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International Journal of Pharmaceutics 158 (1997) 147–155

international journal of pharmaceutics

Controlled release of lidocaine hydrochloride from buccal mucosa-adhesive films with solid dispersion

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Received 18 April 1997; received in revised form 30 June 1997; accepted 24 July 1997

Abstract

Solid dispersion films were prepared with a highly water-soluble medicine, lidocaine hydrochloride (LDC), water-insoluble ethylcellulose (EC) and water-soluble hydroxypropylcellulose (HPC). The release profiles of LDC from the solid dispersion films of different composition, and the suppression mechanism of the release in the LDC-EC-HPC system were studied. The release rate of LDC from the solid dispersion film as drug-reservoir was well controlled at EC/HPC composition ratio of 5/5. The mechanism of controlled release was speculated that there was a little release of HPC together with LDC, and the retained HPC was swelled in the film by the permeating fluid. Then, the release of LDC occurred via diffusion into the swelled HPC phase, causing a marked decrease in the release rate. The film for clinical use, which had the 30% LDC solid dispersion film, adhered almost completely to the buccal mucosa. These observations will provide useful information on clinical application of the LDC-EC-HPC solid dispersion film. © 1997 Elsevier Science B.V.

Keywords: Controlled release; Lidocaine hydrochloride; Polymer film; Solid dispersion

1. Introduction

The solid dispersion method is one of several pharmaceutical techniques for the controlling medicine release, and is used to improve the dissolution properties and bioavailability of slightly water-soluble medicines (Chiou and Riegelman, 1970; Hasegawa et al., 1985; Kai et al., 1996). Nevertheless, we have applied the solid dispersion method to the control of the release of a water-soluble medicine. We have studied solid dispersions composed of a highly water-soluble

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PII S0378-5173(97)00241-X

medicine (oxprenolol hydrochloride (OXP)), water-insoluble ethylcellulose (EC) and water-soluble hydroxypropylcellulose (HPC), and found that the release rate of OXP from solid dispersion markedly decreased because of OXP diffused into the swollen HPC phase formed and retained in the solid dispersion (Yuasa et al., 1991, 1992; Ozeki et al., 1994, 1995).

In this paper, to attempt the clinical use of the solid dispersion film, we prepared the film type preparation with the solid dispersion system as drug-reservoir for the application to the buccal mucosa. Lidocaine hydrochloride (LDC), a regional anesthetic agent, was used as a water-soluble medicine. The release profiles of LDC from the solid dispersion films of different composition, and the suppression mechanism of the release in the LDC-EC-HPC system, and also bioadhesive characteristics in contact with buccal mucosa, were studied.

2. Materials and methods

2.1. Materials

LDC (known as a regional anesthetic drug, 1 g of which dissolves in 0.7 ml of water at 20°C) was purchased from Sigma, St. Louis, MO. EC (Ethocel-10, 9.0–11.0 mPas) was purchased from Wako Pure Chemicals, Osaka, Japan and HPC (HPC-L, 6.0–10.0 mPas) was purchased from Nippon Soda, Tokyo. Ethanol, acetonitrile and methanol were of HPLC grade quality and were purchased from Wako Pure Chemicals. All other chemicals were of analytical grade quality and were purchased from Wako Pure Chemicals. All chemicals were used as received without further purification.

2.2. Preparation of polymer films

A total of 28 types of solid dispersion films consisting of LDC (10, 20, 30, or 40%) and polymers were prepared. The polymers were composed of EC and HPC, in which EC/HPC ratios were 10/0, 9/1, 7/3, 5/5, 3/7, 1/9, and 0/10. The mixed powder (4 g) of the medicine and polymers at various ratios was dissolved in ethanol (40 g) at 40°C, and the ethanol solution was cast on a Teflon mold (50 × 50 mm square, 10 mm deep). The mixed polymer solution was dried at room temperature for 24 h in a desiccator, and the film obtained was stored in the desiccator. The film thickness was measured by using a micrometer (Digimatic Outside Micrometer, Mitutoyo, Tokyo) and evaluated from the average thickness of the four corners and the center of the film with the dimension of 40 × 40 mm.

The film for clinical use was prepared as follows: A 10 mm square piece of the solid dispersion film was adhered to a 20 mm square adhesive and protective film, which was drug free hybrid-type film consisted of ≈ 120 μm thin HPC layer and 30 μm thin EC layer, by using ethanol. The adhesive and protective film was prepared by casting ethanolic solution of EC, after drying ethanolic solution of HPC cast on a Teflon coated flat pan.

