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Effect of Anionic/Siloxy Groups on the Release of Ofloxacin from Soft Contact Lenses

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ABSTRACT: For the treatment of ocular diseases, chemotherapeutic antibiotics, for example, Ofloxacin, are usually administrated through the application of eye drops during ophthalmic perioperative sterilization. However, this approach has several drawbacks, such as the need for frequent application caused by tears draining the drugs out of the eyes or the presence of a possible contraindication of eye drops when contact lenses are worn. To overcome these problems, we have studied contact lenses composed of hydrogels, which function as a type of drug delivery system technology. We synthesized hydrogels to be used as contact lenses with sufficient amounts of drug uptake and release profiles for sterilization treatment during the perioperative period in ophthalmic areas. This study showed that the hydrogels that included side-chain ionic groups and silyl groups were useful materials to prepare drug delivery contact lenses. The ionic groups in the hydrogels could functionally retain a drug if an ionic substituent was present. It is noteworthy that the drug content in the contact lenses could readily be controlled by changing the ratio of ionic monomer contents during polymerization. Furthermore, the controlled drug release of silyl-group-containing hydrogels showed sustained release over 72 h, which indicated that the hydrogels could be used as contact lenses for sustained drug release. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: hydrogel; drug delivery system; contact lens; ofloxacin; ophthalmic sterilization

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INTRODUCTION

The number of patients with ocular diseases, such as retinopathy, glaucoma, and keratitis, has been rapidly increasing. Surgical treatment of ocular diseases requires sterilization of the ophthalmic areas during the perioperative period to prevent postoperative infection. Ocular diseases are treated using chemotherapeutic antibiotics, for example, Ofloxacin, which are usually administrated by applying eye drops during ophthalmic perioperative sterilization. However, this approach has several drawbacks: almost the entire dose of antibiotics can be removed by tears, which would require frequent applications, and contraindication of eye drops could occur if contact lenses are worn. These complications for the application of the antibiotics may lead to poor patient compliance, and sterilization may not be achieved. To overcome these problems, we investigated contact lenses composed of hydrogels that can function as drug delivery systems (DDSs).

DDSs have recently been used to administer drugs, and many drugs in the field of ophthalmology were reported with several methods of drug administration using DDS technology. For example, reports suggested that eye drops enhanced the ocular penetration of the drug by extending the drug residence time in the eye due to the gelation of the eye drops after being dropped (Timoptol®-XE Ophthalmic Solution 0.25%, 0.5% Interview form). DDS devices have been put into practical use as implantable devices composed of biodegradable polymers to treat posterior-eye diseases.[1–3] The drug release is sustained for several months to 1 year because the drug is released as the polymer collapses, not from the hydrogel. The moisture content and softness of hydrogels has led to extensive investigation for their use as drug carriers in DDSs, including in the field of ophthalmology.[4] In the field of ophthalmology, contact lenses composed of hydrogels have been commercialized as medical devices. Thus, the safety and convenience of hydrogels has been shown. Therefore, the commercialization of contact lenses as drug carriers should be useful and convenient.

Contact lenses, which are composed of hydrogels, are three-dimensional networks of crosslinked polymers. Hydrogels provide high structural flexibility and are highly absorbent of water and other solvents. Because of these properties, hydrogels have been studied in a wide range of applications, such as in contact lenses, artificial muscles, artificial breasts, artificial skin, wound

