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Mechanism of medicine release from solid dispersion composed of poly(ethylene oxide)-carboxyvinylpolymer interpolymer complex and pH effect on medicine release[1]

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Abstract

Solid dispersion composed of the poly(ethylene oxide) (PEO)-carboxyvinylpolymer (CP) interpolymer complex containing phenacetin (PHE) was prepared using water/ethanol (1/1, v/v) mixture as a solvent. The release mechanism of PHE from the solid dispersion and the effect of pH on PHE release were studied. The physicochemical properties of the solid dispersion were analyzed by powder X-ray diffractometry, thermal analysis and IR spectroscopy. Transmittance of the polymer solution was measured to study the complexation between PEO and CP. The degree of PEO-CP complex formation by hydrogen bonding varied depending on the PEO/CP ratio. It was found that the PHE release from the solid dispersion was controlled by the degree of the complex formation. With PHE powder, the effect of pH on the dissolution behavior was hardly observed. In contrast, the release rate from the solid dispersion increased with a higher pH. This result is probably caused by the fact that the PEO-CP complex is broken at a higher pH.

Keywords: Solid dispersion; Poly(ethylene oxide); Carboxyvinylpolymer; Complex; Release mechanism; pH

1. Introduction

The solid dispersion method is one of several pharmaceutical techniques for controlling medicine release and has been used to improve the dissolution properties and bioavailability of slightly water-soluble medicines (Sekiguchi and

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Obi, 1961; Chiou and Riegelman, 1970; Fujii et al., 1993; Suzuki et al., 1996; Danjo et al., 1997). We have applied the polymer blending technique to the solid dispersion method, and reported that it is feasible to control the release rate of an extremely high water-soluble medicine (oxprenolol hydrochloride) by combining water-insoluble ethylcellulose and water-soluble hydroxypropylcellulose (HPC) (Yuasa et al., 1991, 1992; Ozeki et al., 1994, 1995a,b).

As for the enhancement of dissolution of a slightly water-soluble medicine, we have also made a study using HPC (Yuasa et al., 1993, 1994) and poly(ethylene oxide) (PEO) (Ozeki et al., 1997), and reported that there is a linear relationship between the release rate of the medicine and the degree of interaction between the polymer and the medicine.

PEO is a class of water-soluble linear resin. It has been used in agricultural engineering, food, dental and pharmaceutical fields because of its aqueous solubility, high gelation and low toxicity, and has recently been used for a directly compressed tablet matrix (Graham and McNeill, 1984; Apicella et al., 1993; Yang et al., 1996). PEO consists of the repeat units of $-CH_2CH_2-O-$ and forms complexes with alkaline metal salts, urea and poly(carboxylic acid) (Smith et al., 1959; Bailey and France, 1961; Osada and Saito, 1976; Osada, 1979; Osada and Saito, 1980; Baranovsky et al., 1991; Bogdanov et al., 1992).

Carboxyvinypolymer (CP) is a kind of poly(carboxylic acid) and has been studied as a bioadhesive and controlled release matrix by using it together with HPC (Machida et al., 1980; Ishida et al., 1981; Satoh et al., 1989; Mortazavi and Smart, 1994), hydroxypropylmethylcellulose (Garcia-Gonzales et al., 1992; Perez-Marcos et al., 1996) and polyvinylpyrrolidone (Takayama and Nagai, 1987).

We have noticed some interaction between the polymer carriers of solid dispersion as well as that between the medicine and the polymers. In the previous paper, we attempted to control the medicine release from solid dispersion by means of the interaction between PEO and CP. We reported that the mixture of water/ethanol (1/1, v/v) was useful as the solvent to prepare solid dispersion, it is feasible to control the release of medicine by varying the PEO/CP ratio, and that interaction between PEO and CP by hydrogen bonding occurred in solid dispersion (Ozeki et al., 1998).

In the present paper, we studied the mechanism of medicine release from the solid dispersion composed of the PEO-CP interpolymer complex and the effect of pH on the medicine release.

