Release of Lidocaine from Polymer Film Dosage Forms

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Received March 27, 1995; accepted June 21, 1995

We investigated the *in vitro* drug release from mixed polymer films using lidocaine (LC), which is poorly water-soluble. The mixed polymer films consisted of various ratios of hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose phthalate (HPMCP).

The effects of the presence glycyrrhizic acid (GL) or polyethylene glycol (PEG) in the films upon LC release were also studied. LC crystallinity decreased in the polymer film and this decrease was remarkable in the presence of GL, resulting in an amorphous state.

During the initial stage, drug release was regarded as a zero-order dissolution. The apparent release rate constant, k_a, varied with the ratios of the two polymers and the amount of additives as well as with the pH of the test solution. The results indicated that GL enhanced the dissolution rate of LC from mixed polymer films, which may be due to the formation of an amorphous state. On the other hand, since PEG is a surfactant, the enhanced wettability of the polymer by the buffered solutions may have caused the increased dissolution rate.

Key words lidocaine; glycyrrhizic acid; polyethylene glycol; drug release; polymer film; amorphous

Many new drug dosage forms have been developed and film dosage forms for the local or systematic delivery of drugs have been the focus of several studies. These forms, applied through the oral mucosa, confer advantages upon drugs which had previously been avoided due to a high first-pass effect or drugs that were unstable in the gastrointestinal tract. However, the permeation and absorption of drugs from the oral mucosa are not high, because the oral mucosa is highly protective, and an enhancer is therefore indispensable for increasing drug permeation and absorption to reach the required blood levels. Azone and other surfactants have been used as enhancers,[1-4] but while they increase drug permeation, they also cause complications and inflammation at the site of administration.

We selected glycyrrhizic acid (GL) as an enhancer which has surface-active action, but has no complications and does not cause inflammation at the site of administration. We described[5] the release of drugs from double-layered film dosage forms consisting of polyvinylacetal-diethylaminoacetate (AEA) and hydoxypropylmethylcellulose phthalate (HPMCP). Saito *et al.*[6] have studied the adhesiveness between oral mucosal and double-layered films of hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC). Ishida *et al.*[7] have prepared a new mucosal dosage form using HPC and Cabopol. In this study, we selected lidocaine (LC) as a model drug which is used as a local and topical anesthetic in dentistry. We prepared mixed polymer film dosage forms of HPC and HPMCP with LC and GL, and examined the release of LC from each.

Materials and Methods

Materials LC (Teikoku Chemical Co., Ltd.) was used as the model drug. The polymers consisted of HPC and HPMCP, which were obtained from Shin Etsu Chemical Co., Ltd. Polyethylene glycol (PEG; Yoneyama Chemical Industries, Ltd.) and GL (Maruzen Pharmaceutical Co., Ltd.) were used as enhancers.

Preparation of Physical Mixture Four hundred milligrams of LC and 200 mg of HPC and HPMCP (ratio of 1 : 1) with and without GL and PEG were mixed with a test tube mixer (Taiyo Automatic Mixer Type s-10) for 10 min at constant amplitude and rate (500 rpm).

Preparation of Mixed Polymer Films One hundred milligrams of LC and 25 (or 180) mg of GL with or without 100 and 200 mg of PEG were dissolved in 10 ml of a mixed polymer solution containing 5% HPC and HPMCP in acetone. The mixed polymer solution containing LC was molded in a Teflon dish (10 cm in diameter, 0.2 cm deep). The mixed polymer solutions were dried at room temperature and stored in a desiccator.

X-Ray Diffraction An RAD-IIVC (Rigaku Denki Co., Ltd.) X-ray powder diffraction analyzer was used with a Ni filter. The X-ray source was CuK_α, with parameters of 40 kV, 20 mA, and a scanning speed of 2°/min.

Differential Scanning Calorimetry (DSC) Analysis The melting point and heat of fusion was measured by means of a Mac Science DSC 3100 apparatus at an incrementally increasing rate of 10 °C/min, in aluminum sample pans. The heat of fusion was determined by weighing the peak area on the thermograph.

