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# Poly(2-hydroxyethyl methacrylate) film as a drug delivery system for pilocarpine

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**Abstract**

This work investigates pilocarpine trapped in a matrix diffusion-controlled drug delivery system using hydrophilic inserts of Poly(2-hydroxyethyl methacrylate) (pHEMA) to ensure an increased bioavailability of pilocarpine and prolong the length of time in which the medication remains in the eyes of the test subjects. The physical and chemical properties of pilocarpine were investigated to elucidate the mechanism of drug–polymer interaction and the effect on drug release behavior of controlled release polymeric devices. In vitro release studies indicated that pilocarpine continued to be released from the inserts for a 24 h period. The results of intraocular pressure tests performed on albino rabbits were consistent with the observed in vitro behavior. The pressure decrease was significant for a period longer than 48 h. It confirms that the inserts, as sustainable releasing devices, are promising carriers for ophthalmic drug delivery systems. 

*Keywords:* pHEMA hydrogel; Pilocarpine; Drug delivery system; Drug release; Glaucoma

## 1. Introduction

Pilocarpine has been widely used as a topical miotic for controlling elevated intraocular pressure associated with glaucoma. However, this drug has a very low bioavailability and a limited active period due to both poor corneal penetration and extensive precorneal loss. Therefore large quantities of pilocarpine have to be administered frequently into the eyes of patients in order to achieve effective therapeutic results. It results in undesirable side effects, however, including miosis, myopia [1–3], and poor patient compliance. The excess pilocarpine, which can't be absorbed by eye tissue, flows out through the lower eyelid and partially penetrates the lacrimonasal canal causing mucosa irritation [4]. The absorption of pilocarpine into the systemic circulation, during the draining process from the precorneal, has also been observed [5].

Using controlled release delivery system as a drug carrier has the potential of lessening the shortcomings of pilocarpine [6,7]. Ideally, a drug carrier should improve the drug–corneal contact time and retard the precorneal drug loss, while the controlled delivery system releases pilocarpine at a constant rate so that the unnecessary high drug concentrations can be avoided. Therefore, high therapeutic efficacy with reduced side effects can be achieved.

A variety of carriers have been explored to modify the response to drugs that are delivered topically to the eye. These include gels, nanoparticles, polymer matrices, liposomes, and the Ocusert device [8]. To prolong pilocarpine's presence in the eye, hydrophilic contact lens [9], the Ocusert system [10], polyvinyl alcohol (PVA) films [4,11], bioerodible systems such as collagen and gelatin [12–14], and water soluble unit [6,15,16] have been used. However, with the exception of Ocusert, none has had wide clinical applications.

Poly(2-hydroxyethyl methacrylate) (pHEMA) hydrogels were first examined and prepared for biological use by Wichterle and Lim [17]. They have then been widely investigated and used in biomedical applications [18]. The well-tolerated safety and biocompatibility of pHEMA hydrogel are evident in its use as contact lens. In addition to its non-toxicity, non-antigenic properties and good biocompatibility, pHEMA has also been developed as a carrier for water-soluble anticancer drugs,

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including 5-fluorouracil [19], topical mitomycin-C [20], and cytarabine [21].

In this study, we report the potential use of pHEMA hydrogel films as a drug carrier for a long acting delivery system for pilocarpine. Two drug delivery systems using pHEMA films at different cross-linking level were prepared and characterized. In addition, the drug-carrier interaction and the in vitro release of pilocarpine from these systems were studied. Finally, the in vivo effects of the prepared delivery systems were investigated in rabbit eyes.

## 2. Materials and methods

### 2.1. Materials

2-Hydroxyethyl methacrylate (HEMA) was supplied by Merck Chemical Inc. and was distilled under a vacuum prior to use. Trimethylolpropane trimethacrylate (TMPTMA) was supplied by TCI Chemical Inc., and pilocarpine nitrate by Sigma Chemical Inc; both were used as received. Ethylene glycol dimethacrylate (EGDMA) was purchased from TCI Chemical Inc. All other chemicals were reagent grade products obtained commercially.

### 2.2. Polymerization

To a mixture of HEMA and distilled water (volume ratio: 4:1) containing pilocarpine nitrate, TMPTMA was added as a cross-linking agent. The concentration of TMPTMA was 0, 6, 10, 20, and 30 wt%, respectively, for each polymer film. The solution was well mixed and added into a plate. It was then exposed to UV irradiation at 365 nm for 11 min. The films were 0.45–0.5 mm thick. The prepared pilocarpine polymer films were dried in a vacuum oven (25°C) for 24 h. EGDMA was also used as a cross-linking agent, for which the concentration was 0, 2, 6, 8, and 10 wt%, respectively, for each polymer film.

