Expert Opinion

Molecularly imprinted therapeutic contact lenses

Charles J White & Mark E Byrne†
Auburn University, Department of Chemical Engineering, Biomimetic and Biohybrid Materials, Biomedical Devices, and Drug Delivery Laboratories, Auburn, AL 36849, USA

Importance of the field: There exists a considerable unmet need for more efficacious delivery of ocular therapeutics. Contact lenses have been developed with high loading and controllable sustained release to overcome limited patient compliance and significant ocular transport limitations. This can best be achieved by extending and controlling the residence time of drugs on the eye surface and thereby limiting drug loss by lacrimation, drainage and non-productive absorption.

Areas covered in the review: Within hydrogels, molecular imprinting can be used to create memory for template molecules embedded within a flexible macromolecular network. Control in therapeutic loading and delay of release have been demonstrated with careful attention to the functional monomer/template ratio, the diversity of functional monomers, and the polymer backbone and network structure. Experimental work has also confirmed that macromolecular memory and not structural differences or phenomena are responsible for delayed drug release kinetics compared with non-imprinted systems. A therapeutically relevant amount of drug can be loaded for release to occur over multiple days, which allows the technique to be applied to daily-wear and extended-wear contact lenses.

What the reader will gain: The focus of this article is to review the emerging field of molecularly imprinted contact lenses and highlight significant accomplishments, trends, as well as future strategies and directions.

Take home message: In the past 8 years, molecular imprinting has been used to produce therapeutic contact lenses with enhanced loading and delayed release. Progress in the field has mostly included low-molecular-weight therapeutics such as anti-glaucoma, antihistamine, antibiotic and anti-inflammatory therapeutics used to treat anterior eye disorders. Recently, high molecular weight comfort molecules have also been successfully demonstrated. Current methods can produce lenses of suitable thickness, water content, and mechanical and optical properties compared with commercial lenses on the market today.

Keywords: antibiotic, antihistamine, anti-inflammatory, beta blocker, combination device, comfort molecule, contact lens, controlled release, drug delivery, macromolecular memory, molecular imprinting, ophthalmology

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1. Introduction: delivering ocular therapeutics by means of contact lenses

The concept of delivering ocular medication by means of contact lenses can be found in the first patent describing the production of soft contact lenses. In 1965, Otto Wichterle and Drahoslav Lim patented a process of creating soft contact lenses by copolymerization of 2-hydroxyethylmethacrylate and ethylene

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Article highlights.

- Hydrogel contact lenses provide an excellent platform to release ocular medication.
- Overcoming the natural barriers of the eye, imprinted contact lenses provide a reservoir of therapeutic on the surface of the eye and control drug release, leading to greater efficiency and effectiveness in topical eye therapy.
- Molecular imprinting can create macromolecular memory for a therapeutic within a flexible polymer network and delay the transport of drug from the matrix through interaction of the drug with functional groups organized within the network.
- Exciting progress in the field has occurred, and therapeutic contact lenses produced by means of molecular imprinting demonstrate higher therapeutic loading and controlled, extended release. Experimental work has included several classes of molecules, including anti-glaucoma, antihistamine, antibiotic, anti-inflammatory and comfort agents.
- The value proposition of imprinted contact lenses is high. Research and development is of significant interest where major emphasis will involve integration into current and future products as well as continued focus on key parameters to overcome hurdles in the rational design and engineering of imprinted lenses.

This box summarizes key points contained in the article.

glycol dimethacrylate [1]. This work significantly altered the direction of the field, with previous efforts in the late 1940s and 1950s focused primarily on the production of hard contact lenses from polymers such as poly(methyl methacrylate). Wichterle and Lim realized that tissue compatibility was a significant problem and that the 'question of structural similarity with the tissue' had not been adequately answered [2]. Their design metrics correctly involved the following: i) a structure with desired and controllable water content; ii) an inert structure resistant to degradation and unfavorable reactions; and iii) a structure with permeability for metabolites [2]. Soft contact lenses had enormous benefits, such as increased comfort with a high water-content structure similar to natural tissue and a better fit, as well as increased transport of oxygen leading to much higher corneal tissue oxygen levels. As early as 1956, Wichterle and Lim were synthesizing and testing hydrophilic, weakly crosslinked hydrogels in ocular applications such as ocular filling after enucleation of the eye and in the manufacturing of contact lenses [2,3].

