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Influence of egg albumin on dissolution of several drugs

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Summary

The dissolution behaviors in water of several drugs in solid dispersion with egg albumin have been studied in comparison with drug alone. The results revealed a marked increase of dissolution rate of acidic drug compared with basic drug The interaction of each drug with egg albumin in aqueous solution and solid state was studied by solubility analysis, thermal analysis and X-ray diffractometry. The solubility of acidic drug was significantly increased with egg albumin concentration. In the solid state, acidic drug dispersed monomolecularly in the matrix of egg albumin. The enhancement of dissolution rate of drug was reflected for the improvement of solubility through complexation and the molecular dispersion of drug in the solid dispersion.

Introduction

The solubilities of poorly water-soluble drugs are found to be increased by their dispersion in a water-soluble carrier (Chiou and Riegelman, 1971; Ford, 1986). The most commonly used carriers are long-chain polymers e.g. polyvinylpyrrolidone or polyethylene glycol (Shefter and Cheng, 1980; Ford et al., 1986; Jachowicz, 1987). However, few attempts to improve the dissolution of drugs using natural polymers have been made in sharp contrast to synthetic polymer. Solid dispersion techniques have been utilized to reduce the particle size of drugs and to increase their dissolution rates (Allen et al., 1978). A natural, innocuous substance is desirable as a carrier from the view point of safety, and a naturally occurring polymer such as protein or polysaccharide may be a good candidate.

Egg albumin (mean molecular weight: 45,000) is a water soluble protein which is widely used in the field of foods, in the pharmaceutical formation. Thus, the present study was undertaken to survey the possible utility of egg albumin as a water-soluble carrier. The solid dispersion of drug with egg albumin was prepared and then the dissolution behavior of the solid dispersion was examined, compared with drug alone. Flurbiprofen, diclofenac acid, pindolol and diltiazem were tested as acidic and basic model drug, respectively.

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Materials and Methods

Materials

The egg albumin was purchased as a guaranteed reagent from Nakarai Chemical Co. Ltd. (Kyoto, Japan). Flurbiprofen (Kaken Pharm. Co. Ltd., Tokyo, Japan), diclofenac acid (Ciba-geigy, Takarazuka, Japan), pindolol (Sankyo Co. Ltd., Tokyo, Japan) and diltiazem (Tanabe Seiyaku Co. Ltd., Osaka, Japan) were used as supplied. The structures and some properties of these compounds were listed in Table 1. All other reagents and solvents were of analytical grade.

Sample preparation

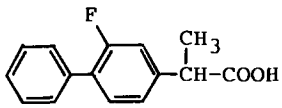
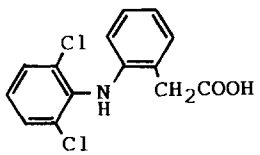
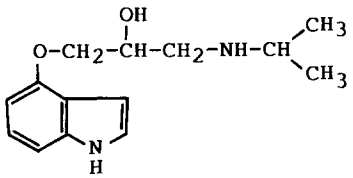
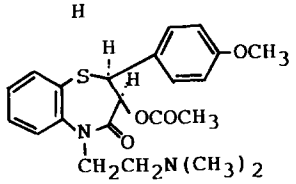
The drug–egg albumin solid dispersions (1 : 1, 1 : 5, 1 : 10 w/w) were prepared by the kneading method. The required amounts of drug and egg albumin were weighed and placed in a mortar, then the mixture was kneaded with 1.4 × that amount of water for 1 h. For example, in the case of drug–egg albumin (1 : 5) solid dispersion, 1 g of drug and 5 g of egg albumin were weighed and kneaded with 8.4 ml of water for 1 h. Drying was carried out under vacuum of 25 °C for 48 h.

