# Intraocular Lens Being Used As A Drug Delivery Reservoir

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***Aim of review:***

To describe the development and use of intraocular lenses (IOLs) as drug delivery systems and to review the current literature on their application and efficacy.

What recent findings: Many drugs have been loaded onto IOLs by coating or by attachment in a separate reservoir. With incorporation of polymeric materials either as a coating or by attachment as a separate reservoir, it is possible to achieve a sustained and controlled release of drugs. Experimental evidence in animal models has shown that IOL drug delivery systems are effective in the prevention and treatment of inflammation, infection and posterior capsule opacification after cataract surgery.

Summary:The use of IOLs as drug delivery reservoirs appears to show great promise. Although excellent results with therapeutic potential have been reported in experimental animal studies, further studies are needed to reach clinical use. HYPERLINK "javascript:showOutline()"

There are many routes for delivery of drugs to the eye including topical, subconjunctival, subtenon's, intracameral, intravitreal, retrobulbar, oral or intravenous administration. The selection of the route of administration depends on the severity of the eye disease. Cataract surgery is the most frequently performed ocular procedure worldwide. The current standard management after cataract surgery includes the use of topical antibiotics and topical corticosteroid. However, topical administration of eye drops can be problematic. There may be a low level of bioavailability due to poor corneal penetration; hence, therapeutic concentration may not be reached. Topical medication often has a short duration of action; hence, frequent application of drops is required. This may result in patientsâ•™ discomfort due to ocular surface toxicity, and is highly dependent on patientsâ•™ compliance, which may not be good in elderly patients, who account for the majority of cases of cataract surgery.

Different drug delivery systems have been investigated to address the limitations related to eye drops and to control infection and inflammation after cataract surgery. Surodex (Oculex Pharmaceuticals Inc., Sunnyvale, CA, USA), a dexamethasone anterior segment drug delivery system, was developed and has been proven effective to treat inflammation after cataract surgery [1]. But this device had several disadvantages: it required an extra step for implantation, it was expensive, removal was difficult and adverse effects such as implant migration and peripheral anterior synechiae were reported.

Recently, there has been growing interest in the use of IOLs as drug reservoirs. Because an IOL is implanted during cataract surgery and remains in the eye after surgery, it is an ideal delivery system for intraocular drugs. The IOL itself, either with a coating or a separate reservoir attached to it, can be used as a drug vehicle. It makes the combination of cataract surgery and postoperative treatments in a single procedure possible, potentially improving the compliance of postoperative management. Moreover, as the drug is supplied directly to the anterior chamber, it will provide a higher, controlled intraocular drug concentration. No extra surgical procedure is required to deliver the sustained drug delivery system and it remains immobilized within the capsular bag. With these advantages, the concept of using IOLs as drug delivery reservoirs has received considerable attention in the last years.

Several drugs have been successfully incorporated with IOLs. These drugs include antibiotics, corticosteroid, indomethacin annexin(to treat postcataract surgery

inflammation)and various drugs, such as rapamycin,matrix metalloproteinases (MMPs),selenocystamine,celecoxib, daunorubicin and thapsigargin [to inhibit posterior capsule opacification (PCO)]

## AN IDEAL DESIGN OF AN INTRAOCULAR LENS DRUG DELIVERY RESERVOIR

First, it should deliver an effective but nontoxic level of the drug for a specific period of time. Hence, it is crucial to understand the pharmacokinetics and to determine the drug concentration of loading as well as the optimum drug release period when designing an IOL drug delivery reservoir. For an antibiotic-loaded IOL, the drug release that achieves the minimal inhibitory concentration 90 (MIC90) is needed. For an IOL with a sustained release system, it is essential that this sustained therapeutic concentration should not cause adverse effects on other nontargeted ocular tissues, such as retina, choroid or corneal endothelium. Second, the drug loading should not affect the optical property of the IOL, such as the dioptric power or the clarity of the IOL, and should not influence the position of the IOL either in the capsular bag or sulcus. Third, the drugs loaded on or the materials incorporated with or attached to the IOLs should be biocompatible, without eliciting further inflammation or toxicity in ocular tissues, such as toxic anterior segment syndrome.

## DRUGS LOADED ON AND RELEASED FROM INTRAOCULAR LENSES

The drug can be loaded on the IOL by two methods: presoaking/coating, or attaching the drug reservoir onto the IOL haptic or optic. The former method is simple, cost effective, and can be applied to either foldable or nonfoldable IOLs, but the drug release occurs over a short period of time . However, some studies have shown that a large burst of drug over a short period was sufficient to have a significant treatment effect . The latter method (using a reservoir) provides a more prolonged, controlled release when it is used in combination with a biodegradable polymer, but the fabrication and amounts of the drug loaded and released ]. In general, IOLs made of hydrophilic materials, such as hydrophilic acrylic (hydrogel), are capable of absorbing and releasing greater amounts of drug , whereas IOLs made of hydrophobic materials, such as silicon, PMMA or hydrophobic acrylic, have poorer drug uptake and release . Davis et al. reported that hydrophilic IOLs had more desirable release pharmacokinetics and a higher cumulative release compared with hydrophobic IOLs. However, both types of IOLs would be capable of providing clinically significant drug levels . For any presoaked IOL, it is important to evaluate the optimum presoaking conditions, such as the drug concentration prior to soaking and the presoaking time.

Intraocular lenses (IOLs) can be modified by combining a variety of biodegradable polymers. The uses of bioinert polymers, such as poly(2-hydroxyethyl methacrylate) (pHEMA) or poly(D,L-lactide-co-glycolide) (PLGA) , are versatile technologies that have shown great promise as intraocular drug delivery polymers.