2. Material and methods

2.1. Materials

PHE (an antipyretic, the density and molecular weight are 1.21 g/cm^3 and 179.22, respectively, and the solubility is 1.31 mg/ml of water at 37°C; Tsukishima Pharmaceutical, Tokyo) was used as the model medicine. PEO (ALKOX™ R-150; the viscosity average molecular weight is about 135000, and the density is 1.24 g/cm^3; Meisei Chemical Works, Kyoto) was supplied by Higuchi, Tokyo. CP (CARBOPOL™ 934P; the nominal average molecular weight is about 3000000, and the density is 1.41 g/cm^3; BF-Goodrich, Brecksville, OH) was supplied by Chugai Boyeki, Tokyo. The densities of PHE, PEO and CP were calculated from the volume measured with an Air Comparison Pycnometer (Model 930, Toshiba-Beckman, Tokyo).

2.2. Preparation of solid dispersions

Solid dispersions were prepared in the same manner as previously reported (Ozeki et al., 1998); that is, powders of PHE, PEO and CP (total amount 5 g) were dissolved in the mixture of water/ethanol (1/1, v/v) (400 ml) at various PEO/CP ratios (w/w), and the solvents were then evaporated. The solid dispersion was ground and dried at 50°C for 24 h under reduced pressure. The granules obtained were sieved (0.85–1.00 mm). The physical mixtures were prepared by

simply mixing the powdered PHE, PEO and CP. Each of them was preliminarily sieved at 75–150 μm.

2.3. Release studies

The release profiles of PHE from PHE powder (sieved at 75–150 μm) and from solid dispersion granules containing 6 mg of PHE were studied with a dissolution tester (TR-5S3, Toyama Sangyo, Osaka), according to the paddle method (JP XIII) at 100 rpm, using 900 ml of the dissolution medium with various pHs at 37 ± 0.5°C. The quantity of PHE was determined spectrophotometrically by measuring the absorbance at 243 nm.

2.4. Powder X-ray diffractometry

Powder X-ray diffraction patterns were measured with a diffractometer (Geigerflex RAD-IB, Rigaku, Tokyo). The operation conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 20 mA and scanning speed, $2\theta = 4°$/min.

2.5. Thermal analysis

Differential scanning calorimetry (DSC) curves were measured with a DSC instrument (SSC/560S, Seiko Instruments and Electronics, Tokyo). The heating rate was 4°C/min and nitrogen gas flowed at the rate of 70 ml/min.

2.6. Transmittance of polymer solution

Transmittance of the polymer solutions at 600 nm was determined with a spectrophotometer (Ubest-30, JASCO, Tokyo). The concentration of the polymer solution was 0.02% (w/v). The PEO-CP mixture was prepared by mixing the respective solutions.

2.7. IR spectroscopy

IR spectra were recorded with an infrared spectrophotometer (IR-810, JASCO, Tokyo). The polymer films were prepared by casting the polymer solution on a Teflon petri dish and directly used for the IR measurement.

2.8. Optical microscopy

An optical microscope (SMZ-10, Nikon, Tokyo) was used to observe the morphology of solid dispersion granules before and after the dissolution test at various pHs.

3. Results and discussion

3.1. Release mechanism of PHE from solid dispersions composed of PEO-CP interpolymer complex with various PEO/CP ratios

The release profiles of PHE from PHE powder and solid dispersion granules with various PEO/CP ratios in distilled water are shown in Fig. 1. The percentage of PHE in solid dispersion was 20%. The release rate of PHE obviously varied depending on the PEO/CP ratio and reached the minimum at the PEO/CP ratio of 50/50. Then, we measured the powder X-ray diffraction patterns and the DSC curves to study the physicochemical properties of the solid dispersions.

The powder X-ray diffraction patterns and the DSC curves of PHE, CP, PEO and their physical mixtures and solid dispersions are shown in Figs. 2 and 3, respectively. In Fig. 2, PHE crystalline

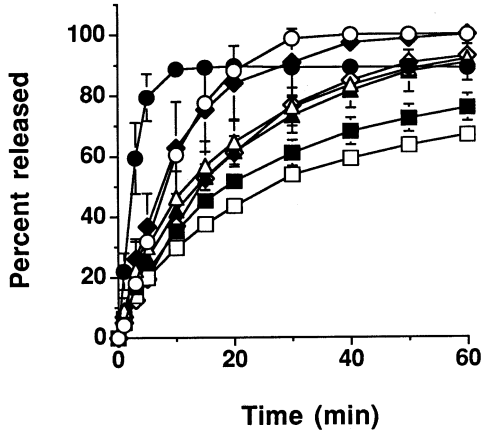

Fig. 1. Release profiles of PHE from solid dispersion granules of PEO-CP interpolymer complex with various PEO/CP ratios. ○, PHE powder. Solid dispersions (PEO/CP: ●, 100/0; △, 75/25; ▲, 62.5/37.5; □, 50/50; ■, 37.5/62.5; ◇, 25/75; ◆, 0/100). Each point represents the mean ± S.D. ($n = 3$).