Dissolution Studies (a) Dissolution of the mixed polymer films was tested with a JPXII apparatus as shown in Fig. 1, by means of a paddle method in which a 1 cm^2 piece of film was bonded with double adhesion tape to the inside of a glass vessel containing 500 ml of medium at 37±0.1 °C. The rotating speed of the paddle was 100 rpm in a release medium consisting of buffered Clark–Lubs solution. The dissolution rate of the polymer films was determined by weighing the film remaining after drying for a constant period. This procedure was repeated three times. (b) LC release was tested with a JP XII dissolution apparatus, using a paddle, in which a 1 cm^2 piece of film was adhered to the inside of a glass vessel at 37±0.1 °C. The release medium was buffered Clark–Lubs solution, and the drug concentration was detected by high performance liquid chromatography (HPLC; Shimadzu LC-9A) under the following conditions: column, Cosmosil 5C18AR; detector, SPD-6A; monitoring wavelength, 220 nm; mobile phase, methanole : water : phosphoric acid = 79 : 20 : 1; flow rate, 1.2 ml/min.

Results and Discussion

Changes in Powder X-Ray Diffraction Patterns The powder X-ray diffraction patterns of the LC, GL and PEG are shown in Figs. 2a, b, and c. Figures 2d, e, and f show the diffraction patterns of a physical mixture of LC and polymers (HPC/HPMCP, 1 : 1) with and without GL or PEG, containing several peaks. The mixed polymer film (HPC/HPMCP, 1 : 1) with LC containing GL was amorphous (Fig. 2g, h, i). This means that there was no crystalline LC in the solid dispersion containing GL. The release rate of drugs is improved by the solid dispersion of drugs in polymers of polyvinylpyrrolidone (PVP),[8] HPMCP[9] and PEG.[10] The powder X-ray diffraction

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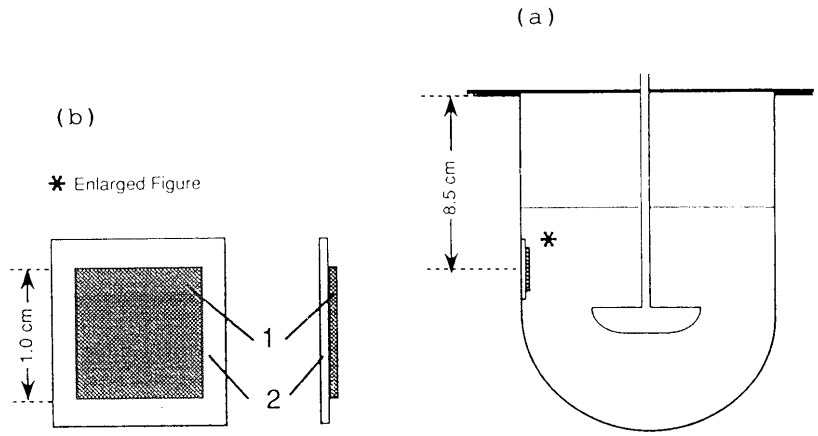

Fig. 1. Schematic Illustration of the Apparatus for the Release Test

(a) Release test apparatus. (b) Polymer film dosage form: 1, mixed film containing lidocaine; 2, double-adhesive tape.