### 2.3. Swelling ratio and cross-linking density

The swelling properties of the unloaded pHEMA films were determined gravimetrically after placing them in 15 ml balanced salt solution (BSS) at 37°C. The specimen were recovered at desired time intervals and weighed on an electronic balance, after excess water being removed. The swelling ratio at indicated time points was calculated using Eq. (1),

$$\text{Swelling ratio} = 100 \times (W_w - W_d)/W_d, \quad (1)$$

where $W_w$ represents the wet weight of the sample, $W_d$ is the dry weight of the sample before swelling. The result is the average of six measurements for each sample.

The cross-linking density, $\rho$ (in moles of cross-links per $cm^3$ of polymer network), of each sample was determined according to the modified Gaussian distribution equation of equilibrium swelling using a reported method [22].

### 2.4. Contact angle measurement

Erma G-1 (Tokyo, Japan) was used for the measurement of static contact angles of prepared pilocarpine-pHEMA films. The tests were taken at 25°C using the sessile drop method.

### 2.5. FTIR analysis

The IR spectra were recorded on an FTIR spectrometer (FTS-135, Bio-rad, USA) using KBr discs. The spectra were recorded from 1850 to 1450 $cm^{-1}$ and a hundred scans were made for each sample.

### 2.6. X-ray diffraction analysis

Powder X-ray diffraction measurements were carried out using R-AXIS IIC (Rigaku, Japan) with Cu $K_\alpha$ radiation and Ni Cu $K_\beta$ filter. The analysis was performed at 20°C, with $2\theta$ varied from 0–40° at a scan speed of 1°/min.

### 2.7. Release studies in vitro

pHEMA films entrapped with pilocarpine nitrate were put into a brown colored vial containing 27 ml BSS. The vial was shaken in a horizontally reciprocating shaker at 37°C (±0.5°C). The polymer films were then transferred into another vial containing 27 ml fresh saline after shaking for 1 h. Transfers were made to equal volumes of saline at 2, 4, 8, 12, and 24 h, respectively. The amount of pilocarpine contained in each vial was then determined by high-performance liquid chromatography (HPLC) using a reported method [14]. Briefly, a group of standard pilocarpine nitrate solutions were made in saline with known concentrations of 100, 70, 50, 30, 10, and 1 μg/ml. The solutions were then analyzed by HPLC (SP4270 integrator with a P-4000 gradient pump and a Spectra 100 detector, all from Spectra-Physics, USA) using two Spherisorb 5-ODS, 5 μm column (Phenomenex, USA) at a flow rate of 1 ml/min. The eluant was prepared by mixing methanol and a monobasic potassium phosphate buffer solution (pH, 3.0) at volume ratio of 4 to 96. The absorbance of pilocarpine at 215 nm was then detected. The concentration versus peak area was drawn as a standard curve. The concentration of pilocarpine nitrate in unknown samples was then estimated from their absorbance at the same wavelength.

### 2.8. Intraocular pressure

A group of seven New Zealand white rabbits (2.5–3.0 kg) were used for the trial. In the first two weeks prior to the insertion of polymer films, the intraocular pressure of each rabbit eye was measured daily. This allowed the experimental eyes to get used to the measurement. Selected polymer films entrapped with pilocarpine nitrate were then inserted into the lower sac of the rabbit eye. The intraocular pressure of each experimental eye was monitored hourly in the first 6 h, then at 12, 24, and 48 h, respectively.

The intraocular pressure measurements were taken in direct contact with cornea using an ophthalmic tonometer (Bio-Rad ophthalmic tonometry division I), after applying the Alcaine® (alcaine 0.5%, proparcaine hydrochloride, Alcon) in rabbit eyes. The eyes were frequently checked when polymer films were kept in. No inflammation was observed in any experimental eyes.

## 3. Results and discussions

### 3.1. Preparation of pHEMA film

#### 3.1.1. Optimal irradiation wavelength and irradiation time of UV light

The polymerization of HEMA has usually been done by irradiation of UV light. For commercial application, UV light with wavelength of 365 and 295 nm are mostly used. In order to identify which of the two wavelengths has less adverse effects on pilocarpine, the 10 wt% pilocarpine solution was irradiated by the two UV strengths for 10 min. It was determined that 295 nm of UV irradiation would destroy pilocarpine. Therefore, for the curing of pHEMA film, 365 nm is the appropriate wavelength of UV light to be applied.

