Published in final edited form as:

J Cataract Refract Surg. 2020 November ; 46(11): 1548–1553. doi:10.1097/j.jcrs.0000000000000366.

Single subconjunctival injection formulation using sol-gel mesoporous silica as a controlled release system for drop-free post-cataract surgery care

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Abstract

Purpose: To develop a mesoporous silica drug delivery system and target drop-free care after cataract surgery with a single subconjunctival injection.

Setting: Laboratory.

Design: Experimental animal study.

Methods: Ketorolac was infiltration-loaded into sol-gel mesoporous silica particles encapsulated with poly(allylamine hydrochloride) and poly(sodium 4-styrenesulfonate) using a layer-by-layer adsorption technique (SG-Ket-LBL). The formulation was subjected to an in vitro and in vivo drug release study in addition to ocular toxicology evaluation.

Results: Thermogravimetric analysis revealed that the drug loading efficiency was 4.4% for the SG-Ket-LBL particles. The in vivo safety study demonstrated that the formulation was well tolerated after subconjunctival injection and aqueous humor pharmacokinetics showed sustained therapeutic drug release for the targeted time window of 6 to 8 weeks.

Conclusion: Findings indicated that sol-gel mesoporous silica could be used as a drug carrier for subconjunctival administration. The tested formulation, SG-Ket-LBL, provided therapeutic ketorolac for 6 to 8 weeks, which might be used for a single subconjunctival injection to replace nonsteroidal anti-inflammatory drug eyedrops after cataract surgery.

Introduction

Cataract surgery is the most common procedure performed in ophthalmology. Roughly 3.6 million cataract procedures each year in the United States¹ and more than 20 million worldwide are performed. To reduce procedure-induced inflammation and to aid in better recovery of vision, steroid and nonsteroidal anti-inflammatory drug (NSAID) eyedrops are routinely used for 4 to 6 weeks^{2–5} postoperatively. Although various commercial

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Disclosures: None of the authors has a financial or proprietary interest in any material or method mentioned.

formulation of steroids and antibiotics are available for intracameral injection before the end of the surgical procedure, it is an intraocular injection and bears inherent risks such as endophthalmitis and additional injection related trauma. In addition, the volume of an intracameral injection is limited and there are high levels of steroid that might increase intraocular pressure (IOP)⁶. We hypothesized that a subconjunctivally injectable drug delivery system would be safer for the patient and release drugs more slowly with lower peak levels. In addition, it is possible to combine particles loaded with different therapeutics for subconjunctival injection to achieve synergistic pharmacological effects. In the current study, we reported a mesoporous silica delivery system containing an NSAID (ketorolac), which could potentially provide 4 to 6 weeks of therapeutic medication after a single subconjunctival injection at the end of a cataract procedure. An additional antibiotic- or steroid-loaded mesoporous silica particle formulation could be an excellent approach to drop-free surgery.

Ketorolac acts as a nonselective cyclooxygenase (COX) inhibitor, and is effective in preventing aqueous flare postoperatively. Ketorolac has also been proven to be effective in suppressing postoperative pain and macular edema following cataract surgery⁷ and has better tissue penetration than other NSAIDs⁸. Therefore, ketorolac might be an ideal payload for mesoporous silica particles. Such a controlled release system will greatly benefit older patients who often have difficulty remembering and properly instilling their eyedrops.

In the current study, we used sol-gel processed silica microspheres, which are different from the etched porous silicon particles used previously^{9, 10}. The sol-gel microspheres have much more homogenous particle sizes, making them friendly for small-gauge injection needles. We have recently reported that these commercially available sol-gel particles have a good ocular safety profile¹¹. We hypothesized that small-molecule drugs could be infiltration-loaded into sol-gel silica particles for a sustained release of 4 to 6 weeks following a single subconjunctival injection.

Methods

Sol-gel micro silica particles

Sol-gel processed silica microspheres were purchased from SiliCycle (<https://www.silicycle.com/products/siliasphere>). These mesoporous silica particles are commercially manufactured in a well-controlled process. Endotoxin testing was performed on these sol-gel silica particles before being used for drug loading.

