Polymer Blend Implant for Ocular Delivery of Fluorometholone

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Ocular implants containing fluorometholone (FLM) were prepared using blends of poly (DL-lactic acid) (PLA) and polyvinyl pyrrolidone (PVP). The effect of the fraction of PVP content on the release of FLM from the implant was investigated *in vitro*. The drug was released from the device by approximately following first order kinetics within the period of 40 d. The release rate gradually increased with an increase in the PVP content. The *in vivo* study after implantation in the anterior chamber of rabbit eyes indicated that the PLA–PVP implant showed a good correlation between the *in vitro* and *in vivo* release of FLM. The present polymer blend implant demonstrated a constant level of FLM in the aqueous humor for one month.

Key words fluorometholone; ocular implant; polymer blend; poly (DL-lactic acid); polyvinyl pyrrolidone

The two major complications after cataract surgery, which involves extracapsular cataract extraction followed by intraocular lens implantation, are inflammation and posterior capsule opacification. Ophthalmic preparations of anti-inflammatory steroids and nonsteroidal drugs are effective for the control of postoperative inflammation after cataract surgery.¹⁾ Furthermore, it has been reported that an indomethacin-coated intraocular lens significantly reduced postoperative inflammation and posterior capsule opacification.²⁾ This lens, however, has two drawbacks: non-transparency of the lens and the short duration of efficacy (24 h).

Fluorometholone (FLM) is an effective topical anti-inflammatory steroid in the eye.³⁾ FLM has high glucocorticoid receptor binding affinity and may rapidly be metabolized to an inactive steroid in ocular tissue.⁴⁾ Biodegradable polymers such as poly(DL-lactic acid) (PLA) and poly(DL-lactic-co-glycolic acid) (PLGA) have been investigated as intravitreal implants since these polymers were well tolerated in ocular tissues.^{5,6)} Shah *et al.* reported that the release rate of steroidal drugs from PLGA film was initially slow and then gradually accelerated according to the weight loss of the polymer.⁷⁾ Recently, blends of a biodegradable polymer with a water soluble polymer have been investigated for altering the degradation and drug release properties of the polymer.^{8,9)}

In this paper, we have studied a controlled release system for FLM which can treat and/or prevent postoperative inflammation. We have prepared rod-shaped ocular implants consisting of blends of PLA and polyvinyl pyrrolidone (PVP) and evaluated the effect of the content of PVP in the PLA–PVP polymer on *in vitro* drug release characteristics. We have also measured the *in vivo* drug release rates and ocular tissue levels of FLM after implantation in the anterior chamber of rabbit eyes in order to compare them with *in vitro* release characteristics.

MATERIALS AND METHODS

Materials FLM and poly(DL-lactic acid) (PLA) (molecular weight, 5000) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). PVP (molecular weight, 40000) was obtained from BASF Japan (Tokyo, Japan). All other chemicals were of reagent grade.

Preparation of Polymer Blend Implants FLM was dis-

solved in 60 ml of a mixture of acetonitrile and ethanol (1 : 1) with various amount of PLA and PVP. The total amount of drug-polymer mixture was 2 g. The solvents were completely removed by two-step drying: under a vacuum at 40 °C for 1 d and at room temperature for another day. After drying, the resultant mass was pulverized in a mortar with a pestle. About 0.5 mg of the drug-polymer mixture was compressed into a rod-shaped implant at 80 °C by a melt-pressing technique.¹⁰⁾ The amount of FLM loaded was 10% by weight and the implant was 2 mm in length and 0.5 mm in diameter (average drug loading level of 50 µg/implant).

***In Vitro* Release Experiments** The implants were incubated in 5 ml of phosphate buffer (50 mM, pH 7.4) with horizontal shakers at 100 cycle/min at 37 °C. At predetermined time intervals, the samples were withdrawn and the elution medium was replaced by fresh medium to achieve a sink condition during the entire period of the release experiment. The concentration of FLM was assayed by HPLC.

***In Vivo* Experiments** Japanese albino male rabbits, weighing 2 to 2.5 kg, were used. The rabbits were anesthetized with a mixture of xylazine hydrochloride (9 mg/kg) and ketamine hydrochloride (34 mg/kg). The implant was inserted into the anterior chamber transcorneally with a 21 gauge needle. At predetermined time intervals, rabbits were sacrificed with an overdose of intravenous sodium pentobarbital. After the eyes were enucleated, approximately 200 µl of aqueous humor was aspirated from the anterior chamber and the implant was then retrieved carefully. The amount of FLM remaining in the implant and the concentration of FLM in the aqueous humor were determined by HPLC.

