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Preparation and evaluation of in situ gelling ophthalmic drug delivery system for methazolamide

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Abstract

Purpose: In this study, a thermosensitive in situ gelling vehicle was prepared to increase the precorneal resident time and the bioavailability of methazolamide (MTA). *Method*: Poloxamer analogs were used as the gelling agents, and the in situ gel was obtained by using a cold method. The gelation temperature, rheological properties, in vitro release as well as in vivo evaluation (the elimination of MTA in aqueous humor and intraocular-lowering effect) of the optimized formulations were investigated. *Results*: The optimum concentrations of poloxamer analogs for the in situ gel-forming delivery system were 21% (w/w) poloxamer 407 and 10% (w/w) poloxamer P188. This formulation was able to flow freely under nonphysiological conditions and underwent sol–gel transition in the cul-de-sac upon placement into the eye. In vitro release studies demonstrated a diffusion-controlled release of MTA from the poloxamer solutions over a period of 10 hours. In vivo evaluation indicated that the poloxamer solutions had a better ability to retain drug than MTA eyedrops did. *Conclusion*: These results suggested that in situ gelling ophthalmic drug delivery system may hold some promise in ocular MTA delivery.

Key words: *Carbonic anhydrase inhibitors; glaucoma; in situ gelling; methazolamide; ocular pharmacokinetics; ophthalmic delivery system*

Introduction

Glaucoma, the leading cause of irreversible blindness worldwide, is one of the most common illnesses in ophthalmology. Carbonic anhydrase inhibitors (CAIs) have been used to treat glaucoma since 1954 because of their ability to lower intraocular pressure (IOP) by reducing aqueous humor formation[1]. Methazolamide (MTA), one of the most common CAIs, has been used as systemically administered antiglaucoma drugs for more than half a century. To obtain the desired lowering in IOP, large oral doses of MTA are used, and this usually leads to severe systemic side effects[2]. Hopefully, topical administration of drug molecules at lower concentrations administered directly to the eye may be able to reduce the incidence of side effects[3]. Significant efforts have been made to improve the ocular bioavailability of MTA. Two formulations of MTA for topical administration have been successfully prepared until now (MTA gel and MTA cyclodextrin eyedrop solutions). When MTA was formulated in a gel and administered directly into the eye, it was shown to increase the precorneal residence time of MTA and to lower the IOP in normotensive rabbits[4]. However, the gel could not be administered easily and accurately by patients[5]. MTA cyclodextrin eyedrop solutions offer numerous advantages over conventional therapeutic approaches[6]; however, eyedrop formulations result in poor bioavailability and therapeutic response owing to a high tear fluid turnover and dynamics causing a rapid precorneal elimination of MTA[7]. Furthermore, there still exists the possibility of tissue irritation and toxicological implications caused by cyclodextrin, the penetration enhancer[8].

Inclusion of excess drug in the eyedrop formulation or increasing times of administration in an attempt to overcome bioavailability problems is potentially dangerous if the drug solution that drained from the eye is systemically absorbed from the nasolachrymal duct[9]. An ideal ophthalmic formulation

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should be one that can be delivered in a drop formulation without causing blurred vision or irritation and possesses a suitable strength to endure the lachrymal fluid dilution without rapid precorneal elimination after administration[10]. These problems can be overcome by using in situ gelling ophthalmic drug delivery systems prepared from polymers that exhibit sol-to-gel phase transitions because of a change in a specific physicochemical parameter in their environment; the cul-de-sac in this case[11,12]. In fact, such a system is liquid at room temperature suitable to be instilled into the eye which, upon exposure to physiological temperature, changes to the gel phase, thus increasing the precorneal residence time and enhancing ocular bioavailability of topically dosed ophthalmic drugs.