Dissolution studies

The dissolution rate of drug from the solid dispersion was determined by the dispersed amount method (Nogami et al., 1969). The equivalent amount of 40 mg of drug as a 100 mesh powder was weighed and put into a dissolution cell. The dissolution medium (100 ml water) was maintained at 37 °C and stirred at 91 rpm. At appropriate intervals, 1 ml samples were removed from the flask, filtered through 1.0 μm membrane filter. The filtrate (0.5 ml) was extracted with 5 ml of chloroform to remove egg albumin. After centrifugation (2000 rpm, 10 min), the organic phase was transfered to a new tube, and the drug concentration was monitored spectrophotometrically at λ_{max} of each drug (shown in Table 1).

TABLE 1

Structures and properties of the compounds

Compound	Structure	Molecular weight	pK_a	λ_{max}	Melting point (°C)
Flurbiprofen		244 27	3 8	247	110–111
Diclofenac acid		296.15	3.5	279	156–158
Pindolol		248.33	9 3	264	171–173
Diltiazem		414.52	7 7	236	104–106

Corrections were applied for cumulative dilution caused by replacing the sample by equal volumes of the original medium.

Solubility studies

Solubility measurements were carried out according to Higuchi and Connors (1965). Excess amounts of drug were added to aqueous solution containing various concentrations of egg albumin and were vigorously shaken at 20 ± 0.5 °C for 3 h, in order to avoid the decomposition of egg albumin, because the decomposition of egg albumin was observed after shaking for 8 h. The solubility of each drug in water after vigorous shaking for 3 h was almost the same as that after usual shaking for 7 days. The suspensions were centrifuged and filtered through a 1.0 μm membrane filter. The filtrate (0.5 ml) was extracted with chloroform and analyzed spectrophotometrically.

Differential scanning calorimetry

Samples, accurately weighed 5 mg, were measured using a scanning rate of 10 °C/min on a Rigaku Thermoflex TG-8110 thermal analyzer (Tokyo, Japan).