Determination of FLM Concentration The concentration of FLM was assayed by HPLC under the following conditions. Column: TSKgel ODS-80Ts (TOSOH Corporation, Tokyo, Japan), mobile phase: a mixture of 45 ml of acetonitrile and 55 ml of 5 mM sodium dihydrogenphosphate aqueous solution (pH 7.2), wave length: 240 nm. The concentration of FLM in the aqueous humor was measured by a modified HPLC method; the mobile phase was the mixture of 55 ml of methanol and 45 ml of 5 mM sodium dihydrogenphosphate aqueous solution (pH 7).

Weight Change of Polymer Blend Implant The weight change of polymer blend implants was determined by measuring the dry weight of the implant after it has been dried

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under vacuum for 1 d.

Scanning Electron Microscopy The implants were sputter-coated with Au-Pd to thickness of 200 Å after being dried under a vacuum. The surface morphology of the implants was examined using a scanning electron microscope (model S-2150, Hitachi, Ltd., Tokyo, Japan) at 25 kV electron beam radiation.

Fig. 1. Effect of PVP Content on the *In Vitro* Release of FLM from PLA-PVP implants

○, PVP 50%; □, 30%; △, 10%; ◇, 0%. Each point represents the mean ± S.D. ($n=4$).

RESULTS AND DISCUSSION

***In Vitro* Release Characteristics of FLM** Figure 1 shows the effect of the PVP content in PLA-PVP implants on the release characteristics of FLM. An increase in the PVP content of the implants resulted in a higher release rate of FLM. About 90% of FLM was released from the FLM-PLA-PVP (1:4:5) implant after 10 d of incubation, while only 25% was released from a pure PLA device.

Fig. 2. Remaining Weight of Polymer Blend Implants

■, FLM-PLA (1:9); □, FLM-PLA-PVP (1:6:3); □, FLM-PLA-PVP (1:4:5). Each column represents the mean ± S.D. ($n=4$).

(A)

(C)

(B)

(D)

Fig. 3. Scanning Electron Photomicrographs of FLM-PLA-PVP Implants

(A), FLM-PLA-PVP (1:6:3) before incubation; (B), FLM-PLA-PVP (1:6:3) at 2 d after incubation; (C), FLM-PLA (1:9) before incubation; (D), FLM-PLA (1:9) at 2 d after incubation.

Heller and Baker reported that the release of hydrocortisone from a biodegradable polyester prepared from diglycolic acid and *trans*-cyclohexane dimethanol involved both drug diffusion and polymer degradation.¹¹⁾ As can be seen from Fig. 1, however, the release profile of FLM from PLA-PVP blend polymer is not biphasic but mono-phasic. This is probably due to the enhanced release rate caused by the initial dissolution of PVP and the resulting channels in the polymer matrix. Figure 2 shows the weight change of the PLA-PVP implants during the *in vitro* release experiment for the first 2 d. The weight of the implants decreased with an increase in PVP content in the implants. The percent weight decrease of the implants after 1 d incubation was approximately identical to the PVP content. In the S.E.M. observation, both the PLA-PVP and the PLA implant showed a relatively smooth surface before incubation, as shown in Fig. 3. The PLA-PVP implant had large pores after incubation for 2 d. However, the pores were not observed in the PLA implant although the PLA implant showed irregular morphology, with cracks which were probably formed by the drying process. These results indicate that the weight change of the implant is due to a rapid dissolution and leaching of PVP in the aqueous solution which may create an extensive water-filled pore structure in the polymer matrix to facilitate the drug release.

***In Vivo* Release of FLM and Weight Change of Implants** The *in vivo* release profiles of FLM from the polymer blend implants in the anterior chamber of rabbits, which was expressed as the decrease of the remaining drug content in the implants, is compared with the weight change of the implant in the anterior chamber (Fig. 4). It is interesting to note that the drug release profile from both the PLA-PVP implant and the PLA implant was approximately identical to the corresponding weight change profiles. This result may indicate that the drug release from the PLA-PVP implants is governed by the diffusion of FLM molecules through water channels produced by the leaching of PVP.