It is quite notable that within Wichterle and Lim's patent they refer to a drug-soaked contact lens and state 'bacteriostatic, bacteriocidal or otherwise medicinally active substances such as antibiotics may be dissolved in the aqueous constituent of the hydrogels to provide medication over an extended period via diffusion' [1]. Also, in 1965, a separate paper was published by Sedlavek that involved a drug-eluting lens [4]. However, there is much evidence that the notion of a dissolved therapeutic within a dressing placed on the surface of the eye has been around for a much longer period of time. For example, honey-soaked linen was used by physicians in ancient Rome as an ophthalmic dressing in the treatment of disease [5], and ancient Egyptians used cloth bandages and patches applied with drug formulation as treatment for ocular swelling and infections [6,7]. Of course, these were not combination devices, such as Wichterle and Lim suggested, but they did provide a drug formulation reservoir on the surface of the eye.

One of the biggest obstacles to using the fluid in the aqueous portion of a polymer gel is maintaining a significant concentration of drug within the fluid to have a therapeutically relevant effect, which is ultimately limited by the solubility and partitioning of the drug. The other obstacle is poor control over the release profile. For these reasons, drug-soaked contact lenses, which have low drug loading and poor control over drug release [8], have not become a clinical or commercial success.

Thus, rationally designing hydrogels to increase drug partitioning or loading by means of polymer adsorption as well as providing control over the release profile are paramount to the development of lenses for ophthalmic drug delivery. Only within the last 8 years has drug loading and control over drug release from soft contact lenses become a reality. One method that has a high probability of success and has experimentally demonstrated the highest drug loading and release duration uses methods adopted from the field of molecular imprinting. Other methods include emulsion- [9,10], liposomal- [11] and particulate- [12] containing lenses as well as ion-exchange lenses [13,14].

Molecular imprinting is a polymer synthesis technique exploiting template-mediated polymerization mechanisms to produce synthetic macromolecular networks with tailored affinity, capacity and selectivity for a template molecule. Most work so far has involved highly crosslinked structures, not weakly crosslinked systems such as hydrogels [15,16].

Molecular imprinting can create macromolecular memory for a therapeutic within a flexible polymer network and delay the transport of drug from the matrix through interaction of the drug with functional groups organized within the network. This paper reviews the emerging field of imprinted contact lenses with a specific focus on papers describing imprinted lenses or films for ocular therapeutics with significant potential for use as contact lenses. For a more broad review of molecular imprinting within hydrogels, the authors recommend the references [15,16].

2. Efficient delivery of ocular medications

In the ocular drug market, there is a considerable unmet need and strong motivation for more efficacious delivery of ocular therapeutics. From a clinical perspective, the challenge is to provide medication conveniently, non-invasively and in therapeutically relevant concentrations for long times with minimal transfer of drug to the systemic circulation.

Topical, targeted therapy to the eye can be best achieved by: i) extending the residence time or duration of drugs on the surface of the eye; and/or by ii) increasing drug transport through ocular barriers such as the cornea, sclera and conjunctiva [17]. The concentration of drug reaching the desired site of action can be significantly improved by altering the kinetics of drug administration, removal and/or absorption. Molecularly imprinted lenses can lead to an increased and controlled residence time of the drug on the surface of the eye. Other strategies to overcome drug removal at the ocular surface have included emulsions [18-21], suspensions [22-25] and liposome carriers [26], viscosity enhancers [27-29], mucoadhesive polymers [30-34], *in situ* gel-forming systems [35-38] and punctal plugs [39-41]. These methods either provide a dispersed reservoir of drug within a polymer or decrease the exiting ocular tear flow rate.