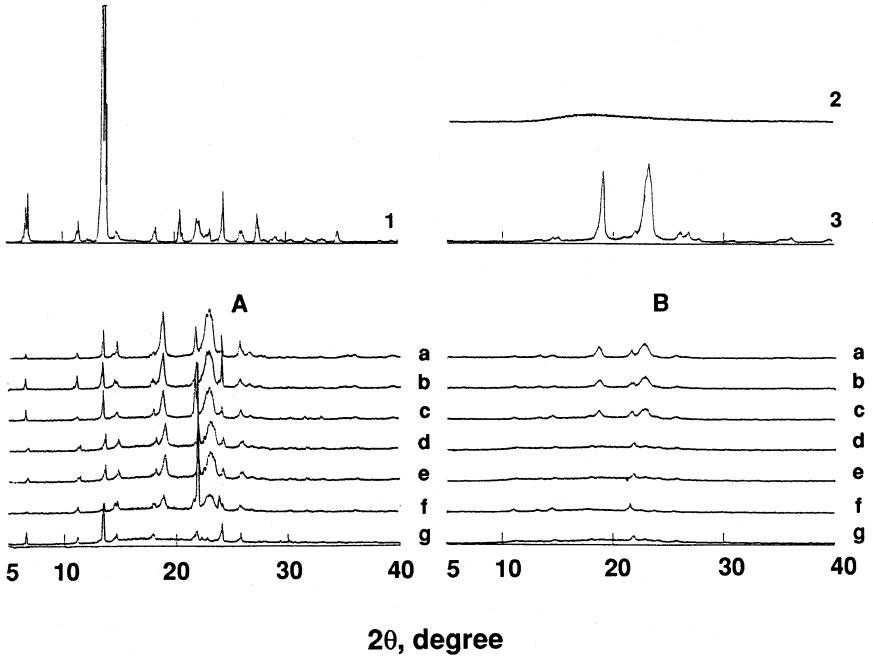

Fig. 2. Powder X-ray diffraction patterns for PHE, CP, PEO, physical mixtures and solid dispersions. 1, PHE; 2, CP; 3, PEO. Physical mixtures (A) and solid dispersions (B) containing 20% of PHE (PEO/CP: a, 100/0; b, 75/25; c, 62.5/37.5; d, 50/50; e, 37.5/62.5; f, 25/75; g, 0/100).

peaks were clearly observed in all the physical mixtures. The peak intensity of PHE in solid dispersions extremely decreased compared with that in physical mixtures. As for the PEO crystalline peaks in solid dispersions, the intensity markedly decreased compared with that in physical mixtures and the peaks were not observed at the PEO ratio of 50% and less. In Fig. 3, no change in the melting endothermic peak based on the PEO crystal around 67°C was observed in physical mixtures. The peak based on the PHE crystal around 136°C was observed in physical mixtures except for the PEO/CP ratio of 100/0 (PHE-PEO system). The reason for the disappearance of the endothermic peak in this system is probably that PHE became amorphous because of the precedent melting of PEO and the enhancement in the molecular mobility during the heating process, which is in agreement with the manner reported by Sugimoto et al. (1980) and the authors (Yuasa et al., 1994; Ozeki et al., 1997). In solid dispersions, no PHE endothermic peak was observed at any PEO/CP ratio. The PEO endothermic peak in solid dispersions was shifted to a lower temperature compared with that in physical mixtures and disappeared at the PEO ratio of 50% and less. These results suggest that the crystallinity of PHE extremely decreased and most PHE existed in the amorphous state in solid dispersions. Further, PEO in the crystalline state disappeared in solid dispersions at 50% and less of PEO.

We previously reported that PEO-CP interaction occurred between the ether group of PEO and the carboxylic group of CP by hydrogen bonding (Ozeki et al., 1998). So, the transmittance of the polymer solution was measured to study the interpolymer complexation at various PEO/CP ratios.