Loading of ketorolac into sol-gel silica

The sol-gel silica particles were coated with 20 layers of alternating poly(allylamine hydrochloride) (PAH) (Sigma) and poly(sodium 4-styrenesulfonate) (PSS) (Sigma) prior to the drug loading. Briefly, stock solutions of PAH and PSS were prepared at concentrations of 2 mg/mL in 0.5 M NaCl. Then, 50 mg of sol-gel particles were incubated in 1 mL of 2 mg/mL PAH solution for 12 minutes. The excess polyelectrolytes were removed by centrifugation (6000 rpm, 3 min) and 2 washes of distilled water. The particles were then incubated in 1 mL of 2 mg/mL PSS solution for 12 minutes, followed again by the same

centrifugation and washing steps. This process was continued, alternating between PAH and PSS, 20 times and then the particles were dried with a lyophilizer overnight. Finally, the particles were transferred into 5 mL of a 25 mg/mL ketorolac (APEX BIO Technology) solution and incubated at room temperature for 24 hours on a roller. The particles (SG-Ket-LBL) were then dried in a vacuum centrifuge at room temperature and loading efficiency was determined by thermogravimetric analysis (TGA).

In vitro release

The release of ketorolac from sol-gel silica preparations was performed in balanced salt solution with a dialysis bag over time. Briefly, 2 mg of SG-Ket-LBL particles were weighed and transferred into a dialysis bag (Fisherbrand Regenerated Cellulose Dialysis Tubing, MWCO 12,000–14,000 D). The dialysis bag was then soaked in 4.5 mL of a balanced salt solution and incubated at 37°C on a shaker. Every day the dialysis bag was transferred to a new tube with the same amount of fresh balanced salt solution, and the old aliquot was stored at –80°C until quantitation. The drug concentrations of ketorolac in the dissolution samples were quantified by high-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS)¹².

In vivo ocular safety and drug release

All animal experiments were carried out in adherence to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Eight albino guinea pigs were used for the study. One eye of each animal received a subconjunctival injection (targeted 0.5 mg in 20 µL) of the drug/release system and the contralateral eye was injected with 20 µL of BSS as control. The particle suspension or balanced salt solution was delivered into the subconjunctival space around 12 o'clock of each guinea pig eye using a 28-gauge needle. The net injected drug amount was calculated by mass balance. At post-injection time points 1 hour, day 3, and weekly up to 9 weeks, the guinea pigs were subjected to regular eye exams, including slitlamp exams, indirect ophthalmoscopy, and intraocular pressure (IOP) measurements. The injection site was photographed prior to collecting 35 µL of aqueous using a 31-gauge insulin syringe at each timepoint. The aqueous humor samples were stored at –80°C until the drug levels were quantified by HPLC-MS/MS. Electroretinograms (ERGs) were taken prior to sacrifice at week 9. After sacrifice, the eyeballs were fixed in 2% paraformaldehyde and 1.25% glutaraldehyde for paraffin embedding and hematoxylin-eosin (H&E) staining.

Data analysis

The safety data, including IOP and ERGs, were compared using paired t-test between the right and left eyes.

Results

Physical characteristics of the particles and drug loading

Figure 1 demonstrated the uniform sol-gel particle size and pore structure before drug loading. The pore size was 10 nm and the particle diameter was 15 µm (Figure 1) with a surface area of 390 m²/g and a pore volume of 1.02 mL/g of particles. To facilitate drug

loading and controlled release, sol-gel silica particles were treated by alternating PAH and PSS to optimize the pore configuration as shown in figure 2. After drug loading, TGA revealed loading efficiency of 4.4% for SG-Ket-LBL (Figure 3).

In vitro drug release profile

Ketorolac was quantitated by HPLC-MS/MS from in vitro release samples. The concentration-time curve demonstrated a very short burst release at the 1-hour time point followed by a sustained release with drug concentrations between 100 ng/mL and 4 ng/mL out to 42 days (Figure 4).

Ocular safety profile

The mass balance analysis revealed that each eye received an average of 0.26 ± 0.02 mg SG-Ket-LBL. After subconjunctival injection, no adverse effects such as conjunctival congestion or aqueous cells/flare was noted during the course of the study. No cornea toxicity was noted from slit-lamp ophthalmic exams at multiple time points up to the end of this study (9 weeks). The retina of all eyes had a normal appearance by indirect ophthalmoscopy. The particles injected under the conjunctiva were seen under a slit-lamp microscope, but difficult to appreciate in photographic images (Figure 5). IOP was monitored during the study course. The average IOP of the right eyes with SG-Ket-LBL was 7.6 ± 0.6 mmHg versus 7.4 ± 0.3 mmHg in the fellow control eyes ($p=0.91$, paired t-test). ERG was performed before sacrifice at 9 weeks. Three types of ERGs including dark-adapted, light-adapted, and flicker ERG were recorded from both eyes of each study animal. There was no significant difference in b-wave amplitude between the study eyes and their fellow control eyes as shown in Figure 6.

