

DISSOLUTION BEHAVIOR OF PHENYTOIN-BILE SALT COMPLEXES PREPARED BY CO-GRINDING

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The physicochemical properties of phenytoin (PHT)-bile salt complexes comprised of sodium dehydrocholate (DHCNa), sodium deoxycholate (DCNa) or sodium cholate (CNa) prepared by co-grinding were investigated by X-ray diffraction analysis, DSC and dissolution kinetics. All X-ray diffraction peak intensities of the co-ground PHT-bile salt [1 mol: 1 mol] mixtures were decreased by grinding for 3 h, and showed a halo pattern of a noncrystalline solid. The solubility of ground products with DCNa, DHCNa and CNa were 212, 56, 68 times higher, respectively, than those of physical mixtures.

KEYWORDS dissolution behavior; mechanochemistry; phenytoin-bile salt complex; molecular interaction; solubility; noncrystalline solid

It is well known that components of bile such as bile salts, which are physiological surfactants, play an important role in intestinal absorption.¹⁾ Many studies^{2,7)} have shown that bile salts markedly increase the solubility and dissolution rate of poorly water-soluble drugs, since the activity of bile salts is mainly due to micellar solubilization.

On the other hand, Miyata et al.^{8,9)} reported that bile acids form multimolecular inclusion compounds with a variety of organic substances in the solid state. Since the solid-state molecular interactions between the drugs and bile salts are affected by the enthalpy of the solid, interactions in the solidstate may affect the dissolution behavior of the drug and the bioavailability of pharmaceutical preparations. In this study, we prepared the phenytoin-bile salt complexes by a co-grinding method, and investigated their dissolution behavior.

EXPERIMENTAL

Grinding Conditions Equimolar mixtures of various kinds of bile salt, sodium dehydrocholate (DHCNa), sodium deoxycholate (DCNa) or sodium cholate (CNa), and phenytoin (PHT) were ground in a 350 ml agate centrifugal ball mill at 360 rpm for 3h.

Characterization Physicochemical properties of the ground complexes were characterized by X-ray powder diffraction analysis and differential scanning calorimetry (DSC).

Dissolution Behavior The dissolution profiles of the ground complexes were measured as follows: The sample powder containing 500 mg PHT was introduced into 200 ml of dissolution medium at $37 \pm 0.5^\circ\text{C}$. The test solution was stirred by a paddle (JPXII) at 150 rpm. The drug concentrations of the samples contained in DCNa, DHCNa and CNa were determined spectrophotometrically at 224 and 280 nm to correct the absorption of the bile salts. Initial dissolution curves were determined as follows: A compressed pellet of the ground sample with DCNa fixed to the holder was set up on the dissolution instrument and rotated at 200 ± 5 rpm in 100 ml of JPXII 2nd fluid (pH 6.8) at $37 \pm 0.5^\circ\text{C}$.

RESULTS AND DISCUSSION

Effects of Co-grinding on Physicochemical Properties of PHT-Bile Salts System

The results of X-ray diffraction profiles of the co-ground PHT-bile salt [1 mol: 1 mol] mixtures were as follows: All diffraction peak intensities of the ground products were decreased by grinding and showed a halo pattern after 3 h grinding, suggesting that the mixtures transformed into a noncrystalline solid during grinding. Yakou et al.⁶⁾ reported that the PHT-DCNa coprecipitate containing more than 3 mol of DCNa was a stable noncrystalline solid, but the coprecipitate containing less than 2 mol of DCNa was not. They did not refer to the stoichiometric PHT complex with bile acid. Therefore, their results suggested that the solid obtained by coprecipitation method was different from the equimolar complex obtained by grinding.

DSC curves of the ground products with PHT-DCNa, DHCNa or CNa showed 30, 20 and 30°C lower melting points, due to that of the complex, respectively, than that of intact PHT, indicating the molecular interactions of these complexes were different from those of intact PHT crystals.

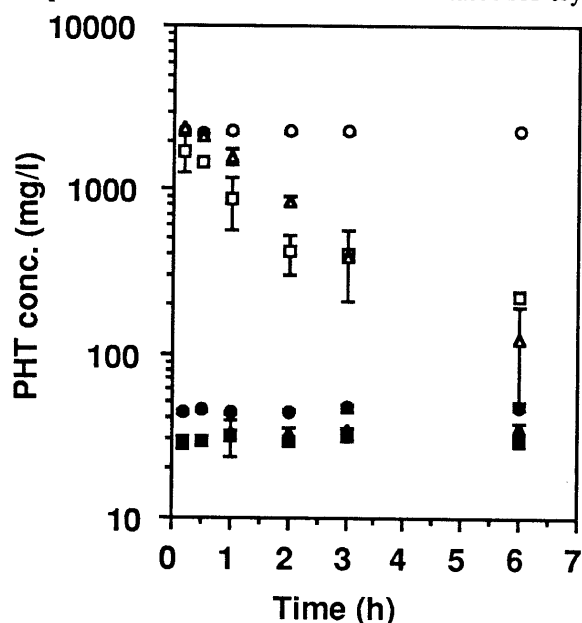


Fig. 1. Dissolution Behavior of Ground PHT-Bile Salt [1:1] Complexes at pH 6.8, 37°C (O, ●), the products with DCNa; (□, ■), with DHCNa; (Δ, ▲), with CNa; open and closed symbols represent the ground products and physical mixtures, respectively. The bars represent standard deviation (n=3).

