



Commercialization challenges for drug eluting contact lenses

Olivia L. Lanier , Keith G. Christopher , Russell M. Macoon , Yifan Yu ,
Poorvajan Sekar & Anuj Chauhan

To cite this article: Olivia L. Lanier , Keith G. Christopher , Russell M. Macoon , Yifan Yu ,
Poorvajan Sekar & Anuj Chauhan (2020) Commercialization challenges for drug eluting contact
lenses, *Expert Opinion on Drug Delivery*, 17:8, 1133-1149, DOI: [10.1080/17425247.2020.1787983](https://doi.org/10.1080/17425247.2020.1787983)

To link to this article: <https://doi.org/10.1080/17425247.2020.1787983>



Accepted author version posted online: 30
Jun 2020.
Published online: 02 Jul 2020.



Submit your article to this journal



Article views: 45



View related articles



CrossMark

View Crossmark data

REVIEW



Commercialization challenges for drug eluting contact lenses

Olivia L. Lanier^a, Keith G. Christopher^a, Russell M. Macoon^b, Yifan Yu^b, Poorvajan Sekar^b and Anuj Chauhan^a

^aChemical and Biological Engineering, Colorado School of Mines, Golden, CO, USA; ^bDepartment of Chemical Engineering, University of Florida, Gainesville, FL, USA

ABSTRACT

Introduction: Eye drops are commonly used for delivering ophthalmic drugs despite many deficiencies including low bioavailability and poor compliance. Contact lenses can deliver drugs with high bioavailability but commercial contacts release drug rapidly, limiting benefits and necessitating modifications to improve the drug release characteristics.

Areas covered: This review covers the common approaches to prolong the release rates of drugs from contact lenses including molecular imprinting, incorporation of nano/microparticles, vitamin-E barriers, and layered/implant contact lenses. It also evaluates their suitability for commercialization and discusses challenges that need to be addressed before commercialization is possible.

Expert opinion: In spite of many benefits of contact lenses compared to eye drops, a drug-eluting contact lens has not emerged in the market due to many reasons including potential safety risks, patient and practitioner acceptance, and production and storage factors. Importantly, changes in the critical lens properties must also be considered such as ion and oxygen permeability, loss in modulus, optical and swelling properties, and protein adherence upon drug loading. Many technologies have addressed scientific and commercialization challenges and are currently being tested both in animal and clinical studies. It is likely that a drug-eluting contact lens will be commercialized in the future.

ARTICLE HISTORY

Received 13 February 2019
Accepted 23 June 2020

KEYWORDS

Contact lenses; vitamin E; molecular imprinting; nanoparticles; multi-layer lenses; commercialization

1. Introduction

The current market for ophthalmic drugs is dominated by eye drop formulations which accounts for about 90% of treatments of common anterior segment diseases such as bacterial and fungal infections, conjunctivitis, dry eye, cystinosis, and glaucoma [1–3]. In the United States, there are over 3 million people plagued by glaucoma alone [4]. The use of eye drops to treat the diseases may require multiple instillations daily, and with glaucoma, the treatment commonly requires multiple drugs [5]. This reduces patient compliance which is a critical issue in managing many diseases. The requirement of multiple instillations results from the low bioavailability of eye drops ranging from about 1–5% [6]. The low bioavailability of eye drops leads to higher therapeutic concentration requirements and thus concerns regarding toxicity. Low bioavailability can be explained as the human tear film has a volume of around 7 µL which is maintained by a balance between tear secretion via lacrimal glands and drainage through the canaliculi into the nasal cavity [7], whereas an eyedrop has a volume of approximately 30 µL. Addition of the 30 µL causes the volume of the tear film to undergo a substantial increase in size and, rapid drainage occurs to restore the steady state volume [8]. This results in a large amount of the drug to drain out through those routes in a short time span. Plus, the drop may spill out of the eye itself as a major route of loss.

The surface of the cornea comprises epithelial cells with tight junctions in between which forms a strong barrier

against permeation of compounds from the tears. The low permeability and rapid clearance of drugs from the tears result in low bioavailability, and a potential for undesired side effects due to transport of the remainder of the drug into blood and then into other tissues [9]. Another drawback with eye drop formulations is the use of preservatives which has been shown to cause cell toxicity [10]. Researchers have devised many modifications of eye drop formulations by encapsulating the drugs in nanoparticles, adding mucoadhesives, or simply increasing the viscosity. However, even increasing the residence time cannot significantly increase transport into the cornea as a large fraction of the drug in the tears also diffuses through the conjunctiva, which has a much larger surface area and permeability than the cornea [11,12]. As the conjunctival stroma is highly vascular, this can lead to elimination of the instilled dose from the pre-corneal area within ~90 seconds and to systemic uptake. Systemic uptake of certain drugs can lead to undesired side effects; for example, systemic uptake of the β -adrenergic receptor blocker, timolol, can cause effects in the heart [13]. Plus, the conjunctiva have structural barriers (i.e. tight junctions) and enzymatic barriers that limit the penetration of therapeutics across the conjunctiva [14]. Thus, even with the above modifications to the formulations, the bioavailability with eye drops remains low. Therefore, this is a critical need for novel drug delivery methods and devices that can increase the bioavailability, reduce or eliminate the need for preservatives, and improve patient compliance.

Article highlights

- Contact lenses are significantly more efficient than eye drops for ophthalmic drug delivery.
- Drug release duration can be extended by many approaches including molecular imprinting, vitamin E barriers, nanoparticles, and multi-layered/implant lenses.
- Commercialization challenges for each method are discussed including manufacturing, storage, and animal studies.
- Impact of drug extension methods on critical lens properties such as transparency and oxygen permeability was explored.
- Expert opinion on future prospects of commercialization

This box summarizes key points contained in the article.

The deficiencies of the eye drop formulations for glaucoma therapy were addressed by Ocusert®, a pilocarpine releasing insert that was placed in the cul-de-sac of the eye. Ocusert® produced a constant reduction in IOP for over 7 days with one-eighth of the eye drop dose, which improved patient compliance [15]. Unfortunately, Ocusert® has been discontinued due to retention problems and burst release issues [16]. Many devices have been explored for delivering ophthalmic drugs including fornix inserts like Ocusert®, puncta plugs, drug-eluting rings, and contact lenses. Each of these types of devices offers advantages compared to eye drops for improved bioavailability, but each has its own set of challenges. Amongst these devices, it is clear that a contact lens will offer the highest bioavailability for delivering drugs to the anterior chamber because of its position in the eye. Drug released by the contact lens toward the cornea will invariably diffuse into the tissue because the time needed for the drug molecules to diffuse out radially is much longer than the time for transport into the cornea. For any other device, the drug released will be exposed to the same clearance pathways as eye drops and so the improvements in bioavailability may not be as high as for contact lenses.

When considering potential devices for delivering drugs to the eyes, contact lenses are an obvious choice because millions of subjects (approximately 100 million people in 2006 [17]) have been safely wearing contacts for decades. Therefore, it is expected that drug-delivering contact lenses would have higher patient compliance than eyedrop formulations which require multiple installments daily. Most contact lenses are hydrogels, often made from silicone, which can be loaded with drugs either through dissolving the drug into the water phase of the lens [18–21] or through binding the therapeutic to the polymer matrix [22,23]. The significant advantage of drug release from contact lenses vs. conventional methods such as eye drops is the drug released from the contact lens has a longer residence time in the post lens tear film (POTL) than eye drop residence time in the tear film; this leads to higher flux into the cornea from lenses than from the application of eye drops [24–27]. Further, contact lenses will reduce the drug inflow into the nasolacrimal sac, which will reduce uptake into the bloodstream [28]. Another advantage is that the release profile from a contact lens could be tuned

for specific diseases and dosing regimens (i.e. to be zero or first-order release). It is therefore not surprising that researchers patented using contact lenses for delivering ophthalmic drugs in 1972 [29]; however, no drug-eluting contact lenses have yet been translated to the market.

There are insufficiencies to the drug-releasing lenses that may explain the lack of commercialization. Initial attempts for delivering drugs by contacts were based on soaking the lenses in drug solution until equilibrium to load the drug, followed by placement on the eye for release. This simple approach can accomplish delivery but cannot be used for extended release beyond a short duration of a few hours [30–37]. The soaked contact lenses may provide more efficient drug delivery than eye drops, but the short duration of release limits the potential benefits particularly for diseases that require multiple eye drops each day. Another major drawback of the soaking approach is that the loading capacity is limited by the equilibrium solubility of the drug in the lens matrix, which could be inadequate for some drugs [18,38–40]. Additionally, the soaking method takes several hours for drug loading into the lens. A further issue with contact lenses is they cause hypoxia, i.e. reduced oxygen and increased carbon dioxide, in POTL when worn for extended time periods. Silicon-hydrogel copolymers with high oxygen transmissibility were synthesized in response to this issue but were still shown to have adverse effects after extended wear such as microbial keratitis [41] and papillary conjunctivitis [42]. As of yet, no drug-eluting lenses have made it to market, although ACUVUE® has released lenses with a photochromic additive [43]. Plus, incorporation of drugs into contact lenses can potentially alter key lens properties such as transparency, ion and oxygen permeability, lubricity, and protein binding.

In the last couple of decades, several techniques, such as molecular imprinting, cyclodextrins [44], liposomal laden lenses [45], vitamin E diffusion barriers [5,34,46], micro and nanoparticle loaded lenses [47], multi-layered lenses [37], and supercritical solvent impregnation [48], have been developed to address the issue of short release durations and inadequate drug loading. These methods have been shown to deliver drugs from contact lenses at controlled rates for extended periods of days, weeks, or even longer. A number of recent reviews of drug-eluting contact lenses have presented accounts of research in this area [28,49–51]. The main focus of this review is to build on previous reviews by covering the technologies that have addressed the described challenges (e.g. short release durations, inadequate drug loading) and the associated considerations for each described technology that must be addressed before commercialization. In particular, molecular imprinting, vitamin-E barriers, micro and nanoparticles, and multi-layer lenses are analyzed for their past studies, benefits, and considerations for commercialization. These are summarized in Table 1.

2. Molecular imprinting

2.1. Background

Molecular imprinting is a technique that involves manipulation of the hydrogel structure to create higher affinity for the

Table 1. Challenges and benefits toward commercialization of the various methods used to prolong drug release from contact lenses.

Method for extending drug release	Challenges for commercialization	Benefits
Molecular imprinting	<ul style="list-style-type: none"> Many studies focused on HEMA, which does not have adequate oxygen permeability for extended wear Further animal studies are required which evaluate safety of the lenses Lenses can deform after drug release Requires optimization of template/functional monomer for each drug system May be difficult to release more than one therapeutic due to the monomer/crosslinker needed Further studies on storage and shelf-life are required 	<ul style="list-style-type: none"> Tunable release profiles Animal studies have demonstrated pharmacokinetics and efficacy Minimal additional manufacturing costs
Vitamin-E barriers	<ul style="list-style-type: none"> Amount of vitamin-E is limited due to its effect on lens properties Further animal studies are required to evaluate drug concentration in the tear film over time Must control 'burst' release in the formulations 	<ul style="list-style-type: none"> Vitamin-E can be directly incorporated into commercial lenses Animal studies demonstrated efficacy Minimal additional manufacturing costs Adds UV protection to the lenses Vitamin-E has been shown to slow cataract development Lenses can be stored in drug solutions due to equilibrium loading method
Nano and microparticles	<ul style="list-style-type: none"> Amount of particles is limited due to effect on lens properties Nanocavities can be created in lenses after particle dissolution Further animal studies demonstrating safety are needed Requires an additional manufacturing step for particle synthesis 'Burst' release Many previous studies used HEMA based lenses 	<ul style="list-style-type: none"> Particles can be made from a variety of materials Animal studies have demonstrated pharmacokinetics and efficacy Storage has been evaluated for some formulations for extended time periods
Multi-layer lenses and implantation	<ul style="list-style-type: none"> Layers are limited by their effect on lens properties PLGA creates acidic environment upon degradation Many studies focused on HEMA Animal studies for long-term safety are required Complex manufacturing 	<ul style="list-style-type: none"> Storage has been successful for dried lenses Animal studies have demonstrated pharmacokinetics and efficacy Zero-order release can be achieved in these systems Incorporation of ring implants preserves overall lens properties Storage has been shown in previous studies

drug of interest [52]. To produce molecularly imprinted hydrogels, the template molecule (i.e. the drug of interest for release) is polymerized with functional monomers and crosslinkers which can interact with the template molecule (Figure 1) [53]. The monomers and crosslinkers can be chosen to mimic the interaction between the drug and the target receptor in the body because it is already known to have a strong binding interaction and results [54,55]. Once polymerized, the unreacted monomer and template molecule are extracted to leave behind the high-affinity pockets. The lenses are then soaked in a template molecule solution to load the drugs of interest. Some of the most common monomers and crosslinkers used to customize the gel matrix are acrylic acid (AA), acetic acid (HAc), acrylamide (AC), N,N-diethylacrylamide (DEAA), methacrylic acid (MAA), methyl methacrylate (MMA), N-vinyl 2-pyrrolidinone (NVP), 4-vinyl-pyridine (VP), N-(3-aminopropyl) methacrylamide (APMA), hydroxypropyl methylcellulose (HPMC), N,N-diethylaminoethyl methacrylate (DEAEM), poly(ethylene glycol) (200) dimethacrylate (PEG200DMA), and N,N'-methylenebisacrylamide (NN-MBA) [55–58].