2.3. In vitro dissolution study

Solid dispersion films with 20 × 20 mm and thickness of 130 ± 20 μm were used for the dissolution test. Four such films, which were fixed on plastic films (180 μm thick) using a wax (Maves Inlay Wax, Maves) so that the surface area exposed to the dissolution medium would remain constant, were bonded with double-adhesive tape to the inside of a glass vessel, as shown in Fig. 1a. The release behavior of LDC from the solid dispersion films was observed with a dissolution tester (Model PTW-II, Pharmatest), according to the paddle method (JP XII) at 100 rpm, using 500 ml of 1/15 M phosphate buffer (pH 7.0) as the dissolution medium at 37 ± 0.3°C. The LDC concentration was determined by high performance liquid chromatography under the following conditions: apparatus (TOSOH, Tokyo); pump, CCPS; detector, UV-8010; column, TSKgel ODS-80Ts (5 μm, 150 × 4.6 mm I.D.); detection wavelength, 220 nm; column temperature, 40°C; mobile phase, acetonitrile/methanol/0.02 M phosphate buffer (pH 6.0) = 40/20/40; flow-rate, 0.8 ml/min. The LDC content in the films was calculated from the composition ratio of LDC and the weight of the film.

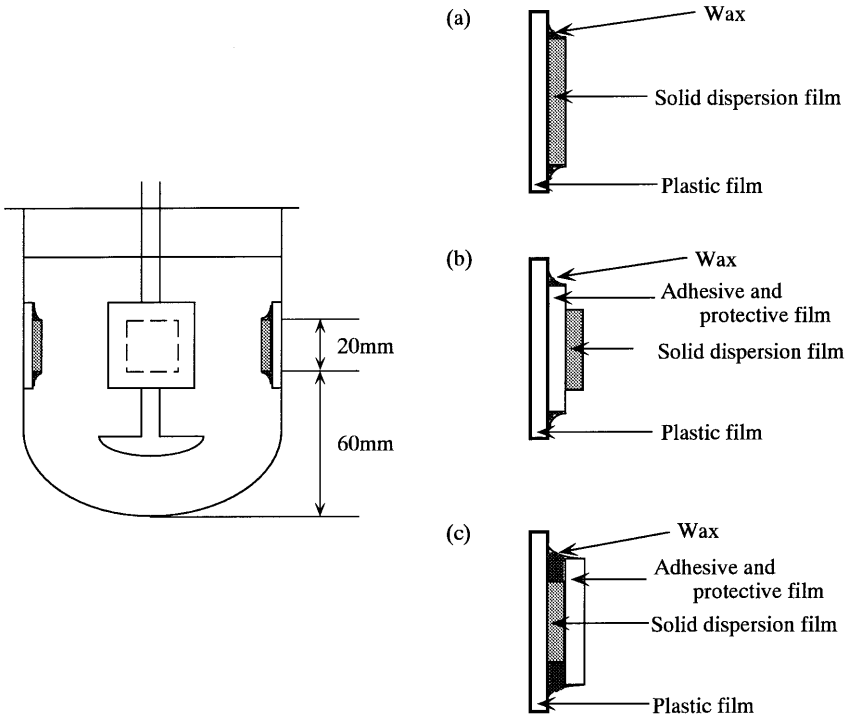

Fig. 1. Schematic illustration of dissolution test apparatus. (a) solid dispersion film; (b) solid dispersion film with adhesive and protective film for clinical use and (c) reversed setting of (b).

In case of the film for clinical use, the dissolution test was carried on the same manner of solid dispersion film in the two different adhesion modes, shown in Fig. 1b, c.

2.4. Powder X-ray diffractometry

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

Physical mixtures, as control of the solid dispersion films, were prepared by simply mixing the powdered LDC and polymers at the same composition ratios as those of the solid dispersions.

2.5. Thermal analysis

Differential scanning calorimetry (DSC) curves were obtained with a DSC instrument (SSC/560S, Seiko Instruments and Electronics) at the heating rate of 4°C/min, in aluminum sample cells under the N_2 gas flow. Physical mixtures of the medicine and polymers at various ratios were prepared as the same manner of powder X-ray diffractometry.

