pH 1.2 and 6.8 media regardless of the mole fraction of PB, above 90% within 5 min. Bioavailability after the oral administration of PB-PC to rabbits with a dose of 15 mg/kg equivalent to PB was compared with that of PB crystals. The area under the plasma concentration curve was bigger, but not significant. The maximum concentration was significantly higher, and the time to maximum concentration was significantly faster. These results indicate that the absorption rate became high with PB-PC because the dissolution was rapid.

Keywords phenobarbital; phosphatidylcholine; solid dispersion; dissolution rate; amorphous; oral administration; rabbit; bioavailability

We previously reported the physicochemical properties of phenobarbital (PB) solid dispersion with phosphatidylcholine (PC).1) PB resembles indomethacin (IM) with a plane like molecular shape. PB is present in an amorphous state in solid dispersion with PC (PB-PC) when its mole fraction is less than 0.75, to the same extent as IM. The interaction between PC and PB is similar to that between PC and phenytoin (PHT) which also has an oxopyrimidine ring.

We examined the dissolution behavior of PB from solid dispersion and compared it with IM2) or PHT3) solid dispersion with PC (IM-PC, PHT-PC). Also, the plasma concentration of PB after its oral administration to rabbits was studied.

Experimental

Materials The same PB and PC as in the previous report were used.1) Other chemicals were of reagent grade.

Preparation of Solid Dispersion PB-PC and a physical mixture of PB and PC were prepared by the method previously reported.1) The figure in parentheses following PB-PC is the mole fraction of PB. In the case of PB-PC (0.50), the prepared PB-PC was held at 70°C for 10 min or at 160°C for 10 min to obtain the stable and metastable forms, respectively.

Solubility Studies An excess amount of sample (equivalent to 300 mg of PB) was put into 50 ml of the 1st fluid (pH 1.2) or the 2nd fluid (pH 6.8) of the JP XI disintegration test kept at 37±0.1°C. Details have been previously reported.2,3) The concentration of PB was determined by ultraviolet absorption at 252 nm after diluting with 0.1 N NaOH solution. The determination was done within 2 h after diluting for PB degrades in alkaline solution. The results represent the mean of 3 experiments.

Dissolution Studies The dissolution patterns were tested by a method similar to PHT-PC.3) A sample equivalent to 250 mg of PB was dispersed in 4 ml of test solution and the suspension was dropped into 500 ml of test solution at 37±0.1°C with stirring by a paddle at 100 rpm. The method for the determination of PB concentration is described in the solubility studies section. All studies were done in triplicate.

Animal Experiments Four white male rabbits (body weight 2.6-3.0 kg) were fasted for 24 h but allowed to take water freely. A sample equivalent to 15 mg/kg of PB suspended in 4 ml of water was orally administered to a rabbit followed by the administration of 26 ml of water. About 100 g of food was given after 24 h of blood sampling. Doses were administered by the cross-over arrangement after a two-week interval.

Determination of PB in Plasma The plasma concentration of PB was determined by high performance liquid chromatography (HPLC)2,3,9) The stationary phase, Bondapak C18 (3.9 x 150 mm), was kept at 50°C. The mobile phase was a mixture of acetonitrile: pH 5.4 phosphate buffer solution (17:83, v/v). The flow rate was 1.0 ml/min. PB was detected

Fig. 1. Solubility Behavior of PB-PC in pH 1.2 (a) and 6.8 (b) Medium

Δ, PB crystals; □, physical mixture (0.75); ○, PB-PC (0.25); ●, PB-PC (0.50); ◯, PB-PC (0.75).

© 1991 Pharmaceutical Society of Japan
at 230 nm. PB concentrations were calibrated by an external standard method on the basis of peak height measurement.

Statistical Analysis Statistical analysis was performed using a one-way analysis of variance. Follow-up analysis was performed using Dunnett's test. A p value of < 0.05 was accepted as demonstrating statistical significance.

Results and Discussion

Solubility and Dissolution Studies Figure 1 shows the time courses of the PB concentration in pH 1.2 and pH 6.8 media. The solubilities of PB in pH 1.2 and pH 6.8 media were 1.7 and 2.2 mg/ml, respectively. The PB concentrations with the physical mixture (0.75) were 1.7 mg/ml (pH 1.2) and 2.1 mg/ml (pH 6.8), and agreed with the PB solubilities. When PB-PC (0.25) was used, the PB concentrations rose temporarily to 2.2 mg/ml (pH 1.2) and to 2.8 mg/ml (pH 6.8) initially. When PB-PC (0.50) or (0.75) was used, the PB concentrations were slightly higher than the PB solubilities, 1.9 mg/ml (pH 1.2) and 2.5 mg/ml (pH 6.8). When PB-PC was used, PB concentrations after 24 h agreed with the solubility regardless of the PB mole fraction in PB-PC.