The process of molecular imprinting increases the overall partition coefficient of the drug in the lens and decreases the effective diffusivity through the hydrogel. Some of the early work on the use of molecular imprinting for controlled release from contact lenses focused on timolol, which is a commonly used drug for managing glaucoma [59–61]. Hiratani et al. used dimethyl acrylamide (DMA) and methacryloxypropyl-tris-

(trimethylsiloxy) silane (TRIS), as backbone monomers, MAA as the functional monomers, and ethylene glycol dimethacrylate (EGDMA) for the crosslinking agent [59]; all synthesized formulations with template molecule timolol had optical transparency, comparable mechanical strength, and similar water contents. This study showed that adjustment of the template:functional monomer ratio and the functional monomer/cross-linker ratio can significantly affect the drug release profile, extending the release duration from 5 to 72 h [59]. Timolol binding to the MAA is expected to be ionic or by hydrogen binding with the amino, ether, and hydroxy groups of the timolol; this study found that when using a lower timolol: MAA ratio, more effective cavities can be created with greater multi-point association. Plus, Wulff et al. found that after the removal of the template molecules, the cavities can relax and lose their original structure [62]. Matrix swelling can also cause an irreversible change in the shape of cavities so that they cannot take up the template again. This supports that finding that the ratio of template/functional monomer is critical in the formation of molecularly imprinted hydrogels as they must maintain the conformation to have a high enough affinity to recognize the template while also allowing the template to be removed and reloaded [63]. Another study [60] produced 2-hydroxyethylmethacrylate (HEMA) lenses with EDGMA crosslinker in the presence of MAA (functional monomer), MMA (functional monomer), and timolol maleate, and showed that use of MAA as a comonomer increased the

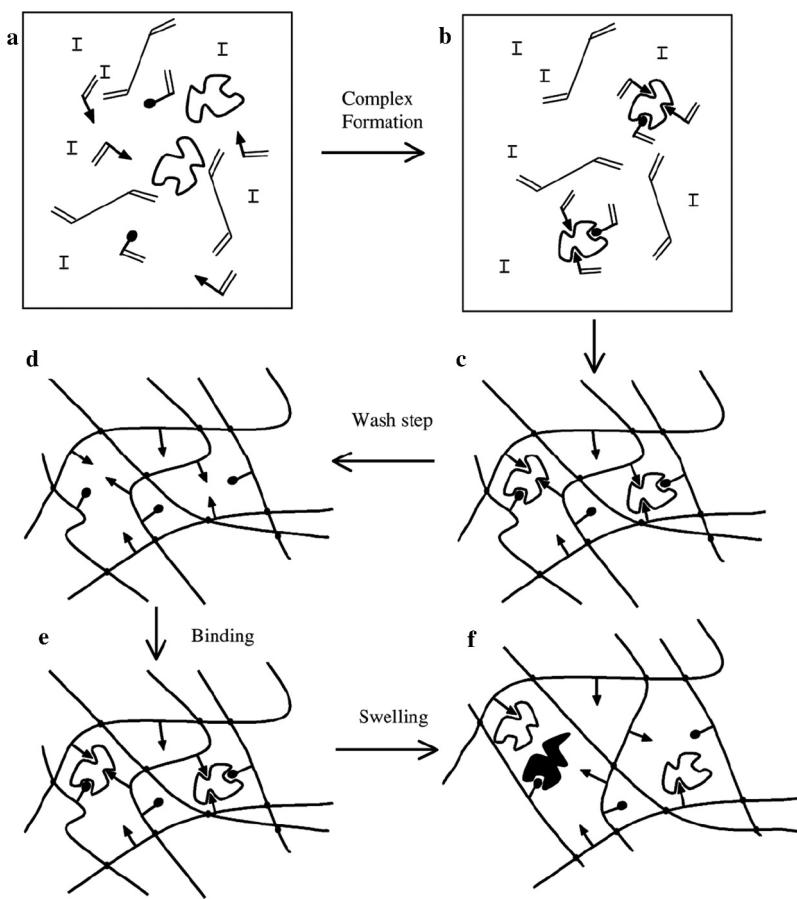


Figure 1. Imprinting Process. (a) Solution mixture of template, functional monomer(s) (triangles and circles), crosslinking monomer, solvent, and initiator (I). (b) The pre-polymerization complex is formed via covalent or non-covalent chemistry. (c) The formation of the network. (d) Wash step where original template is removed. (e) Rebinding of template. (f) In less crosslinked systems, movement of the macromolecular chains will produce areas of differing affinity and specificity (filled molecule is isomer of template). Reprinted from Advanced Drug Delivery Reviews, Vol 4 Issue 1, Mark Bryne, Kinam Park, Nicholas A. Peppas, Molecular Imprinting within Hydrogels, 149–161, Copyright 2002, Reference [53] with permission from Elsevier.

timolol loading to therapeutically relevant levels and maintained suitable release characteristics. Moreover, a study by Yañez et al. [61] used isothermal titration calorimetry to identify the optimal timolol: functional monomer (AA) ratios for sustained release from HEMA-based hydrogels. Ratios of 1:6 and 1:8 loaded less timolol than smaller ratios 1:12, 1:16 and 1:32, but sustained release for longer time periods (up to 2 weeks for the 0.9 mm thick hydrogels).

There are many other studies that focused on hydrophilic, hydrophobic, and amphiphilic drugs and showed increases in drug release durations [64–66]. For example, Tieppo et al. [64] synthesized molecularly imprinted HEMA lenses with DEAEM (functional comonomer) and PEG200DMA (crosslinker) for the sustained release of non-steroidal anti-inflammatory drug (NSAID) diclofenac sodium. This study showed that without DEAEM there was negligible binding, and by manipulating the DEAEM: diclofenac ratio, macromolecular memory sites within the gel could be engineered for optimal release kinetics (i.e. zero-order release for 2 days). Another study [65] created HEMA lenses with VP and AMPA to release NSAIDs ibuprofen and diclofenac and showed that incorporating the functional monomers did not significantly affect viscoelastic properties of the hydrogel

but did significantly increase loading of the NSAIDs. The developed HEMA gels were able to sustain release of ibuprofen up to 24 h and up to 1 week for the diclofenac. A study by Hui et al. [66] synthesized some of the first molecularly imprinted silicone-based hydrogels with AA and HAc comonomers for the release of antibiotic ciprofloxacin. Release was achieved up to 14 days dependent on the concentration of functional monomer and functional monomer:template ratio. Greater monomer: template ratio (8:1 and 16:1) resulted in longer release periods where lower ratios (4:1) released higher amounts of ciprofloxacin into solution over a shorter time period [66]. While most research has focused on delivery of single small molecule drugs, a study by White et al. [67] developed molecularly imprinted silicone lenses for the simultaneous release of hydroxypropyl methylcellulose (HPMC), trehalose, ibuprofen, and prednisolone. This study also shows the feasibility of releasing high molecular weight molecules such as HPMC using molecular imprinting [67]; other studies have also released relatively high weight molecules such as antimicrobial peptides [68] and hyaluronic acid (HA) [57]. Overall, these studies have shown that molecular imprinting can be used to prolong the release of several relevant

ophthalmic drugs from contact lenses. They have also demonstrated findings which are imperative to the design of functional molecularly imprinted lenses: the choice of template and functional monomer must be compatible, the template: functional monomer ratio must be optimized to produce cavities with high enough affinity for the molecule but also allow for the template to be removed and reloaded, and amount of cross-linker must also be optimized for the hydrogel to maintain its structure while also allowing the template molecule to be released. The functional monomer–crosslinker interaction must also be considered, as the crosslinker choice has been linked to changes in the template recognition behavior [69].

2.2. Considerations for commercialization

It is important to evaluate the effect of molecular imprinting on the properties of the contact lens before commercialization. Contact lenses must have very defined optical and mechanical properties, in addition to ion and oxygen permeability. Thus, the functional monomers that can be used and the degree of crosslinking are restricted. This may also limit the maximum amount of drug loaded. A majority of optimization studies have been focused on HEMA which is not ideal for extended wear. However, more recent studies have been performed with silicone hydrogels which is more oxygen-permeable [66]. A study by Venkatesh et al. [70] showed that molecular imprinting did not have a significant effect on the swelling ratios of the hydrogel compared to control HEMA gels; a study by Alvarez-Lorenzo et al. [60] also showed that molecular imprinting did not significantly affect swelling and transparency of HEMA lenses. Another study using molecularly imprinted silicone lenses to release hydroxypropyl methylcellulose showed that using EGDMA and PEG200DMA as cross-linking molecules resulted in lenses with acceptable optical clarity and modulus values [71]; the authors noted that numerous other crosslinking agents were evaluated that did not result in acceptable lens properties [72]. A further study [59] using silicone-based lenses made from TRIS and DMA for timolol release showed that the lenses retained optical transparency and good mechanical strength after being imprinted with MAA and crosslinker EGDMA; the water content of the lenses was shown to be dependent on the amount of EGDMA used. Taken together, these results indicate the ideal lens properties can be maintained through the molecular imprinting process but that optimization for each lens/monomer/template will need to be performed. Moreover, it also needs to be considered that there can be a change in module following drug release.

Importantly, animal studies have demonstrated safety and pharmacokinetics from the imprinted contact lenses [58,63]. An in vivo study [63] using Male Nippon albino rabbits and *N,N*-diethylacrylamide (DEAA) lenses modified with MAA and EGDMA for timolol release provided measurable timolol concentrations in the tear fluid 2 and 3 times longer than control lenses and eyedrops. Another in vivo study [58] used Male New Zealand white rabbits to test the efficacy of HEMA lenses with AA, AM, NVP, and PEG200DMA to release ketotifen fumarate; the results showed the lenses could sustain a constant

concentration of drug in the tear film for up to 26 h, whereas non-imprinted lenses only sustained release for 10 h. Before commercialization, more in vivo studies will be required to show safety of these molecularly imprinted systems and that they do not induce corneal hypoxia, irritation, inflammatory responses, or adverse changes in tear volume or intraocular pressure.

As for manufacturing, the imprinted lenses can be manufactured using the same approach as current manufacturing protocols for lenses and stored for extended periods without any impact on subsequent drug release. The imprinted lenses could be produced through the same approach of polymerization in molds as is currently done in contact lens industry. One study showed molecularly imprinted HEMA lenses could be stored in water for 24 h with minimal release of therapeutic, but have relevant release profiles in lacrimal fluid [73]. Due to the required optimization process for template/polymer/monomer/crosslinker, the design and scale-up of molecularly imprinted lenses could be tricky when the treatment requires more than one drug. In addition, implementing more than one therapeutic may negatively impact the lens' optical and physical properties due to the required monomer/crosslinker needed. However, an advantage of imprinting is control over release rate via polymer properties. The degree of control using the imprinting process has been shown to be higher than other methods and is one of the main attractions of this method.

Altogether, molecularly imprinted lenses have promise for commercialization as they extend therapeutic release to clinically relevant time periods and increase corneal bioavailability. However, more in vivo studies are required to assure the safety of the lenses, and it may be difficult to commercialize any lenses with multiple therapeutics which may limit their utility.