The pHEMA film was prepared by irradiating the HEMA monomer with UV light. Various reaction times have been tested for the preparation of pHEMA film. It was found that less than 11 min caused a low degree of polymerization, great than 20 min caused too much heating. Based on the result of testing, the polymerization of pHEMA film is implemented by irradiation of UV light for 11 min, which could produce a stable film with the proper shape.

### 3.2. The interaction of pilocarpine and pHEMA film

Pilocarpine is entrapped in pHEMA film with different concentrations (5, 10, 15, 20, and 30%). The FT-IR spectrum (1850–1450 $cm^{-1}$) is employed to analyze the change of pilocarpine entrapped in pHEMA film. The absorption of C=O stretching of pilocarpine is maintained at 1770 $cm^{-1}$ while the drug content is increased. When the drug content reaches 20 wt%, the absorption of the C=O stretching shifts to 1771 $cm^{-1}$ and the peak becomes broad. As the amount of pilocarpine reaches 30-wt%, the absorption of C=O stretching becomes 1777 $cm^{-1}$ and can move no further. The shift of carbonyl stretching absorption to low wave number can be explained as follows: hydrogen bonding is formed by the interaction of the oxygen atom of pilocarpine carbonyl group with the hydrogen atom of HEMA hydroxy group. At 20 wt%, most of the pilocarpine entrapped in pHEMA is molecularly dispersed with intermolecular hydrogen bonding while only a little fraction of drugs were crystalline dispersed that the absorption of C=O group is broad. The pilocarpine entrapped in pHEMA is crystalline dispersed at the 30 wt% drug content, and the absorption of the carbonyl group is unaffected by the hydrogen bonding. Therefore the absorption peak of C=O group is sharp.

The X-ray diffraction was used to measure the crystalline property of pilocarpine entrapped in pHEMA. Diffraction peak of pilocarpine does not appear in pHEMA film with limited amounts of pilocarpine. It is therefore evident that pilocarpine is molecularly dispersed within the polymer. In addition, crystals are not formed until the content of the pilocarpine exceeds 20 wt%. Notably, pilocarpine is not destroyed during the preparation of pHEMA film. Also the formation of pilocarpine crystals is disadvantageous to the control of drug release, since the drug release rate would definitely be accelerated through the porous structure after the crystalline drug was dissolved by water. Based on the X-ray diffraction results, 20 wt% is the maximum amount of pilocarpine in the pHEMA film.

### 3.3. The drug release characteristic of pHEMA film

Fig. 1 demonstrates pHEMA film's drug release. With an increased concentration the drug release rate accelerates, which thereby decreases drug release time. This is due to the following: the additional matter (pilocarpine) added to the polymer alters the hydration behavior and the material tortuosity, which is the main force that retards drug release. The increase of pilocarpine will decrease the material's tortuosity, which in turn reduces the effect of retardant of the drug release.

The pilocarpine diffusion release rate of polymer hydrogel could be retarded by the increase of polymer cross-linking density. EGDMA is one of the most commonly used cross-linking agents in HEMA cross-linking. As illustrated in Table 1, increasing of the EGDMA concentration reduces the swelling ratio of the polymer film, with equilibrium reached after 2 h. Therefore, it is clear that the addition of EGDMA increased the cross-linking density of pHEMA.

The effect of various EGDMA densities upon the release behavior of pHEMA is indicated in Table 2. During the first hour the drug release amount of pHEMA is

