Application of Polymer Gels Containing Side-Chain Phosphate Groups to Drug-Delivery Contact Lenses

Takao Sato,[1,2] Rei Uchida,[1] Haruyasu Tanigawa,[1] Kenji Uno,[1] Akira Murakami[2]

[1]*Research and Development Section, SEED Company, Limited, Saitama, Japan*
[2]*Department of Ophthalmology, Juntendo University School of Medicine, Tokyo, Japan*

Received 9 August 2003; accepted 13 December 2004
DOI 10.1002/app.22080
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Hydrogels that contain phosphate groups in side chains were studied for their usefulness in drug-delivery soft contact lenses (SCLs). Naphazoline, a model drug having a cationic group, was incorporated into an SCL because of its phosphate groups and was released over a period of about 14 h. For the SCL, the naphazoline content was equivalent to the phosphate group content. It is suggested that drug-delivery SCLs can be designed to contain the needed amount of a drug through the choice of the ionic group for the ligand. Furthermore, the SCL having amide groups and phosphate groups had high transparency and an unchanged shape. It is suggested that amide groups and phosphate groups must be introduced into the polymer in equimolar amounts to give the necessary polymer–drug interaction. Therefore, hydrogels having a drug-delivery system were synthesized by the inclusion of a phosphate group and an amide group. These hydrogels are also applicable to SCL materials. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 98: 731–735, 2005

Key words: biomaterials; drug delivery systems; hydrogels; ion exchangers

INTRODUCTION

Recently, the population of soft contact lens (SCL) users has reached over 1.5 billion, and SCLs have been recognized as medical devices that have infiltrated our daily lives. The number of SCL users is increasing with the increasing popularity of disposable SCLs. SCLs are hydrogel-based devices, but not all of them are made of 2-hydroxyethyl methacrylate (HEMA). SCLs have a weak point; that is, their shape is altered by changes in the pH, temperature, and osmotic pressure.[1,2] The shape change is a problem for the wearing of SCLs, so the shape of SCLs is essential for proper fit. The incidence of corneal infection has increased with increased use of SCLs, particularly extended-wear SCLs, with the highest incidence occurring with the use of extended-wear SCLs in aphakic eyes. Because of the increasing proportion of the elderly population wearing contact lenses, the incidence of corneal infection may rise.

On the other hand, eye diseases such as glaucoma and cataracts in elders are increasing year by year.[3,4] Eye drops are commonly used to treat these diseases. However, administering eye drops presents many problems, such as poor adsorption of the drug, eye irritation, and the possibility of overdosing.

Correspondence to: T. Sato (takao_sato@seed.co.jp).

Journal of Applied Polymer Science, Vol. 98, 731–735 (2005)

To find a solution to these problems, the drug-delivery system (DDS) has been studied by many researchers.[5–7] For example, a complex of cationic and anionic polymers can swell or shrink, depending on the pH, the ionic strength, the types of ionic groups present, and the ionic concentration.[8,9] This phenomenon is used in drug-delivery hydrogels. However, these drug-delivery hydrogels do not have high transparency or a uniform shape.

In this study, we synthesized hydrogel SCLs that were used to correct vision while delivering medication through the controlled release of a drug. That is, we tried to develop a drug-delivery SCL material containing an ophthalmic drug, studied its synthesis, and evaluated its suitability for use as a drug-delivery SCL. We have previously reported a drug-delivery hydrogel with phosphate groups.[10,11] Its phosphate groups served as ligands, and these ligands were most useful in other anionic groups. In this article, we report on the complex strength of phosphoric acid in a hydrogel cationic drug and the interaction between methacrylamide (MAm) and a model drug.

EXPERIMENTAL

Materials

HEMA, MAm, and 2,2′-azobisisobutyronitrile (AIBN) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). 2-Methacryloxyethyl phosphate (MOEP) was purchased from Johoku Chemical Co.,

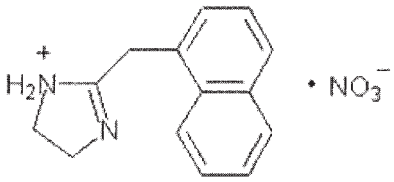

Figure 1 Chemical structure of 2-(1-naphthyl methyl)-2-imidazoline (naphazoline).

Ltd. (Tokyo, Japan). Methacrylic acid (MAA) and ethylene glycol dimethacrylate (EDMA) were purchased from Mitsbishi Rayon Co., Ltd. (Tokyo, Japan). These monomers were purified according to standard methods. All other chemicals were reagent-grade.