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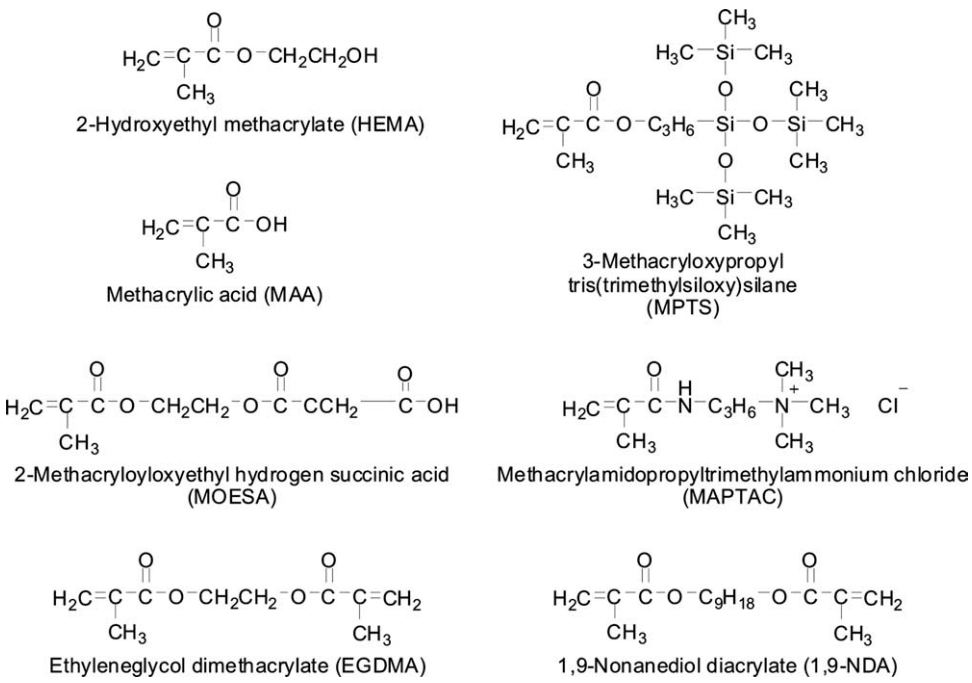

Figure 1. Chemical structures of the materials.

healing agents, and drug carriers for DDSs. Water-containing hydrogels that comprise contact lenses are required to have high biocompatibility, transparency, strength, and dimensional stability for use as contact lenses. Recently, the number of contact lens users has increased; therefore, contact lenses applied as devices for drug administration in the field of ophthalmology is a key issue for reducing burdens on patients and improving compliance.

Several attempts were reported that attempted to commercialize contact lenses and combine their use with eye drops or drug solutions for DDSs.[5–7] However, it is difficult to retain the transparency and shape of contact lenses, which are standard functional requirements for contact lenses. The driving force of drug retention manifests through a variety of interactions with the contact lenses. For instance, Alvarez's group reported the drug-imprinted contact lenses which are created imprinted cavities in hydrogels for uptake drug.[8,9] We previously reported that contact lenses composed of a zwitterionic, transparent, shape-retaining hydrogel could potentially be compatible with ophthalmic drug installation.[10,11] In addition, we have investigated contact lenses as a DDS composed of hydrogels having several ionic groups, which interact with the drugs and function as contact lenses.[12,13] In those reports, the drug was encapsulated in a hydrogel due to ionic interactions between the cationic groups of the hydrogel and the anionic drug. Repetitive exchange reactions between ions in tear film showed that the drug was initially released gradually into the eye. In contrast, the anionic groups restrained the electric charge inside the hydrogel and compromised the lens' dimensional stability and durability. However, some drugs require higher amounts to be uptaken and the release period to be longer.

In this report, we synthesized hydrogels that had ionic groups and silyl side-chain groups to increase drug uptake and to change the release profile. The hydrogels are to be used as contact lenses for sterilization treatments during the perioperative period in the field of ophthalmology. Furthermore, we measured the amount of drug uptake and the release behavior of a cationic drug by the contact lenses.

MATERIALS AND METHODS

Materials

Methacrylic acid (MAA) and 2-methacryloyloxyethyl hydrogen succinic acid (MOESA) were obtained from Kyoeisha Chemical (Osaka, Japan) as the anionic monomer. For the cationic monomer, methacrylamidopropyltrimethylammonium chloride (MAPTAC) from Mitsubishi Rayon was used. 3-Methacryloxypropyl tris(trimethylsiloxy)silane (MPTS) was obtained from Gelest (PA). 2-Hydroxyethyl methacrylate (HEMA) was obtained from Mitsubishi Gas Chemical Company (Tokyo, Japan). Ethyleneglycol dimethacrylate (EGDMA) from Mitsubishi Rayon (Tokyo, Japan) and 1,9-nonanediol diacrylate (1,9-NDA) from Kyoeisha Chemical were used as crosslinking agents. 2,2′-Azobisisobutyronitrile (AIBN) from Wako Pure Chemical (Osaka, Japan) was used as the polymerization initiator. The structures are shown in Figure 1. Ofloxacin ((*RS*)-7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo[7.3.1.0]trideca-5(13),6,8,11-tetraene-11-carboxylic acid) was obtained from Wako Pure Chemical Industries (Tokyo, Japan). Ofloxacin is a zwitterionic drug with p*K*a values of 5.74 and 7.90 (Tarivid® ophthalmic solution 0.3% Interview form) as shown in Figure 2.