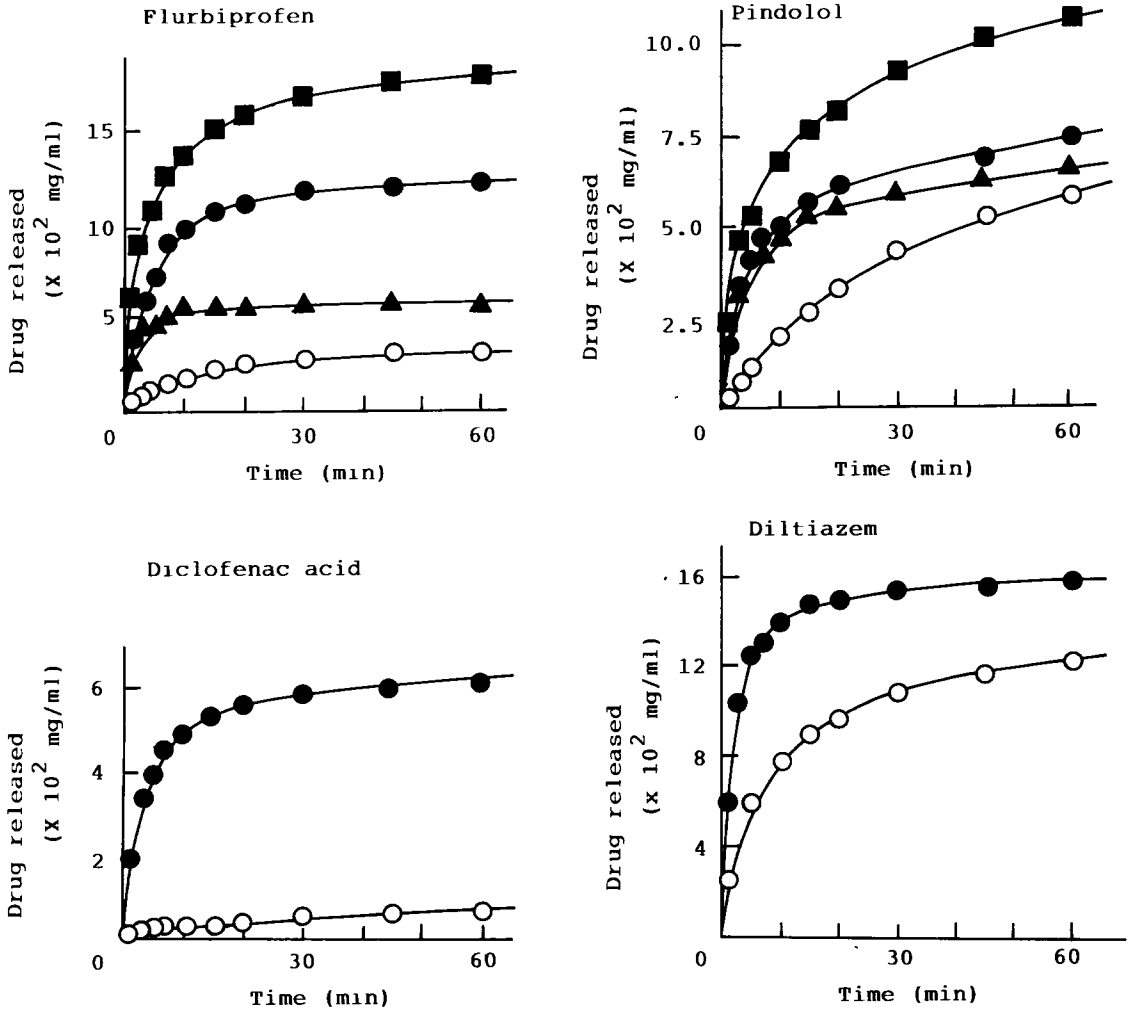


Fig. 1. Dissolution profiles of drug and its solid dispersion with egg albumin in water at 37 °C measured by the dispersed amount method ○, drug alone, ▲, drug egg albumin (1 : 1), ●, drug egg albumin (1 5); ■, drug · egg albumin (1 : 10).

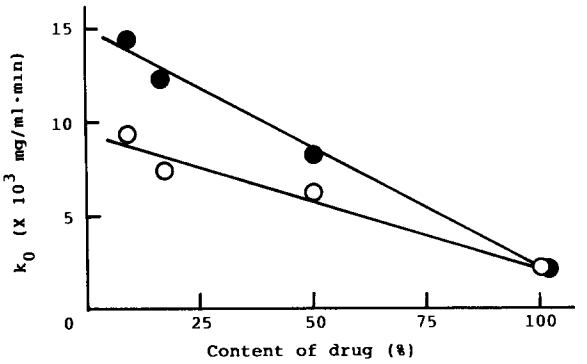


Fig. 2. Initial dissolution rate of drug from solid dispersion with egg albumin as a function of content of drug. ●, flurbiprofen; ○, pindolol.

X-ray diffraction studies

The powder X-ray diffraction patterns were obtained by scanning at 1°/min through the 2θ angle on a Rigaku Denki Geiger Flex-2012 diffractometer (Tokyo, Japan), using Cu-Kα-radiation.

Result and Discussion

Fig. 1 shows the dissolution profiles of each drug from its solid dispersion with egg albumin and drug powders in water at 37°C. The solid dispersion exhibited a significantly greater dissolution rate than that of the drug alone. Interestingly, the remarkable increase of the dissolution rate by egg albumin was observed for acidic drug compared with basic drug. In the case of 1 : 5 solid dispersion with acidic drug, the drug concentration after 60 min of dissolution exceeded that of drug alone as much as 4- and 10-fold for flurbiprofen and diclofenac acid, respectively. On the other hand, the basic drug concentration after dissolution of 1 : 5 solid dispersion exceeded that of drug alone as little as 1.2–1.3 times. The dis-