2.6. IR spectroscopy

IR spectra were recorded with an IR spectrophotometer (IR-810, JASCO, Tokyo) by the KBr disk method.

2.7. Measurement of pore size distribution

Pore size distribution in the solid dispersion films before and after the dissolution test was measured by mercury intrusion porosimetry (Yuasa et al., 1993), employing a mercury porosimeter (Autoscan-33, Quantachrome). The contact angle of mercury with the samples and the

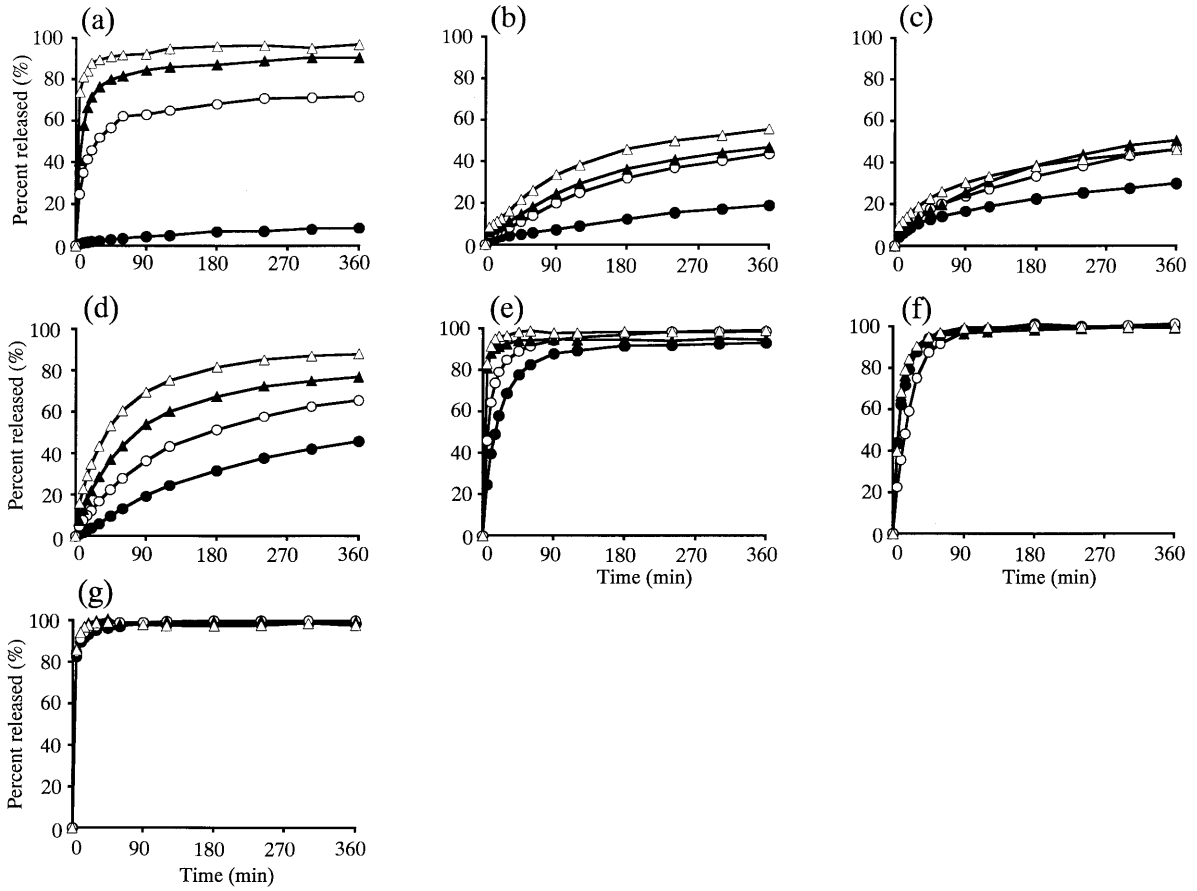

Fig. 2. Release profiles of LDC from solid dispersion films. LDC components are (●) 10%; (○) 20%; (▲) 30% and (△) 40%. Ratios of EC/HPC in the polymer component are (a) 10/0; (b) 9/1; (c) 7/3; (d) 5/5; (e) 3/7; (f) 1/9 and (g) 0/10. Each point represents the mean of three experiments.

surface tension of mercury were taken to be 140° and 480 dyn/cm, respectively (Ritter and Drake, 1945).