PB was present in an amorphous state in PB-PC when its mole fraction was under 0.75. When PB-PC was used, PB concentrations were temporarily higher than PB solubilities because of an amorphous state of PB, and the equilibrium concentrations agreed with solubilities. These time-concentration curves were similar to those of IM-PC and PHT-PC.3

In the case of IM-PC, the degree of supersaturation became higher when the mole fraction of the drug became higher as long as IM was present in an amorphous state.2

It was considered that the diffusion of the drug in solid dispersion was the rate-limiting step because PC was insoluble in water. However, in the case of PB-PC, the degree of supersaturation was the largest when the mole fraction of PB was as low as 0.25. Thus, it was not explained merely by diffusion. When the mole fraction of PB was under 0.50, it was considered that the hydrogen bond exists between PB and a polar head group of PC.12 Thus, PB exists first near the polar head group of PC and the remaining PB exists near the hydrophobic part of PC. It was considered that water has a higher affinity to the polar head group of PC than to the hydrophobic part, so that the PB existing near the polar head group dissolved faster than the PB existing near the hydrophobic part of PC; hence the dissolution might change.

PB-PC (0.50) showed two energy conditions, a metastable and a stable state.13 They were induced by heating PB-PC at 70°C (stable) or 160°C (metastable). Figure 2 shows the effect of conditions on the solubility behavior in pH 6.8 medium. PB-PC (0.50) in the stable state showed no supersaturation. On the other hand, PB-PC in the metastable state showed similar solubility behavior to PB-PC. It became apparent that there is a difference in the solubility between the two conditions, and a metastable state was of greater advantage for the improvement of the solubility behavior of PB.

Figure 3 shows the dissolution patterns. In pH 1.2 medium, the dissolution percent of PB within 5 min was 35% from PB crystals, whereas it was above 90% from PB-PC. The dissolution was a little faster from PB-PC (0.25) than from PB-PC (0.75), but there was no marked difference. In pH 6.8 medium, the dissolution from PB crystals was faster than that in pH 1.2 because of the higher solubility. In contrast, dissolution from PB-PC (0.50) did not affect the pH; 90% of the PB dissolved within 5 min. PB dissolved almost completely from PB-PC though PHT dissolved only 75% from PHT-PC (0.25) in pH 6.8 medium,19 although the same interaction pattern was indicated by infrared spectra and thermal analysis. It was considered to be because the solubility of PB is very much higher (about 100-fold) than PHT, and/or PB, but not PHT, is ionized in pH 6.8.

As mentioned above, the maximum concentration of PB with PB-PC was only 1.2 times the PB solubility, but the dissolution rate was improved, particularly in the pH 1.2 medium.

Bioavailability Studies PB is absorbed well by oral

---

Fig. 2. Solubility Behavior of PB-PC (0.50) in Different Conditions ---, conventional PB-PC (0.50); --, stable; ---, metastable.

Fig. 3. Dissolution of PB from PB-PC in pH 1.2 (a) and 6.8 (b) Medium Δ, PB crystals; □, physical mixture (0.75); ○, PB-PC (0.25); ●, PB-PC (0.75).
administration, but sometimes the absorption is delayed because of slow dissolution. There were not many problems in steady-state therapy of the convulsant, but some problems arose if PB was used as a hypnotic. The dissolution rate of PB is improved in both pH 1.2 and 6.8 by using PB-PC. Thus, the plasma concentration of PB following PB-PC administration was compared with that following PB crystals. PB-PC (0.75) was used because the dissolution rate showed no marked difference between the mole fraction of PB, the physicochemical property showed no change with time as did PB-PC (0.25) or (0.50), and the amount of PC in PB-PC was minimum so that the influence of PC is thought to be small.

Figure 4 shows the plasma concentrations of PB following oral administration at a dose of 15 mg/kg PB equivalent. The bioavailability parameters (maximum concentration \( C_{\text{max}} \), time to maximum concentration \( T_{\text{max}} \) and area under the plasma concentration curve (\( AUC \)) are shown in Table I. Following the administration of PB as PB-PC (0.75), the plasma concentration after 1 h was 20 mg/ml, and was 2-fold following an administration of PB crystals. \( C_{\text{max}} \) became significantly higher and \( T_{\text{max}} \) was faster than those with PB crystals. This suggests the improvement of the absorption rate. \( AUC_{0-48h} \) after an administration of PB-PC (0.75) tended to be higher, but not significantly so. It was considered that the improvement of the dissolution rate affected the absorption rate.

Table I. Bioavailability Parameters after Oral Administration of PB at a Dose of 15 mg/kg

<table>
<thead>
<tr>
<th></th>
<th>( C_{\text{max}} ) (µg/ml)</th>
<th>( T_{\text{max}} ) (h)</th>
<th>( AUC_{0-48h} ) (µg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB crystals</td>
<td>18.8 ± 2.2</td>
<td>5.0 ± 0.6</td>
<td>567 ± 63</td>
</tr>
<tr>
<td>PB-PC (0.75)</td>
<td>25.3 ± 0.6</td>
<td>2.0 ± 0.9</td>
<td>692 ± 7</td>
</tr>
</tbody>
</table>

Each value represents mean ± S.E. of 4 rabbits. a) Significantly different (p < 0.05) from PB crystals.

References and Notes