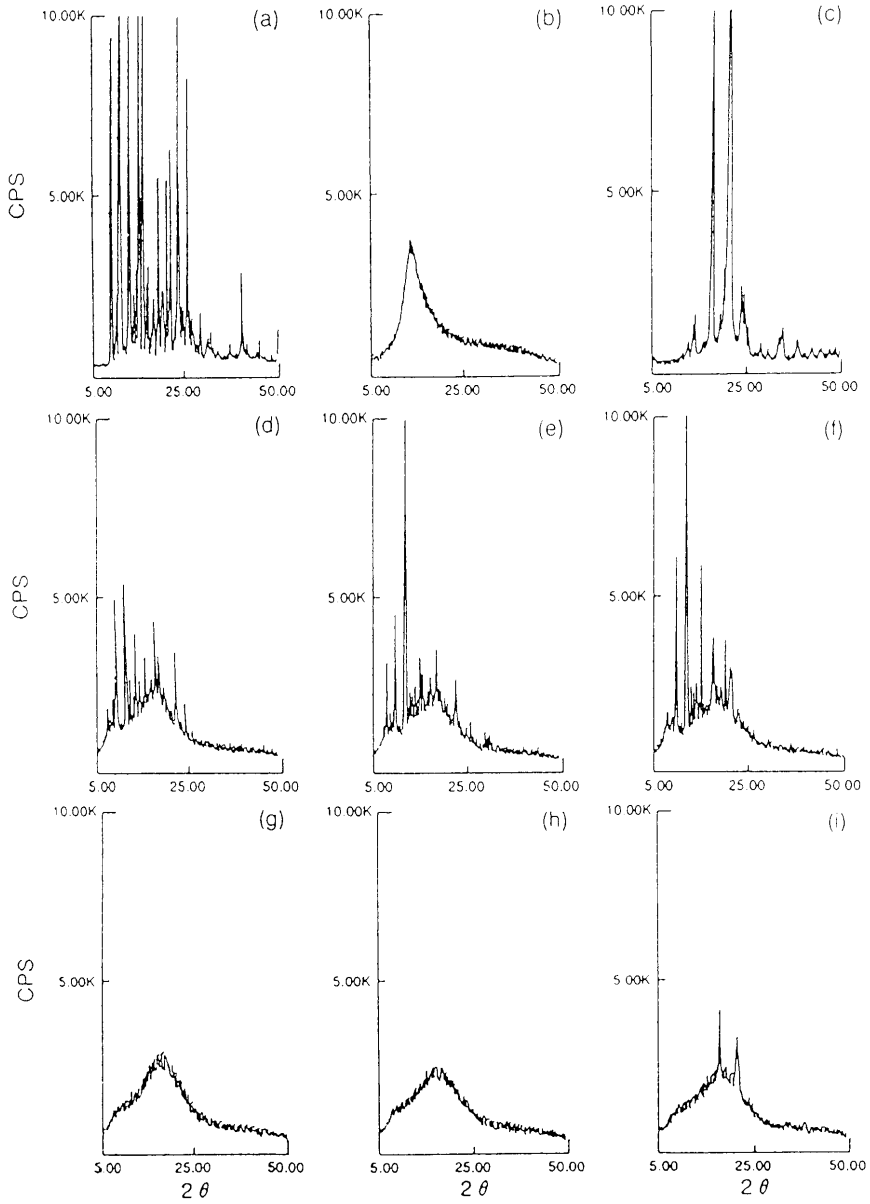

Fig. 2. X-Ray Diffraction Patterns

(a) LC; (b) GL; (c) PEG; (d) physical mixture of LC and mixed polymer (HPC : HPMCP = 1 : 1); (e) physical mixture of LC, GL and mixed polymer (HPC : HPMCP = 1 : 1); (f) physical mixture of LC, PEG, and mixed polymer (HPC : HPMCP = 1 : 1); (g) mixed polymer film (HPC : HPMCP = 1 : 1) with LC; (h) mixed polymer film (HPC : HPMCP = 1 : 1) with LC and GL; (i) mixed polymer film (HPC : HPMCP = 1 : 1) with LC and PEG.

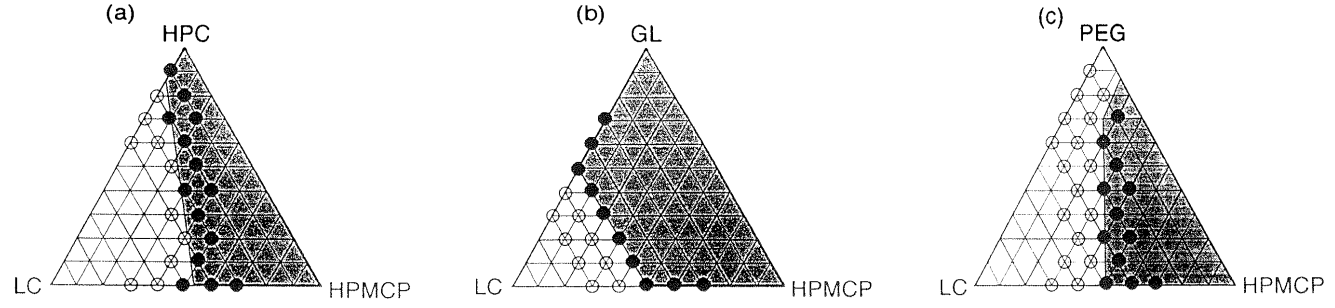

Fig. 3. Phase Diagrams

(a) LC/HPMCP/HPC system; (b) LC/GL/HPMCP; (c) LC/HPMCP/PEG. ○, with LC crystalline peaks in X-ray diffraction pattern; ●, without LC crystalline peaks in X-ray diffraction pattern.