2.8. Adhesion of films for clinical use

After explanation of the experimental protocol, six healthy adult volunteers, five males and one female, agreed to participate in the study. The subjects, ranged between 25 and 47 years (mean 35.5 ± 7.8 years) old, were clinically examined and found to have no hepatic, renal or cardiovascular disease or to be receiving treatment with any other medication. A piece of the film was placed in the buccal mucosa after removing of moisture with a dry tissue paper. The site of application was monitored for an adhesive period and a feeling of nuisance.

3. Results and discussion

3.1. In vitro release of LDC from films

The release profiles of LDC from the solid dispersion films of different composition of EC and HPC are shown in Fig. 2. The release rates of LDC at the EC/HPC composition ratio of 10/0 (LDC-EC system) (Fig. 2a) were scarcely at the LDC 10% film and considerably large in the early

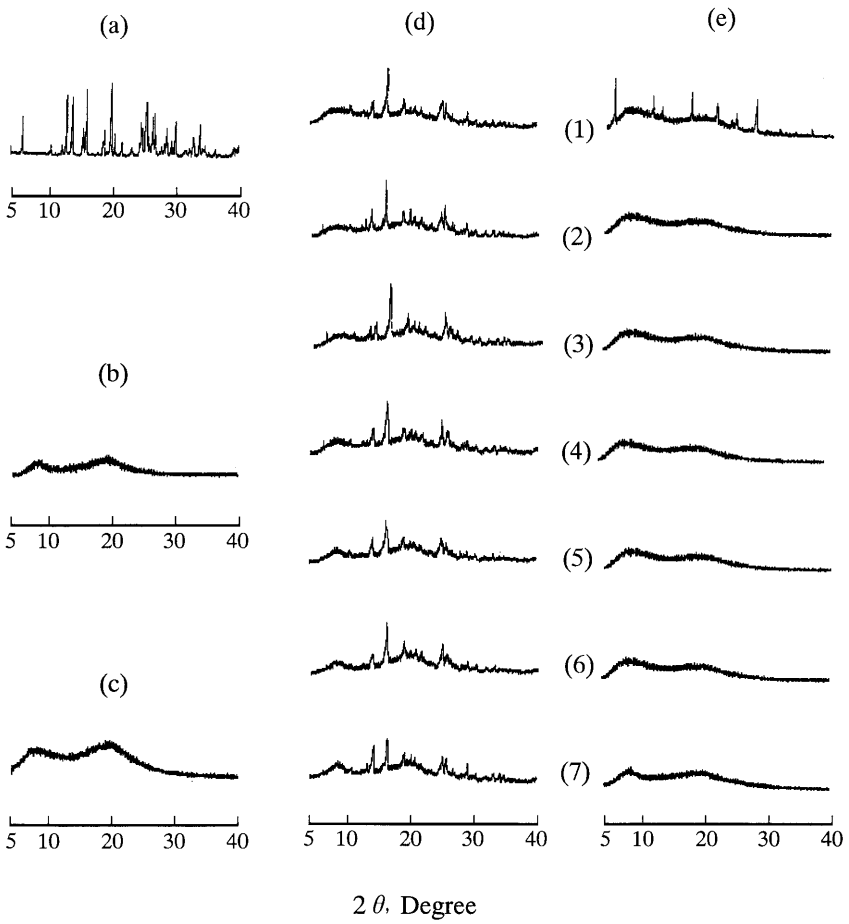

Fig. 3. Powder X-ray diffraction patterns of powder of (a) LDC; (b) EC; (c) HPC; (d) LDC-EC-HPC physical mixtures and (e) LDC-EC-HPC solid dispersion films. LDC components are 30% in both (d) and (e). Ratios of EC/HPC in the polymer component are (1) 10/0; (2) 9/1; (3) 7/3; (4) 5/5; (5) 3/7; (6) 1/9 and (7) 0/10.

stages of the release process at the LDC 20–40% films, in a so-called initial burst. When the EC/HPC composition ratios were 9/1, 7/3, 5/5, 3/7, and 1/9 (LDC-EC-HPC system) (Fig. 2b–f), the controlled release of LDC were obtained except 3/7 and 1/9 films, and the release rate of LDC increased with increasing HPC composition ratio. In such cases the composition ratio of HPC was more than that of EC, the release rate of LDC increased drastically in the early stages of the release process. The release rates of LDC at the EC/HPC composition ratio of 0/10 (LDC-HPC system) (Fig. 2g) were drastically large. Thus, it is difficult to control the release rate when HPC or EC is absent in the film. These results suggest that the release rate of LDC is well controlled at EC/HPC composition ratio of 5/5, and increases with the decrease of polymer ingredient.