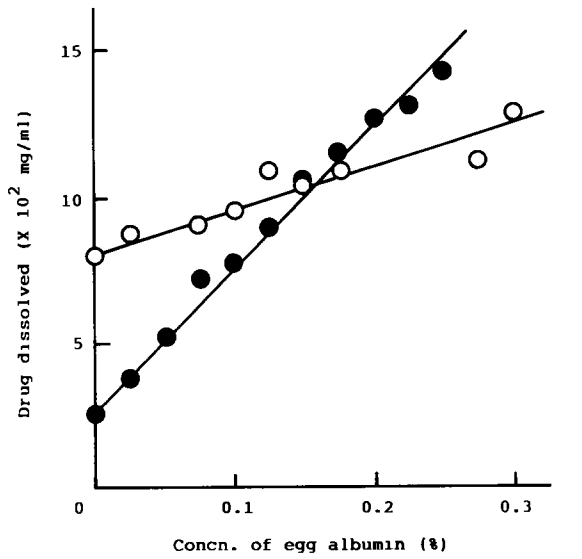


Fig. 3. Phase solubility diagrams of drug–egg albumin systems in water at 20°C. ●, flurbiprofen; ○, pindolol.

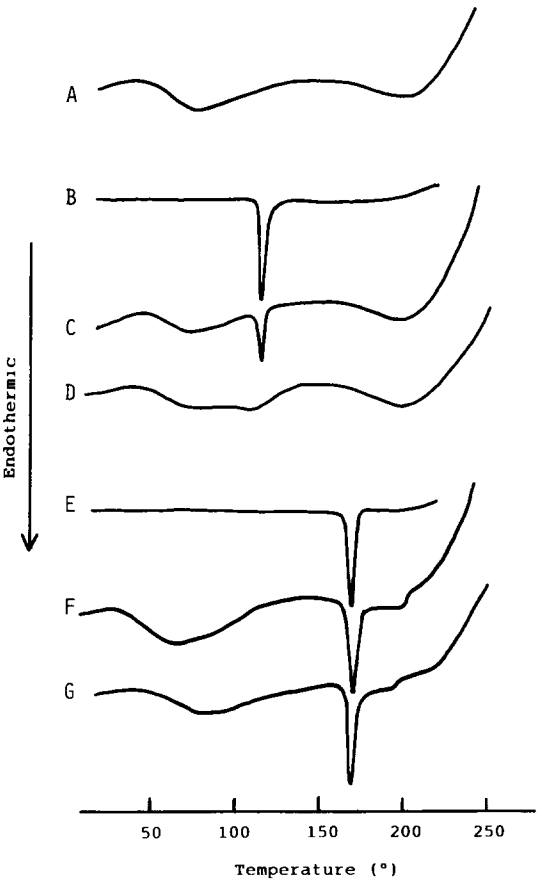


Fig. 4. DSC Thermograms of drug–egg albumin systems. A egg albumin B. flurbiprofen. C· physical mixture of flurbiprofen and egg albumin. D· solid dispersion of flurbiprofen with egg albumin. E· pindolol F: physical mixture of pindolol and egg albumin. G: solid dispersion of pindolol with egg albumin.

solution rates of drugs from solid dispersion increased with egg albumin amount added. To characterize the differences of these dissolution behaviors, the dissolution was expressed using the apparent initial dissolution rate. The initial rates were calculated from dissolution curves as a function of content of drug in the solid dispersion, using the data in Fig. 1 (Fig. 2). The slope for flurbiprofen was greater than that for pindolol, indicating that the effect of egg albumin on the dissolution rate of acidic drug was greater than that of basic drug. So, in order to elucidate the dissolution mechanism of drug from egg albumin solid dispersion, the interaction of drug with egg albumin was studied in the aqueous solution and in the solid state.