Concentration dynamics of ketorolac in aqueous humor

After subconjunctival injection of the SG-Ket-LBL, aqueous humor was sampled over time and the ketorolac was quantitated as shown in figure 7. There was a very short burst release at the first hour after injection. Thereafter, the release became sustained with approximately 10 ng/mL for the duration of 56 days.

Histology study—At the end of the 9-week study the animals were euthanized and their eyes fixed in a solution of 2% paraformaldehyde and 1.25% glutaraldehyde. The globes were dissected into two halves through the injection site before paraffin embedding. H&E stained sections under the light microscope revealed normal structures at the injection site including conjunctiva, sclera, and ciliary body (Figure 8). No inflammatory cell infiltration was noted in any of the study eyes.

Discussion

In this study, sol-gel mesoporous silica particles were investigated for drug loading and release toward subconjunctival application. Porous silica can be made from electrochemical etching as we reported⁹, or made by sol-gel synthesis.^{13, 14} Sol-gel synthesis has the advantage to produce large amounts of particles with better control of the particle diameter. Uniform particle size plays an important role in ophthalmic drug administration because the

eye has a very limited volume which is prone to overdosing or underdosing if the formulation is a particulate suspension with a nominal concentration¹⁵. Uniform particle size allows for better control of dosing to achieve the concentrations. In addition, uniform particle size has less friction among the particles and can be delivered by a smaller needle which is an important aspect because larger needles introduce more injection-related risks such as injection hole leaking or vitreous hemorrhages. In the current study, we used sol-gel silica particles for infiltration loading of ketorolac in conjunction with a layer-by-layer adsorption technique to encapsulate the particle. We knew that without proper encapsulation, the infiltration loaded drug could quickly leach out and even cause toxicity.⁹ Encapsulation would slow down and extend the period of release as we have shown.² For the current study, we are aiming to provide local anti-inflammation treatment after cataract surgery. Therefore, 4 to 8 weeks of sustained drug delivery is targeted because this is the time window for anti-inflammatory drops post-cataract surgery. The current in vitro release demonstrated that ketorolac release lasted for 42 days in vitro. However, the in vivo release profile demonstrated that ketorolac provided 8 weeks of therapeutic concentrations (10 ng/mL). The EC50 for ketorolac to inhibit COX-1 and COX-2 were reported to be 3.5 to 6 ng/mL and 10 to 23 ng/mL, respectively.¹⁶¹⁷

Although nano-porous silica has been investigated as an important long acting ocular drug delivery system, thus far, no studies have tested the application of porous silica in the subconjunctival space. The current study demonstrated that sol-gel processed porous silica particles were well tolerated under the conjunctiva without lingering irritation or inflammation. The loaded drugs can be detected in aqueous humor and no aqueous flare or cells were noted during the whole course of the study. This indicates that porous silica particles have good biosafety in the subconjunctival space as seen in our histology images.

The current study selected ketorolac as payload. Ketorolac is commonly used drug after cataract surgery and is a nonsteroidal anti-inflammatory drug (NSAID) which inhibits the COX pathway¹⁸ to reduce inflammation with additional analgesic effects. It has been reported that 0.45% topical ketorolac was more effective than 0.1% diclofenac, another NSAID, in preventing macular edema following cataract surgery.¹⁹ Duong, et al also found that ketorolac tromethamine demonstrated better patient satisfaction, compliance, and pain control compared to the NSAID nepafenac.²⁰ After cataract surgery, ketorolac eye drops were prescribed to be used at least twice a day for 2 to 4 weeks.^{21–23} Extended use of topical NSAIDs have been associated with corneal sensitivity decrease or superficial punctate keratitis.^{24–26} With the current SG-Ket-LBL formulation, a single subconjunctival injection may provide a therapeutic concentration of ketorolac for 8 weeks; and the release duration as well as release rate may be adjusted by varying the injection volume or drug loading rate. This technology also opens the door for subconjunctival administration of a dose of mixed silica particles with different drug loading such as ketorolac, steroid, or antibiotics. NSAID, steroids, and antibiotics are the local medication for intra- or peri-cataract surgery. Various formulations of combined steroids and antibiotics²⁷ or antibiotics release lens²⁸ or sustained release form of steroids⁶ including intracanalicular implant²⁹ have been investigated; however, a formulation providing steroid, antibiotics, and NSAID simultaneously is not available yet.