3. Vitamin-E barriers

3.1. Background

Nanoaggregates of vitamin-E can be incorporated into contact lenses to function as diffusion barriers for drugs and slow down their release (see Figure 2). Vitamin-E (D- α tocopherol), a yellow-brown viscous liquid is a lipid-soluble antioxidant and a commonly used dietary supplement. Besides serving as a diffusion barrier, prior research shows the ocular benefits of vitamin-E including slowing down the progression of cataract development [74] and inhibiting keratocyte apoptosis following photorefractive keratectomy (PRK) surgery [19]. Being lipophilic in nature, vitamin-E readily dissolves in organic solvents such as ethanol; thus, vitamin-E is integrated into contact lenses by soaking an unmodified control lens in vitamin-E concentrated ethanol solution. The hydrogel lens swells in ethanol owing to polymer relaxation, enabling pore size expansion within the hydrogel matrix. This allows the vitamin-E to partition into the lens and bind to the long-chain polymer units in the matrix. The soaked hydrogel is left for 24 h to ensure equilibration at room temperature (25°C). The swollen gel is later removed from the vitamin-E/ethanol solution and

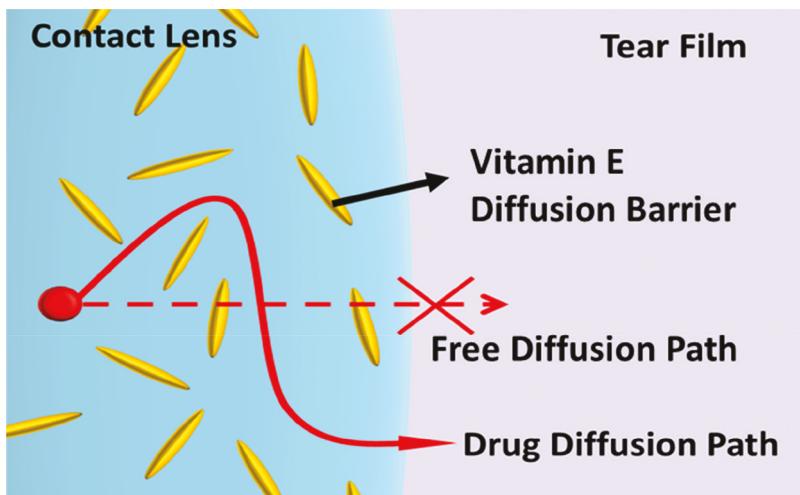


Figure 2. Vitamin-E diffusion barriers in a contact lens create a longer diffusion path for the drug into the tear film. Image courtesy of Kuan-Hui Hsu.

rinsed in PBS to shrink it to the pre-deformed shape and stored in phosphate-buffered solution or dried until further experiments [19,20,75–78]. The vitamin-E remains in the lens due to the inherent hydrophobicity, high viscosity, and negligible solubility in PBS solution [5,19,46,75–80].

Chauhan et al. investigated the effect of vitamin-E diffusion attenuators in commercial lenses including ACUVUE® NIGHT&DAY™, ACUVUE® OASYS™, ACUVUE® ADVANCE™, O₂ OPTIX™, and PureVision™ on extended delivery of ophthalmic drugs [77]. Timolol (beta-blocker and a glaucoma medication), fluconazole (anti-fungal), and dexamethasone 21-disodium phosphate (anti-inflammatory corticosteroid) were the test drugs in these studies. Release experiments were conducted by soaking the drug and vitamin-E loaded lens in 2 ml of PBS and measuring the dynamic drug concentration in solution using an UV-Vis spectrophotometer. Thus, it should be noted that *in vivo* studies may show different release results. Studies on ocular delivery of timolol by vitamin-E-loaded lenses demonstrated an increase in release durations from ~1.5 h with no vitamin-E to ~43 h for 27% vitamin E loading and ~192 h for 74% vitamin E loading in the NIGHT&DAY™ lens [77]. Similar results were observed for transport of both fluconazole and dexamethasone 21-disodium phosphate. It was also demonstrated for the investigated drugs that the extent of time scale of release showed a quadratic increase when correlated with the fraction of vitamin-E loading in commercial lenses [77]. The disparities in release durations of these three drugs are attributed to differences in molecular weight and partition coefficient. Interestingly, vitamin-E also attenuates the release of hydrophobic drugs such as dexamethasone, but the relative increase in the release durations is much less than that for the hydrophilic counterpart [78]. In this case, solute dissolution into the hydrophobic nanoaggregates of vitamin-E provides additional resistance to solute transport through the gel matrix. The release duration of dexamethasone increases from 4.5 h (with no vitamin E) to 12 days in NIGHT&DAY™ lenses with 27% vitamin-E loading [78]. Vitamin-E-loaded lenses have also been synthesized and shown to increase release duration

of cyclosporine (for dry eyes treatment) [75], betaine (osmoprotectant) [80], dexpanthenol (moisturizing agent) [80], cysteamine (for treatment of cystinosis) [81], pirenadol (anti-inflammatory, antifibrotic) [34], and more.

A recent study combined vitamin-E technology with cationic surfactants, cetalkonium chloride, and stearylamine, in order to improve the drug loading capacity of three different NSAIDS (ketorolac tromethamine, flurbiprofen sodium, and diclofenac sodium) into ACUVUE® OASYS™ and ACUVUE® TruEye™ lenses [82]. First, it was shown that for lenses with 11% and 21% vitamin-E loading, release of ketorolac tromethamine and flurbiprofen sodium is extended from hours to several days but that the overall amount of drug released was reduced. By incorporating the cationic surfactants, the authors were able to extend release while maintaining drug loading capabilities of the lenses [82]. Another recent study loaded vitamin-E barriers into ACUVUE® OASYS™ and ACUVUE® TruEye™ lenses for the extended release of ofloxacin to treat corneal infections [83]. The results showed that incorporation of the vitamin-E barriers significantly prolonged release profiles for both lens types ($p < 0.05$) and release was achieved for up to 4 days [83].

Overall, these studies have shown that vitamin-E can be incorporated into commercially available contact lenses as nanoaggregate diffusion barriers. This type of delivery system has been developed for numerous drugs, including hydrophilic and hydrophobic.

3.2. Considerations for commercialization

Important considerations for commercialization are the properties of these lenses such as transparency, water content, tensile strength, oxygen permeability, and ion permeability. Since the vitamin-E barriers can be directly incorporated into commercial lenses, it will likely reduce regulatory barriers for their commercialization, especially if proven that the properties of the commercial lens are retained. Chauhan and coworkers demonstrated that vitamin-E barriers can be created in

extended wear contact lenses without any impact on the transparency for vitamin-E loadings as high as 42% (w/w) [77]. Plus, these lenses were shown to block UV light, adding an additional benefit of UV protection to the lenses [77]. Indirect evidence suggests that the vitamin-E phase separates into high aspect ratio disc-shaped nano-barriers, 21 nm in thickness and 350 nm in radius [19,77]. Since the aggregates are smaller than the wavelength of the visible light, the lenses remain transparent [39]. A further study [79] showed that ACUVUE® OASYS™ and ACUVUE® TruEye™ remain transparent after vitamin-E loading, but ACUVUE® Moist™ become hazy; SEM images showed that the vitamin-E barriers in the ACUVUE® Moist™ lenses are micron sized which explains the loss of transparency in these lenses. Thus, the property of transparency should not be a barrier for commercialization.

However, increase in size and decrease in ion permeability limit the maximum vitamin-E loaded in these lenses. Specifically, for NIGHT&DAY lenses, a 30% vitamin-E loading led to a 6.5% increase in lens size, 75% vitamin-E loading led to ~40% reduction in oxygen diffusion, and 10% vitamin-E loading led to 50% reduction in the ion permeability [77]. This study also showed that the water content at equilibrium for each lens decreased with vitamin-E loading compared to the control lenses, but it was different for each commercial lens type evaluated [77]. These values are still adequate to allow movement of the lens on the eye and prevent corneal hypoxia. The study which combined vitamin-E barriers and cationic surfactants did not evaluate the effect on contact lens wettability, water content, material modulus, base curve, power, or diameter, and thus this will need to be done before moving to in vivo testing of these lenses [82].

Before widespread commercialization, in vivo and clinical studies must be performed to prove the efficacy and safety of the technology. Pilot in vivo studies were done to demonstrate the efficacy of glaucoma drug delivery via vitamin-E-modified lenses in Beagle dogs [5,20,76]. These studies also showed that vitamin-E-modified contact lenses with a lower drug payload are as efficacious as topical drops in regard to the intraocular pressure reduction for glaucoma treatment. Lenses with a 20% vitamin-E loading increase the release duration from 2–3 to 24 and 36 h, respectively, for individually loaded timolol and dorzolamide lenses [5]. However, the time-scale of release increased to 42 h for both drugs delivered contemporaneously. Glaucomatous Beagle dogs were treated by these lenses over the course of 288 h [5]. Studies revealed that intraocular pressure upon treatment with vitamin-E-modified lenses was roughly 5 mmHg lower than that of the untreated eyes for up to 21 days, which is clinically significant for effective glaucoma management [5].

Another study showed that NIGHT & DAY™ lenses loaded with timolol were able to reduce intraocular pressure by 5 mmHg, and showed that use of contact lenses reduced systemic uptake compared with eye drops [20]. A third study [76] with beagle dogs used 20% vitamin-E loaded ACUVUE® TruEye™ lenses for the release of timolol; the lenses were replaced every 24 h or worn continuously for 4 days. The results showed that the lenses resulted in comparable decrease in intraocular pressure to eye drops but with only

20% of the dose [76]. The decrease in dose could both reduce disease-associated costs and reduce systemic side effects. An in vivo study using New Zealand white rabbits and ACUVUE®OASYS™ lenses loaded with 20% vitamin-E and cysteamine (for ocular cystinosis treatment) showed no sign of irritation, congestion, lacrimation or blepharospasm or photophobia, no inflammatory response, no significant change in tear volume or intraocular pressure, and no significant change in endothelial cell count [79]. Finally, ex vivo studies for commercial lenses loaded with ofloxacin and vitamin-E barriers were performed on excised New Zealand rabbit eyes inoculated with *S. aureus* or *P. aeruginosa* and showed that the lenses were effective at eliminating the bacteria [83]. Taken together, these in vivo results show that the lenses can increase corneal bioavailability and be used safely, although human clinical studies will need to be performed. Plus, further animal studies are required which measure the drug concentration over time in the tear film and systemically.

For scaling up production, it is important to consider that the fabrication of vitamin-E-modified lenses involves an additional step of integrating barriers through ethanol soaking in comparison to manufacturing control lenses. However, the loading of the drugs into the lenses is a one-step process, and it does not have the problem of early release while packaged because it is based on an equilibrium loading mechanism and can be stored in drug solution [77]. Vitamin-E lenses are loaded by soaking the lens in drug solution and are only loaded up until equilibrium. This can be done after the monomer extraction and sterilization steps. Plus, it can be done in already commercially available lenses. The simple modification protocol does not induce significant property changes, thus retaining patient compliance and tolerability upon lens insertion. Though cleanroom facilities will require initial investment, manufacturing costs of modified lenses are comparable to those involved for control lens fabrication with only added costs for the vitamin-E and ethanol which is relatively inexpensive. The high efficacy and simplicity of the technology have attracted industrial investment. Another potential drawback for the vitamin-E-loaded lenses is they typically display first-order 'burst' kinetics; this will need to be evaluated and controlled to avoid toxicity and to maintain a clinically relevant dose of therapeutic over time.

Altogether, the major advantages of integrating vitamin-E barriers in the lens matrix include class-1 UV blocking, attenuated drug delivery rates, and improved corneal bioavailability compared to eye drops. Key properties of the commercial lenses were minimally altered especially at low vitamin-E loading percentages; mechanical strength will need to be studied further. A shelf-life study will also need to be done prior to commercialization. Plus, the amount of vitamin-E will need to be optimized specifically for each lens/drug combination in order to achieve clinically relevant release profiles for different ophthalmic diseases.