Fig. 3 shows the phase solubility diagrams obtained from flurbiprofen and pindolol with egg albumin. The drug solubility increased with increasing egg albumin concentration, the increase being more apparent for flurbiprofen. In addition, flurbiprofen quenched the intrinsic fluorescence of egg albumin that might arise from tryptophan residues (not shown). Therefore, egg albumin may interact more strongly with an acidic drug such as flurbiprofen than the basic drug through hydrophobic and electrostatic interaction, as expected from drug–serum albumin interaction (Tanford, 1973; Vallner, 1977). This leads to the suggestion that complex formation between egg albumin and acidic drug is more likely to occur in the diffusion layer of a dissolving solid dispersion.

Interaction of flurbiprofen and pindolol with egg albumin in solid state was examined by DSC and X-ray diffractometry. Fig. 4 shows the DSC thermograms of drug–egg albumin (1 : 5) solid dispersion and the physical mixture (drug–egg albumin 1 : 5). The physical mixture showed a sharp endothermic peak corresponding to the melting point of each drug, and a broad endothermic peak at about 70 °C which is thought to represent the vaporization of moisture from the egg albumin. The disappearance of the flurbiprofen peak from the solid dispersion indicates that flurbiprofen has interacted with egg albumin and this excludes the presence of a crystalline drug in the dispersion. Such disappearance of drug peak was obtained in the diclofenac acid–egg albumin solid dispersion. On the other hand, pindolol and diltiazem peak existed in solid dispersion curve as well as physical mixture curve. This indicates that the basic drug probably scarcely interacts with egg albumin and then a crystalline drug is present in the dispersion. In order to get further evidence on the possible interaction of acidic drug with egg albumin, X-ray diffractometry study was performed on drug–egg albumin (1 : 5) solid dispersion and physical mixture (Fig. 5). Since the diffraction pattern of egg albumin shows a halo pattern, the diffraction peaks in the physical mix-

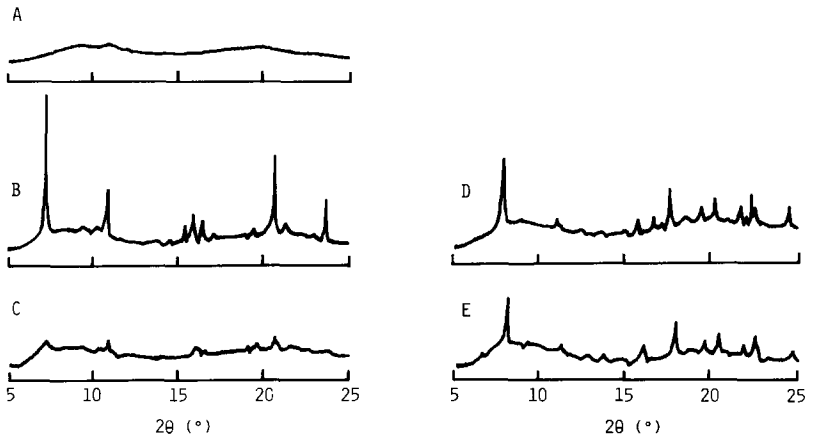


Fig 5. X-Ray diffraction patterns of drug–egg albumin systems. A· egg albumin B: physical mixture of flurbiprofen and egg albumin C: solid dispersion of flurbiprofen with egg albumin. D· physical mixture of pindolol and egg albumin. E: solid dispersion of pindolol with egg albumin.

ture were characterized for the drug. The absence of flurbiprofen peaks in the solid dispersion indicated that an amorphous form only existed in solid dispersion. On the other hand, by comparing the spectra of pindolol–egg albumin solid dispersion with physical mixture, it was found that the solid dispersion contains separated pindolol crystals. Similarly, the absence of the diclofenac acid peak, and the presence of the diltiazem peak were found for each dispersion. These results indicated that the acidic drug disperse monomolecularly in the matrix of egg albumin while basic drug disperse for separated crystals.

The data presented here have shown that the acidic drug solid dispersion with egg albumin increase the dissolution rate by the formation of the water-soluble complex and the lowering of the crystallinity. This result suggests that egg albumin is useful for the enhancement of the apparent absorption rate following the dissolution of some poorly water-soluble acidic drugs in the GI tract.

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