Influence of pH and Phospholipid Species on Release of Acetaminophen from Tablets Containing Phospholipids

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The release of acetaminophen (AAP) from tablets containing phospholipids was examined using hydrogenated soybean phospholipid (HSL) and its main components, phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylinositol (PI), although the PI was not well purified (PI rich). Tablets compressed with 400 kgf had about 9% porosity and 2—4 kgf hardness. The release patterns of AAP from the tablets were fitted to Higuchi's square root of time law. The release rate was influenced by the pH of the medium, though solubility of AAP did not change with pH. PC tablets showed faster release at pH of less than 3 than that at pH of above 3, whereas PI rich and HSL tablets showed faster release at pH of above 3 than that at pH of less than 3. The release rate from PE tablets was little affected by pH. A linear relationship exists between the release rate of AAP and the rate of water absorption by the tablet. The ionization state of the phospholipids changes with the pH of the medium, and affects the hydration characteristics. The fully ionized state, at pH of less than 3 in the case of PC and above 3 in the case of PI is most effective on hydration. PE does not fully ionize because of intermolecular hydrogen bonding.

Key words phospholipid; controlled release; pH dependence; phosphatidylcholine; phosphatidylethanolamine; phosphatidylinositol

Lipids are often used as controlled release excipients. Inert wax matrices such as carnauba wax or hydrogenated castor oil wax have been used in sustained release dosage formulations, but they are so hydrophobic that additives, like surfactants or water-soluble materials must also be used for efficient release to occur.[1-6] Soybean phospholipids and their hydrogenated forms have also been used as sustained release excipients in granules,[7] tablets,[8] suppositories[9] and microcapsules.[10] Phospholipids are amphoteric and so do not have the disadvantages of wax matrices. However, in most cases, the soybean phospholipids used in the studies are mixtures of phospholipids. Soybean phospholipids are largely mixtures of phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylinositol (PI), and also contain other lipids such as glycolipids or triglycerides. Their composition depends on the raw soybeans from which they are derived and the separation method used to prepare them.[11-13] The structures of PC, PE and PI differ structurally only in terms of the hydrophilic group, but their hydrophilic and hydrophobic balances are different. Thus, their uses as excipients differ; for example, PC is useful as an emulsifier in o/w emulsions, but PE and PI are useful as emulsifiers in w/o emulsions.[14] Therefore, the phospholipid composition might affect the release rate because of the differences in the degree of hydrophilicity among phospholipids. Moreover, phospholipids are weak electrolytes and their degree of dissociation depends on pH, so pH might also affect release rate.

In this study we used several phospholipids, PC, PE, a PI rich fraction, and commercial hydrogenated phospholipids (HSL), and compared the release patterns of a drug in solution at various pHs to determine the effect of phospholipid species and pH on release rate. All phospholipids are hydrogenated type, because they are stable to oxidation. A direct compressed tablet with no other additives was used as dosage form to simplify the experimental conditions. Acetaminophen (AAP) was used as a model drug, because the solubility of AAP does not change with pH.

Experimental

Materials AAP was of JP XII grade. HSL was a gift from Nikko Chemicals Co., Ltd., Tokyo, Japan (Lecinol S-10 lot. 2951). PC was also from Nikko Chemicals Co., Ltd.(hydrogenated type, Lecinol S-10EX). PE and PI-rich fraction (PI rich) were obtained from HSL by a method previously reported.[15,16] The fatty acyl composition in the phospholipids was about stearic acid : palmitic acid = 85 : 15. The other chemicals used were of reagent grade.

Measurement of Phospholipid Composition The PC content was determined by the Reinecke salts method.[17] PE was determined by the DNP-ethanolamine derivative method.[18] The total phospholipid concentration was determined by P-moribdate complex method.[19] The phospholipid contents are shown in Table 1.

Preparation of Tablets The AAP powder sieved through 150 mesh and the appropriate phospholipid were mixed well in a glass mortar. The weight ratio of AAP to phospholipid was fixed at 16 : 84. One hundred mg of the mixture was compressed at 50—1000 kgf by the direct compression method, with a tablet-hitting pressure displacement measuring system (N-20 E, Okadaseiko Co., Ltd., Tokyo, Japan) as a single-punch tablet machine equipped with a flat-face punch (diameter, 7 mm).