In summary, the current study demonstrated the safety of a sustained ketorolac delivery system using sol-gel porous silica particles, which is designed for a single subconjunctival injection application following cataract surgery. This technology may eliminate undertreatment or overtreatment associated with poor patient compliance and risk of corneal abrasions by using eye drops³⁰. Another benefit to using this system is that it would eliminate the possibility of eye drop contamination or exposure to preservatives present in many eye drops which are a source of toxic keratopathy.³¹ With this technology, three different drugs loaded silica particles may be mixed for a single subconjunctival injection or ketorolac loaded porous silica particles used with current intraoperative formulation of steroid and/or antibiotics to achieve drop-free care for cataract surgery.

Acknowledgments

Funded by National Institutes of Health (NIH) grant EY020617, unrestricted funds to Jacobs Retina Center from Research to Prevent Blindness, National Institutes of Health under core grant P30EY022589, and Research to Prevent Blindness (UCSD).

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What was known

- Steroid and nonsteroidal anti-inflammatory eyedrops are the current standard care after cataract surgery
- The commercial formulation of steroids is available for intracameral injection during surgery or intracanalicular implant immediately after surgery, which bears risks of corneal edema and intraocular pressure rise.

What This Paper Adds

- A sol-gel porous silica-based delivery system that can host nonsteroidal anti-inflammatory agent ketorolac was used for controlled release over 6–8 weeks after a single subconjunctival injection.
- Subconjunctival injection had a better safety profile than transscleral and intracameral injections and might offer the possibility of better drop-free care for post-cataract surgical patients.

Figure 1. Morphology of the SG-Ket-LBL particles. Light microscopy (left) of the particles shows that they are uniform in size and shape. SEM image (right) reveals a highly porous surface.

Figure 2. SEM image of SG-Ket-LBL particle. After layer-by-layer treatment, surface configuration of the sol-gel silica looked less porous with the openings of the pores plugged with PAH/PSS compared with the image (right panel) in figure 1. Some irregular deposits of PAH/PSS were seen on the particle surface.

Figure 3. Thermogravimetric analysis (TGA). TGA curves of SG-LBL (unloaded sol-gel coated with PSS and PAH), and SG-Ket-LBL (sol-gel coated with PSS and PAH and loaded with ketorolac). The loading efficiency of the SG-Ket-LBL particles was 4.4%.

Figure 4. Concentration-time plot from ketorolac in vitro release. The ketorolac dissolution from SG-Ket-LBL in PBS showed an initial burst release with a subsequent sustained release of ketorolac over 90% of the release time. Each error bar is constructed using one standard error from the mean.

Figure 5.

Clinical observational images. A: The right eye showing conjunctival bleb immediately after 20 μ L subconjunctival injection of SG-Ket-LBL. The needle entry hole can be appreciated (thin arrow). B: The same eye 4 weeks after the subconjunctival injection without congestion and comparable to the left eye image (C) taken at the same time. D: fundus of the right eye 4 weeks after the injection, showing a transparent avascular retina and the choroidal vessels underneath. In the center of the fundus image, the round whitish area corresponds to the optic nerve head (thick arrow) of the guinea pig eye, mostly overlapped by a light reflex ring generated from the pre-positioned fundus lens during the photography.

Figure 6. Box-plot of b-amplitudes of dark-adapted, light-adapted, and flicker ERG from SG-Ket-LBL injected right eyes versus BSS injected left eyes.

Figure 7.

In vivo pharmacokinetics. SG-Ket-LBL shows a sustained release of ketorolac at around 10 ng/mL up to 56 days. The dashed line is the concentration of ketorolac to inhibit PGE₂ production by 50% (EC₅₀). Each error bar is constructed using one standard error from the mean.

Figure 8. Histology. The top image is the H&E stained section from the SG-Ket-LBL injected eyes while the bottom image is the contralateral control eyes injected with BSS. The structures at the injection site of the injected eyes are comparable to their fellow control eyes. The scale bar is 500 μm.