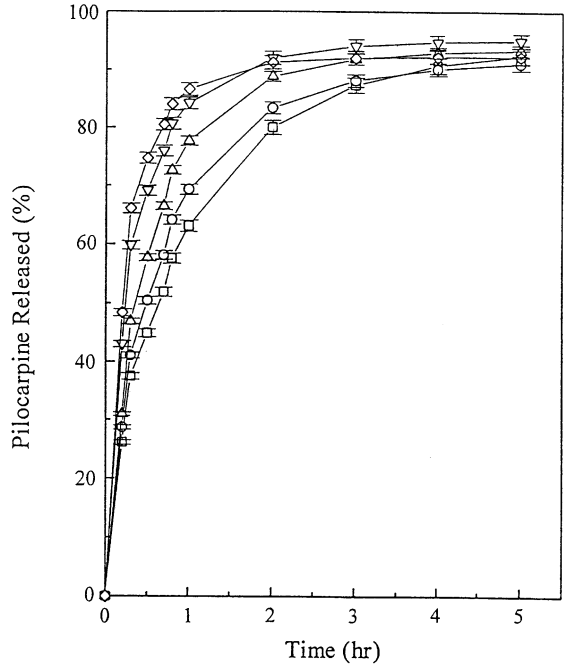


Fig. 1. The drug release diagram of pilocarpine entrapped pHEMA film. The concentration of drug: (□) 5 wt%; (○) 10 wt%; (△) 15 wt%; (▽) 20 wt%; (◇) 30 wt%.

Table 1
The swelling ratio of EGDMA and TMPTMA crosslinking pHEMA film in saline

| Content (wt%) | Swelling ratio (%) | |
|---|---|---|
| | EGDMA | TMPTMA |
| 0 | 52.0 | 52.0 |
| 2 | 33.9 | — |
| 6 | 27.0 | 31.9 |
| 8 | 26.3 | — |
| 10 | 21.5 | 25.7 |
| 20 | — | 17.0 |
| 30 | — | 12.4 |

reduced from 54.3 to 30.1% when EGDMA is added. The release time of the polymer film is expanded to 24 h, which is good for the release control of the polymer film. However, the EGDMA cross-linked polymer film has a burst effect, which is found in many releasing systems. For the EGDMA cross-linked pHEMA film, approximately 30% of the drug content is released during the first hour, which exceeded the initial amount targeted for release control.

In contrast, TMPTMA has the optimal release effect. TMPTMA, a three-function group cross-linking agent, is added to the polymer film. The swelling ratio in equilibrium is illustrated in Table 1. The swelling ratio of the 6 wt% TMPTMA cross-linking film attains equilibrium after 5–6 h. Equilibrium of cross-linking film of other TMPTMA contents occurs after approximately 7–8 h. Optimal swelling ratio occurs at a solution of 10 wt% TMPTMA. Therefore, the cross-linked film with 10 wt% TMPTMA has the optimal release effect.

The drug release of the polymer film at different time was demonstrated in Table 2, which is cross-linked using TMPTMA. With 10 wt% TMPTMA, the drug releases for one day. However, with an increase of TMPTMA, controlled drug release occurs for two days. The initial release amounts of the polymer film with TMPTMA of 10 and 6 wt% are approximately 21.7 and 32.4%, respectively. With the use of 20 and 30 wt% TMPTMA, during the first hour the drug release amount is less than the amount with a lower TMPTMA content. The release time for these amounts is more than 48 h. This indicates that the burst effect of the polymer film with TMPTMA is less than that with other cross-linking agents. Due to the length of the release time, it could be controlled by changing the content of the cross-linking agent.

### 3.4. The release kinetics

A simple semi-empirical equation is introduced to represent the drug release process of swelling polymer:

$$M_t/M_\infty = kt^n,$$

Table 2
The release amount of pilocarpine of EGDMA and TMPTMA cross-linking film at different times

| Content (wt%) | 1 h | | 4 h | | 8 h | | 12 h | | 24 h | |
|---|---|---|---|---|---|---|---|---|---|---|
| | EGDMA (%) | TMPTMA (%) | EGDMA (%) | TMPTMA (%) | EGDMA (%) | TMPTMA (%) | EGDMA (%) | TMPTMA (%) | EGDMA (%) | TMPTMA (%) |
| 0 | 68.5 | 69.6 | 88.9 | 90.6 | 89.8 | 92.3 | — | — | — | — |
| 2 | 56.5 | — | 86.1 | — | 94.4 | — | 96.3 | — | 98.1 | — |
| 6 | 48.1 | 32.5 | 79.6 | 69.2 | 89.8 | 84.6 | 92.6 | 90.6 | 96.3 | 96.6 |
| 8 | 45.8 | — | 76.8 | — | 87.0 | — | 90.7 | — | 95.4 | — |
| 10 | 29.6 | 21.8 | 55.6 | 58.1 | 71.3 | 77.8 | 77.8 | 85.5 | 86.6 | 94.9 |
| 20 | — | 12.8 | — | 31.6 | — | 46.2 | — | 54.7 | — | 68.4 |
| 30 | — | 8.1 | — | 19.7 | — | 28.2 | — | 35.0 | — | 47.0 |