In preliminary study, we tried to prepare the solid dispersion films consisting of 50 or 60% LDC. When the EC/HPC ratios were 10/0 and 0/10, no film was formed because of its brittleness of LDC-EC system or stickiness of LDC-HPC system. On the other hand, although the polymer films were formed in the LDC-EC-HPC system, the LDC was crystallized on the surface of films.

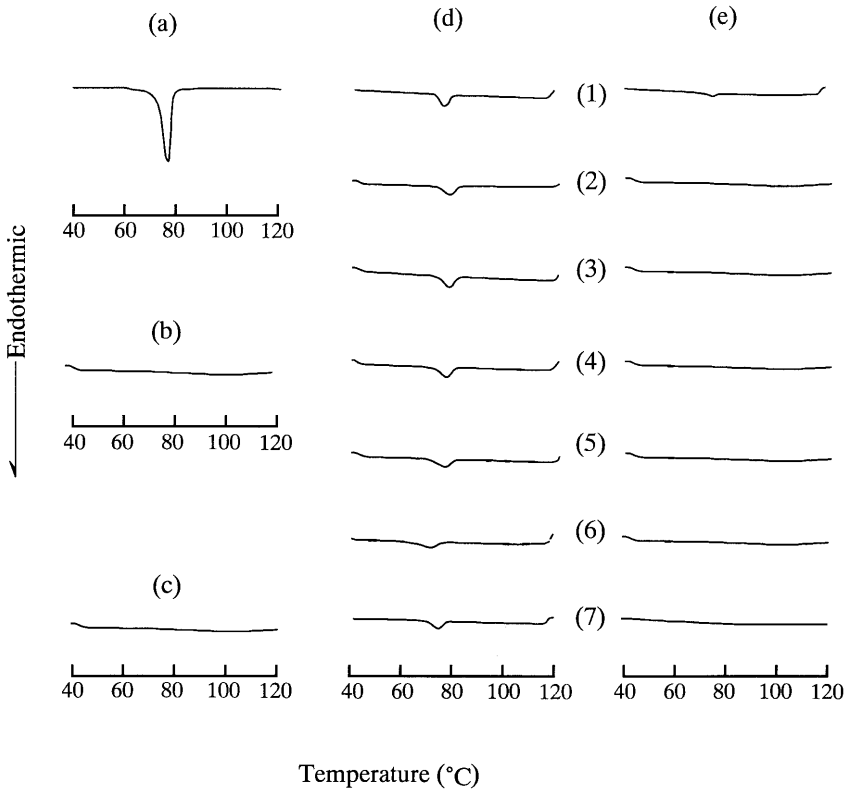

Fig. 4. Differential scanning calorimetry curves of powder of (a) LDC; (b) EC; (c) HPC; (d) LDC-EC-HPC physical mixtures and (e) LDC-EC-HPC solid dispersion films. LDC components are 30% in both (d) and (e). Ratios of EC/HPC in the polymer component are (1) 10/0; (2) 9/1; (3) 7/3; (4) 5/5; (5) 3/7; (6) 1/9 and (7) 0/10.

3.2. Physical properties of LDC in solid dispersion film

The powder X-ray patterns and the DSC curves of LDC powder, EC powder, HPC powder, and the physical mixtures and solid dispersion films of 30% LDC are shown in Figs. 3 and 4, respectively. In Fig. 3, the LDC crystalline peaks were not observed in the solid dispersion films except LDC-EC system, although the peaks appeared in the physical mixtures. In Fig. 4, no melting endothermic peak based on LDC crystal was observed in the solid dispersion films except LDC-EC system, although the peaks appeared in the physical mixtures. These results suggest that LDC exists as an amorphous form in the solid dispersion films containing HPC.