The objective of this study was to develop a thermosensitive in situ gelling system using poloxamer analogs for local release of MTA, one of the most common CAIs used in the preoperative management of closed-angle glaucoma or as an adjunct therapy in the treatment of open-angle glaucoma. The in vitro evaluation (rheological behaviors, in vitro MTA release) and the in vivo evaluation (the elimination of MTA in aqueous humor, the IOP-lowering effect) were characterized to evaluate sustained release effect of the thermosensitive in situ gelling system.

Materials and methods

Materials and animals

Materials

Poloxamers (P407 and P188) obtained from BASF Corp. (Ludwigshafen, Germany) were used as received. MTA was purchased from Hangzhou Aoyipollen Pharmaceutical Co., Ltd. (Hangzhou, China). Brinzolamide 10 mg/mL eyedrops (AZOPT®) were purchased from Alcon (Puurs, Belgium). All other chemicals and solvents were of reagent grade.

Animals

Male and female New Zealand albino rabbits, weighing 2.5–3.0 kg, were provided by Animal Experimental Center of Nanjing Medical University. The animals, housed in standard cages in an air-conditioned and light-controlled room at 25 ± 1°C and at 70 ± 5% relative humidity, were given a standard pellet diet and were provided with water ad libitum. All studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication no. 92–93, revised in 1985). The local ethics committees for animal experimentation approved all experiments.

Preparation of formulations

Selection of vehicle

Poloxamers (trade name Pluronic®), ABA triblock copolymers consisting of hydrophilic polyoxyethylene (PEO) and hydrophobic polyoxypropylene (PPO) units, are known for exhibiting the phenomenon of reverse thermal gelation under certain concentrations (critical micellization concentration) and temperatures (critical micellization temperature)[13]. At a concentration of 18% (w/w) or higher in an aqueous solution, poloxamer 407 (P407) is transformed from a low-viscosity solution to noncross-linked hydrogel upon being exposed to ambient temperature. Considering the lachrymal fluid dilution, a relative higher polymer concentration is essential for the P407 solution to form gel under physiological conditions. In this case, however, the preparations would already form gels at room temperature and are difficult to instill into the eye. If the preparation was stored in refrigerator to make the administration easier, the potential irritation of low temperature to the sensitive ocular tissues must be taken into consideration[14]. Therefore, different series of poloxamers[14] or polyethylene glycol[15] were added to P407 as regulatory substances to increase the gelation temperature (GT) of P407.

Sample preparation

The formulations were prepared on a weight/weight basis using the cold method[16,17]. A certain volume of bidistilled water was cooled down to 4°C. Appropriate amounts of P407 and P188 were then slowly added to the cold water with continuous stirring. The dispersions were stored in a refrigerator until clear solutions were obtained. For preparation of drug-containing polymer solutions, 5% (w/v) mannitol and 0.01% (w/v) benzalkonium bromide were first dissolved in a certain volume of bidistilled water[18], which were used as isotonicity agent and preservative, respectively. The required amount of MTA was added later, and then the polymer solutions were prepared as described above.

The conventional commercial eyedrop bottle delivers an average drop volume of about 40 μL[19], whereas the available tear fluid is 7 μL. To understand the in vivo phase transition process of thermosensitive gels, the rheological parameters were measured as a function of temperature before and after the poloxamer formulations diluted by simulated tear fluid (STF) at a ratio of 40:7. The composition of STF was sodium chloride 0.670 g, sodium bicarbonate 0.200 g, calcium chloride·$2H_2O$ 0.008 g, and bidistilled water q.s. 100 g[20].

Measurement of gelation temperature

A transparent vial containing 10 mL of sample solution and a magnetic bar was placed in a low-temperature

water bath. A thermometer with an accuracy rating of 0.1°C was immersed in the sample solution. The solution was heated at the rate of 1°C/1–2 min with constant stirring of 5 rpm (Tachometer, RET Control Visc C, IKA, Germany). The temperature at which the magnetic bar completely stopped moving because of gelation was regarded as the GT[21]. Each sample was measured at least in triplicate.