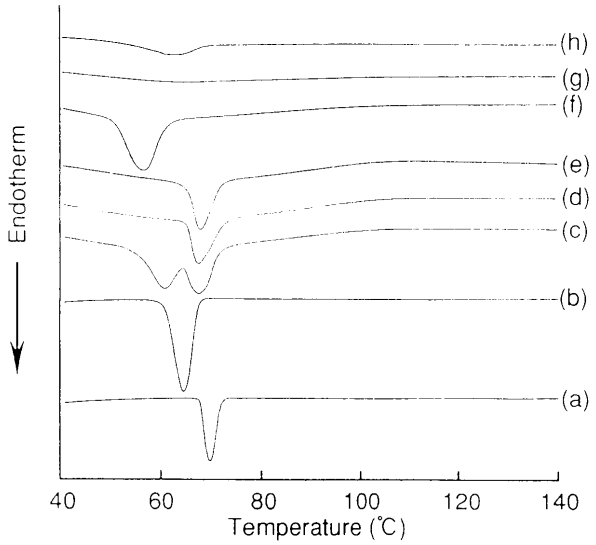

Fig. 4. DSC Thermograms

(a) LC; (b) PEG; (c) physical mixture of LC, PEG, and mixed polymer (HPC:HPMCP=1:1); (d) physical mixture of LC, GL, and mixed polymer (HPC:HPMCP=1:1); (e) physical mixture of LC and mixed polymer (HPC:HPMCP=1:1); (f) mixed polymer film (HPC:HPMCP=1:1) with LC and PEG; (g) mixed polymer film (HPC:HPMCP=1:1) with LC and GL; (h) mixed polymer film (HPC:HPMCP=1:1) with LC.

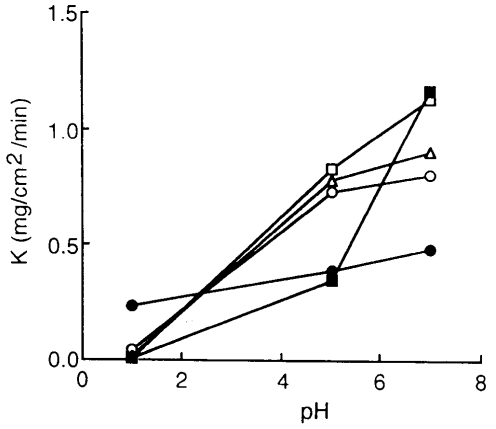

Fig. 5. Relationship between the Dissolution Rate of Polymer Films and pH

○, HPC:HPMCP=2:1; △, HPC:HPMCP=1:1; □, HPC:HPMCP=1:2; ●, HPC; ■, HPMCP.

patterns indicated that the crystalline LC changed into an amorphous state upon admixture with the polymer and GL.

Here, we studied the interaction of LC and the polymers (GL, HPC, HPMCP) using a phase diagram of the three-component crystallinity system as shown in Fig. 3. In the system, LC/HPC/HPMCP, LC amorphism was promoted when the ratio of HPMCP/LC was 1:1, and when the ratio of HPC/LC was above 85% as shown in Fig. 3a. On the other hand, in the system, LC/HPMCP/GL, LC amorphism was promoted when the ratio was 1:1, as shown in Fig. 3b. We assume that the amorphism of LC was promoted by solid dispersion due to an acid–base interaction between GL, HPMCP, and LC, the latter two agents containing carboxylic acid and an amino group, respectively.

We performed thermoanalyses of mixed polymer film dosages by DSC. The DSC curves of LC in the physical mixture and in the mixed polymer film with GL are shown in Fig. 4. LC showed an endothermic peak of 70 °C due to the crystalline form melting. However, for the mixed polymer film with LC and GL, no peaks were found. These results indicated that LC changed to an amorphous form because of the interaction of LC, HPMCP, and GL. On the other hand, in the presence of PEG, endothermic peaks appeared at 60 and 68 °C in the physical mixture of only LC and PEG, as shown in Fig. 4c. However, for the film dosage form, it appeared that crystalline LC had become amorphous, since only one endothermic peak appeared at about the same melting point as that of PEG (Fig. 4f).