2-(1-Naphthyl methyl)-2-imidazoline nitrate (naphazoline) was purchased from Lancaster Synthesis (England). Figure 1 shows the chemical structure of naphazoline. In this study, this compound was used as the model drug. Naphazoline is known as a sedative used in the eye to relieve congestion, and it is applied as an eyewash solution.

Preparation of the anionic hydrogels

MOEP or MAA (1, 3, 5, 7, or 10 mol %; ligand monomer) and EDMA (0.3 mol %; crosslinker) were dissolved in HEMA (90.7–98.7 mol %, based on the monomer). This solution, which had been previously heated to 40°C and to which AIBN (0.25%; initiator) had been added, was transferred into a mold in the form of a contact lens (20 mm in diameter and 0.3 mm thick). The reaction was degassed under nitrogen and allowed to polymerize at 50–100°C for 25 h. After polymerization, the molds were removed, and the hydrogels obtained were soaked in deionized water and then washed successively with 0.1*M* NaOH and deionized water. Each type of washing lasted for 2 days, during which the washing solution was replaced every 10 h; the complete washing period was 3 days.

Preparation of the poly(2-hydroxyethyl methacrylate-*co*-2-methacryloxyethyl phosphate-*co*-methacrylamide) [poly(HEMA-*co*-MOEP-*co*-MAm)] hydrogels

MOEP (3 mol %; ligand monomer), different amounts of MAm (0, 0.07, 0.15, 0.2, 0.3, 0.45, and 0.6 mol %; functional monomer), and EDMA (0.3 mol %; crosslinker) were dissolved in HEMA (98.8–99.4 mol %, based on the monomer). This solution, which had been previously heated to 40°C and to which AIBN (0.25%; initiator) had been added, was transferred into a contact lens mold (20 mm in diameter and 0.3 mm thick). The reaction was degassed under nitrogen and allowed to polymerize at 50–100°C for 25 h. Figure 2 shows the chemical structure of poly(HEMA-*co*-MOEP-*co*-MAm). After polymerization, the molds were removed, and the hydrogels obtained were soaked in deionized water and then washed successively with 0.1*M* NaOH and deionized water. Each type of washing lasted for 2 days, during which the washing solution was replaced every 10 h; the complete washing period was 3 days.

Binding of drugs to the hydrogel and drug release

A piece of the hydrogel was reduced and then immersed in a 0.5% naphazoline aqueous solution at 25°C for 2 days to allow naphazoline adsorption. Free naphazoline was removed from the hydrogel by consecutive washing with an aqueous solution at 25°C for 24 h. Next, each hydrogel was immersed in 10 mL of a 0.9% NaCl aqueous solution at 37°C for 40 h. Samples were withdrawn from this solution at regular intervals, and their naphazoline concentration was measured by high-performance liquid chromatography (Jasco International Co., Ltd., Tokyo, Japan). The end of the release from the hydrogel was confirmed by the direct measurement of the hydrogel sample with a spectrophotometer at 254 nm.

Characterization of a sample hydrogel for an SCL

For a hydrogel to be used as an SCL material, the hydrogel has to satisfy the following requirements. First, the shape of the hydrogel must not be altered by a change in the pH, temperature, or osmotic pressure.[12,13] Second, the hydrogel must have transparency and good visual power. Consequently, we measured the shape of the sample hydrogel and its eyesight. Its size and base curve were measured with a contact lens analyzer (Optimic, UK). The eyesight was measured with a power meter (OL-7, Nikon, Tokyo, Japan).

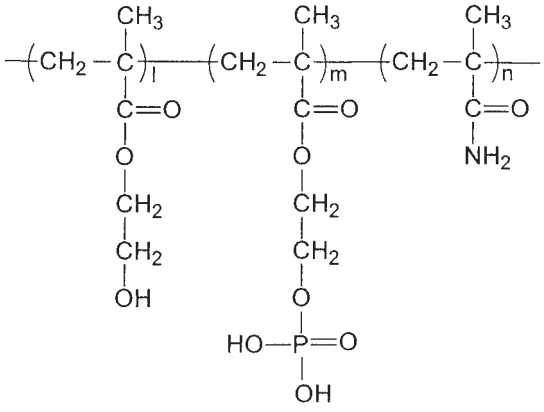

Figure 2 Chemical structure of poly(HEMA-*co*-MOEP-*co*-MAm).