Rheological studies

The dynamic viscosity of the compositions under different shear rates (6, 12, 30, 60 rpm) was determined under a nonphysiological condition (25 ± 0.1°C) and a physiological condition (35 ± 0.1°C) using a rotating cylinder viscometer (Shanghai Precision Instrumentation Co. Ltd., Shanghai, China). To simulate the physiological dispersion of gels more literally, the polymer solutions were diluted by STF in a ratio of 40:7[10] before the rheological studies were conducted at 35 ± 0.1°C. The average of two readings was used to calculate the viscosity. Evaluations were conducted in triplicate.

In vitro release studies of MTA

According to previous reports[7,10], the in vitro release of MTA from the formulations used a dissolution testing apparatus (ZRS-8G, Tianjing University Precision Instrument Factory, Tianjin, China). The dissolution medium was freshly prepared STF (pH 7.4). Cellophane membrane (cutoff 12,000, Merck, Darmstadt, Germany), previously soaked overnight in STF, was fixed in a self-made polytef sample cell (30 mm i.d. and 5 mm i.d.). A 2-mL volume of the cold formulation was accurately pipetted into this container in triplicate and each container was placed into a 1000 mL beaker. Care was taken to make sure that no air bubbles were inside the solutions. The container was immersed in 500 mL dissolution medium maintained at 35 ± 0.1°C with a rotating speed of 100 rpm. Aliquots (5 mL) were withdrawn from the release mediums at each sampling time and replaced by an equal volume of the release medium. The samples were filtered through 0.45 μm syringe filters and subjected to high-performance liquid chromatographic (HPLC) analysis to determine the MTA concentrations.

Elimination of MTA in aqueous humor

New Zealand albino rabbits were divided into nine groups of four rabbits each, and 50 μL of MTA in situ gel-forming preparation (1.5 mg/mL) and MTA-containing STF (1.5 mg/mL) were dropped into the conjunctival sac of each eye, gels in the left and solutions in the right. The animals were then killed at each of the following time intervals: 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12.0, 16.0, and 24.0 hours after drug administration. The surface of the eye was carefully washed with 5 mL 0.9% sodium chloride solution, the excess of which was blotted with filter paper. An aliquot of 150 μL of aqueous humor was withdrawn with a 27 gauge, 1.3 cm needle attached to 1 mL disposable syringe inserted through the corneoscleral junction and slightly upward into the anterior chamber. The collected aqueous humor was centrifuged at 5600 × *g* for 15 minutes. Twenty microliter of the supernatant was analyzed by HPLC.

IOP-lowering effect

Six New Zealand albino rabbits were used as model animals. IOP was measured using an indentation tonometer (YJI, Suzhou Mingren Medical Apparatus and Instruments Co. Ltd., Suzhou, China), by the same operator, using the same tonometer, after instilling one drop of 0.2% (w/v) lidocaine hydrochloride to the eye as local anesthetic. All measurement periods began during the same hour on each day. The resting IOP level was determined in both eyes as the mean of IOP measurements taken every 30 minutes over a 2-hour period before administration of drugs to the eye.

Two drops of MTA-containing polymer solutions or STF were dosed from a micropipette. To avoid experimental bias, the left eye (treatment eye) of each rabbit was first administered with drug-containing vehicle, followed by the application of the control vehicle (formulation with no drug) to the right eye (control eye). All the solutions were administered at room temperature and were instilled in the lower conjunctival sac, approximately midway between the inner and outer canthus. At regular intervals, the IOP was measured by the same method. No animal was used more than once at each drug concentration and at least 1-week washout period was employed between experiments. Change in IOP (ΔIOP) is expressed as follows: $\Delta IOP = IOP_{\text{control eye}} - IOP_{\text{treatment eye}}$. To assess the extent of total pharmacological response of different formulations, areas under the ΔIOP time curve ($AUC_{0\rightarrow 12\ \text{hours}}$) were calculated. The IOP-lowering effect of AZOPT® (commercially available topical CAI) was determined the same way as the MTA test solutions.