Preparation of Contact Lenses

To the liquid monomer (mixtures composed of HEMA as the main component), the ionic monomers were mixed with composition ratios of 1–10 wt % of MAA or MOESA as anionic monomers and 1–10 wt % of MAPTAC as the cationic monomer. EGDMA and 1,9-NDA (0.1–10 wt %) (crosslinking agents) were

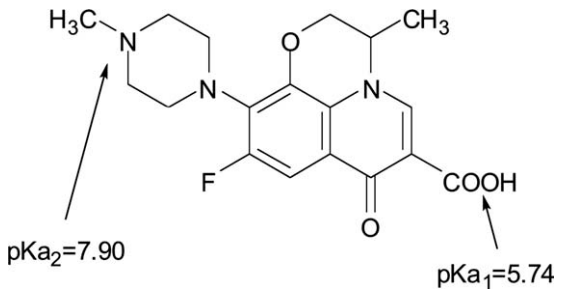

Figure 2. Structure of Ofloxacin with pKa values indicated (Tarivid® ophthalmic solution 0.3% Interview form).

added, to prevent the contact lenses from reaching water contents that were too high due to the addition of ionic monomers. These crosslinking agents could also adjust water contents of contact lenses. Generally, the more crosslinking agents are added, the less water contents of contact lenses become. AIBN (0.4 wt %) was added to the mixtures and stirred for 1 h under nitrogen. As described in previous reports,[11–13] the liquid monomer mixtures were poured into a plastic mold for contact lenses and heated in the range of 50–100°C for 24 h to obtain the polymers. The polymers were cooled to room temperature, removed from the mold, and then soaked in distilled water at 60°C for more than 4 h to hydrate the samples.

Uptake of Ofloxacin into Contact Lenses

Contact lenses were immersed in a 0.3 wt % Ofloxacin and 0.85% NaCl solution for 3 h after the hydration step for Ofloxacin uptake. Then, contact lenses with the Ofloxacin solution were heat-treated in the same way as general contact lenses. The Ofloxacin solution was adjusted to pH 6.5 by the addition of 0.5 *M* HCl. As shown below, the pH was adjusted by the addition of 0.5 *M* HCl or NaOH to 5.0, 6.5, 7.0, and 8.0 to determine the effects of pH on the solution.

Measurement of the Water Content of Contact Lenses

The weights of the contact lenses containing Ofloxacin [W_w] were measured, and then, the weights of the dry lenses [W_d] were measured after the removal of water by heating the lenses at 120°C for 2 h. The water content of the contact lenses was calculated by the following formula:

$$\text{Water content } (\%) = (W_w - W_d)/W_w \times 100$$

Measurement of Ofloxacin Uptake and the Amount Released from Contact Lenses

To measure the amount of Ofloxacin uptake by the contact lenses, each contact lens containing Ofloxacin was soaked in MeOH for 24 h. After all, the Ofloxacin had been removed from the contact lens, as determined by the absence of absorption in the UV spectrum, the drug concentration in the MeOH was measured by high-performance liquid chromatography (HPLC, JASCO, Japan).

The sustained-release behavior of Ofloxacin from the lenses was measured as follows. Each contact lens was soaked in 2 mL of 0.9% NaCl solution at room temperature for the release of the drug. After 1 h, each contact lens was soaked in fresh 2 mL of 0.9% NaCl solution under the same conditions. Under the same conditions, each contact lens was continuously resoaked in a fresh solution for 2, 4, 8, and 24 h. The drug concentrations in the 0.9% NaCl solutions were measured using HPLC. The ratio of the released drugs at each time was calculated by setting the uptake amount of the contact lens as 100%.