Measurement of Tablet Hardness The stress required to break a tablet by compression was defined as the tablet hardness. It was measured using a semiautomatic tablet hardness tester (Model TS-50 N, Okadaseiko Co., Ltd.).

Measurement of Tablet Porosity The thickness and diameter of the tablets were measured with a micrometer, and the tablet volume calculated. The bulk density of the tablets was calculated from their weight and volume. The true density of the tablets was measured with a pycnometer (AccuPyc 1330, Micromeritics, Georgia, U.S.A.). The porosity was calculated from the bulk density and the true density.

Table 1. Phospholipid Contents of Samples Used in This Study

	Sample name			
	PC	PE	PI rich	HSL
Phosphatidylcholine	>95%	< 1%	7%	20%
Phosphatidylethanolamine	< 2%	>90%	20%	21%
Total phospholipid	99%	>95%	77%	80%

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Dissolution Study The release patterns were determined in a JP XII dissolution test apparatus (NTR-VS6P, Toyama Sangyo Co., Ltd., Osaka, Japan) controlled by a TCP flow personal computer system with a spectrophotometer (UV-160 with cell positioner and controller, Shimadzu Co., Kyoto, Japan). The test solution (500 ml) was kept at 37 °C and stirred at 100 rpm with a paddle. At appropriate time intervals, the test solution was filtered through a fine filter (20 μm, F-72, Toyama Sangyo) and circulated through the spectrophotometer, and the absorbance at 243 nm was determined. A test solution at pH 1.2 was the 1st fluid used in the disintegration test in the JP XII, at pH 2 was HCl-KCl buffer solution and at pH 3—7 were 0.1 M phosphate buffer solution combination of H_3PO_4–NaH_2PO_4 (pH 3), H_3PO_4–K_2HPO_4 (pH 4—6) and KH_2PO_4–NaOH (pH 7). Each experiment was carried out for 23 h. In all cases, the pH at the end of the test was the same as the initial pH.

Water Absorption Study The same apparatus as used in the release test was used in the water absorption test. At appropriate time intervals, the tablet was carefully taken out of the test solution with a spatula, put on paper (Kim-wipes®) for a few seconds to remove test solution from the surface of and was weighed. The amount of water absorbed was calculated as (weight − 100 mg).

Results and Discussion

Relationship between Compression Force and Tablet Properties The relationship between the compression forces and the tablet hardness was examined to determine the compression force. The results are shown in Fig. 1. The hardness of the PC tablets and the other phospholipid tablets increased with compression force up to 100 and 400 kgf, respectively, and above that remained almost constant even with change in compression force. The maximum hardness differed with the type of tablet; it was about 4 kgf in the PC and PE tablets, which was higher than the 2 kgf for the PI rich and HSL tablets.

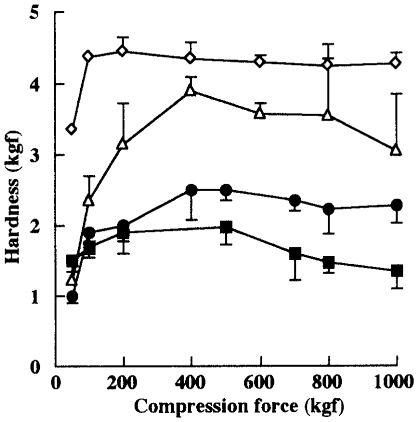

Fig. 1. Relationship between Compression Force and Tablet Hardness
◇, PC; △, PE; ■, PI rich; ●, HSL.

It is well known that the release of a drug from a matrix depends on the porosity of the matrix. Therefore, the porosity of PC and HSL tablets was determined. In the case of a compression force of 50 kgf, the porosities of the PC and HSL tablets were 13 and 15%, respectively. When the compression force was 400 kgf or above, the porosities of the PC and HSL tablets were 9 and 8%, respectively. The release profiles of AAP from PC and HSL tablets compressed at various forces are shown in Fig. 2. In PC tablets the release pattern was affected by neither porosity nor compression force; in HSL tablets, release was fast when the compression force was 50 kgf because the tablets were not as hard and disintegrated easily. Therefore, the compression force was set at 400 kgf.