Fig. 4 shows the transmittance of aqueous and ethanolic polymer solutions with various PEO/CP ratios. These solvents were used for the prepara-

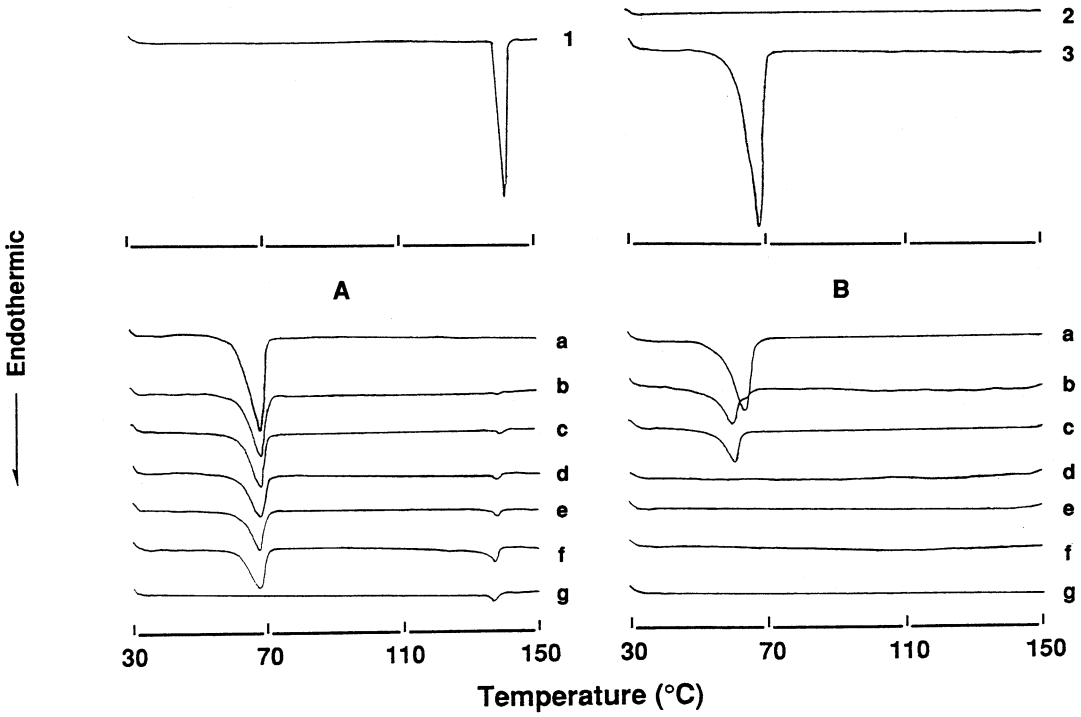

Fig. 3. DSC curves for PHE, CP, PEO, physical mixtures and solid dispersions. 1, PHE; 2, CP; 3, PEO. Physical mixtures (A) and solid dispersions (B) containing 20% of PHE (PEO/CP: a, 100/0; b, 75/25; c, 62.5/37.5; d, 50/50; e, 37.5/62.5; f, 25/75; g, 0/100).

tion of solid dispersions. In the case of PEO or CP alone, a high transmittance was observed in both solutions. In PEO-CP mixtures, the transmittance varied depending on the PEO/CP ratio and showed the minimum value at the ratio of 50/50, indicating the maximum degree of the complex formation between PEO and CP. Fig. 5 shows the relationship between the transmittance and the time required to release half of the amount of the medicine (T_{50}). A good correlation was observed between these two factors ($r = 0.868$). These results indicate that the degree of formation of the water-insoluble complex between PEO and CP by hydrogen bonding varies depending on the PEO/CP ratio, causing changes in the release rate of PHE from solid dispersions.

We subsequently studied the effect of pH of the dissolution medium on the medicine release from solid dispersions at the PEO/CP ratio of 50/50, where the release rate showed the minimum.

3.2. Effect of pH on release behavior of PHE from PHE powder and solid dispersions

The release profiles of PHE from PHE powder and solid dispersion granules with various pHs and the plots of T_{50} are shown in Figs. 6 and 7, respectively. The percentage of PHE in solid dispersion was 20%. The effect of pH on the dissolution behavior of PHE powder was hardly observed. However, the release rate from solid dispersion increased with a higher pH.