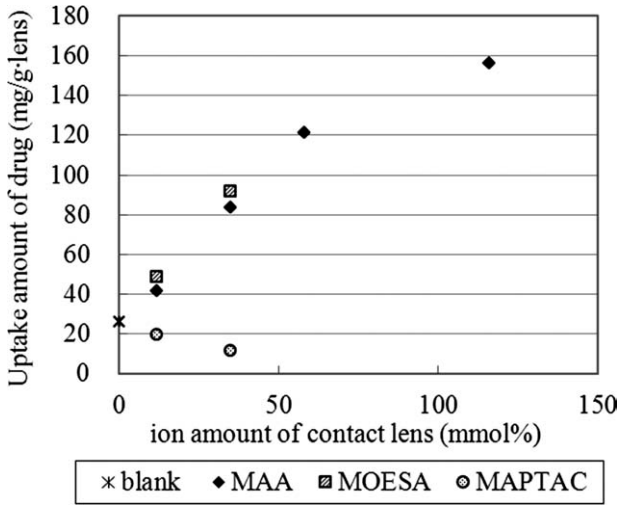

Figure 3. Uptake amount of Ofloxacin for contact lenses. Contact lenses were consisted of HEMA and crosslinking agents (blank lens), added with 1–10 wt % of MAA, MOESA, or MAPTAC, respectively.

RESULTS AND DISCUSSION

Effect of Ionic Interaction Between the Drug and Hydrogels for Contact Lenses

A 0.3 wt % Ofloxacin ophthalmic solution of pH 6.5 was commercially available (Tarivid® ophthalmic solution 0.3% Interview form). To clarify the mechanism of Ofloxacin uptake for hydrogels with anionic or cationic groups, uptake amounts of Ofloxacin were measured for contact lenses consisting of hydrogels containing MAA and MOESA anionic groups or MAPTAC cationic groups (Figure 3).

Compared with the blank lens, which consisted of HEMA and EDGMA, the contact lenses containing MAA or MOESA as anionic groups had a capacity of Ofloxacin that was dependent on the amount of anionic monomers, whereas the uptake of the contact lenses containing MAPTAC as cationic groups decreased. The results were consistent with the observation that the majority of Ofloxacin existed as a cation in a solution of pH 6.5 because the ratios of ionized to unionized Ofloxacin are COO^- : COOH = 9 : 5 and N^+ : NH = 80 : 1, according to calculations from the Henderson–Hasselbach equation. Therefore, the uptake process of Ofloxacin into the hydrogels with ionic groups can be explained by ionic interactions between the cationic groups of Ofloxacin and the anionic side chains in hydrogels as shown in Figure 4.

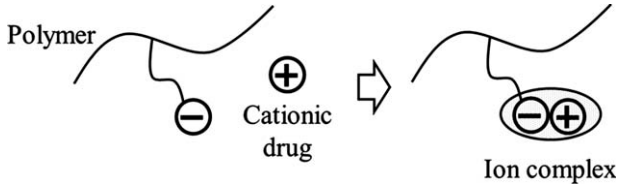

Figure 4. Uptake process of Ofloxacin for a hydrogel with ionic groups.

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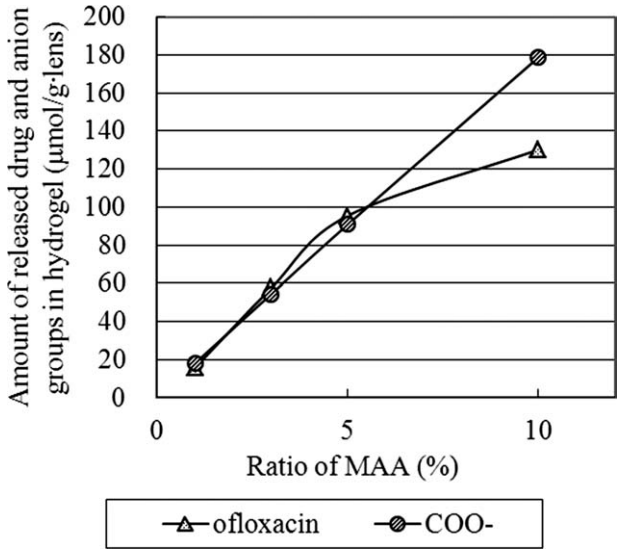

Figure 5. Amount of released drug caused by ionic interaction and COO^- (MAA). The released drug caused by ionic interaction were calculated by subtracting the amount of released drug from blank lens. The amount of COO^- (MAA) were calculated at the condition of pH 6.5.