HPLC conditions

The HPLC system consisted of LC-10AT *vp* pump (Shimadzu, Japan), a SPD-10A *vp* detector (Shimadzu, Kyoto, Japan), and a 2010 Chromatography Workstation (Zhejiang University, Zhejiang, China). The HPLC separation was performed on a reversed-phase LiChrospher-C18 column (5 μm, 150 × 4.6 mm, Jiangsu Hanbang SciTech Co., Huaiyin, China). The mobile phase consisted of a mixture of methanol and water (30 : 70, v/v).

The mobile phase was filter through a 0.45 μm microporous membrane and was deaerated ultrasonically before use. The detector was set at 290 nm and the flow rate was set at 1.0 mL/min. The column temperature was set at 40°C.

Treatment of data

Pharmacokinetic analyses were performed using the 3p87 Pharmacokinetic Program (Chinese Society of Mathematical Pharmacology 1987, Beijing, China). Statistical comparisons were analyzed by one-way analysis of variance or the Student's *t*-test, where appropriate, and statistically significance differences between groups were defined as $P < 0.05$.

Results and discussion

Selection of vehicle

Gelation temperature of poloxamer solutions

Poloxamer solutions with a sufficiently high concentration were converted to gels at or above GT, which attribute to the interaction between hydrophilic PEO and hydrophobic PPO blocks[22]. When the concentration and the temperature of the polymer are above a critical value, poloxamer molecules in the aqueous solution will self-assemble to form spherical micelles with a dehydrated PPO core surrounded by hydrated swollen PEO chains. Poloxamer analogs possess a different PEO:PPO ratio, and the different PEO:PPO ratios will lead to a different GT. Therefore, the aim of the modulation of GT can be reached by mixing various amounts of P407 and P188 in aqueous solution without affecting the gelling mechanism.

Figure 1 shows that the GT of the mixed poloxamer formulations decreased as the P407 concentration increased. This can be explained as follows: both the quantity of micelles and the probability that micelles entangled and packed with each other increased as the P407 concentration increased, which made the GTs to decrease proportionally. However, as the P188 concentration increased gradually with constant P407 content, the GT initially increased to maximum at the concentration of approximately 10% P188 and then decreased. The same result was reported by Wei et al.[14] A possible reason for this could be that the incorporation of a slight amount of P188 may change the PEO:PPO ratio, which causes the increase of the GT. Therefore, by increasing the P188 concentration sequentially, not only does the PEO:PPO ratio change, but the micellization P188 molecules are also able to participate in the construction of the gel, leading to the decrease of GT.

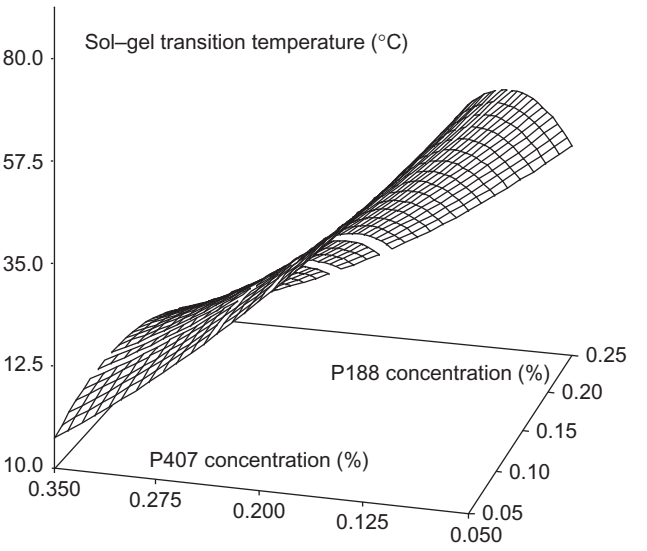

Figure 1. Effect of compositions on the gelation temperature of poloxamer thermosensitive gels.