4. Micro and nanoparticles

4.1. Background

A promising technology for controlled ophthalmic drug delivery are drug-laden particles dispersed in a contact lens gel

matrix. Drugs of interest can be encapsulated into nano or microparticles and dispersed into the polymerizing medium of unreacted monomers. When the lens has completed the polymerization process and is applied to an eye, drug diffuses out of the dispersed particles, travels through the lens matrix, and then reaches the POLTF. Due to the slow rate of diffusion of drug molecules from particles and through the lens matrix, continuous drug release from the lenses can occur for extended periods of days or weeks [24,84]. The particles used for drug encapsulation can be synthesized using a myriad of different materials including polymers [24] and liposomes [85].

Liposomes are one of the most common and well-researched carrier particles for drug delivery. They are celebrated for their highly adaptable properties as well as their ability to stabilize therapeutic species of hydrophobic, hydrophilic, or amphiphilic nature [25,86]. Liposome particles consist of a lipid bilayer which include molecules with hydrophilic heads and hydrophobic tails. This structure is advantageous because hydrophilic drugs can be encapsulated in the aqueous center surrounded by hydrophilic heads. Alternatively, hydrophobic drugs can localize in the region of hydrophobic tails (Figure 3). Liposomes deliver therapeutics using two main mechanisms. Either the particles break down and drug freely diffuses through the gel matrix before releasing into the POLTF or the liposomal particles diffuse through the lens and through the lipid layers of target cells before rupturing and releasing the encapsulated medicament [85,87]. An advantage of these drug-laden particles have over common treatments is that the surface of the liposome can be functionalized with specific ligands to increase intracellular uptake into target cells [88]. Examples of liposomes adaptable

properties include modifications to the particles using surface charge, polymer chains, antibodies, or proteins to ensure stability both in vitro and in vivo [89,90]. Another advantage to these types of particles is that the large aqueous center and lipid bilayer exterior can allow for the incorporation of macromolecules. These macromolecules include drugs, peptides, proteins, plasmic DNA, antisense oligonucleotides, or ribozymes which can be used for gene therapies and regenerative medicine approaches [91].

Multiple studies in the literature have incorporated liposomes into contact lens formulations. A study by Gulsen et al. [85] synthesized HEMA hydrogels with dimyristoyl phosphatidylcholine (DMPC) liposomes and showed that ophthalmic drugs were released for up to 8 days, which is significantly greater than control lenses. Another study by Danion et al. [92] immobilized PEG-biotinylated lipid liposomes to the surface of a commercial contact lens (Hioxifilcon B). First, polyethylenimine was covalently bounded onto the hydroxyl groups; then, NHS-PEG-biotin molecules were bound to the surface amine groups by carbodiimide chemistry. NeutrAvidin was bound to the PEG-biotin layer and the liposomes were bound to the NeutrAvidin. Consecutive layers of NeutrAvidin and liposomes were created. The lenses showed release of carboxyfluorescein for up to 12 days [92].

Nanoparticles and microparticles can also be used for extended drug release from contact lenses. Numerous particle materials have been explored in the literature, and some are reviewed below. Nanoparticle loaded gels may be useful for hydrophobic drugs since they can be encapsulated within the particle instead of directly into the lens. The particles can be used to encapsulate relatively high amounts of therapeutic and provide an additional barrier for release, essentially

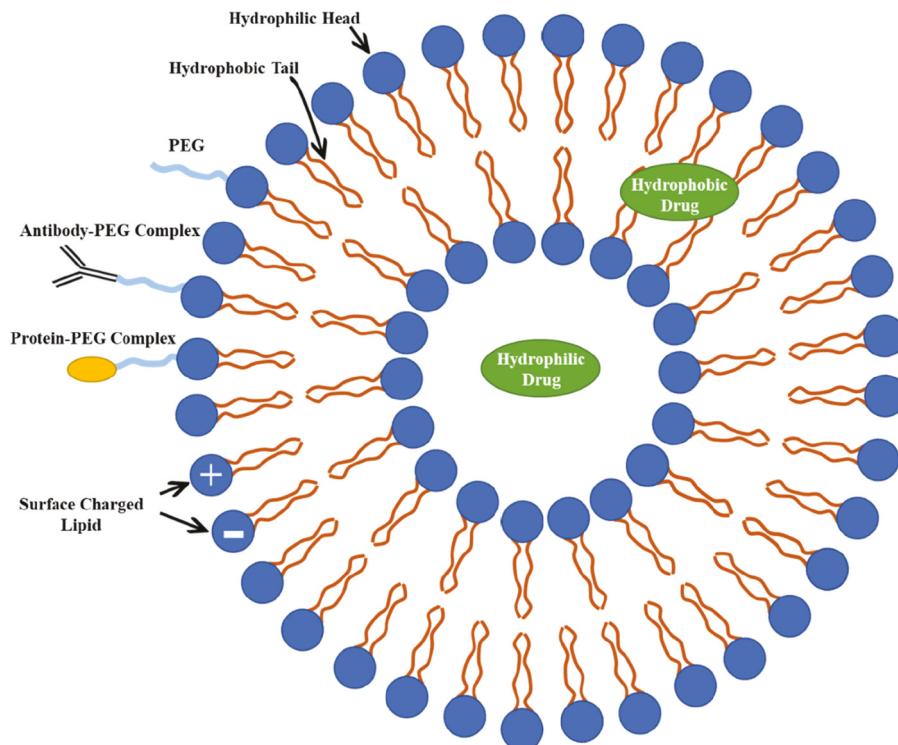


Figure 3. Schematic of liposome with encapsulated hydrophilic or hydrophobic drug.



leading to extended-release periods. For some formulations, stabilized emulsions can be formed to create particles that can then be added to the polymerization mixture. An oil-water (O/W) microemulsion effectively encapsulates hydrophobic drugs within a polymer matrix because the drug readily solubilizes in the oil phase droplets [24]. This study [24] synthesized HEMA lenses with hexadecane particles (with and without silica shell for stabilization) for release of lidocaine. Results showed that drug was released for up to 10 days, and increasing nanoparticle concentration in the gel from 0.23 to 1.2 mg/g did not significantly affect release profiles [24]. Plus, the silica shell was shown to improve stability of the formulation. A study by Jung Jung and Chauhan [84] produced HEMA lenses with dispersed particles made from propoxylated glyceryl triacrylate (PGT) and EGDMA encapsulating timolol for its extended release (2–4 weeks). The goal of this study was to produce lenses that would release drug upon application to the eye and not during prior storage, which was an issue in previous studies due to destabilization of soft particles [24,85]. The results showed first-order release for up to 30 days with a temperature-dependent rate constant [84].

A study by Maulvi et al. [93] incorporated gold nanoparticles into HEMA lenses for increased uptake and release of timolol through absorption of timolol onto the gold nanoparticle surface. The incorporation of gold nanoparticles was shown to improve loading of timolol, but not to prolong its release [93]. A further study by this group [94] incorporated Eudragit S100 (pH-sensitive) nanoparticles-laden into HEMA contact lenses for the sustained release of cyclosporine. The nanoparticle lenses could release cyclosporine up to 6 days where the control lenses could only release up to 4 days [94]. This group also synthesized ketotifen loaded microemulsion laden HEMA hydrogels and silica shell nanoparticle-laden (prepared from microemulsion using octyltrimethoxysilane) HEMA hydrogels for sustained release of ketotifen (anti-allergy drug) [95]. The results showed that silica nanoparticle hydrogels sustained release of ketotifen the longest (up to 9 days), followed by the microemulsion hydrogels (7 days), and the control lenses releasing for the shortest time period (5 days). Further, another study [96] prepared HEMA lenses with ethylcellulose particles for release of timolol; the particle-laden hydrogels had less loading than control gels but were able to extend release from 22 to 48 h with zero-order release [96]. Recently, Maulvi et al. also investigated using Pluronic-F68 for improved loading and release of hydrophobic drug, gatifloxacin [97,98]. Incorporation of Pluronic F68 into the lens with the monomers reduced the optical and physical properties, and therefore this approach should be avoided [97]. However, when Pluronic F68 was added to the packaging solution, the optical and swelling properties of the lens were improved after 7 days of sterilization, indicating that Pluronic F68 can form micelles over time which dissolve the gatifloxacin precipitates within the lens matrix [97]. A follow-up study showed that incorporation of the Pluronic F68 into the monomer solution improved drug loading despite reducing optical and physical properties, and based on these collective results used software to determine the ideal amount of Pluronic F68 which should be used in the packaging and monomer solutions [98].

This study showed that gatifloxacin could be released from silicone-based lenses for up to 72 h, whereas release from the control lenses without Pluronic F68 showed sustained release for up to 48 h [98].

Overall, these studies have shown that liposomes and particles can be incorporated into or immobilized onto contact lenses for the extended release of drugs from the lenses. The release rates vary from days to weeks depending on the drug/particle and hydrogel formulation. Moreover, zero-order and first-order release have been achieved.

4.2. Considerations for commercialization

Using particles to load the drug and control release rates is certainly very appealing. There is considerable literature on using colloidal particles for controlled release that could be adapted into contact lenses. Yet, before commercialization, contact lens properties with incorporated particles must be evaluated, and many past studies have evaluated these properties. A study by Gulsen and Chauhan [24] showed that HEMA hydrogels with incorporated hexadecane-drug particles or hexadecane-drug particles stabilized with a silica shell maintained 66% and 79% transmittance, respectively; this is compared to 88% transmittance for pure HEMA control gels. An additional study that synthesized silica nanoparticle loaded HEMA hydrogels and showed that the nanoparticles did not significantly affect the transmittance, swelling, wettability, or ion permeability compared to control hydrogels, but the presence of particles did affect cell viability [95]. This study also showed that direct drug loading into the hydrogels caused changes in these properties compared to control lenses that were not present with the nanoparticle-loaded lenses [95]. Another study producing HEMA hydrogels with dispersed EGDMA/PGT nanoparticles for timolol delivery showed that the lenses retained optical transparency in the visible light range but had an increase in storage modulus with particle loading [84]. Importantly, the study showed that loading only 4.6% particles resulted in a zero-frequency storage modulus value (0.95 MPa) comparable to commercial lenses [84]. However, it should be noted that leaching of drug can even occur from the nanoparticles with time, as the lens is in aqueous media. Generally, soaking method is used to uptake the nanoparticle inside the lens, so high burst release is observed.

Another study that incorporated gold nanoparticles into HEMA lenses showed that the lenses had minimal increase in swelling compared to control lenses and maintained optical transparency [93]. Further, a study [94] using Eudragit S100 nanoparticles in HEMA lenses to release cyclosporine showed that only a ratio of 1:1 Eudragit S100: cyclosporine created lenses with ideal swelling/optical properties, and with more Eudragit S100 added, the properties of the lens were undesirably altered. This is because nanochannels/cavities were created within the lens when the nanoparticles dissolved, which will be an interesting consideration for all lenses with incorporated particles. The study by Maulvi et al. [96] that synthesized HEMA lenses with ethylcellulose microparticles for the sustained release of timolol showed that the microparticles affected the optical and physical properties of the hydrogels

proportionally to the amount of particles incorporated. This issue could potentially be solved by reducing the particle size to the nanoscale. Recent studies by Maulvi et al. optimized the amount of Pluronic-F68 surfactant used in monomer and packaging solutions for improved transmittance, swelling, and drug loading in lenses for the extended release of gatifloxacin micelles in the lenses since gatifloxacin is a hydrophobic drug which affects these lens properties when loaded [97,98]. These studies show that the material properties of the particles affect the hydrogel properties, but can be tailored to minimize their effect and still be within acceptable values for lens commercialization.