Release Pattern of AAP from Tablets Figure 3 shows the release pattern of AAP from various types of tablets at pH 1.2—7.0. In all cases, the release profile of AAP was fitted to Higuchi's square root of time law when the % released was less than 80. The release rates were calculated from the linear part of the plots and are shown in Fig. 4. In all cases except that of the PE tablets, the release pattern changed at pH 3. The release from the PC tablets in the pH 1.2 and 2 solutions was faster than that in the other solutions, almost 100% was released within 10 h. The tablets became small and some of the PC dispersed in the pH 1.2 and 2 solutions at the end of the tests. Among the pH 3—7 solutions, the release rates were almost the same, and the tablets were slightly larger when the test over (23 h) than when it had started. The release from the PE tablets was slow over the entire pH range, and the PE tablets did not disintegrate but expanded slightly after 23 h. In contrast, the release from the PI rich tablets was slow at low pH, and then became constant; almost 100% was released within 8 h at pHs of above 3. The PI rich tablets at the end of the tests were slightly smaller than they were at the beginning. The release from the HSL tablets was faster at pH 7 than at pH 1.2, but the pH dependence of the release rate was not as strong as in the PC and PI rich tablet cases. This is because HSL is a mixture of phospholipids of which pH dependency is the opposite.

Water Absorption of Tablets In the release tests, the tablets tended to expand and the degree of expansion differed depending upon the type of tablet and the pH of the solution. Water penetration into the matrix is important for the release of a drug from an inert matrix. The water absorption of each type of tablet was therefore

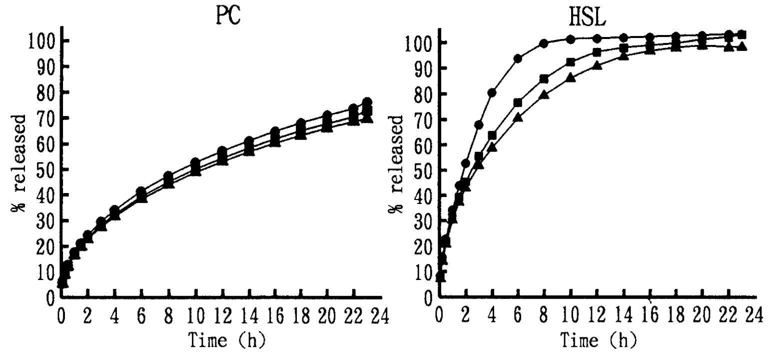

Fig. 2. Release Profiles of AAP from PC and HSL Tablets Compressed at 50 kgf (●), 400 kgf (■), and 1000 kgf (▲) in pH 7 Test Solution