Figure 5 compares the *in vitro* and *in vivo* profiles of FLM release and the weight loss of the implants. A good correlation between the *in vitro* and *in vivo* profiles were observed for both release and weight change. These findings suggest

Fig. 4. *In Vivo* Release profiles of FLM from the Implants (Closed Key) and Weight Change of the Implants (Open Key)

(Square), FLM-PLA-PVP (1:6:3); (Circle), FLM-PLA (1:9). Each point represents the mean $\pm$ S.D. ($n=4$).

that the *in vivo* release rate can be predicted from the *in vitro* data.^{12,13)}

Concentration of FLM in Aqueous Humor after Implantation Figure 6 shows the concentration of FLM in the aqueous humor after implantation of the devices in the rabbit eye. The present ocular device achieved a maximum concentration, 46 ng/ml, 3 d after implantation. The FLM concentration was maintained within levels of 30 and 25 ng/ml during 5 to 14 d, and then decreased gradually, while the PLA implant showed a drug concentration lower than the therapeutic level, although prolonged action was achieved. It has been reported that the maximum concentration of FLM in the aqueous humor is 10 ng/ml at 15 min after the instillation of 0.1% FLM eye drops to rabbit eyes, the FLM concentration is used clinically, and that FLM then disappeared in the aqueous humor within 150 min.¹⁴⁾ These results may indicate that the drug level and the duration of maintaining a constant drug level in the aqueous humor can be controlled by varying the composition ratio of PLA and PVP in the implant when both the drug loading level and the size of the device are constant.

Fig. 5. Correlation of the *In Vivo* and *In Vitro* Release of FLM (Square) and Weight Change of the FLM-PLA-PVP (1:6:3) Implant

Open Key, *In vitro* experiment; Closed Key, *In vivo* experiment. Each point represents the mean $\pm$ S.D. ($n=4$).

Fig. 6. Concentration of FLM in the Aqueous Humor after Implantation of the Implants *In Vivo*

□, FLM-PLA-PVP (1:6:3) Implant; ○, FLM-PLA (1:9) Implant. Each point represents the mean $\pm$ S.D. ($n=4$).

CONCLUSION

The effects of the content of PVP in the PLA-PVP blend polymer rod on the release of FLM have been investigated both *in vitro* and *in vivo*. The release rate of FLM from the polymer blend implant was controlled by varying the PVP content in the implant. Furthermore, the PLA-PVP implant showed a good correlation between the *in vitro* and *in vivo* release of FLM in the rabbit eye. The increase in the release rate of FLM by adding PVP in the biodegradable PLA implant was well explained by the weight change of the polymer due to PVP dissolution and leaching.

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REFERENCES

- 1) Roberts C. W., Brennan K. M., *Arch. Ophthalmol.*, **113**, 725—727 (1995).
- 2) Nishi O., Nishi K., Yamada Y., Mizumoto Y., *J. Cataract Refract. Surg.*, **21**, 574—578 (1995).
- 3) Schlagel C. A., *J. Pharm. Sci.*, **54**, 335—354 (1965).
- 4) Polansky J. R., Alvarado J. A., *Curr. Eye Res.*, **4**, 267—279 (1985).
- 5) Kimura H., Ogura Y., Hashizoe M., Nishikawa H., Honda Y., Ikada Y., *Invest. Ophthalmol. Vis. Sci.*, **35**, 2815—2819 (1994).
- 6) Rubsamen P. E., Davis P. A., Hernandez E., O'Gray G. E., Cousins S. W., *Arch. Ophthalmol.*, **112**, 407—413 (1994).
- 7) Shah S. S., Cha Y., Pitt C. G., *J. Controlled Release*, **18**, 261—270 (1992).
- 8) Park T. G., Cohen S., Langer R., *Macromolecules*, **25**, 116—122 (1992).
- 9) Pitt C. G., Cha Y., Shah S. S., Zhu K. J., *J. Controlled Release*, **19**, 189—200 (1992).
- 10) Asano M., Fukuzaki H., Yoshida M., Kumakura M., Mashimo T., Yuasa H., Imai K., Yamanaka H., Kawaharada U., Suzuki K., *Int. J. Pharm.*, **67**, 67—77 (1991).
- 11) Baker R. (ed.), "Controlled Release of Bioactive Molecules," Academic Press, New York, 1980, pp.1—17.
- 12) Wang G., Tucker I. G., Roberts M. S., Hirst L. W., *Pharm. Res.*, **13**, 1059—1064 (1996).
- 13) Kunou N., Ogura Y., Hashizoe M., Honda Y., Hyon S-H., Ikada Y., *J. Controlled Release*, **37**, 143—150 (1995).
- 14) Okuda I., Tanaka H., *Atarashii Ganka*, **7**, 1051—1053 (1990).