## EXPERIMENTAL STUDIES ON THE INTRAOCULAR LENS DRUG DELIVERY SYSTEMS

Research on the use of an IOL drug delivery reservoir can be divided to those used in the prevention of postcataract surgery infection, in the treatment of postcataract surgery inflammation and in the prevention of postcataract surgery PCO.

## POSTCATARACT SURGERY INFECTION

The use of IOLs as drug delivery vehicles to prevent postoperative infectious endophthalmitis has been described. As the IOL is implanted during the time of cataract surgery, and itself serves as a substrate for the adhesion and proliferation of bacteria in endophthalmitis , it is reasonable to attempt to add directly antibacterial drugs onto the IOL to prevent postoperative infection. It is thought that the antibiotic-loaded IOLs increase the chance of attaining the MIC90level because the antibiotics can easily reach the target site. Kleinmann showed the

efficacy and safety of a hydrophilic acrylic IOL as a drug delivery system for fourth-generation fluoroquinolones. IOLs were presoaked with gatifloxacin (3â•Šmg/ml) or moxifloxacin (5â•Šmg/ml) solution for 24â•Šh, and then were implanted into rabbits. The drug concentrations in aqueous samples in presoaked IOL groups were statistically significantly higher than those in which topical eye drops were applied for both antibiotics at all postoperative time points (postoperative 4, 8 and 12â•Šh). These concentrations were above the MIC90 for Staphylococcus epidermidis, the most common bacteria isolated from clinical cases of postoperative endophthalmitis Hydrophilic acrylic IOLs were immersed in levofloxacin (5 and 15â•Šmg/ml) or gatifloxacin (3 and 5â•Šmg/ml) solution for 24h.

## POSTCATARACT SURGERY INFLAMMATION

Corticosteroids have been the drug of choice for the prevention and treatment of postoperative inflammation. It has been reported that coating a silicone IOL with dexamethasone for 40â•Šmin significantly reduced postoperative inflammatory markers in the aqueous (i.e. prostaglandin E2, cells, and protein content) for several days following cataract surgery in a rabbit model.

The short-term safety and pharmacokinetic behavior of IOLs with polymeric corticosteroid drug delivery systems has been investigated. Siqueira loaded dexamethasone into PLGA polymers, and these small polymeric devices were attached to the IOL optic rings. After implantation into the posterior chamber of the rabbit eye, therapeutic concentration was achieved in the aqueous and vitreous, and there was no acute damage to the cornea or retina based on histological evaluation. The therapeutic concentration in the vitreous indicated the possible benefits for patients with other combined ocular diseases, for example, diabetic retinopathy or uveitis . In addition, the long-term use of a polymeric corticosteroid-releasing drug delivery reservoir has also been reported.

One major concern of such reservoirs is the difficulty in reversal of the effects of corticosteroids, and it may be a problem if patients suffer from corticosteroid-related glaucoma or signs of ocular infection. Although previous literature has shown an absence of intraocular pressure (IOP) elevation after corticosteroid-loaded IOL implantation in rabbits, further clinical assessments of IOP in humans are required.

Other anti-inflammatory drugs have also been incorporated with IOLs. An indomethacin-containing PLGA disc placed below an IOL was put into the rabbit capsular bag, and it significantly decreased aqueous flare.

## POSTCATARACT SURGERY POSTERIOR CAPSULE OPACIFICATION

PCO is caused by proliferation, migration and epithelial mesenchymal transition of residual lens epithelial cells. The process is initiated by the presence of growth factors such as TGFÎ²2 , and is accompanied with the activation of an inflammatory reaction and MMPs. A pharmacological agent that can block or hinder this cascade may act as a potential therapeutic tool to prevent PCO. A wide variety of drugs have been investigated in vitro/in vivo to inhibit the formation of PCO with variable success, including antimetabolites (daunomycin, 5-fluorouracil, mitomycin C, colchicine and methotrexate), anti-inflammatory agents (dexamethasone, indomethacin and diclofenac sodium), osmotic agents and so on.

It has been demonstrated that indomethacin-coated IOLs significantly reduced PCO histopathologically in a rabbit model, although the in-vitro experiments showed that all the indomethacin was released from the IOL within 24h. It reduced PCO formation by approximately 50% in terms of PCO wet mass measured at 8 weeks, postoperatively. However, some endothelial cell loss was noted. The toxic effect of the antimetabolite drug on the surrounding intraocular tissues, especially on the corneal endothelium, might limit its clinical application.

## FUTURE APPLICATIONS

The incorporation of other drugs with IOLs for the treatments of other ocular diseases deserves further

investigations. These potential medications may include other NSAIDs, hypotensive drugs , antiviral drugs such as ganciclovir or antiangiogenic agents such as anti-vascular endothelial growth factor . Furthermore, the development of an IOL delivery system containing both an antibiotic and a corticosteroid is also being explored. Although drug delivery systems attached to a three-piece IOL haptics have been successfully designed , it may be a challenge to attach such drug delivery systems onto foldable IOLs and safely loaded into IOL injector systems. Foldable IOLs are the more commonly used types of IOLs by surgeons nowadays, and application of a sustained release platform on such IOLs is under investigation.

## CONCLUSION

The use of IOLs as drug delivery reservoirs appears to be a promising way to treat inflammation, infection and posterior capsule opacification after cataract surgery. It enables the combination of cataract surgery and postoperative treatments in a single procedure. It can achieve a high therapeutic index in the immediate postoperative period, and may provide a sustained, rate-controlled drug release when incorporated with a polymeric-based reservoir. Besides eliminating the dependency of patients compliance, it presents great advantages for patients with other combined ocular diseases, such as uveitis or diabetic retinopathy undergoing cataract surgery. Further studies are warranted to evaluate their potential applications in humans to reach clinical practice.

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