Fig. 5 shows the IR spectra of LDC powder, physical mixtures and solid dispersion films of 30% LDC at 1600–1800 per cm. LDC powder and physical mixtures have the carbonyl stretching band at 1650 per cm because of being in (secondary amide of) LDC. In the solid dispersion films, these carbonyl stretching bands were shifted to a higher wave number. These results can be explained similarly to the OXP in the previous paper (Ozeki et al., 1995). That is, LDC and EC and/or HPC were dissolved in ethanol during the preparation of the solid dispersion, and, when this ethanol solution was evaporated, the solid dispersion was formed while LDC and EC and/or HPC were interacting with each other by hydrogen bonding.

In the analysis by IR spectroscopy, LDC interacted with EC and HPC by hydrogen bonding in the solid dispersion.

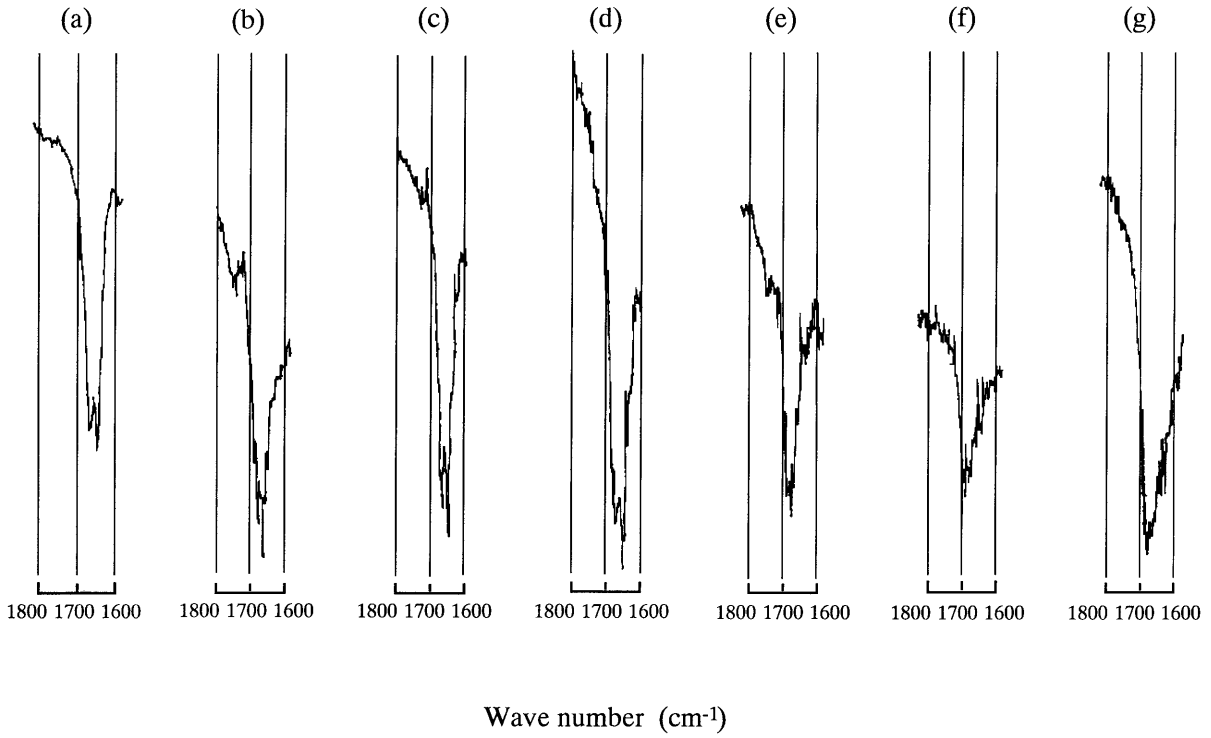

Fig. 5. IR spectra of (a) LDC powder; (b) LDC/EC (30:70) physical mixture; (c)LDC/HPC (30:70) physical mixture; (d) LDC/EC/HPC (30:35:35) physical mixture; (e) LDC/EC (30:70) solid dispersion film; (f) LDC/HPC (30:70) solid dispersion film and (g) LDC/EC/HPC (30:35:35) solid dispersion film.