The transmittance of the polymer aqueous solution (PEO/CP = 50/50) with various pHs was measured to study the effect of pH on the complex formation and is shown in Fig. 8. The transmittance gradually increased up to pH 5.5 and drastically increased in the region between pH 5.5 and 6.8. After that, a very slight decrease in the transmittance was observed. These results are thought to have occurred as follows. The pK_a of CP is about 6.0. With the increasing pH value, the

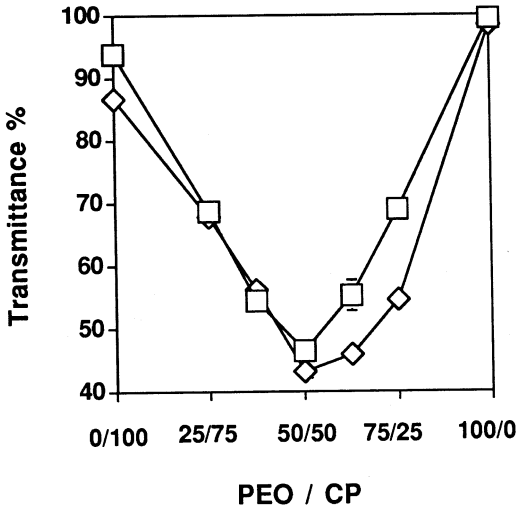

Fig. 4. Transmittance of polymer solution at 600 nm as a function of PEO/CP ratio. The solvent: □, water; ◇, ethanol. Each point represents the mean ± S.D. ($n = 3$).

proton of the carboxyl group of CP began to dissociate and the ionization drastically progressed around the pK_a. Thus, the complex formation was suppressed. At higher pH values around neutrality, where almost all carboxyl groups are ionized, the counterions reduced the electrostatic repulsion among the polymer chains

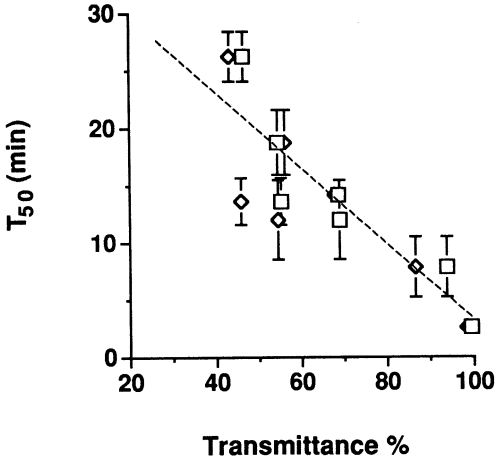

Fig. 5. Relationship between T_{50} in PHE release from solid dispersions and transmittance of polymer solution. The solvent: □, water; ◇, ethanol. Each point represents the mean ± S.D. ($n = 3$).

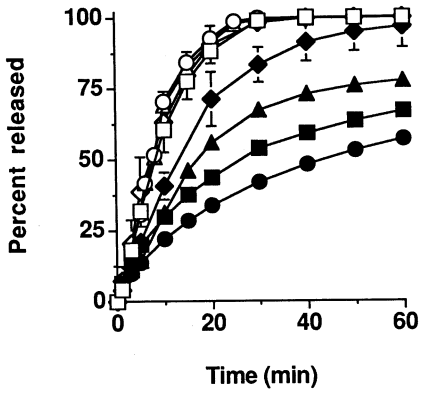

Fig. 6. Effect of pH on release profiles of PHE from PHE powder and solid dispersion granules (PEO/CP = 50/50). PHE powders: ○, pH 1.2; □, pH 5.5; △, pH 6.8; ◇, pH 9.0. Solid dispersions: ●, pH 1.2; ■, pH 5.5; ▲, pH 6.8; ◆, pH 9.0. Each point represents the mean ± S.D. ($n = 3$).

and the expansion of the chains was prevented. Therefore, the transmittance was slightly decreased (Bell and Peppas, 1996). To understand the effect of pH on the interaction between PEO and CP in more detail, we measured the IR spectra.