To study the effect of poloxamer compositions on the GT ($T_{sol-gel}$), the following linear equation was drawn from multiple regression analysis:

$$T_{sol-gel} = 277.0824C_{P407}^2 - 737.0321C_{P188}^2 - 409.0255C_{P407} + 1.0655C_{P188} + 566.0918C_{P407}C_{P188} + 97.7780 (r = 0.9968). \quad (1)$$

Both P407 and P188 had significant effects ($P < 0.01$) on $T_{sol-gel}$. As described above, 10% of P188 was able to increase the GT of poloxamer solutions with a constant P407 content to maximum. For the purpose of using the minimum possible amount of poloxamers, the concentration of P188 was fixed at 10% in this investigation. Based on Equation (1), approximately 22.4% of P407 was required to obtain a formulation with the GT about 25°C.

Influence of ingredients on the gelation temperatures of poloxamer solutions

MTA is the active component of this pharmaceutical preparation, and its concentration in this preparation is 0.15% (w/v). At this concentration level, MTA can exist in molecular form. Isotonic ophthalmic preparation is preferred by the majority of the patients as it causes less irritation to the eyes. Therefore, incorporation of 5.0% (w/v) mannitol was taken into consideration and 0.01% (w/v) benzalkonium bromide was incorporated as a bacterial inhibitor. In this section of the experiment, the influence of MTA, mannitol, and benzalkonium bromide on the GTs of poloxamer solutions was investigated.

As shown in Figure 2a, 0.15% MTA and 0.01% benzalkonium bromide both had slight influence on the GTs. However, the GT decreased by 2–3°C in the presence of 5% mannitol. When designing a concentration-dependent drug delivery system for ophthalmic use, lachrymal dilution must be considered. The GT increased at least 7°C after STF dilution. Because of the decreasing effect of GT of 5% mannitol, the pharmaceutical preparation based on 22.4/10 poloxamer mixture had a GT lower than room temperature. To offset the effect of mannitol, based on Equation (1), approximately 21% of P407 and 10% of P188 were required to obtain a formulation with the GT of about 28°C. Similar phenomena were observed in 22.4/10 and 21/10. As can be seen in Figure 2b, the GTs of poloxamer gels (21/10) containing 5% mannitol before and after STF dilution were within the temperature range of 25–35°C.

Rheological studies

For thermosetting gels, the viscosity at various conditions is an important rheological parameter involved in its utilization and in vivo performance. For instance, if viscosity is too high it will lead to difficult instillation; on the contrary, if viscosity is too low it will give rise to increased drainage[23]. The dynamic viscosity of poloxamer formulations was measured as the change of shear rate under a nonphysiological condition and a physiological condition. As shown in Figure 3, the viscosity of poloxamer formulations was very low before STF dilution at 25°C, which showed the character of Newtonian fluid. The same result was reported by Edsman et al.[24] The gels formed at physiological conditions, and the viscosity of the formulations decreased as the shear rate increased, which showed the character of pseudoplastic fluid. Because the ocular shear rate is very large ranging from 0.03/second during interblinking periods to 4250–28,500/second during blinking[7], viscoelastic fluid with a viscosity that is high under low shear rate conditions and low under high shear rate conditions is preferred. The pseudoplastic property of poloxamer formulations under physiological conditions is in favor of sustaining drainage of drugs from the conjunctival sac of the eye, simultaneously without the unwanted blinking tendency for undergoing shear thinning.