The contact lenses containing MAA showed that the uptake of Ofloxacin decreased at 10 wt % MAA, in contrast to an increase for contact lenses with 1–5 wt % MAA, which was dependent on the amount of MAA. Figure 5 shows the amount of COO^- of MAA at pH 6.5 and released drug obtained by subtracting the amount of released drug from blank lens. Because uptake drug of blank lens was caused by only water in hydrogel, the amount of released drug obtained by subtracting the amount of released drug from blank lens were caused by ionic interaction with COO^-. The decreasing uptake at 10 wt % MAA is supposed to be caused by the drug high-concentration, which

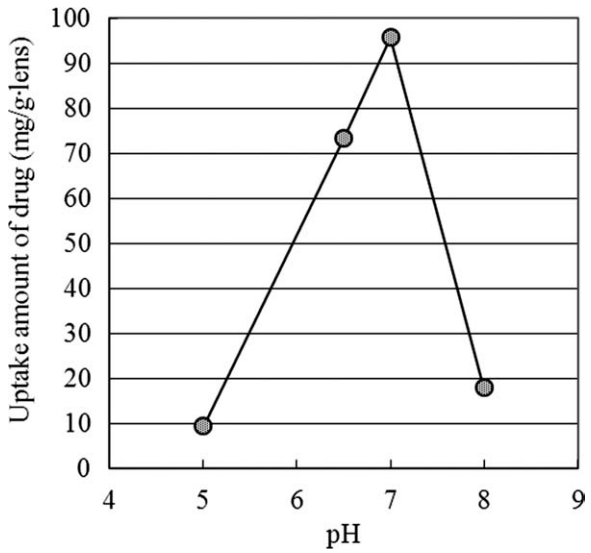

Figure 6. Uptake amount of Ofloxacin at each pH. Contact lenses containing MAA were soaked in a 0.3 wt % Ofloxacin solution of pH 5.0, 6.5, 7.0, and 8.0.

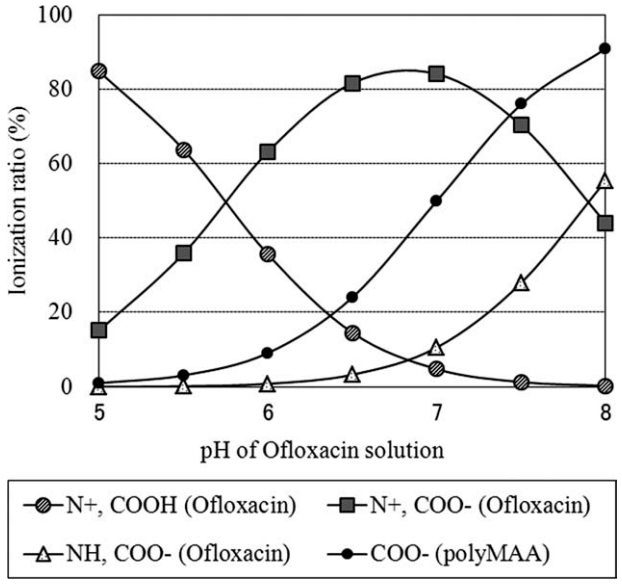

Figure 7. Ion dissociation curves of Ofloxacin and poly MAA.

reached saturated levels within the hydrogel due to the bulkiness of the drug. Once drug have interaction with ionic groups of side chains in hydrogels, excluded volume of side chains are increased. Thus, it was difficult to occur additional drug uptake, although there were still free anionic groups that had not interacted with the drug.

Effect of pH on the Uptake of Ofloxacin into Hydrogels with Anionic Groups

To evaluate the effects of pH on Ofloxacin uptake, contact lenses containing anionic MAA monomer were soaked in a 0.3 wt % Ofloxacin solution of pH 5.0, 6.5, 7.0, and 8.0. The each uptake amounts were measured (Figure 6). Although uptake amounts of Ofloxacin were less than 20 mg/g·lens at pH 5.0 and 8.0, uptake amounts were 73.4 mg/g·lens at pH 6.5 and