Fig. 9 shows the IR spectra of the PEO-CP system at 1300–1900 cm^{-1} before and after soaking into the dissolution medium with various pHs for 60 min. Before soaking, the carbonyl stretching bands of CP were observed at 1710 cm^{-1} and

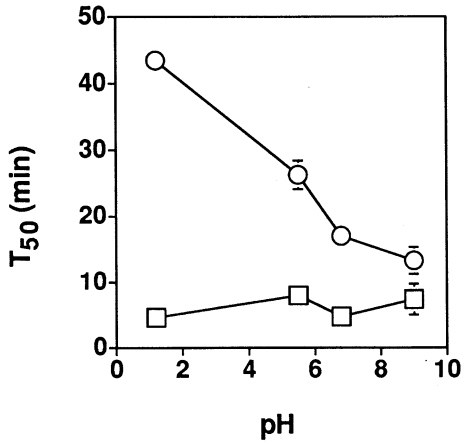

Fig. 7. Effect of pH on T_{50} in PHE release. □, PHE powders; ○, solid dispersions. Each point represents the mean ± S.D. ($n = 3$).

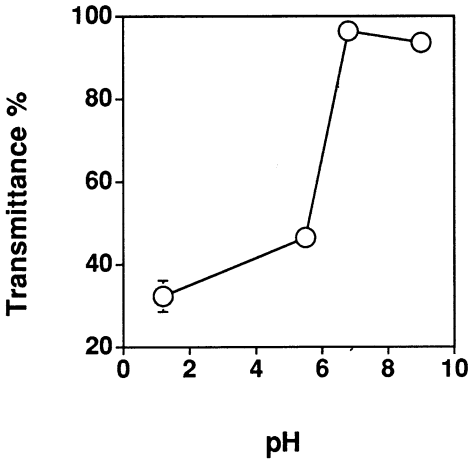

Fig. 8. Effect of pH on transmittance of polymer aqueous solution (PEO/CP = 50/50). Each point represents the mean ± S.D. ($n = 3$).

1734 cm^{-1}. The peak at 1710 cm^{-1} was due to dimers. The peak at 1734 cm^{-1} was due to the carbonyl group shifted by hydrogen bonding between the ether group of PEO and the hydroxyl group of the carboxyl group of CP (Ozeki et al., 1998). After soaking into the medium with pH 1.2 or 5.5, the ratio of the peak at 1734 cm^{-1} to that at 1710 cm^{-1} decreased with a higher pH, suggesting that the hydrogen bonds between PEO and CP were partly broken by penetration of the dissolution medium. However, no difference was observed in the wave number of the bands. In contrast, after soaking into the medium with pH 6.8 or 9.0, these two peaks disappeared. Further, a new peak was observed around 1580 cm^{-1} and the peak intensity at about 1400 cm^{-1} markedly increased. These peaks were due to $-COO^-$ (Nakanishi, 1960). These results indicate that the carboxyl groups of CP were ionized, in agreement with the results of the transmittance in Fig. 8.

Fig. 10 shows the optical micrographs of solid dispersion granules before and after the dissolution test at various pHs. In the case of pH 1.2, the swelling of the granules was hardly observed although the dissolution medium penetrated into the granules. In the case of pH 5.5, a slight swelling was observed compared with that at pH 1.2. However, the degree of swelling was extremely small. In the cases of pH 6.8 and 9.0, a remarkable swelling of the granules was observed.

From the results of the transmittance, the IR spectra and the optical micrographs, it is suggested that the PEO-CP complex formed by hydrogen bonding was broken at a higher pH, causing a promotion of the permeation of the

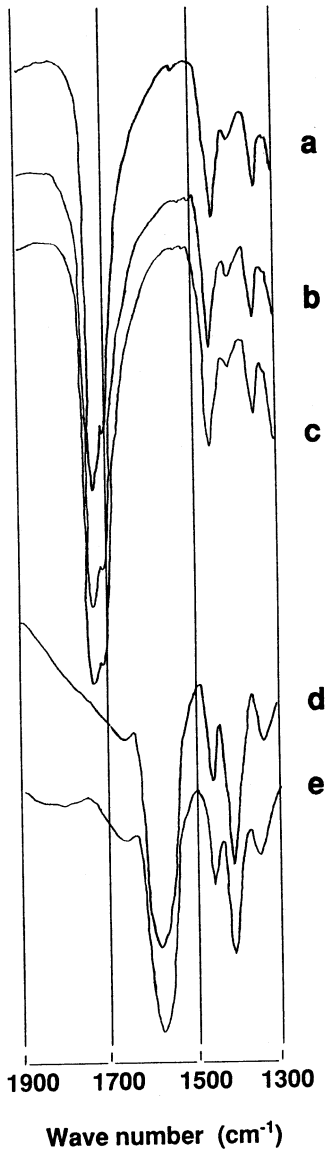

Fig. 9. IR spectra of PEO-CP system before and after soaking into dissolution medium with various pHs. Before: a; after: b, pH 1.2; c, pH 5.5; d, pH 6.8; e, pH 9.0.