Moreover, animal and clinical studies must be done before commercialization. An *in vivo* study [93] using New Zealand white rabbits was performed with HEMA lenses with incorporated gold nanoparticles for timolol release. The study showed that lenses with 0.025 mM gold nanoparticles had 1685 µg/ml timolol in the tear solution after 1 h of exposure compared to none for the eye drop formulation. The nanoparticle loaded lenses also invoked reduced intraocular pressure for up to 72 h. The authors noted further studies to access the toxicity of the lenses are required with monitoring of heart rate and timolol plasma concentration over time [93]. Another study [94] used New Zealand white rabbits to test HEMA lenses with Eudragit S100 nanoparticles to release cyclosporine and showed that the drug could be released into the tear film for up to 14 days without any obvious histopathological changes in conjunctiva and cornea due to contact lenses. The authors note that to get a better viewpoint of what histopathological changes the nanoparticle-loaded lenses will induce, a long-term study with silicone-based lenses should be performed [94]. Another animal study used Swiss albino mice and New Zealand white rabbits to test HEMA hydrogels with silica nanoparticles loaded for ketotifen (anti-allergy) release [95]. The results showed no abnormal behavior in test groups, no symptoms of ocular irritation such as opacity of the cornea, inflammation or swelling of the iris, conjunctivae redness, chemosis, and discharge were observed after instillation of test extract at various time intervals. Control groups showed redness and chemosis of conjunctivae of grade 1 in the ocular irritation study. The nanoparticle loaded lenses released ketotifen into the tear film up to 10 days [95]. *In vivo* studies of the gatifloxacin-loaded lenses with Pluronic F68 micelles were performed in New Zealand white rabbits and showed that release could be sustained in the tear fluid up to 24 h (with the release amount being less than HPLC detection limit after this timepoint); however, more in-depth studies of this and long-term safety studies are required before commercialization [98]. These studies collectively suggest that particle-loaded lenses can be used for extended release *in vivo*, but more safety and long-term toxicity studies are required before clinical trials can be done.

One drawback of the particle approach is the stability of the particles within the lens. The ability for a particle to retain an encapsulated drug is dependent on its ability to maintain its structure. This structure breaks down chemically over time due to hydrolysis and oxidation [99]. Plus, the past study

showed that dissolution of the particles caused formation of nanocavities which caused optical/physical properties to change in the hydrogel [94], which could cause adverse effects to the patient. Premature release is also a concern when considering the viability of particles as a therapeutic. When a modified lens is applied, the particles in the outermost layer of the lens diffuse to the target region. This is undesirable because it leads to an initial burst release of drug, and reduces the capability of the system to provide extended drug release [24]. To circumvent some of these potential drawbacks, particles may be further modified or go through additional processes. These include surface modifications and coatings, as well as altering the composition of a particle or incorporation of other species [100]. Although these modifications have shown some improvements on stability or release duration, each type of particle may require a unique, intensive optimization process. Plus, it should be noted that many of the past studies on particle-loaded lenses were done with HEMA lenses which do not have adequate oxygen permeability for extended wear, and further studies with silicone-based lenses are needed. Another drawback for commercialization of particle-loaded lenses is the manufacturing will require two steps: one for particle formulation and one for lens formulation.

Another critical challenge with this approach is the potential for release of the incorporated drug during packaging and/or early breakdown of the particles [35]. Some of the problems of early release could be addressed by designing particles to eliminate the release of the drug during packaging. For example, Jung et al. [47] designed polymeric particles with covalently attached timolol through an ester bond, which can be hydrolyzed to release the drug. Storing the lenses in a refrigerator reduced the rate of hydrolysis allowing storage of the lenses for longer than 6 months without any premature drug release. Another study that produced lenses with immobilized liposomes containing carboxyfluorescein showed minimal drug release at 4°C for 1 month [92], showing that lenses can be stored without releasing the drug. Plus, the study that produced HEMA lenses with Eudragit S100 particles showed that the lenses could be stored for 3 months without drug leaching due to the pH-sensitive properties of Eudragit S100 [94]. These results suggest that particle-loaded lenses can be tailored for extended storage without drug leaching. These results display that it is possible to store particle loaded lenses for extended time periods without drug leaching when the system is properly tailored.

Altogether, these studies show that particle-loaded lenses can be used to extend release of drugs while maintaining appropriate optical and physical properties for the hydrogel. Previous studies have also shown that the lenses can be tailored to minimize release of drug during storage for extended time periods. The preliminary *in vivo* studies suggest these lenses can be used for extended release of drugs, although more long-term and safety studies are needed. Many of the previous studies used HEMA lenses which do not have adequate oxygen permeability for extended wear, so more focus should be made on developing these systems in silicone-based lenses. It should also be considered that the release rate in these types of systems will decay, and thus optimization for clinically relevant release curves is

required for each therapeutic. Further, a cost/benefit analysis must be done since the manufacturing of these lenses will require the extra step of particle synthesis.

5. Multilayer lenses and implantation

5.1. Background

Another approach to extend drug release from contact lenses that have been utilized by researchers is to create multi-layer lenses. The layers are made of multiple hydrogel layers with encapsulated drug or include an encapsulated polymeric layer or implant for extended release. An example of this technology is Ciolino et al. developed a multi-layer contact lens by sandwiching a drug-loaded poly-(lactic-co-glycolic acid) (PLGA) film in a HEMA contact lens [36]. PLGA has become a common choice for drug release because it is biodegradable, biocompatible, and has been FDA approved for drug delivery applications [101]. The drug-loaded PLGA films were prepared by a solvent casting method and subsequently incorporated inside poly-HEMA contact lens by placing the drug-loaded film in a mold filled with the monomer, crosslinker, and initiator [36]. The fabricated device had an optically clear central aperture in the center of the PLGA film. Fluorescein and ciprofloxacin were eluted from the device for an extended-release period of roughly a month at a steady rate with a minimal burst release [36]. The authors used the same approach [37] to release econazole, an antifungal, for an extended period (up to 10 days) and was able to inhibit the growth of a fungus in vitro. These layered lenses were also used to release latanoprost for extended duration (up to 8 days) [102].

Similarly, contact lenses with ring-implants have been synthesized for improved drug delivery. In one study, Maulvi et al. [103] developed HEMA-based lenses with a HA ring implant as shown in Figure 4. The HA implant was incorporated to extend the release of HA for treatment of dry eye syndrome. The lenses were designed by analyzing the effects of the amount of EGDMA crosslinker and thickness of the HA implant on HA leaching, 50% toxic dose (t_{50}), and effective ion diffusivity. The optimized lenses showed release up to 9 days in the therapeutic range [103]. The lenses were also tested in vivo as discussed below. In another study, HEMA lenses were modified with HA rings as well as timolol-loaded rings [104]. The therapeutic-loaded rings were prepared from the hydrogel components (HEMA, DMA, TRIS, NVP, EGDMA, and Irgacure D) but the EGDMA (crosslinker) and Irgacure D (photo-initiator) were used in higher amounts in the rings than in the base lens [104]. The lenses showed in vitro release of timolol and HA up to 96 h [104]. A similar study by this research group produced HEMA lenses with implanted rings loaded with moxifloxacin hydrochloride and HA and showed release of the therapeutics for up to 96 h [105]. Further, another study by this group [106] incorporated ethyl cellulose nanoparticles encapsulating timolol maleate into the HEMA/MA ring implant and then incorporated this ring into the HEMA/MA hydrogel lens. This was done to extend release using the nanoparticle system while minimizing the effect of the nanoparticles on the total lens properties. Release data showed timolol to be released within the therapeutic

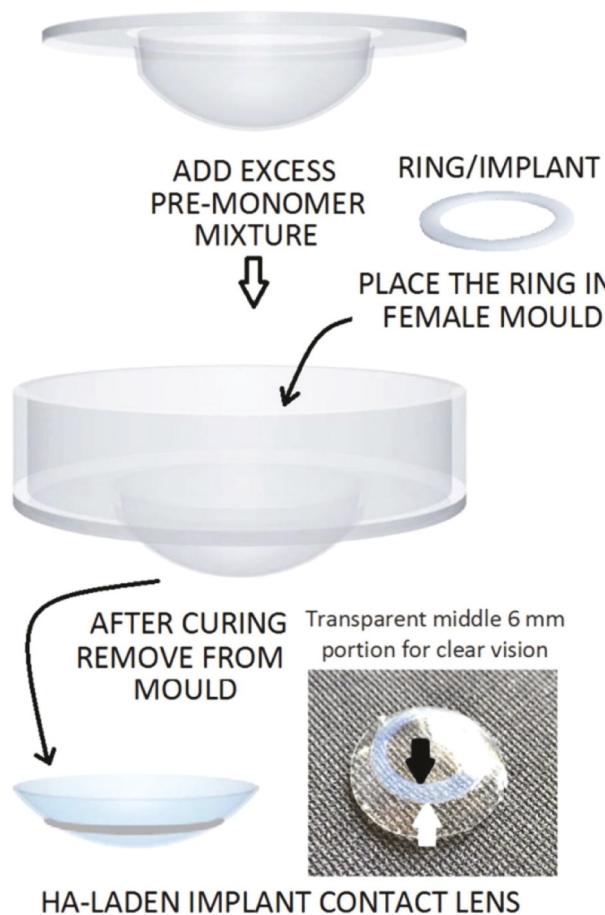


Figure 4. Illustration of fabricating HA-laden implant contact lenses using modified cast molding technique. Blank arrow points to the inner margin of the ring implant and white arrow points the outer margin. Reprinted from Maulvi, F.A., et al., [103] Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome: In vitro and in vivo evaluation, 211–221, Copyright 2017, with permission from Elsevier.

range up to 7 days [106]. The study showed that the combination of the nanoparticle-laden ring into the hydrogel extended release longer than the ring only or nanoparticles only [106]. Recently, another study with a PLGA ring loaded with dexamethasone was inserted into a methafilcon lens for extended delivery to the retina and was shown to extend release up to 7 days [107]. Stability and in vivo studies with these lenses are discussed below in the considerations for commercialization.

A different approach combined the multi-layers with vitamin-E diffusion barriers for release of moxifloxacin hydrochloride [108]. The produced lenses were composed of three-layer bimodal amphiphilic co-networks (β -APCNs) where the center layer contained the drug and the outer layers contain vitamin-E barriers. The β -APCNs were made of a co-continuous morphology of percolating hydrophilic poly(*N,N*-dimethylacrylamide) (PDMAAm) and hydrophobic polydimethylsiloxane (PDMS) networks, in order to improve oxygen permeability. This type of system was shown to eliminate any type of initial diffusional burst release and the resulting release profile was zero-order for up to 30 h (at which timepoint 25% of encapsulated drug was released) [108].

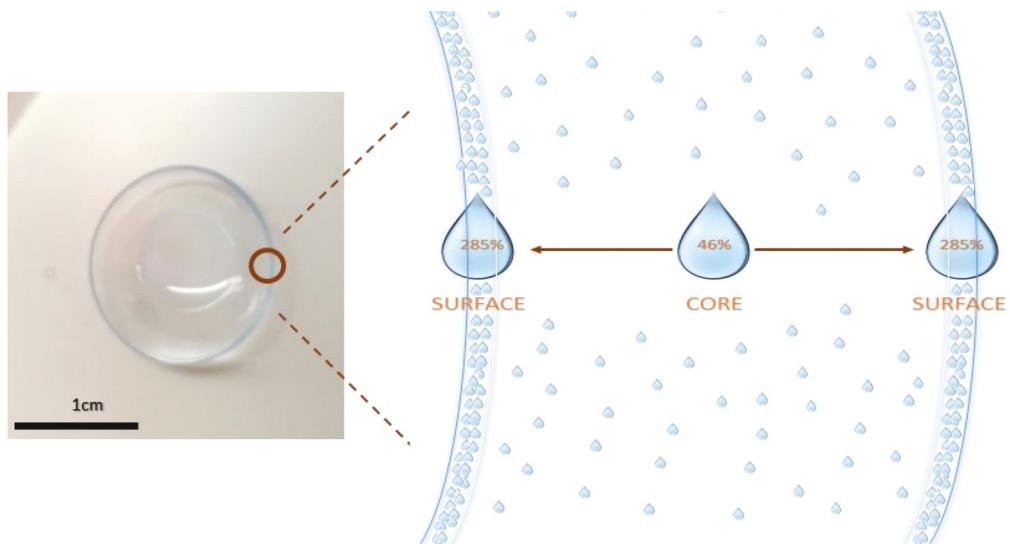


Figure 5. Multi-layer lens structure of commercial lens with dimethylacrylamide surface layers as synthesized in reference [106].

Multi-layer lenses have also been synthesized to improve wettability and protein deposition of current contact lenses. A study by Hu et al. [109] assembled chitosan/HA multi-layers by layer-by-layer deposition on the surface of a contact lens, which increased water retention and decrease protein absorption. The lenses released loaded norfloxacin up to 1 h and timolol in 30 minutes [109]. Thus, although they improve properties of the lenses, the drug release was not significantly improved for extended release. Other studies also have sought to add layers to contact lenses for property improvement, but did not measure drug release from the lenses [110,111]. The structure of the layered lenses from Yu et al. [111] that added dimethylacrylamide surface layers to the commercial lenses can be seen in Figure 5. This demonstrates the layers can potentially have different drug loadings in the future as the water content is different.