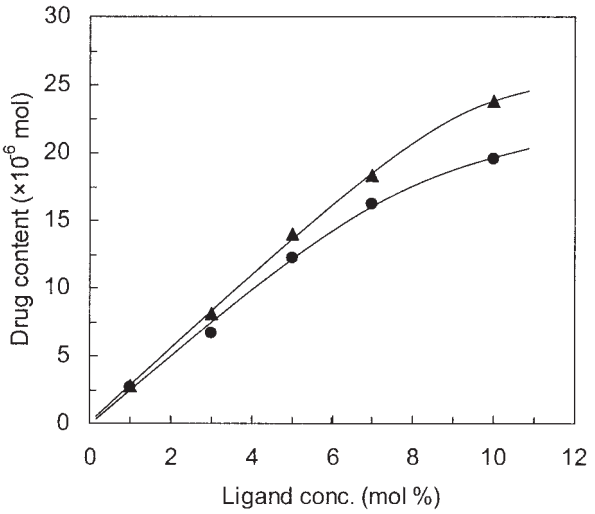

Figure 3 Dependence of the drug content on the ligand concentration of the hydrogels: (▲) MAA and (●) MOEP.

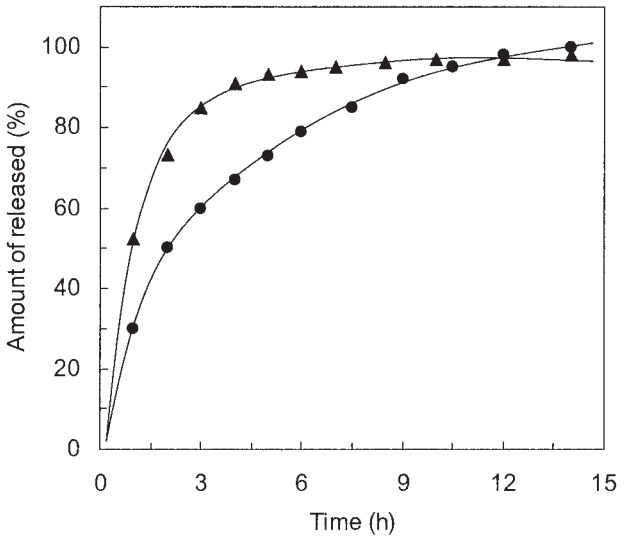

Figure 4 Release profiles of naphazoline delivered from hydrogels. The ligand monomer concentration was kept constant at 3 mol %: (▲) MAA and (●) MOEP.

RESULTS AND DISCUSSION

Anionic hydrogels

Figure 3 shows the relationship between the MAA and MOEP ligand concentration and the naphazoline content of the hydrogel. The naphazoline content increased with increasing ligand content, independently of the carbonic acid group and phosphate group. Consequently, it was suggested that the ionic complex was formed by an anionic group on the polymer side chain and naphazoline; naphazoline, having a cationic group, was released by an ion-exchange reaction in a 0.9% NaCl aqueous solution. For the same ligand content, the MAA hydrogel had a higher naphazoline content than the MOEP hydrogel. This phenomenon tended to increase the ligand content. The MAA hydrogel had a high naphazoline content, so its ligand had strong ionic strength and ionized easily. On the contrary, the MOEP hydrogel had less naphazoline content, so its ligand had weak ionic strength and ionized with difficulty. The naphazoline content in these hydrogels depended on the dissociation constant of MAA and MOEP. Furthermore, for the MOEP hydrogel, the naphazoline content was equivalent to the phosphate group content. It was suggested that drug-delivery contact lenses could be designed to contain the needed amount of a drug through the choice of the ionic group for the ligand.

Figure 4 shows the drug-release behavior of each hydrogel. For MAA hydrogels, naphazoline in the hydrogels was released for over 5 h, but for MOEP hydrogels, naphazoline was continuously released for 14 h. At first, MAA hydrogels formed a complex with the carbonic acid group and naphazoline. After immersion in a 0.9% NaCl aqueous solution, the ion-exchange reaction by Na^+ was greater than the reaction by phosphate groups with the MOEP hydrogels. This reaction was dependent on pK_a. Figure 5 shows the change in the ionic structure with the pH change. MOEP, having a pK_a value of 6.80, was dissociated in the NaCl solution. Its phosphate acid