Table 3
The diffusion exponent ($n$), diffusion kinetic constant ($k$), coefficient of determination ($r^2$), and $T_{50\%}$ of EGDMA crosslinking pHEMA film in saline

| EGDMA (wt%) | $n$ | $k$ | $r^2$ | $T_{50\%}$ (h) |
|---|---|---|---|---|
| 0 | $0.507 \pm 0.008$ | $0.092 \pm 0.003$ | 0.9989 | 0.50 |
| 2 | $0.389 \pm 0.006$ | $0.099 \pm 0.003$ | 0.992 | 1.07 |
| 6 | $0.427 \pm 0.018$ | $0.079 \pm 0.006$ | 0.996 | 1.24 |
| 8 | $0.415 \pm 0.002$ | $0.070 \pm 0.001$ | 0.999 | 1.94 |
| 10 | $0.481 \pm 0.005$ | $0.040 \pm 0.001$ | 0.949 | 3.26 |

Table 4
The diffusion exponent ($n$), diffusion kinetic constant ($k$), coefficient of determination ($r^2$), and $T_{50\%}$ of TMPTMA crosslinking pHEMA film in saline

| TMPTMA (wt%) | $n$ | $k$ | $r^2$ | $T_{50\%}$ (h) |
|---|---|---|---|---|
| 0 | $0.507 \pm 0.008$ | $0.092 \pm 0.003$ | 0.9989 | 0.50 |
| 6 | $0.544 \pm 0.037$ | $0.036 \pm 0.006$ | 0.9954 | 2.16 |
| 10 | $0.611 \pm 0.019$ | $0.019 \pm 0.006$ | 0.9813 | 3.54 |
| 20 | $0.533 \pm 0.034$ | $0.016 \pm 0.003$ | 0.9832 | 10.91 |
| 30 | $0.511 \pm 0.029$ | $0.011 \pm 0.002$ | 0.9847 | 27.39 |

The diffusional kinetic constant $k$ defines the characteristics of a polymer network system. The diffusional coefficient $n$ represents the mechanism of the transportation. In the equation, $n = 0.50$ is the Fickian release, and $n = 1.00$ is the Case-II release. Between these two limiting cases, the anomalous release behavior is found in the intermediary between Fickian and Case-II. It is defined as the anomalous release when $n$ is between 0.50 and 1.0 in the semi-empirical equation.

In the case without any cross-linking agent, the $n$ value of the pHEMA film containing 10 wt% pilocarpine is 0.517, $k$ is 0.093, and $T_{50\%}$ is 30 min. Table 3 represents the drug release ratio of pHEMA film containing pilocarpine, in which EGDMA is the cross-linking agent. The drug release rate diminished ($k$ is decreased) while EGDMA increased. The increase of EGDMA prolonged $T_{50\%}$. When EGDMA is added, $T_{50\%}$ of pHEMA film is approximately 1 h, twice the amount without EGDMA. $T_{50\%}$ of the polymer film with 10 wt% EGDMA lasted three and half-hours, and released 80–90% of the total drug content after 24 h. The $n$ value of the cross-linked pHEMA film, however, is much less than that of the pHEMA film without EGDMA. Accordingly, the release mechanism of the pHEMA film using EGDMA as the cross-linking agent is therefore based on the Fickian diffusion. It is indicated that EGDMA impedes the release mechanism. EGDMA enhanced the network structure of pHEMA, which prolongs the release time. However, it also brings the release mechanism out of Case-II transportation. Therefore, EGDMA is not a suitable cross-linking agent.

Table 4 presents the drug release mechanism of the cross-linking pHEMA film, for which TMPTMA is used as the cross-linking agent. The diffusional kinetic constant $k$ is decreased with the increase of TMPTMA, which reduces the drug release rate and prolongs the release time. $T_{50\%}$ is increased along with the increase of TMPTMA, which could reach 27 h. When TMPTMA is initially added, the diffusional coefficient $n$ is increased for the increase of TMPTMA. As TMPTMA becomes more than 10 wt%, the $n$ value decreased. Also during this period, the change of the $n$ value represents pHEMA film as being close to the desired Case-II transportation.