Another study used multiple implants in HEMA-based lenses for the multi-drug release of timolol, bimatoprost, and hyaluronic acid at therapeutically relevant doses without high burst release for treatment of glaucoma [112]. The drugs were loaded into three separate implants by adding the required amount of drug to the monomer mixture [Irgacure 184, EGDMA, DMA, NVP, Siloxane, and HEMA (up to 1 ml)]. Then, the implants were cut and placed around the periphery of the lens which was cast in a polypropylene mold [112]. Release was shown for up to 72 h, with a lower burst release compared to the control lens which was loaded by the traditional soaking method [112].

As shown by these studies, considerable efforts have been made using a multitude of layer and implant approaches. The layers and implants indeed can extend drug delivery, but other parameters must be evaluated before commercialization.

5.2. Considerations for commercialization

Considerable issues may arise in the multi-layer lenses as they are often not transparent besides the aperture in the center of

the lens and could potentially reduce oxygen and ionoflux permeability of the lenses. The study that synthesized β -APCNs [108] sought to solve this issue for the multi-layer lenses by using a highly oxygen permeable material. Indeed, the work showed that the lenses maintained appropriate oxygen permeability during drug release and also maintained transparency [108]. Plus, the ring implantation technology explored by Maulvi et al. [103] is intended to extend release while maintaining the overall optical and physical properties of the HEMA lenses. HEMA lenses with HA and timolol ring implants maintained similar swelling characteristics and transparency, and had decreased surface roughness compared to Freshlook® control lenses [104]. However, when the ethylcellulose nanoparticles were incorporated into the rings, the effective ion diffusivity decreased [106]. Plus, as discussed in previous sections, HEMA lenses are not ideal for extended wear, and silicone lenses should be further explored. Another study that incorporated three implants for multi-drug release around the periphery of the lens showed that optical transmittance was maintained [112]. By placing the implants around the periphery, many issues with optical and physical properties of the lenses changing with drug loading can be bypassed.

Storage is another important consideration for manufacturing. The layered lenses with PLGA films inserted could require lyophilization to prevent drug elution or degradation. One study with a PLGA layer showed that the anti-fungal econazole maintained its anti-fungal activity after 24 h following lyophilization [37]. The study by Maulvi et al. [103] that produced HEMA lenses with HA ring implants showed that the lenses could be stored for up to 6 months with insignificant HA leaching. Another study for HEMA lenses with timolol and HA loaded rings showed that the monomer extraction and autoclave steps caused a major amount of timolol to leach from the lenses; thus, the lenses were sterilized using radiation and dehydrated for dry storage [104]. A similar study that produced HEMA lenses with moxifloxacin hydrochloride and HA loaded lenses showed that the moxifloxacin also leached



out and thus these lenses also needed to be sterilized by radiation and dehydrated for storage [105]. Further, the study which incorporated ethyl cellulose nanoparticles into the ring [106] showed negligible release of timolol into the stimulated tear fluid packaging solution after 90 days; however, release profiles were dissimilar from these lenses and the authors proposed packaging the lenses dry would be preferable [106]. Generally, these lenses can thus be stored dry, but there are possible ways to optimize the formulation for wet storage conditions.

Next, animal and clinical studies must be done before commercialization to ensure safety and efficacy of the lenses. Multi-layer lenses composed of a PLGA film with encapsulated latanoprost within the periphery of a methafilcon hydrogel have been tested successfully in a monkey model to reduce intraocular pressure [37]. The study did not measure systemic drug concentrations or measure other parameters for optical safety such as endothelial cell count. More recently, lenses with a PLGA ring insert were shown to deliver dexamethasone to the front and back of the eye for up to a week in New Zealand white rabbits, and moreover inhibited retinal vascular leakage in the posterior segment of the eye [107]. Plus, this study also showed that the lenses could be worn continuously for up to 4 weeks without toxicity [107]. The HA ring implant lenses were tested in vivo in a rabbit model for treatment of dry eye syndrome [103]. The results showed release of HA into the rabbit eye for up to 15 days, and the HA ring lenses showed faster and more complete healing of dry eye syndrome compared to control lenses [103]. New Zealand white rabbits were used for animal testing of the HEMA lenses with implanted HA and timolol loaded rings [104]. The ring-loaded lenses showed presence of timolol in the tear fluid for up to 72 h and showed significant reduction of intraocular pressure compared to control lenses and eye drops [104]; signs of ocular irritation and chemosis were not observed for the study period of 168 h. The authors note heart rate studies will need to be conducted to ensure no systemic side effects are occurring.

New Zealand white rabbits were also used to test the HEMA lenses with HA and moxifloxacin hydrochloride ring implants for treatment of bacterial conjunctivitis [105]. The results showed moxifloxacin to be released into the tear fluid up to 48 h and that the ring-laden lenses had equivalent healing effects to the high dose eye drops [105]. Further, the ethylcellulose nanoparticle loaded ring lenses for release of timolol were tested in a rabbit model and shown to release timolol into the tear fluid for up to 192 h and also to reduce intraocular pressure for this time period [106]. Further animal studies were conducted in New Zealand white rabbits for the multi-drug release of timolol, bimatoprost, and hyaluronic acid from lenses with multiple HEMA implants which showed that the implant-loaded lenses provided a significantly lower burst release and improved drug residence times compared to eyedrop therapy [112]. Plus, these lenses showed reduction of IOP up to 120 h [112]. These in vivo studies collectively show that multi-layer and ring-laden lenses can be efficacious at treating different eye conditions, but in most cases, more safety studies need to be preformed before moving to clinical trials. However, authors of the recent study with the PLGA ring lenses for dexamethasone release note that actions

have been taken toward moving to Phase I/II clinical trials to treat recurrent cystoid macular edema, as their in vivo studies showed adequate efficacy and safety [107]. This is currently listed as a study in the NIH Clinical Trials database.

The multi-layer and implant approach has the advantage and capability of being adapted to any therapeutic, and potentially providing a zero-order release for extended durations. There are however multiple drawbacks including the complex, multistep manufacturing, which is not consistent with the currently used, high throughput manufacturing of contact lenses. Plus, many of the above devices include PLGA in the formulation. PLGA degrades by hydrolysis into acidic monomers and can cause acidic pH change which may cause toxicity [113]. The commercialization barriers for the layered contact lenses include cost of manufacturing and the potential for degradation of the drug layer during packaging. The degradation could be minimized by storing the lens dry and hydrating it just prior to insertion. The transport of other critical molecules including oxygen, ions, and water and comfort enhancers could be impeded by the multi-layers, which could limit the use of this technology, although the preliminary research shows that these parameters can be optimized by varying the synthesis conditions. Plus, further animal studies are needed to show safety of the technology for extended wear.

6. Conclusion

Eye drops continue to be the most common approach for managing ophthalmic diseases. However, low corneal bioavailability and reduced patient compliance of topical treatment demand development of noninvasive drug-eluting devices. In addition to addressing concerns of low bioavailability, the ophthalmic devices should also eliminate potential toxic effects by reducing systemic drug absorption. The location of a contact lens in the immediate vicinity of the cornea make it the optimal device for targeting anterior segment. Both mathematical models and animal studies have demonstrated that about 50% of the drug loaded in the contacts react the cornea compared to about 1–5% for eye drops. In addition to controlled drug elution, drug-eluting contact lenses can also correct vision making it an ideal platform for patients that also need vision correction.

Lenses that uptake drugs purely by the soaking method are only capable of release for a few hours. Different methods such as the ones reviewed in this paper (molecular imprinting, vitamin-E barriers, micro and nanoparticles, and multilayer lenses) have been employed for extending the release of drugs up to days or weeks; however, it is important to note that these may induce undesired changes in the optical and physical properties of the lenses which can cause potential barriers to commercialization. Plus, the lenses all require further in vivo and clinical studies and have important considerations for their scale-up for large-scale manufacturing. In addition to the technological challenges, there are other factors that must be critically analyzed, particularly patient and physician acceptance.

7. Expert opinion

The considerations for commercialization of each modified lens type for extended delivery have been discussed.

Although there are other general issues with contact lenses that need to be addressed before commercialization. There are numerous risks associated with ongoing contact lens wear: microbial keratitis [114], corneal erosion [114], hypoxia [115], hypercapnia [115], dry eye syndrome [116], and conjunctivitis in patients with allergies [117]. Incorporation of drugs that may alleviate these risks could therefore increase chances of successful commercialization. In fact, Johnson & Johnson recently completed positive phase 3 clinical studies for commercial lenses that release the antihistamine ketotifen [118]. It is well known though that many of contact lens wearers drop out each year due to discomfort. Contact lens discomfort has been linked to friction [116]. Thus, approaches to minimize the end of the day discomfort by improving the lubricity and wettability of the surface must be explored and optimized for commercialization. Lenses that release comfort molecules [57] or are modified for higher surface wettability [111] may be able to address this challenge. Thus, lenses that elute drugs to mitigate the issues with contact lens wear may be the answer to the risks associated with contact lenses. Although, for ophthalmic diseases, these molecules may be needed with additional therapeutics for disease treatment, and lens design for multiple therapeutics is generally more complicated.

In addition, there may be issues with public and physician acceptance of the technology, especially for extended wear. Some subjects particularly the elderly make even have difficulties in inserting and taking out the contact lenses. However, a survey of glaucoma physicians suggested that if a drug-eluting contact lenses became available for glaucoma therapy, doctors would consider it as a useful addition to their arsenal of choices for managing the disease in their patients [119]. Plus, it should be noted that promising safety evaluations of drug-loaded lenses for human trials were conducted with soaked contact lenses [120]. This is promising that drug-releasing lenses will soon be commercialized, and the extension of drug release through the reviewed methods will be able to further enhance the utility of this technology.

Importantly, the drug-eluting contact lenses must be evaluated for their optical and physical properties such as water content/swelling, mechanical strength, transparency, and ion and oxygen permeability. All platforms will require optimization to obtain clinically relevant release profiles for each drug and corresponding ophthalmic disease while maintaining these key properties. One barrier for commercialization is indeed the time it takes for optimization of these parameters, followed by animal and clinical studies. The costs associated with animal and clinical studies are not insignificant and thus the potential benefits of the technology must be significant enough for the investment. Many of the reviewed studies had associated animal studies with rabbits or monkeys and were able to show therapeutic efficacy of the drug-eluting lenses. Yet, in many cases, further studies on long-term safety are required before clinical studies can be done. Also, many studies analyzed storage conditions and shelf-life of their drug-eluting lenses, but this must be done for any formulation that is being considered for commercialization. While each technology discussed in this review can be successful, there are some clear differences and pros and cons, which are summarized in Table 1. A downfall of these studies is that protein

adherence and modulus of the lenses were typically not evaluated. Further, many of the studies used HEMA materials which have a relatively low oxygen permeability; a study showed that using silicone-based hydrogels with higher oxygen permeability can be worn for extended time periods up to 4 months without any signs of hypoxia [42].

Moreover, even if drug-eluting contact lenses can be successfully commercialized, they face competition from other devices such as the puncta plugs and the corneal rings. Puncta plugs are rather small in size which considerably limits the mass of drug that can be delivered. Corneal rings have some of the same benefits as contact lenses but may not offer the same increase in bioavailability as contacts. There are also manufacturing issues that need to be considered. Vitamin-E barriers and molecular imprinting techniques will add minimal steps to the manufacturing process, but nano and microparticles as well as multi-layer lenses face the issue of complex manufacturing which may be difficult for scale-up. Even further to consider are the regulatory hurdles that these types of technology face, with acquiring the relevant intellectual property rights to getting the product approved by the FDA.

With an aging world population, there is a growing need for developing more efficient drug delivery systems for treating diseases both in the front and the back of the eyes, and contact lenses are well positioned to play an important role in this field. The future appears to be promising but several challenges remain such as balancing optimization for critical optical and physical lens properties with adequate drug loading and release, processing and storage issues, regulatory hurdles, high costs of clinical studies, and potential lack of acceptance by the elderly.