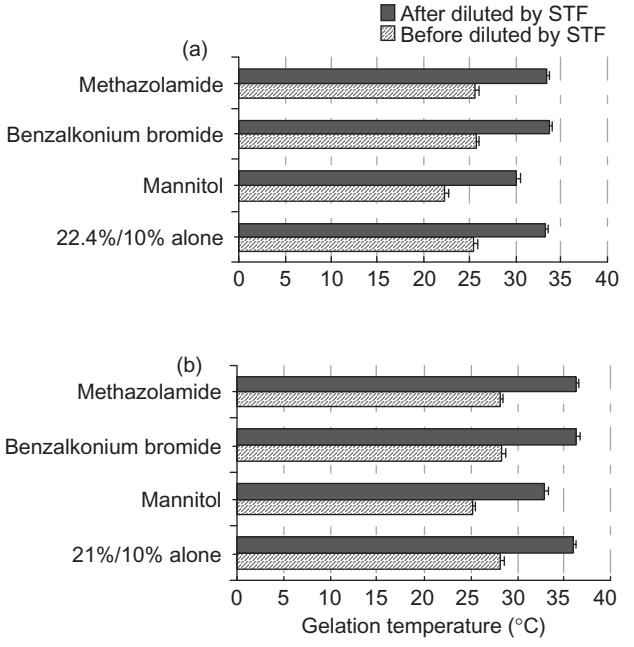

Figure 2. Influence of ingredients on the gelation temperatures of poloxamer mixtures. Different ingredients were added to the mixtures of P407/P188, (a) 22.4/10 and (b) 21/10, before and after dilution with STF. Each bar represents the mean ± SD ($n = 3$).

In vitro release studies

Figure 4 shows the cumulative amount of MTA released versus time profiles for MTA-containing poloxamer solution and MTA-containing STF. Both the poloxamer solution and the STF contained 0.15% (w/v) MTA. For the drug-containing STF, almost all the MTA is released immediately after the start of the release study. The drug released about 89.23% to the medium after 1 hour. In the case of drug-containing poloxamer solution, the drug released about 44.9% to the medium after 1 hour, approximately 86.63% after 6 hours, and the release profile continued to rise thereafter. These results indicate that poloxamer formulation has a better ability to

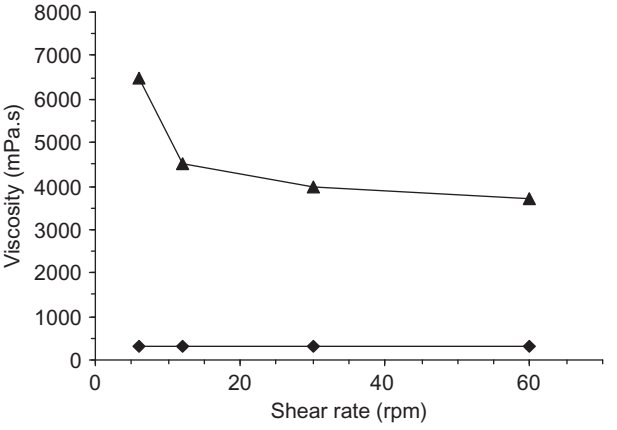

Figure 3. The rheological profiles of 21% P407/10% P188 poloxamer formulations measured under a nonphysiological condition and physiological condition. (◆): 25°C and before STF dilution; (▲): 35°C and after STF dilution. All the measurements were performed in triplicate and the standard deviations were all within 3%.

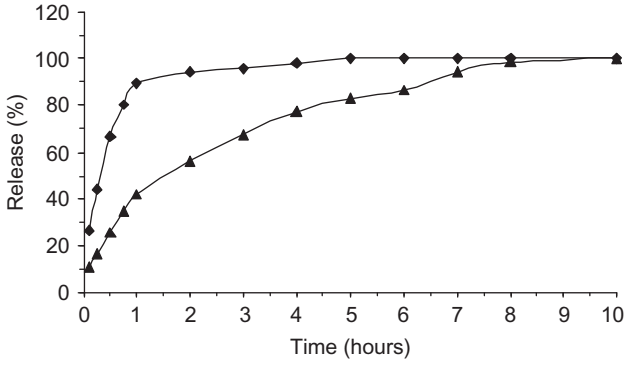

Figure 4. Cumulative amount of MTA released from poloxamer formulations and control. (▲): MTA-containing 21% P407/10% P188 solution; (◆): MTA-containing STF. Each point represents the mean ± SD ($n = 3$). MTA indicates methazolamide.