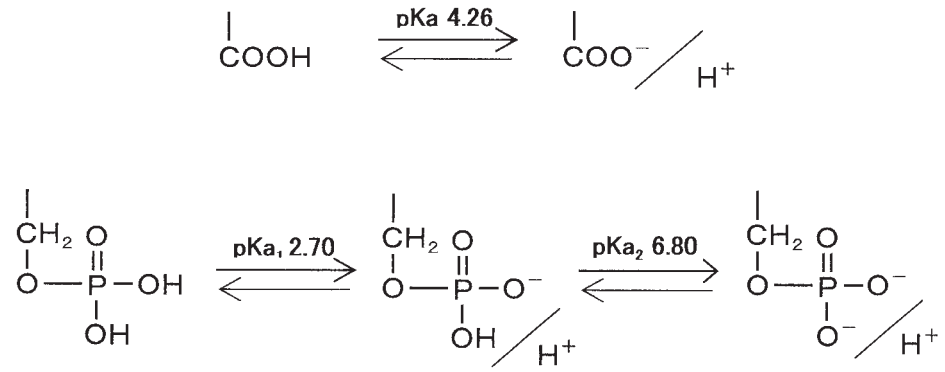

Figure 5 Chemical structure with pH change.

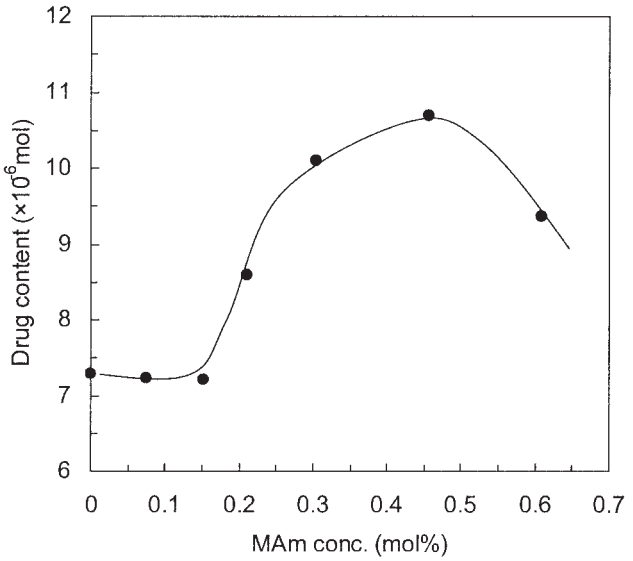

Figure 6 Dependence of the drug content on the MAm concentration of the MOEP hydrogel. The MOEP concentration was kept constant at 3 mol %.

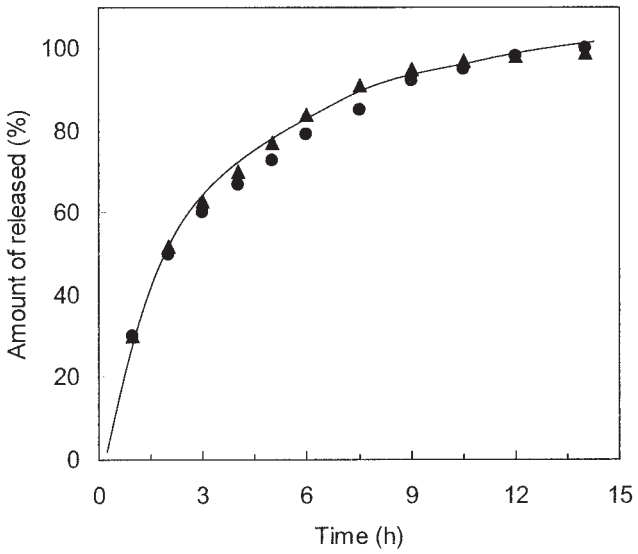

Figure 7 Release profiles of naphazoline delivered from hydrogels. The MAm concentration was (▲) 0.4 or (●) 0 mol %. The MOEP concentration was kept constant at 3 mol %.

ion was stronger than the carbonic acid ion of MAA. The naphazoline-release behavior was dependent on the diffusion velocity of the hydrogels. Thus, it is thought that MAA, having a short residue, has a rapid release and diffusion velocity, but MOEP, having a long residue, has a long release and a protracted effect on the diffusion resistance of gels. It is suggested that phosphate groups, as side chains, have good ion interactions under physiological conditions.