Funding

The authors acknowledge financial support from the CMMI program of the National Science Foundation (Grant#1762625).

Declaration of interest

A Chauhan is a coinventor on patent US20100330146A1, 'Contact lenses for extended release of bioactive agents containing diffusion attenuators.' The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Glossary of common eye and vision conditions. Am Optom Assoc. <https://www.aoa.org/patients-and-public/eye-and-vision-problems/glossary-of-eye-and-vision-conditions>
2. Gahl WA, Kuehl EM, Iwata F, et al. Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. Mol Genet Metab. 2000;71:100–120.

3. Patel A, Cholkar K, Agrahari V, et al. Ocular drug delivery systems: an overview. *World J Pharmacol.* 2013;2:47–64.
4. Glaucoma facts and stats. *Glaucoma Res Found*; 2017.
5. Hsu K-H, Carbia BE, Plummer C, et al. Dual drug delivery from vitamin E loaded contact lenses for glaucoma therapy. *Eur J Pharm Biopharm.* 2015;94:312–321.
6. Hsu KH, Gause S, Chauhan A. Review of ophthalmic drug delivery by contact lenses. *J Drug Deliv Sci Technol.* 2014;24:123–135.
7. Man Lam S, Tong L, Duan X, et al. Extensive characterization of human tear fluid collected using different techniques unravels the presence of novel lipid amphiphiles 1. *J Lipid Res.* 2014;55:289–298.
8. Zhu H, Chauhan A. A mathematical model for ocular tear and solute balance. *Curr Eye Res.* 2005;30:841–854.
9. Gause S, Hsu KH, Shafor C, et al. Mechanistic modeling of ophthalmic drug delivery to the anterior chamber by eye drops and contact lenses. *Adv Colloid Interface Sci.* 2016;233:139–154.
10. Tripathi BJ, Tripathi RC, Kolli SP. Cytotoxicity of ophthalmic preservatives on human corneal epithelium. *Lens Eye Toxic Res.* 1992;9:361–375.
11. Watsky MA, Jablonski MM, Edelhauser HF. Comparison of conjunctival and corneal surface areas in rabbit and human. *Curr Eye Res.* 1988;7:483–486.
12. Prausnitz MR, Noonan JS. Permeability of cornea, sclera, and conjunctiva: a literature analysis for drug delivery to the eye. *J Pharm Sci.* 1998;87:1479–1488.
13. Frishman WH, Kowalski M, Nagnur S, et al. Cardiovascular considerations in using topical, oral, and intravenous drugs for the treatment of glaucoma and ocular hypertension: focus on β -adrenergic blockade. *Hear Dis.* 2001;3:386–397.
14. Hosoya KI, Lee VHL, Kim KJ. Roles of the conjunctiva in ocular drug delivery: a review of conjunctival transport mechanisms and their regulation. *Eur J Pharm Biopharm.* 2005;60:227–240.
15. Saettone MF, Salminen L. Ocular inserts for topical delivery. *Adv Drug Deliv Rev.* 1995;16:95–106.
16. Leydhecker W. Ocuser. Synopsis of a round-table discussion. *Klin Monbl Augenheilkd.* 1975;167:917–918.
17. Alvarez-Lorenzo C, Hiratani H, Concheiro A. Contact lenses for drug delivery: achieving sustained release with novel systems. *Am J Drug Deliv.* 2006;4:131–151.
18. Kim J, Conway A, Chauhan A. Extended delivery of ophthalmic drugs by silicone hydrogel contact lenses. *Biomaterials.* 2008;29:2259–2269.
19. Peng CC, Burke MT, Chauhan A. Transport of topical anesthetics in vitamin E loaded silicone hydrogel contact lenses. *Langmuir.* 2011;28:1478–1487.
20. Peng -C-C, Ben-Shlomo A, Mackay EO, et al. Drug delivery by contact lens in spontaneously glaucomatous dogs. *Curr Eye Res.* 2012;37:204–211.
21. Karlgard CCS, Wong NS, Jones LW, et al. In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA hydrogel contact lens materials. *Int J Pharm.* 2003;257:141–151.
22. Dutta D, Cole N, Kumar N, et al. Broad spectrum antimicrobial activity of melimine covalently bound to contact lenses. *Investig Ophthalmol Vis Sci.* 2013;54:175–182.
23. Willcox MDP, Hume EBH, Aliwarga Y, et al. A novel cationic-peptide coating for the prevention of microbial colonization on contact lenses. *J Appl Microbiol.* 2008;105:1817–1825.
24. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. *Investig Ophthalmol Vis Sci.* 2004;45:2342–2347.
25. Bourlais CL, Acar L, Zia H, et al. Ophthalmic drug delivery systems—recent advances. *Prog Retin Eye Res.* 1998;17:33–58.
26. McNamara NA, Polse KA, Brand RJ, et al. Tear mixing under a soft contact lens: effects of lens diameter. *Am J Ophthalmol.* 1999;127:659–665.
27. Creech JL, Chauhan A, Radke CJ. Dispersive mixing in the posterior tear film under a soft contact lens. *Ind Eng Chem Res.* 2001;40:3015–3026.
28. Xinming L, Yingde C, Lloyd AW, et al. Polymeric hydrogels for novel contact lens-based ophthalmic drug delivery systems: a review. *Contact Lens Anterior Eye.* 2008;31:57–64.
29. Neece CW. Contact lenses for ocular drug delivery. USA; 1972. p. 1–4. **• This is the original patent that first proposed using contact lenses as drug delivery systems.**
30. Sedláček J. Possibility of the application of ophthalmic drugs with the use of gel contact lenses. *Cesk Oftalmol.* 1965;21:509–512.
31. Hillman JS. Management of acute glaucoma with pilocarpine-soaked hydrophilic lens. *Br J Ophthalmol.* 1974;58:674–679.
32. Ruben M, Watkins R. Pilocarpine dispensation for the soft hydrophilic contact lens. *Br J Ophthalmol.* 1975;59:455–458.
33. Schultz CL, Nunez IM, Silor DL, et al. Contact lens containing a leachable absorbed material. Johnson and Johnson Vision Care Inc; 1995.
34. Dixon P, Ghosh T, Mondal K, et al. Controlled delivery of pirenzipine through vitamin E-loaded contact lens ameliorates corneal inflammation. *Drug Deliv Transl Res.* 2018;8:1114–1126.
35. Fathalla D, Soliman GM, Fouad EA. DLatanoprost liposomes for glaucoma treatment development and in vitro/in vivo evaluation of liposomal gels for the sustained ocular delivery of latanoprost. *J Clin Exp Ophthalmol.* 2015;6:390.
36. Ciolino JB, Hoare TR, Iwata NG, et al. A drug-eluting contact lens. *Invest Ophthalmol Vis Sci.* 2009;50:3346–3352.
37. Ciolino JB, Hudson SP, Mobbs AN, et al. A prototype antifungal contact lens. *Invest Ophthalmol Vis Sci.* 2011;52:6286–6291.
38. Paradiso P, Galante R, Santos L, et al. Comparison of two hydrogel formulations for drug release in ophthalmic lenses. *J Biomed Mater Res Part B Appl Biomater.* 2014;102:1170–1180.
39. Paradiso P, Serro AP, Saramago B, et al. Controlled release of antibiotics from vitamin E-loaded silicone-hydrogel contact lenses. *J Pharm Sci.* 2016;105:1164–1172.
40. Boone A, Hui A, Jones L. Uptake and release of dexamethasone phosphate from silicone hydrogel and group I, II, and IV hydrogel contact lenses. *Eye Contact Lens Sci Clin Pract.* 2009;35:260–267.
41. Lim L, Loughnan M, Sullivan L. Microbial keratitis associated with extended wear of silicone hydrogel contact lenses. *Br J Ophthalmol.* 2002;86:355–357.
42. Fonn D, MacDonald KE, Richter D, et al. The ocular response to extended wear of a high Dk silicone hydrogel contact lens. *Clin Exp Optom.* 2002;85:176–182.
43. Stark A. U.S. Food and Drug Administration [Internet]. FDA clear. first contact lens with Light. Technol. 2018. Available from: <https://www.fda.gov/news-events/press-announcements/fda-clears-first-contact-lens-light-adaptive-technology>
44. Rosa Dos Santos JF, Alvarez-Lorenzo C, Silva M, et al. Soft contact lenses functionalized with pendant cyclodextrins for controlled drug delivery. *Biomaterials.* 2009;30:1348–1355.
45. Jain R, Shastri J. Study of ocular drug delivery system using drug-loaded liposomes. *Int J Pharm Investig.* 2011;1:35–41.
46. Sekar P, Chauhan A. Effect of vitamin-E integration on delivery of prostaglandin analogs from therapeutic lenses. *J Colloid Interface Sci.* 2019;539:457–467.
47. Jung HJ, Abou-Jaoude M, Carbia BE, et al. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. *J Control Release.* 2013;165:82–89.
48. Braga MEM, Costa VP, Pereira MJT, et al. Effects of operational conditions on the supercritical solvent impregnation of acetazolamide in Balafilcon A commercial contact lenses. *Int J Pharm.* 2011;420:231–243.
49. Guzman-Aranguez A, Colligris B, Pintor J. Contact lenses: promising devices for ocular drug delivery. *J Ocul Pharmacol Ther.* 2013;29:189–199. **• This review article covers relevant areas including methods for extending drug release from contact lenses, critical lens properties, and ophthalmic diseases requiring drug intervention.**
50. Maulvi FA, Soni TG, Shah DO. A review on therapeutic contact lenses for ocular drug delivery. *Drug Deliv.* 2016;23:3017–3026.

51. Hu X, Hao L, Wang H, et al. Hydrogel contact lens for extended delivery of ophthalmic drugs. *Int J Polym Sci*. 2011;2011:814163.

52. Clegg JR, Wechsler ME, Peppas NA. Vision for functionally decorated and molecularly imprinted polymers in regenerative engineering. *Regen Eng Transl Med*. 2017;3:166–175.

53. Byrne ME, Park K, Peppas NA. Molecular imprinting within hydrogels. *Adv Drug Deliv Rev*. 2002;1:149–161.

54. Singh B, Chauhan N, Sharma V. Design of molecular imprinted hydrogels for controlled release of cisplatin: evaluation of network density of hydrogels. *Ind Eng Chem Res*. 2011;50:13742–13751.

55. Ribeiro A, Veiga F, Santos D, et al. Receptor-based biomimetic NVP/DMA contact lenses for loading/eluting carbonic anhydrase inhibitors. *J Memb Sci*. 2011;383:60–69.

56. Hiratani H, Alvarez-Lorenzo C. The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. *Biomaterials*. 2004;25:1105–1113.

57. Ali M, Byrne ME. Controlled release of high molecular weight hyaluronic acid from molecularly imprinted hydrogel contact lenses. *Pharm Res*. 2009;26:714–726.

58. Tieppo A, White CJ, Paine AC, et al. Sustained in vivo release from imprinted therapeutic contact lenses. 2012.

59. Hiratani H, Mizutani Y, Alvarez-Lorenzo C. Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities. *Macromol Biosci*. 2005;5:728–733.

60. Alvarez-Lorenzo C, Hiratani H, Gómez-Amoza JL, et al. Soft contact lenses capable of sustained delivery of timolol. *J Pharm Sci*. 2002;91:2182–2192.

61. Yañez F, Chauhan A, Concheiro A, et al. Timolol-imprinted soft contact lenses: influence of the template: functional monomer ratio and the hydrogel thickness. *J Appl Polym Sci*. 2011;122:1333–1340.

62. Wulff G. Molecular imprinting in cross-linked materials with the aid of molecular templates—a way towards artificial antibodies. *Angew Chemie Int Ed English*. 1995;34:1812–1832.

63. Hiratani H, Fujiwara A, Tamiya Y, et al. Ocular release of timolol from molecularly imprinted soft contact lenses. *Biomaterials*. 2005;26:1293–1298.

- This article includes the synthesis of molecularly imprinted DEAA lenses modified with MAA and EGDMA for timolol release and tests the lenses in an *in vivo* model.

64. Tieppo A, Pate KM, Byrne ME. In vitro controlled release of an anti-inflammatory from daily disposable therapeutic contact lenses under physiological ocular tear flow. *Eur J Pharm Biopharm*. 2012;81:170–177.