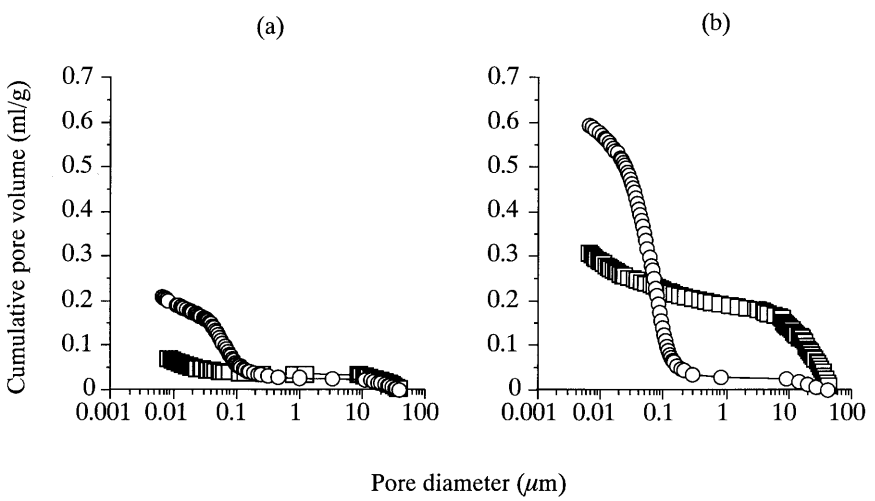

Fig. 6. Pore size distribution of solid dispersion films (a) before and (b) after dissolution test. (○) LDC/EC (30:70) and (□) LDC/EC/HPC (30:35:35).

3.3. Release mechanism of LDC from solid dispersion film

Fig. 6 shows the pore size distribution before and after the dissolution test in the LDC 30% solid dispersion films at LDC-EC system and LDC-EC-HPC system. Before the dissolution test, as a control, a small pore volume and the approximately same shape of the distribution were observed in the both solid dispersion films. After the dissolution test, the volume of pores with pore diameters of less than about 0.2 μm, which were formed by the release of LDC, markedly increased in the LDC-EC system, but scarcely increased in the LDC-EC-HPC system. In the LDC-EC-HPC system, after the dissolution test, the volume of the pores with diameter of several to several tens of μm evidently increased. This result suggests that HPC was released from the EC matrix in the dissolution process, i.e. the LDC molecules enclosed by HPC were released together with HPC erosion. After the dissolution test, the volume of the pores were ≈ 0.6 ml/g in the LDC-EC system and ≈ 0.3 ml/g in the LDC-EC-HPC one, respectively. While, the released portion of LDC were $\approx 90\%$ in the LDC-EC system and $\approx 75\%$ in the LDC-EC-HPC one, respectively. This phenomenon was speculated as follows: there was a little release of HPC together with LDC, and the retained HPC was swelled in the film by the permeating fluid, so the release of LDC occurred via diffusion into the swelled HPC phase, causing a marked decrease in the release rate. The conjecture supports the results of OXP in our previous paper (Ozeki et al., 1994).

3.4. Adhesion of films for clinical use

The film for clinical use, which had the LDC/EC/HPC = 30/35/35 solid dispersion film as the LDC reservoir, adhered almost completely to the buccal mucosa for 60–120 min, and was not detached from the buccal mucosa without tongue scratching. In all of the volunteers, a sign of numbness as a pharmacological effect of LDC was observed and continued throughout the adhesion. However, the disagreeable sensation based on the adhering of film was scarcely found, and the bitter taste based on the LDC was no found in all of the volunteers. In the dissolution test, the LDC release profile from the film for clinical use was almost the same as that of the solid dispersion film, while the protective film was drastically prevented LDC release from the solid dispersion film to dissolution medium over 6 h. Thus, this film for clinical use shows significant bioadhesive characteristics in contact with buccal mucosa and substantial prevention of LDC diffusion through the protective film.

In conclusion, a new buccal mucosa-adhesive film for the controlled release of LDC was developed using EC and HPC. The release rate of LDC from the solid dispersion film as drug-reservoir was well controlled at EC/HPC composition ratios of 5/5. The mechanism of controlled release was speculated as follows: there was a little release of HPC together with LDC, and the retained HPC was swelled in the film by the permeating fluid, so the release of LDC occurred via diffusion into the swelled HPC phase, causing a marked decrease in the release rate. The film for clinical use, which had the 30% LDC solid dispersion film, adhered almost completely to the buccal mucosa. The results obtained in this study will provide useful information on clinical applicability of the LDC-EC-HPC solid dispersion film.

Acknowledgements

The authors thank Professor Norio Ohshima, Institute of Basic Medical Sciences, University of Tsukuba, for many valuable suggestions.

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