When anionic hydrogels were applied to SCL materials, eye lesions were reported with the use of SCLs because of adsorbed cationic proteins in the tear fluid. The adsorption was caused by ion interactions between the anionic SCL surface and the cationic protein.[12,13] In this study, the MOEP hydrogel, having a phosphate group as a side chain, suppressed the induction of eye lesions because of the stabilized ion complex and ion balance. It has been suggested that MOEP hydrogels can be used as drug-delivery SCLs.

Poly(HEMA-*co*-MOEP-*co*-MAm) hydrogel

As previously described, the phosphate ligand on the MOEP hydrogel has been found useful for drug-delivery SCLs. When the hydrogel is used as an SCL material, its shape must be stabilized for the purpose of correcting eyesight and for safety. In this study, we synthesized a novel hydrogel with nitrogen atoms as side chains for unchanged shapes of hydrogels. Figure 6 shows the relationship between the MAm content and naphazoline content of the MOEP hydrogel (3 mol % MOEP), which had phosphoric acid as the ligand. The naphazoline content of the MOEP hydrogel (3 mol % MOEP) was the same as that of eye drops. Figure 6 shows that the naphazoline content in the hydrogel did not change until about 0.2 mol % MAm. The naphazoline content increased over 0.2 mol % MAm and decreased over 0.6 mol % MAm. It has been suggested that the polymer–drug complex forms an interaction of an amide group into MAm, a phosphate group into MOEP, and a hydroxyl group into HEMA and naphazoline residue. The polymer chain, before the naphazoline content, is kept stable by ionic interactions; when naphazoline of a cationic drug is introduced into the hydrogel, the polymer–drug complex

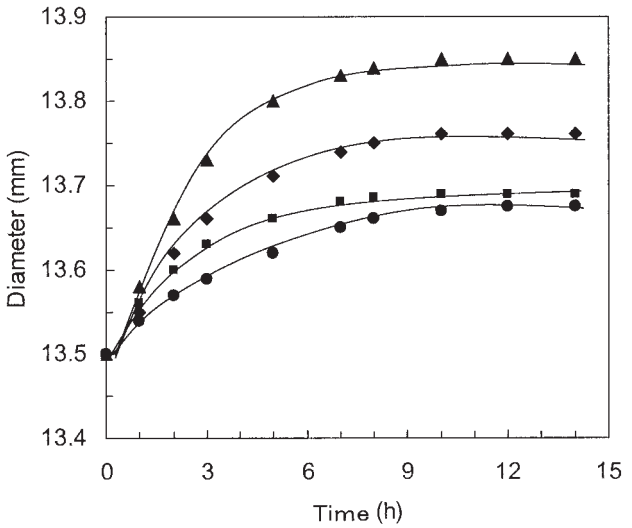

Figure 8 Dependence of the change in the diameter of the hydrogels with the release of naphazoline. The MOEP concentration was kept constant at 3 mol %. The MAm concentration was (▲) 0, (♦) 0.2, (■) 0.3, or (●) 0.4 mol %.