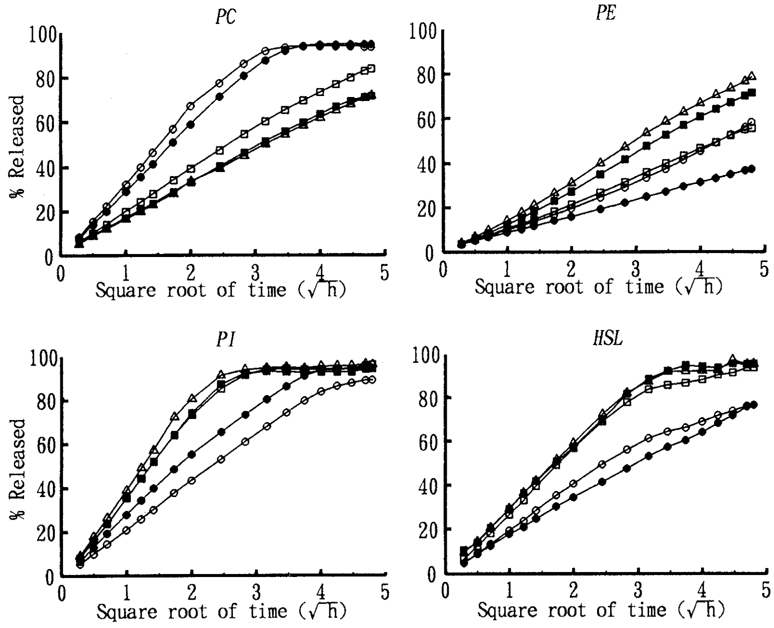

Fig. 3. Release Profiles of AAP from Various Types of Phospholipid Tablets Compressed at 400 kgf, in Test Solutions at Various pHs
○, pH 1.2; ●, pH 2; □, pH 3; ■, pH 4; △, pH 7.

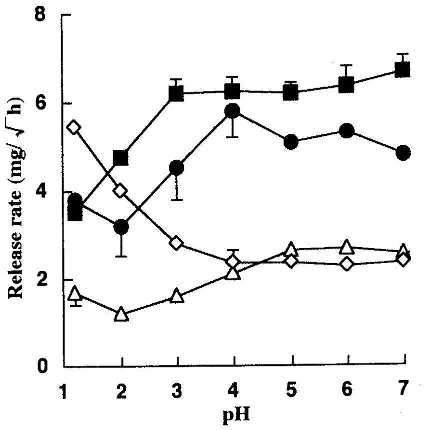

Fig. 4. Relationship between Release Rate of AAP and pH of Test Solution
◇, PC; △, PE; ■, PI rich; ●, HSL.

determined at pH 1.2 and pH 7; the highest and lowest release rates of AAP are shown in Fig. 5. When the amount of water absorbed exceeded 100 mg, the tablets became too breakable to weigh in the same procedure. The amount of water absorbed by the PC tablets was greater at pH 1.2 than at pH 7, and the amount of that absorbed by the PI rich and HSL tablets was greater at pH 7 than at pH 1.2. The PE tablets absorbed little water at both these pHs. The water absorption *vs.* the square root of time profiles showed a linear relationship in all cases.

The water penetration rate into a tablet is shown as the Washburn equation;

$$L^2=(R\gamma\cos\theta/2\eta)t$$

where L is the wetting length of capillary at the time t, R is the radius of the capillary, γ is the surface tension of the solution, η is the viscosity of the solution and θ is the contact angle between the solid and the liquid. The slope of the plot of water absorption *vs.* square root of time, the water absorption rate, shows the square root of $(R\gamma\cos\theta/2\eta)$. When the pH of the solution was changed, the R did not change and the change in γ and η in this case must be negligible; therefore, the influence of pH on the water absorption rate by pH must depend on the contact angle between solid and liquid, that is, interface tension between the phospholipid and the test solution.

Effect of Phospholipid Ionization on Water Absorption Rate Phospholipids have hydrophobic long-chain fatty acids and polar head groups, and therefore are amphophilic. The polar regions exist in various states of ionization, depending on the pH of the bulk. Dissociation constants (pK) for various phospholipids have been reported, determined by various measurement methods.[20,21] The pK value of the phosphate groups of PC, PE and PI was reported to be about 3. The amine group of the choline moiety in PC is positively charged at all pHs. The amine group of the ethanolamine moiety in PE is positively charged at a pH of less than 10—11, and therefore was positively charged over the entire pH range used in this study. PI has no other ionizable groups. PC and PE are zwitterions at pH values above 3. The phosphate groups in PC and PE are protonated at pH values less than 3; however, complete protonation is not achieved in the case of the PE phosphate groups at pH values above 0.5.[21,22] PI is an anion at pH values above 3, and neutral at pH values less than 3.