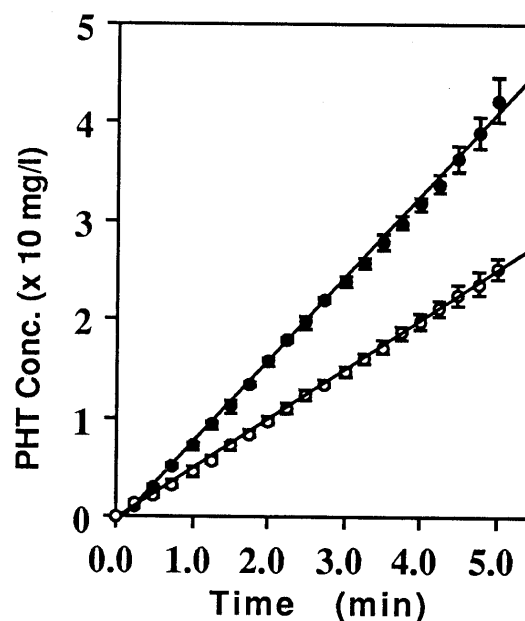


Fig. 2. Initial Dissolution Curves of Ground PHT-DCNa Complex at pH 6.8 and 37°C by the Rotating Disk Method (●), PHT-DCNa (1:1); (O), PHT-DCNa (1:2); the bars represent standard deviation (n=3).

Dissolution Behavior of PHT-Bile Salt Complexes Obtained by Co-Grinding

Figure 1 shows the dissolution profiles of PHT ground products with various kinds of bile salts at pH 6.8; all PHT-bile salt ground products dissolved vary rapidly. The ground product with DCNa dissolved completely without any residue, and gave a constant drug concentration at 2460 ± 11 mg/l during drug dissolution for 6 h, indicating the solubility was higher than this constant value. On the other hand, the concentration of the ground products with DHCNa or CNa increased rapidly to give maximum concentrations of 1700 ± 420 and 2350 ± 24.7 mg/l, respectively, at 10 min and then declined to 223 ± 14 and 162 ± 2.9 mg/l after 6 h. The solubility of physical mixtures with DCNa, DHCNa and CNa were 47.9 ± 1.8 , 29.7 ± 1.0 and 35.3 ± 2.2 mg/l, respectively. The maximum concentration of all ground products were much

higher than those of the respective physical mixtures. Yakou et al.⁶⁾ reported that the solubility of the PHT-DCNa complex (weight ratio, 1:5) obtained by coprecipitation in buffer at pH 6.8 was 120 mg/l. Therefore, from these results it seems that the ground products were much more soluble than the solids obtained by co-precipitation, indicating that molecular interactions in the ground products with bile salts were different from those obtained by the co-precipitation method. The ground complex with DHCNa or CNa dissolved rapidly at the initial dissolution stage; after that, the PHT concentration decreased with the elapse of time, since it was transformed into the stable form. However, the PHT concentration profile of the ground complex with DCNa showed a plateau. The dissolution behaviors suggested that the ground [1:1] complex with DHCNa or CNa was metastable in water, but that with DCNa was very stable.

Evaluation of Solubility of PHT-Bile Salt Complexes by Initial Dissolution Kinetics

In the previous section, the solubility of the ground PHT complexes [1:1] with DHCNa or CNa was estimated from Fig. 1, but the solubility of the ground PHT-DCNa complex was not determined, since all solid was dissolved in the solution. Therefore, to estimate the solubility of the ground PHT-DCNa complex, dissolution rate experiments were performed by the rotating disk method as reported by Sekiguchi and Kanke.¹⁰⁾

$$C_{as} = J_a C_{hs} / J_h \quad \text{eq. 1}$$

where C_{as} is the solubility of meta-stable form, C_{hs} is the solubility of the stable form, J_a is the initial dissolution rate constant of the metastable form, and J_h is the initial dissolution rate constant of the stable form.

The solubility of the crystalline form of PHT was measured in pH 6.8 buffer at 37°C by the powder dispersion method and estimated to be 27.2 ± 0.17 mg/l (n=5). Figure 2 shows the initial dissolution rate curves of ground PHT-DCNa [1:1] and [1:2] complexes in pH 6.8 buffer at 37°C. The solubility of the ground PHT: DCNa [1:1] and [1:2] complexes were calculated from the initial dissolution rate constant using eq. 1 and estimated to be 10200 ± 590 and 6064 ± 200 mg/l (n=3), respectively. The solubility of the ground PHT-DCNa [1:2] complex was lower than that of the [1:1] complex. This result suggests that PHT:DCNa [1:1] complex formed the most water-soluble complex in the solid state, indicating that the finding was not due to micellar solubilization, but due to formation of [1:1] molecular complex. Therefore, we concluded that the solubility of PHT complexes with DCNa, DHCNa and CNa obtained by grinding were 212, 56 and 68 times higher than those of the physical mixtures, respectively. These results suggested that PHT formed water-soluble complexes with bile salts by mechanochemical treatment.

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