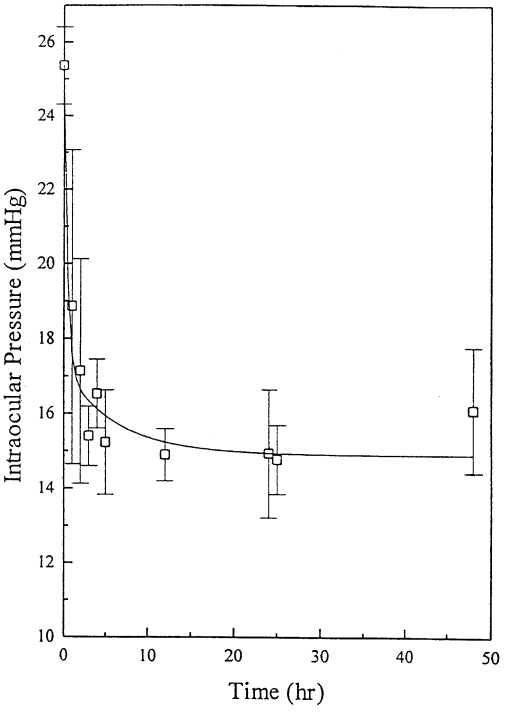


Fig. 2. The intraocular pressure of rabbit eye treated with pilocarpine entrapped TMPTMA cross-linking film.

With TMPTMA higher than 10 wt% the mechanism became non-Fickian. Hence, 10 wt% of TMPTMA is the optimal condition for the drug release.

### 3.5. In vivo animal experiment

A pHEMA film containing pilocarpine is placed into the rabbit's eyes. Fig. 2 represents the intraocular pressure. In spite of the initially slow release of pilocarpine in vitro test, the intraocular pressure is rapidly decreased from 25.4 mm Hg to approximately 15 mm Hg (approximately 5 h to reach equilibrium). The reduction of the intraocular pressure lasts for 24 h and even longer than 48 h during equilibrium. The released amount of drug is not much at equilibrium condition, however, it is sufficient to maintain pressure at 16 mm Hg. Reduction in

Table 5
The diameter of rabbit pupil after treatment with pHEMA film

| | 0 h | 1 h | 24 h | 48 h |
|---|---|---|---|---|
| Diameter (cm) | 1.1 | 0.94 | 0.73 | 0.8 |

intraocular pressure can be stabilized with only a little amount of pilocarpine. An applied concentration of conventional eyedrop formulation of pilocarpine is about 1–4%. To decrease intraocular pressure, it just needs less than 1/5 of the drug dosage given the fact that at least 80% (by volume) of the administered eyedrops drain rapidly through the nasolacrimal duct. Accordingly, the required amount of drug to reduce intraocular pressure is about 3–10 μg. The intraocular pressure will reach a steady state on the period when the required dosage is provided. In this study, the polymer film with 20% drug content contains more than 600 μg of pilocarpine. It retained about 10% of its original amount after 24 h that there is sufficient amount of drug released to reduce the intraocular pressure. After 24 h, the pressure is decreased slowly. However, the eye pressure continued to reduce to 9 mm Hg after 48 h.

Since pilocarpine is a miotic, the miosis could be observed after the treatment of the drug-contained pHEMA film. The diameter of rabbit pupil was measured and illustrated in Table 5. It is observed that the pupil has become smaller after only 1 h of the treatment. After 24 h, there is still an effect to the pupil. For a long period of placing the polymer film in the eye, inflammation does not occur.

## 4. Conclusion

The characteristic of pilocarpine entraped in pHEMA remains unchanged during the preparation process. Pilocarpine exists in pHEMA with molecular or noncrystal dispersion. The carbonyl group of pilocarpine and the hydroxy group of pHEMA form the hydrogen bonding. According to drug release kinetics, the amount of pilocarpine affects the hydrogen bonding, and thus affects the drug release mechanism of the pHEMA film. The effective drug release time increased with the increase of the cross-linking density. Also, the drug is continuously released for 24 h with the concentration of cross-linking agent higher than 10 wt% (w/w). The 10% (w/w) TMPTMA cross-linking pHEMA film has the highest diffusional coefficient, which indicates that the release mechanism occurs mainly with Case-II transportation. In this study, we have prepared the pilocarpine-contained cross-linked pHEMA film, and shown that the drug release ability can continue for 24 h such that the concentration of pilocarpine maintained an effective dose. Moreover, the in vivo animal experiment confirmed that the polymer film effectively reduced the intraocular pressure.

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