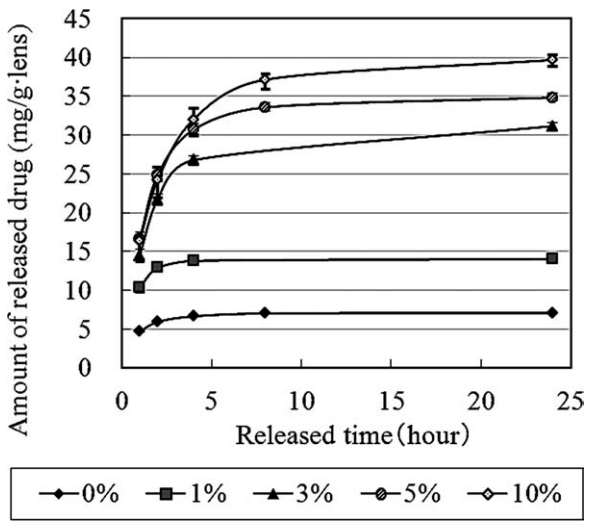

Figure 8. Release behavior of Ofloxacin from contact lenses. Contact lenses included 0, 1.0, 3.0, 5.0, and 10.0 wt % of MAA. Their water contents were 37 ± 2%. Data are shown as average ($n = 3$).

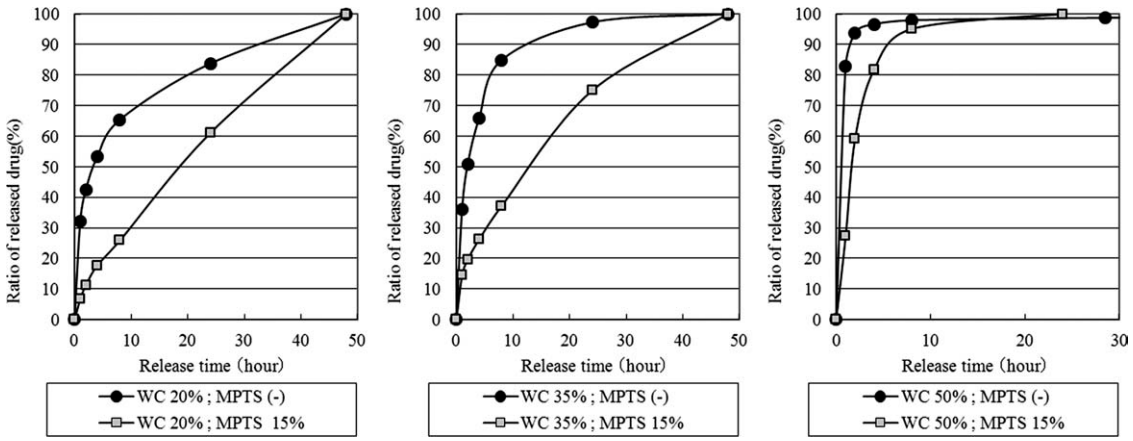

Figure 9. Sustained-release behaviors of each water content of contact lenses. Contact lenses were consisted of HEMA and 1–10 wt % of MAA or MOESA, which included 0 or 15 wt % of MPTS.

95.7 mg/g·lens at pH 7.0. This effect is not due to solubility. The Ofloxacin molecules existed as zwitterions under the pH conditions described above. The relative solubility characteristics of Ofloxacin at room temperature, as defined by USP nomenclature, indicate that Ofloxacin is considered to be soluble in aqueous solutions between pH 2 and 5 and in aqueous solutions greater than pH 9. Ofloxacin is sparingly to slightly soluble in aqueous solutions of pH 7, which is 4 mg/mL. Figure 7 shows the ionized ratio of each ionic group of Ofloxacin and polyMAA. The ionized Ofloxacin exists in three forms: N^+/COOH, N^+/COO^-, and NH/COO^-. In aqueous solutions with pH 6.5 and pH 7, ~ 90% of Ofloxacin exists as N^+/COOH and N^+/COO^-, which the MAA-containing contact lenses can uptake due to the ionic interactions. Therefore, the uptake amount at pH 6.5 and pH 7.0 increased, especially for the pH 7.0 solution, which was at a maximum because the carboxylic acid of the MAA-containing contact lenses were ionized at 50%. In contrast, the lack of Ofloxacin uptake at pH 5.0 and pH 8.0 were caused by a low ratio of ionization. Namely, the Ofloxacin existed as cationic molecules in solution at pH 5.0, but the carboxylic acids of the contact lens with MAA did not ionize. In the solution at pH 8.0, almost all the carboxylic acids of the MAA-containing contact lens ionized but were anionic (NH/COO^-) more than cationic.