Dissolution of Single and Mixed Polymer Films The dissolution rate of the polymer films, *K*, without drug was determined by weighing the remaining film after it had been dried for a fixed period. Figure 5 shows the effect of pH on the dissolution rate, *K*, of the polymer films. The single HPC film dissolved after a lag time of 30—60 min, and *K* increased slightly with the pH value. On the other hand, the dissolution rate of the HPMCP single film increased significantly at higher pH values. We considered that the carboxybenzoyl group in HPMCP contributed to the progress of the dissolution of mixed polymer films at a higher pH. Therefore, *K* for the mixed polymer films increased with increasing pH values at all ratios tested. At pH 7, the *K* values of mixed polymer films increased with the increasing ratio of HPMCP:HPC, while the *K* value of the HPMCP single film was similar or a little larger than those of the mixed polymer films. However, the *K* values of the mixed polymer films were lower than those of the HPC single film at pH 1.

Effects of GL and PEG on the Release of LC from Mixed

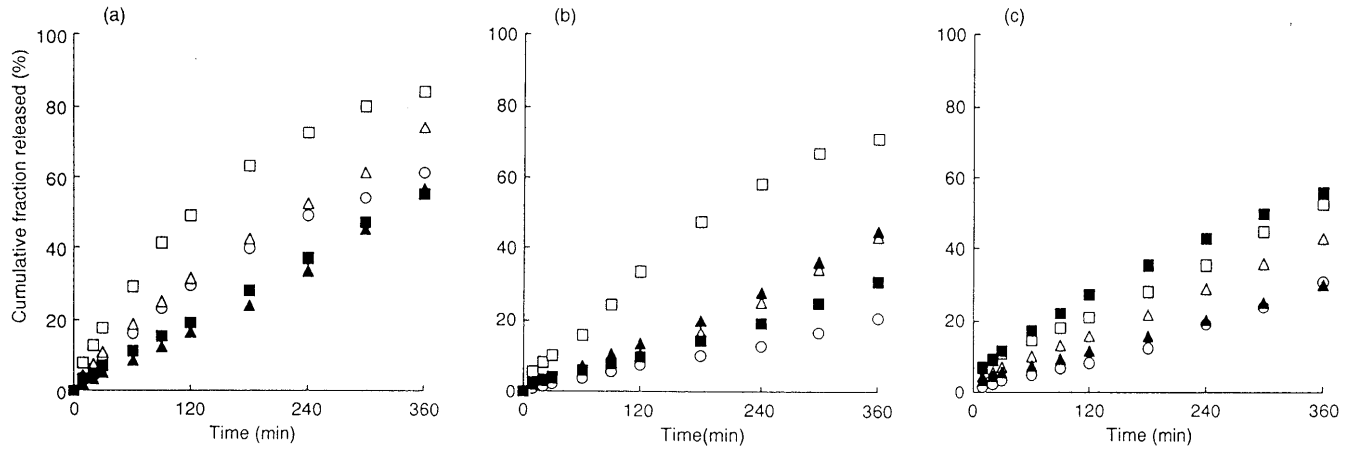

Fig. 6. Release Profiles of LC from Mixed Polymer Films at pH 1.0

(a) HPC : HPMCP = 2 : 1; (b) HPC : HPMCP = 1 : 1; (c) HPC : HPMCP = 1 : 2. ○, without GL and PEG; △, with GL at 4 mg/cm^2; □, with GL at 8 mg/cm^2; ▲, with PEG at 8 mg/cm^2; ■, with PEG at 16 mg/cm^2.