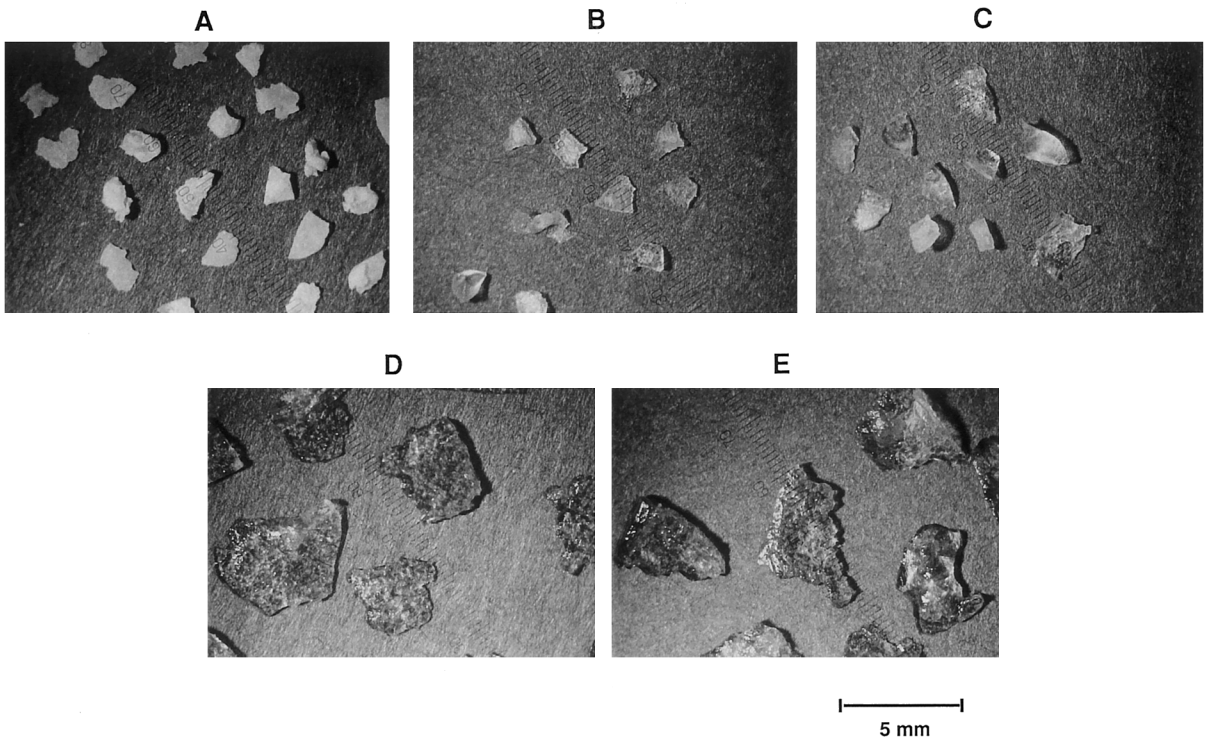

Fig. 10. Optical micrographs of solid dispersion granules before and after dissolution test with various pHs. Before: A; after: B, pH 1.2; C, pH 5.5; D, pH 6.8; E, pH 9.0.

dissolution medium into solid dispersions. This action might have increased the diffusion rate of PHE in solid dispersions and the release rate increased with a higher pH.

4. Conclusion

It was found that the degree of the PEO-CP complex formation by hydrogen bonding varied depending on the PEO/CP ratio. PHE was released by diffusion into solid dispersions and the release was controlled by the degree of the complex formation. Although the dissolution behavior of PHE powder was hardly affected by pH of the dissolution medium, the release rate from solid dispersions increased with a higher pH. This result is probably caused by the fact that the PEO-CP complex is broken with a higher pH.

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