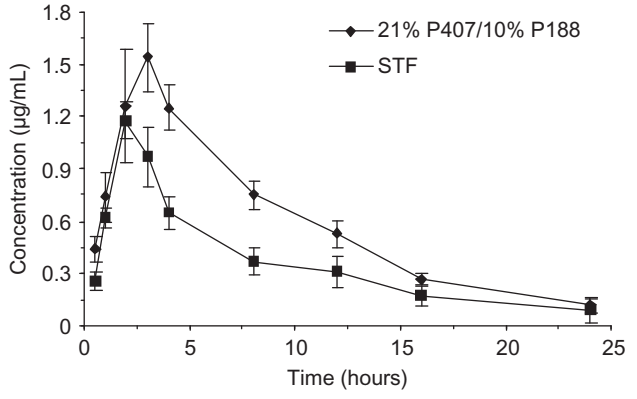

Figure 5. MTA concentrations in rabbit aqueous humors at different times after topical application of 0.15% MTA-containing STF and 0.15% MTA-containing poloxamer formulation. Each point represents the mean ± SD ($n = 5$). MTA indicates methazolamide.

retain drugs than pure STF. Furthermore, it can be shown that the cumulative amount is proportional to the square root of the time (up to 83% of total drug released for drug-containing poloxamer formulation), demonstrating a linear relationship with a correlation coefficient higher than 0.99. Similar results were also demonstrated by other researchers in other poloxamer systems[10,25]. The linear relationship in conjunction with the slow dissolution rate suggests that the in vitro drug release from poloxamer formulation under physiological conditions occurs primarily by diffusion.

Elimination of MTA in aqueous humor

Figure 5 shows the level of MTA in aqueous humor after instillation of 50 μL of 1.5 mg/mL MTA in situ gel and 1.5 mg/mL MTA-containing STF, and the corresponding kinetic parameters are summarized in Table 1. The

Table 1. Pharmacokinetic parameters of MTA in aqueous humor of rabbits ($n = 4$).

Pharmacokinetic parameters	MTA-containing STF	MTA-containing poloxamer formulation
C_{max} (μg/mL)	1.21 ± 0.08	1.54 ± 0.15*
T_{max} (hours)	2.01 ± 0.02	3.11 ± 0.21*
MRT (hours)	10.99 ± 1.96	10.38 ± 1.20
$AUC_{0-24\ hours}$ (μg·h/mL)	8.64 ± 0.83	13.92 ± 0.90*
$AUC_{0-\infty}$ (μg·h/mL)	9.75 ± 0.67	15.36 ± 0.48*

Both the poloxamer solution and the STF contain 0.15% (w/v) MTA. Poloxamer formulation contains 21% P407 and 10% P188. MTA indicates methazolamide. C_{max}: maximum aqueous humor concentration; T_{max}: time to reach C_{max}; MRT: mean residence time; AUC: area under the moment curve. Statistically significant difference from the reference solution (STF) at the level of $^*P < 0.05$. The values are mean ± SD.

concentration–time profiles of MTA of both in situ gel and solution can be described by a two-compartment model with first-order transcorneal absorption. The aqueous humor content of MTA was significantly higher ($P < 0.05$), at 3, 4, 8, 12 hours, after administration of MTA in situ gel formulations than those obtained after the instillation of MTA solutions. In comparison to aqueous solution, the in situ gel exhibited 1.27-fold and 1.55-fold greater maximum level of MTA in aqueous humor (C_{max}) and time required to reach maximum concentration (T_{max}), respectively. The $AUC_{0-24\ hours}$ and $AUC_{0-\infty}$ values of in situ gel were 1.61 times and 1.58 times greater than that of STF-containing MTA, respectively. However, it was shown that the mean residence time of MTA in situ gel was not significantly different from that of STF-containing MTA ($P > 0.05$). This suggests that with the use of in situ gel, a higher amount of drug can be absorbed into the eye before being washed out of the conjunctival sac by tears, as compared to the use of MTA-containing STF.