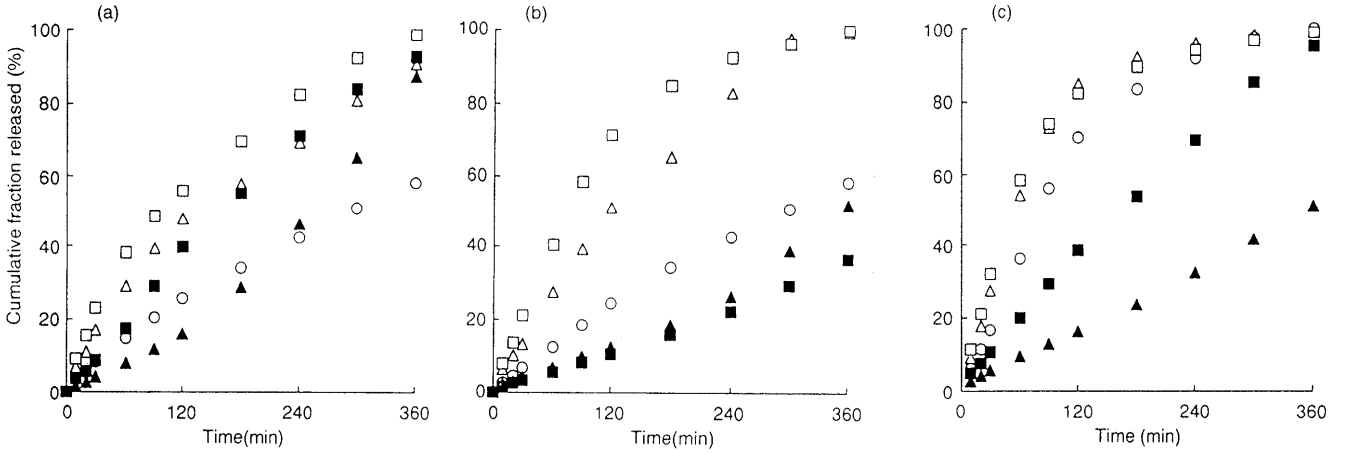

Fig. 7. Release Profiles of LC from Mixed Polymer Films at pH 5.0

(a) HPC : HPMCP = 2 : 1; (b) HPC : HPMCP = 1 : 1; (c) HPC : HPMCP = 1 : 2. ○, without GL and PEG; △, with GL at 4 mg/cm^2; □, with GL at 8 mg/cm^2; ▲, with PEG at 8 mg/cm^2; ■, with PEG at 16 mg/cm^2.

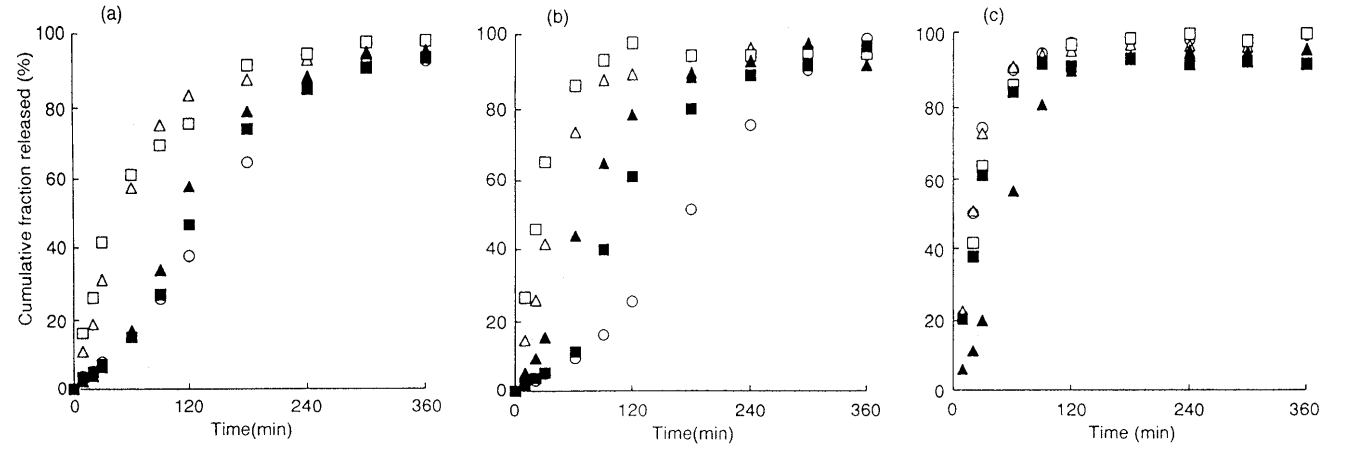

Fig. 8. Release Profiles of LC from Mixed Polymer Films at pH 7.0

(a) HPC : HPMCP = 2 : 1; (b) HPC : HPMCP = 1 : 1; (c) HPC : HPMCP = 1 : 2. ○, without GL and PEG; △, with GL at 4 mg/cm^2; □, with GL at 8 mg/cm^2; ▲, with PEG at 8 mg/cm^2; ■, with PEG at 16 mg/cm^2.