The ionization state of phospholipids affects the hydration characteristics of the phospholipids, with the fully ionized state having the greatest effect on them. Thus, it was inferred that PI tablets, being negatively charged at a pH of 7, showed high water absorption rates in solutions with a pH of 7, and being neutral at acidic pH, showed low water absorption rates in acidic solutions. In contrast, PC tablets showed low water absorption rates in solutions with a pH of 7, because PC is a zwitterion at this pH, and

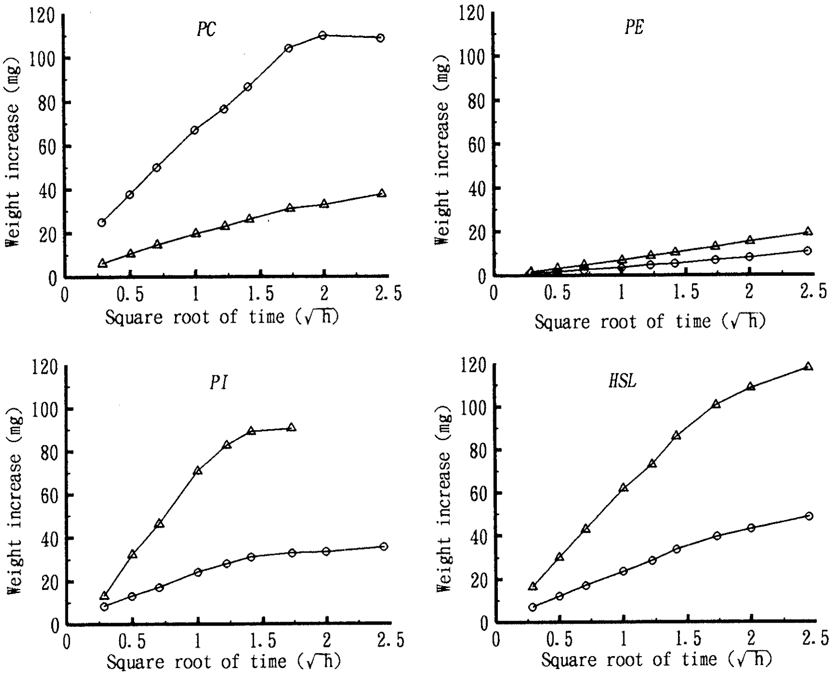

Fig. 5. Water Absorption Profiles of Various Types of Phospholipid Tablets
○, pH 1.2; △, pH 7.

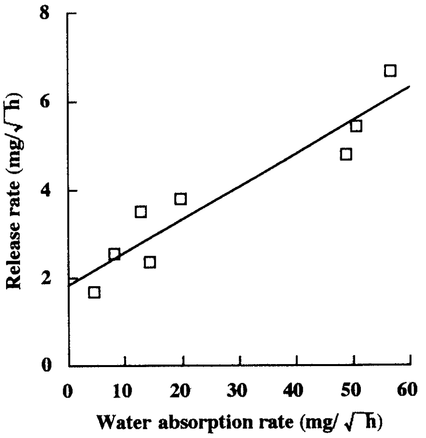

Fig. 6. Relationship between Water Absorption Rate and AAP Release Rate

high water absorption rates in solutions with a pH of 1.2, because it is protonated and positively charged at this pH. PE tablets should show a dependence on pH similar to that of PC tablets; however, they showed lower water absorption rates than did PC tablets in acidic solutions. PE is not completely protonated at a pH of 1.2, and intermolecular hydrogen bonding occurs between the protonated and unprotonated phosphate groups. Thus, PE shows only a small hydration effect and low water absorption rates at pH 1.2—7.

The state of ionization or the phospholipids changed with the changing pH of the solution, and therefore affected the hydration characteristics. Interface tension between the phospholipid and the test solution might be affected by the hydration characteristics of phospholipids. The water absorption rate was about 50 mg/$\sqrt{\text{h}}$ when the phospholipids were positively or negatively charged, and was about 15 mg/$\sqrt{\text{h}}$ when they were neutral or zwitterionic.

The Relationship between Release Rate and Water Absorption Rate The relationship between release rate and water absorption rate is shown in Fig. 6. A linear relationship exists between the water absorption rate and the release rate. Therefore, the water absorption rate is an important factor in the release of AAP from the phospholipid tablets. The main route of release of AAP from the tablets was believed to be diffusion through the water absorbed by the tablet.

The change in the ionization state with a change in the pH of the medium is different with different phospholipids because of different molecular structures. The state of ionization affects the water absorption rates, and consequently the release rates. It is therefore important to know the characteristics of phospholipids when they are used as ingredients for controlled release.

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