Evaluation of the Release Periods for the Contact Lens

Figure 8 shows sustained-release behaviors of Ofloxacin from the contact lenses, which included 0, 1.0, 3.0, 5.0, and 10.0 wt % of MAA. The water contents were 37 ± 2%. The contact lenses released 85% of the Ofloxacin within 4 h. The results from Figure 3 indicate that the carboxylic acid groups of MAA could not extend the drug-release periods, while the carboxylic acid groups could increase the uptake amount of Ofloxacin.

Using the same method, sustained-release behaviors from contact lenses that included or did not include the silyl groups were measured (Figure 9). The contact lenses without silyl groups (with water contents of 20, 35, and 50%) did not release the drug as well as the MAA-containing contact lenses (with a water content of 37 ± 2%). By contrast, the silyl-group-containing contact lenses effectively controlled the initial burst-release of Ofloxacin for each percent of water content. In addition, low-water content lenses (20 and 35%) showed prolonged release of the drug in which under 30% of the total amount of Ofloxacin was released within 4 h. Drug release continued for

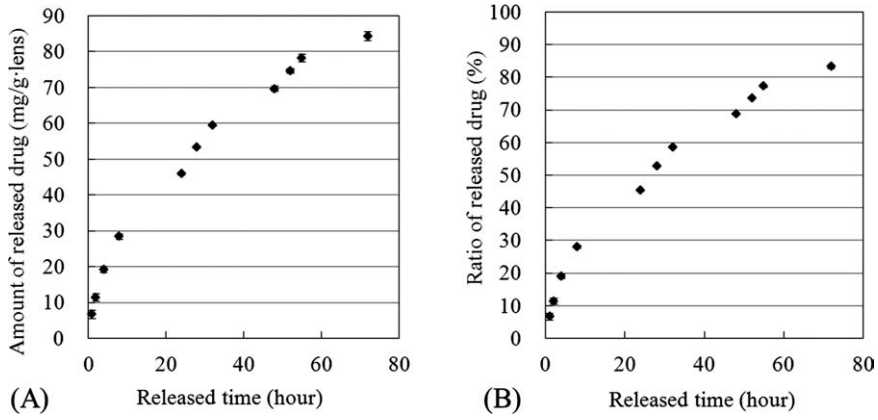

Figure 10. Amount (A) and ratio (B) of sustained-release behaviors of the contact lenses. Contact lens were consisted of HEMA and crosslinking agents with 10 wt % of MAA and 15 wt % of MPTS. Data are shown as average ($n = 2$).

an additional 48 h. Because the hydrogels with a hydrophobic side-chain silyl group were able to suppress the initial burst-release of the drug normally present in many hydrogels, the hydrophobic groups in the hydrogel can possibly affect the drug release rate. Generally, the driving force of releasing a water-soluble drug from a hydrogel is an exchange between water solvating the drug in the hydrogel and water out of the gel. Because water-exchange efficiency in hydrogels affects the rate of drug release from the hydrogel, hydrogels with side-chain silyl groups reduce the efficiency of water exchange in the hydrogel through hydrophobic interactions. As a result, it could be possible to control the drug release rate.

Evaluation of the Optimized Drug Delivery Contact Lens for Ofloxacin Release

As shown earlier, anionic groups and silyl groups in a hydrogel could increase the uptake amount of drugs and extend the release periods. In order to be applied for viable contact lenses, hydrogels were optimized as DDSs for Ofloxacin release, which should also be wearable, that is, transparent, dimensionally stable, and durable. The sustained-release behaviors of the contact lenses were measured by the same method (Figure 10). The contact lenses released 73.7 mg/g·lens in 72 h, which was a sufficient amount of Ofloxacin compared with a dosage of 0.3 wt % Ofloxacin solution over 3 days (one drop at a time, three times a day). Furthermore, the initial burst-release of Ofloxacin was efficiently controlled. The amount of released Ofloxacin in 4 h was 20% of the total amount and 84% at 72 h.

CONCLUSION

This study demonstrated that the hydrogels containing ionic groups and silyl groups in the side chains were useful materials to prepare drug delivery contact lenses. The ionic groups in the hydrogels functioned by retaining a drug with an ionic substituent. It is noteworthy that the drug content in the contact lenses could readily be controlled by changing the ionic monomer content during polymerization. Furthermore, the controlled release of the drug from the silyl groups on the hydrogels showed sustained release over 72 h, which indicated that it is useful as a contact lens for sustained drug release. These results indicate that contact lenses can be tailored for optimized drug interaction by adding functional groups.

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