Polymer Films Figures 6, 7, and 8 show the effects of GL and PEG on the release of LC from mixed polymer films at pH 1, 5, and 7, respectively. The release of LC from mixed polymer films decreased with increasing ratios of HPMCP : HPC at pH 1, as shown in Fig. 6. With GL, LC was released more rapidly than when there was no GL. LC was released more slowly at higher HPMCP/HPC ratios, probably because the solubility of HPMCP in an acidic solution[11] had some influence. At pH values of 5 and 7, the release profiles with GL at HPC : HPMCP ratios

Table 1. Apparent Release Rate Constant, k_a ($\mu g \cdot cm^{-2} \cdot min^{-1}$)

HPC : HPMCP		pH 1.0	pH 5.0	pH 7.0
2 : 1	Without GL and PEG	0.2427	0.2192	0.3046
	With GL 4 mg/cm^2	0.2584	0.3928	0.9507
	With GL 8 mg/cm^2	0.3979	0.4580	1.3484
	With PEG 8 mg/cm^2	0.1343	0.1305	0.3736
	With PEG 16 mg/cm^2	0.1546	0.3280	0.2930
1 : 1	Without GL and PEG	0.0614	0.2006	0.1749
	With GL 4 mg/cm^2	0.0851	0.4204	1.2187
	With GL 8 mg/cm^2	0.2608	0.5996	2.1400
	With PEG 8 mg/cm^2	0.1077	0.0983	0.7491
	With PEG 16 mg/cm^2	0.0738	0.0843	0.1910
1 : 2	Without GL and PEG	0.0615	0.6006	2.6401
	With GL 4 mg/cm^2	0.0703	0.7056	2.4903
	With GL 8 mg/cm^2	0.1250	0.6604	2.1595
	With PEG 8 mg/cm^2	0.0720	0.1216	1.0447
	With PEG 16 mg/cm^2	0.1836	0.3103	2.0207

of 2 : 1 and 1 : 1, were similar to that at pH 1 without GL, as shown in Figs. 7 and 8. However, with GL, LC was released much more quickly at pH 7 than at pH 5.

When the HPC/HPMCP ratio was 1 : 2, the difference in the LC release was very small, since HPMCP dissolved easily at pH 7. The efficacy of PEG was clear in the solution at pH 1. However, in solutions at pH 5 and 7, the release rate of LC was not affected by PEG. At HPC and HPMCP ratios of 1 : 1 and 1 : 2 at pH 5, the release of LC was slower than without the enhancer. We assumed that the release of LC from a mixed film proceeded with the dissolution of the polymer, according to the Noyes–Whitney equation.

In this release system, the surface area is constant, and the release mechanism is of the so-called zero-order type. The apparent release rate constant, k_a, was a straight line for the first part of the relationship between the release time and percent drug release, as shown in Figs. 6, 7, and 8 and Table 1. The k_a increased with an increasing concentration of GL for all dosage forms. We then clarified the effect of GL on the release of LC from polymer films. Solid dispersions of drugs are made with polymers, which markedly enhance the dissolution rate of a drug,[12-14] or its sustained release.[15-17] Here, the solid dispersion of LC with polymer in the presence of GL resulted in the transformation of the drug into a GL amorphous form, as shown in Fig. 2. Thus, the improvement of LC release from polymer films with GL is due not only to improved wettability, but also to the amorphism of LC due to the formation of a solid dispersion.

Conclusion

The partition coefficient of LC indicated that this drug would be comparatively easily absorbed from the oral mucosa, since the pH of this tissue is 5 to 7. The film dosage forms of LC showed sustained release when the HPC to HPMCP ratio in the polymer was changed, and the dissolution of this drug was increased by GL, due to the formation of amorphous LC.

It is thus possible to make a sustained or rapid drug release form by changing the HPC to HPMCP ratio in the polymer. GL can be used as an enhancer of drug release, and PEG is inferior to GL as an enhancer of release.

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