65. Andrade-Vivero P, Fernandez-Gabriel E, Alvarez-Lorenzo C, et al. Improving the loading and release of NSAIDs from pHEMA hydrogels by copolymerization with functionalized monomers. *J Pharm Sci*. 2007;96:802–813.

66. Hui A, Sheardown H, Jones L, et al. Acetic and acrylic acid molecular imprinted model silicone hydrogel materials for ciprofloxacin-HCl delivery. *Materials (Basel)*. 2012;5:85–107.

67. White CJ, Dipasquale SA, Byrne ME, et al. Controlled release of multiple therapeutics from silicone hydrogel contact lenses. *Optom Vis Sci*. 2016;93:377–386.

68. Malakooti N, Alexander C, Alvarez-Lorenzo C. Imprinted contact lenses for sustained release of polymyxin b and related antimicrobial peptides. *J Pharm Sci*. 2015;104:3386–3394.

69. Shoravi S, Olsson GD, Karlsson BCG, et al. On the influence of crosslinker on template complexation in molecularly imprinted polymers: a computational study of prepolymerization mixture events with correlations to template-polymer recognition behavior and NMR spectroscopic studies. *Int J Mol Sci*. 2010;15:10622–10634.

70. Venkatesh S, Saha J, Pass S, et al. Transport and structural analysis of molecular imprinted hydrogels for controlled drug delivery. *Eur J Pharm Biopharm*. 2008;69:852–860.

71. White CJ, McBride MK, Pate KM, et al. Extended release of high molecular weight hydroxypropyl methylcellulose from molecularly imprinted, extended wear silicone hydrogel contact lenses. *Biomaterials*. 2011;32:5698–5705.

72. White C. Extended release of macromolecular comfort agents from silicone hydrogel contact lenses. Auburn University; 2011.

73. Alvarez-Lorenzo C, Yañez F, Barreiro-Iglesias R, et al. Imprinted soft contact lenses as norfloxacin delivery systems. *J Control Release*. 2006;113:236–244.

74. Ohta Y. Possibility of clinical application of vitamin E to cataract prevention. *J Clin Biochem Nutr*. 2004;35:35–45.

75. Peng -C-C, Chauhan A. Extended cyclosporine delivery by silicone-hydrogel contact lenses. *J Control Release*. 2011;154:267–274.

76. Peng -C-C, Burke MT, Carbia BE, et al. Extended drug delivery by contact lenses for glaucoma therapy. *J Control Release*. 2012;162:152–158.

77. Peng CC, Kim J, Chauhan A. Extended delivery of hydrophilic drugs from silicone-hydrogel contact lenses containing Vitamin E diffusion barriers. *Biomaterials*. 2010;31:4032–4047.

- This article investigates vitamin-E diffusion attenuations in commercial lenses for the extended release of multiple ophthalmic drugs including timolol, fluconazole, and dexamethasone 21-disodium phosphate.

78. Kim J, Peng CC, Chauhan A. Extended release of dexamethasone from silicone-hydrogel contact lenses containing vitamin E. *J Control Release*. 2010;148:110–116.

79. Dixon P, Fentzke RC, Bhattacharya A, et al. In vitro drug release and in vivo safety of vitamin E and cysteamine loaded contact lenses. *Int J Pharm*. 2018;544:380–391.

80. Hsu K-H, Lazon de la Jara P, Ariyavidana A, et al. Release of betaine and dexamethasone from vitamin E modified silicone-hydrogel contact lenses. *Curr Eye Res*. 2015;40:267–273.

81. Hsu KH, Fentzke RC, Chauhan A. Feasibility of corneal drug delivery of cysteamine using vitamin E modified silicone hydrogel contact lenses. *Eur J Pharm Biopharm*. 2013;85:531–540.

82. Torres-Luna C, Hu N, Tammareddy T, et al. Extended delivery of non-steroidal anti-inflammatory drugs through contact lenses loaded with Vitamin E and cationic surfactants. *Contact Lens Anterior Eye*. 2019;42:546–552.

83. Ubani-Ukoma U, Gibson D, Schultz G, et al. Evaluating the potential of drug eluting contact lenses for treatment of bacterial keratitis using an ex vivo corneal model. *Int J Pharm*. 2019;565:499–508.

84. Jung HJ, Chauhan A. Temperature sensitive contact lenses for triggered ophthalmic drug delivery. *Biomaterials*. 2012;33:2289–2300.

85. Gulsen D, Li CC, Chauhan A. Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. *Curr Eye Res*. 2005;30:1071–1080.

- This study synthesizes HEMA hydrogels with DMPC liposomes for extended release of ophthalmic drugs up to 8 days, which is significantly greater than control lenses.

86. Singh K, Mezei M. Liposomal ophthalmic drug delivery system I. Triamcinolone acetonide. *Int J Pharm*. 1983;16:339–344.

87. Sercombe L, Veerati T, Moheimani F, et al. Advances and challenges of liposome assisted drug delivery. *Front Pharmacol*. 2015;6:286.

88. Monteiro N, Martins A, Reis RL, et al. Liposomes in tissue engineering and regenerative medicine. *J R Soc Interface*. 2014;11:20140459.

89. Meisner D, Mezei M. Liposome ocular delivery systems. *Adv Drug Deliv Rev*. 1995;16:75–93.

90. Agarwal R, Iezhitsa I, Agarwal P, et al. Liposomes in topical ophthalmic drug delivery: an update. *Drug Deliv*. 2014;23:1–17.

91. Ulrich AS. Biophysical aspects of using liposomes as delivery vehicles. *Biosci Rep*. 2002;22:129–150.

92. Danion A, Brochu H, Martin Y, et al. Fabrication and characterization of contact lenses bearing surface-immobilized layers of intact liposomes. *J Biomed Mater Res A*. 2007;82A:41–51.

93. Maulvi FA, Patil RJ, Desai AR, et al. Effect of gold nanoparticles on timolol uptake and its release kinetics from contact lenses: in vitro and in vivo evaluation. *Acta Biomater*. 2019;86:350–362.

94. Maulvi FA, Choksi HH, Desai AR, et al. pH triggered controlled drug delivery from contact lenses: addressing the challenges of drug

leaching during sterilization and storage. *Colloids Surf B Biointerfaces*. 2017;157:72–82.

- **This study synthesized HEMA hydrogels with Eudragit S100 (pH-sensitive) nanoparticles incorporated for the extended release of cyclosporine, and tested the synthesized lenses in a New Zealand white rabbit model showing release into the tear film for up to 14 days.**

95. Maulvi FA, Mangukiya MA, Patel PA, et al. Extended release of ketotifen from silica shell nanoparticle-laden hydrogel contact lenses: in vitro and in vivo evaluation. *J Mater Sci Mater Med*. 2016;27:113.

96. Maulvi FA, Soni TG, Shah DO. Extended release of timolol from ethyl cellulose microparticles laden hydrogel contact lenses. *Open Pharm Sci J*. 2015;2:1–12.

97. Maulvi FA, Parmar RJ, Shukla MR, et al. Plackett-Burman design for screening of critical variables and their effects on the optical transparency and swelling of gatifloxacin-pluronic-loaded contact lens. *Int J Pharm*. 2019;566:513–519.

98. Maulvi FA, Parmar RJ, Desai AR, et al. Tailored gatifloxacin Pluronic® F-68-loaded contact lens: addressing the issue of transmittance and swelling. *Int J Pharm*. 2020;581:119279.

99. Toh M-R, Chiu GNC. Liposomes as sterile preparations and limitations of sterilisation techniques in liposomal manufacturing. *Asian J Pharm Sci*. 2013;8:88–95.

100. Nasr FH, Khoei S, Dehghan MM, et al. Preparation and evaluation of contact lenses embedded with polycaprolactone-based nanoparticles for ocular drug delivery. *Biomacromolecules*. 2016;17:485–495.

101. Choi JS, Seo K, Yoo JW. Recent advances in PLGA particulate systems for drug delivery. *J Pharm Investigig*. 2012;42:155–163.

102. Ciolino JB, Ross AE, Tulsan R, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. *Ophthalmology*. 2016;123:2085–2092.

103. Maulvi FA, Shaikh AA, Lakdawala DH, et al. Design and optimization of a novel implantation technology in contact lenses for the treatment of dry eye syndrome: in vitro and in vivo evaluation. *Acta Biomater*. 2017;53:211–221.

- **This study developed HEMA based lenses with a HA ring implant for the extended release of HA for treatment of dry eye syndrome. In a rabbit model, the lenses were shown to extend release up to 15 days.**

104. Desai AR, Maulvi FA, Pandya MM, et al. Co-delivery of timolol and hyaluronic acid from semi-circular ring-implanted contact lenses for the treatment of glaucoma: in vitro and in vivo evaluation. *Biomater Sci*. 2018;1580–1591. DOI:10.1039/C8BM00212F

105. Maulvi FA, Singhania SS, Desai AR, et al. Contact lenses with dual drug delivery for the treatment of bacterial conjunctivitis. *Int J Pharm*. 2018;548:139–150.

106. Maulvi FA, Lakdawala DH, Shaikh AA, et al. In vitro and in vivo evaluation of novel implantation technology in hydrogel contact lenses for controlled drug delivery. *J Control Release*. 2016;226:47–56.

107. Ross AE, Bengani LC, Tulsan R, et al. Topical sustained drug delivery to the retina with a drug-eluting contact lens. *Biomaterials*. 2019;217:119285.

108. Guzman G, Es-haghi SS, Nugay T, et al. Zero-order antibiotic release from multilayer contact lenses: nonuniform drug and diffusivity distributions produce constant-rate drug delivery. *Adv Healthc Mater*. 2017;6:1600775.

109. Hu X, Tan H, Li D, et al. Surface functionalisation of contact lenses by CS/HA multilayer film to improve its properties and deliver drugs. *Mater Technol Adv Perform Mater*. 2014;29:8–13.

110. Lin CH, Cho HL, Yeh YH, et al. Improvement of the surface wettability of silicone hydrogel contact lenses via layer-by-layer self-assembly technique. *Colloids Surf B Biointerfaces*. 2015;136:735–743.

111. Yu Y, Macoon R, Chauhan A. Improving wettability and lubricity of commercial contact lenses by polymerizing a thin film of dimethylacrylamide. *Colloids Surf A Physicochem Eng Aspects*. 2019;583:123974.

112. Desai AR, Maulvi FA, Desai DM, et al. Multiple drug delivery from the drug-implants-laden silicone contact lens: addressing the issue of burst drug release. *Mater Sci Eng C*. 2020;112:110885.

113. Fu K, Pack DW, Klibanov AM, et al. Visual evidence of acidic environment within degrading poly(lactic-co-glycolic acid) (PLGA) microspheres. *Pharm Res*. 2000;17:100–106.

114. Markoulli M, Papas E, Cole N, et al. Corneal erosions in contact lens wear. *Contact Lens Anterior Eye*. 2012;35:2–8.

115. Mandell RB. Contact lens practice. 4th ed. Springfield (IL): Charles C Thomas Pub Ltd; 1988.

116. Markoulli M, Kolanu S. Contact lens wear and dry eyes: challenges and solutions. *Clin Optom*. 2017;9:41–48.

117. Urgacz A, Mrukwa E, Gawlik R. Adverse events in allergy sufferers wearing contact lenses. *Postep Dermatolgi Alergol*. 2015;32:204–209.

118. Sekston A. Johnson & Johnson Vision [Internet]. Johnson Johnson Vision's Investigig. Antihistamine-releasing contact lens demonstr. Posit. Phase 3 Results. 2019. Available from: <https://www.jjvision.com/press-release/johnson-johnson-visions-investigational-antihistamine-releasing-contact-lens>

- **Johnson & Johnson recently completed positive phase 3 clinical studies for commercial lenses that release the antihistamine ketotifen.**

119. Taniguchi EV, Kalout P, Pasquale LR, et al. Clinicians' perspectives on the use of drug-eluting contact lenses for the treatment of glaucoma. *Ther Deliv*. 2014;5:1077–1083.

120. Schultz CL, Poling TR, Mint JO. A medical device/drug delivery system for treatment of glaucoma. *Clin Exp Optom*. 2009;92:343–348.