IOP-lowering effect

Figure 6 shows the pharmacological response (the decrease in IOP, ΔIOP) versus time profiles for MTA-containing 21% P407/10% P188 solution, MTA-containing STF, and AZOPT®. It can be seen from this figure that approximately before 1.5 hours, the decrease in IOP was greater for AZOPT® than for both MTA-containing poloxamer solution and STF. After that, the decrease in IOP became larger for the MTA-containing poloxamer solution than for AZOPT® and the MTA-containing STF, although the general shape of the profiles was similar. Despite the fast in vitro release rates for MTA in STF (Figure 4), higher initial in vivo pharmacological responses were not observed; because several factors

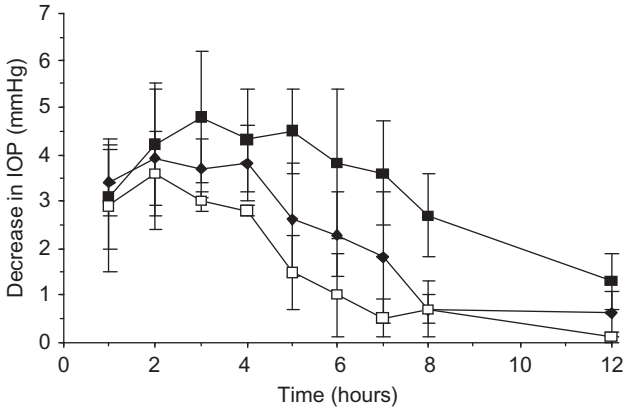

Figure 6. Decrease in IOP versus time for different formulations. (■): MTA-containing 21% P407/10% P188 solution; (◆): brinzolamide 10 mg/mL eyedrops (AZOPT®); (□): MTA-containing STF. Each point represents the mean ± SD ($n = 5$). MTA indicates methazolamide.

affecting the in vivo drug performance, including the blinking of eyes, lachrymal secretion as well as nasolachrymal drainage, were not considered in the performance of in vitro dissolution experiment. The results of this experiment demonstrated that 21% P407/10% P188 solution prolonged the IOP-lowering effect to 12 hours after administration, which was significantly better than STF (7 hours) and relatively better than AZOPT® (>8 hours).

The $AUC_{0\rightarrow12\ hours}$ values for different formulations are listed in Table 2. It can be seen that a 2.29-fold increase in $AUC_{0\rightarrow12\ hours}$ was obtained for MTA-containing 21% P407/10% P188 solution relative to the drug-containing STF. Less-pronounced enhancement of $AUC_{0\rightarrow12\ hours}$ was obtained for AZOPT® (1.44-fold) as compared to the STF. These in vivo results along with in vitro results demonstrate that the 21% P407/10% P188 solution may significantly prolong the drug contact time and thus increase its pharmacological response.

Table 2. The area under ΔIOP versus time profiles in 12 hours ($AUC_{0\rightarrow12\ hours}$) for different formulations.

Formulations	$AUC_{0\rightarrow12\ hours}$ (mmHg·h)	Ratio
MTA-containing poloxamer solution	36.11 ± 4.16	2.29
AZOPT®	22.75 ± 3.71	1.44
MTA-containing STF	15.80 ± 3.02	

MTA indicates methazolamide. Each value represents the mean ± SD for five determinations.

Conclusions

MTA, a CAI used in the treatment of glaucoma, was successfully formulated as thermosensitive in situ gel-forming ophthalmic solutions (0.15%, w/v) using 21% P407 and 10% P188. The formulation is able to flow freely under nonphysiological conditions as it undergoes sol–gel transition in the cul-de-sac upon instillation into the eye. Both in vitro and in vivo results indicated that the poloxamer analog solutions performed better in retaining MTA than did STF. The developed formulation is a viable alternative to conventional MTA eyedrops, by virtue of its ability not only to be readily administered (decreasing the frequency of administration, resulting in better patient acceptance) but also to be able to prolong the precorneal residence time, to attain higher bioavailability, thus reducing the systemic side effects caused by the drainage from the nasolachrymal duct.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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