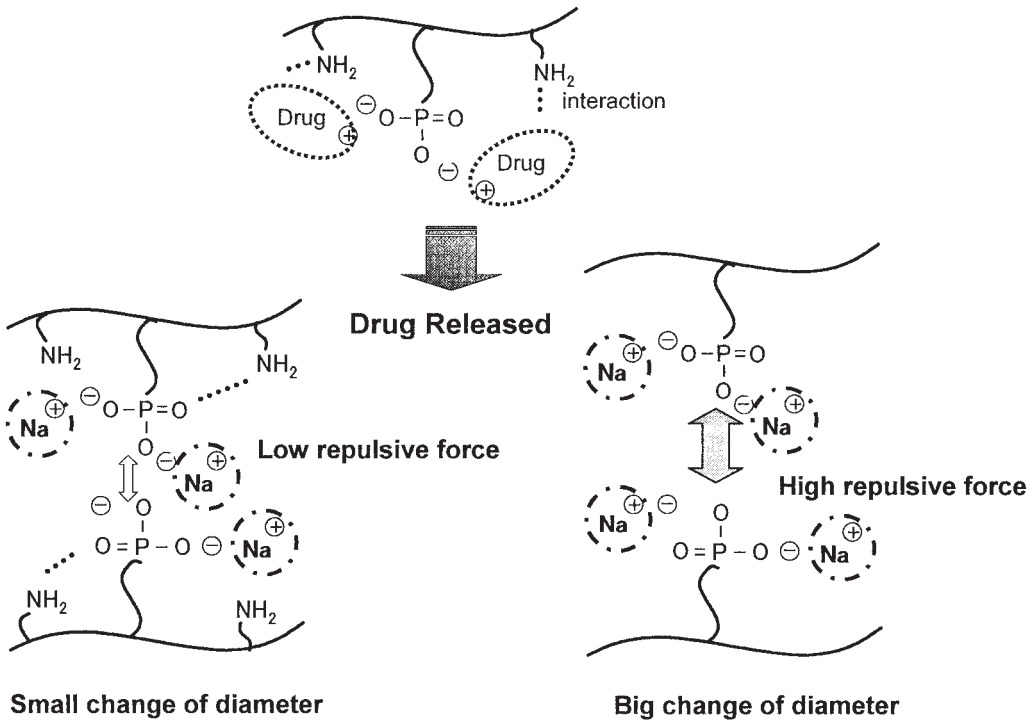

Figure 9 Schematic representation of the proposed mechanism for the change in the hydrogel diameter.

is formed. At this time, the polymer–drug complex formation is due to a ligand (MOEP)–naphazoline interaction and a hydroxyl group (HEMA)–amide group (MAm) interaction. Thus, it has been suggested that equimolar amounts of MAm and the phosphate group of MOEP must be introduced into the polymer to give reasonable polymer–drug interactions.

Figure 7 shows the behavior of naphazoline released from a hydrogel containing 0.4 mol % MAm and a hydrogel without MAm. By the inclusion of MAm, the naphazoline content was increased, but the same behavior was indicated when naphazoline was released. The behavior of the naphazoline release may been governed by an ion-exchange reaction.

Figure 8 shows the size changes dependent on the MAm content when naphazoline was released. The change in size was reduced with increasing MAm content. Figure 9 shows a schematic representation of the proposed mechanism for the change in the hydrogel diameter. The small change in size may have been produced by ionic repulsion depressed on phosphate groups as side chains, so its polymer conformation of over-release was formed by an ionic interaction. The amide group in MAm interacted with naphazoline and made space for naphazoline content by a short side chain. As mentioned previously, if hydrogels are used as SCLs, the hydrogels have to satisfy the following requirement: the shapes of the hydrogels are not altered by changes in the pH, temperature, or osmotic pressure, and the hydrogels must have transparency and good eyesight. As can be seen in Figure 8, the problem was much improved by the introduction of 0.3–0.4 mol % MAm to the polymer having a phosphate group as a side chain.

From these results, hydrogels having DDS have been synthesized to include phosphate and amide groups. These hydrogels are applicable to SCL materials. By the use of drug-delivery SCLs, these drugs are expected to permeate the cornea, in comparison with eye drops.

References

1. Sato, T.; Saito, N.; Shirogane, T.; Tanigawa, H.; Uno, K.; Kanai, A. J Jpn Contact Lens Soc 2001, 43, 7.
2. Cerulli, L.; Pocobelli, A.; Ricci, F.; Missiroli, A.; Sabbatini, L.; Zambonin, P. Contact Lense Association of Ophthalmologists J 1992, 18, 101.
3. Kanai, A.; Igawa, S. J Jpn Contact Lens Soc 1998, 40, 1.
4. Tsubai, T.; Murai, M.; Watanabe, A. Orbit 1997, 16, 91.
5. Uchida, R.; Sato, T.; Tanigawa, H.; Uno, K. J Controlled Release 2003, 92, 259.
6. Deshpande, S. G.; Shirolkar, S. J Pharm Pharmacol 1989, 41, 197.
7. Miyazaki, S. Chitin Chitosan Res 2001, 7, 1.
8. Jaskari, T.; Vuorio, M.; Kotturi, K.; Urtti, A.; Manzanares, J. A.; Hirvonen, J. J Controlled Release 2000, 67, 179.
9. Yamakawa, T.; Nishimura, S. J Controlled Release 2003, 86, 101.
10. Sato, T.; Kobayashi, D.; Kobayashi, K.; Tanigawa, H.; Uno, K. Drug Delivery Syst 2002, 17, 264.
11. Sato, T.; Uchida, R.; Tanigawa, H.; Uno, K. J Polym Sci Technol 2003, 60, 235.
12. Honda, S.; Suto, Y.; Uchida, K.; Shirogane, T.; Syaku, H.; Watanabe, Y.; Tanigawa, H.; Uno, K.; Fujimoto, M.; Kanai, A. J Jpn Contact Lense Soc 2001, 43, 2.
13. Sano, K. J Jpn Contact Lens Soc 2000, 42, 68.