For permeation enhancement through ocular membranes or absorption strategies as well as additional information on the aforementioned methods, the reader is directed to the ocular administration and delivery reviews [17,42-47,103] and ocular pharmacokinetics texts [48,49].

The caveat of topical delivery is that bioavailability tends to be low owing to various factors and ocular protective mechanisms. The eye is pharmacokinetically isolated from the rest of the anatomy, which makes successful drug delivery difficult. Protective mechanisms lead to poor drug absorption on the surface of the eye despite it being a very accessible organ to treat topically. As a result, ocular bioavailability of drugs applied topically to the eye is very poor, with < 1 – 7% of the applied drug being absorbed, and the rest entering the systemic circulation [43,48]. Tear drainage and to some extent the absorption through the eyelids and adnexa lead to less drug on the surface of the eye available to transport through the cornea, conjunctiva and sclera [49]. The human eye surface and conjunctival sac hold a tear volume that ranges from 7.0 to 30.0 µl with a tear turnover rate of 0.5 – 2.2 µl/min [48,50]. This translates to a therapeutically relevant drug residence time of < 5 min with complete exchange of tear volume in ~ 14 min assuming normal lacrimation and blinking rates. Blinking aids in contaminant removal and promotes a well-mixed tear fluid. If the topical medication or the mechanical forces of the instilled drop irritate the eye, lacrimal secretion will increase and further dilute the dosage. The movement of fluid in the eye depends on the flow of the aqueous phase, which is secreted by the lacrimal glands above the eye, spread over the eye surface through surface tension and blinking, and drains out of the eye through the lacrimal puncta with the aid of a pumping mechanism [51]. Up to 95% of topically applied drug can be washed away from the eye surface within minutes (**Figure 1**) [52].

Topically applied drugs in the forms of solutions, suspensions and ointments account for 90% of ophthalmological formulations on the market today [42]. The most common method of delivery is eye drops administered to the eye surface, and there are > 100 topical eye drop formulations on the market today [17]. Topical solutions and suspensions have remained effective by the administration of very high concentrations of drug multiple times a day, leading to decreased compliance, increased toxicity, burning, itching sensations and gritty feelings experienced by the patient [17]. Although ointments can lead to slightly increased bioavailabilities over drops, they are difficult to apply, uncomfortable to use and severely reduce vision. Also, eye drop formulations typically contain preservatives to prevent pathogenic contamination, which can cause adverse reactions and be toxic to ocular tissue.

Patient compliance remains one of the biggest drawbacks of topical drop administration, with evidence suggesting a large percentage of patients have significant periods of ineffective drug concentration levels. The volume of instilled dose is also highly variable from application to application, which depends on the squeeze force, the angle of administration and the ability to resist blinking, which leads to spillage from the eye [53]. These issues compound into quick drug loss along with tear flow rate and ocular protective mechanisms. Also, the tear drainage rate has been show to increase linearly with instilled volume [48,49]. **Figure 2** highlights these effects on the concentration profile of topically instilled drug in the eye as well as the concentration profiles of drug-soaked and imprinted contact lenses.

3. Molecular imprinting within hydrogels: creating macromolecular memory

Hydrogels are insoluble, crosslinked polymer network structures composed of hydrophilic homo- or heteropolymers, which have the ability to absorb significant amounts of water and retain their shape without dissolving. Crosslinks (also known as tie-points or junctions) can be covalent bonds, permanent physical entanglements, non-covalent interactions, or microcrystalline regions incorporating various chains and are primarily responsible for preventing the dissolution of the polymer in water [54]. Most hydrogel contact lenses are covalently crosslinked, and it is within these types of gel that imprinting has had the most success.

The concept of molecular imprinting within gels involves the creation of macromolecular memory for a template molecule within a polymer network. Effective self-assembly of the functional monomer(s)–template complex is crucial to non-covalent imprinting efficacy. Macromolecular memory is primarily due to two synergistic effects: i) shape specific cavities that match the template molecule, which provide stabilization of the chemistry in a crosslinked matrix; and ii) chemical groups orientated to form multiple non-covalent complexation points with the template (**Figure 3**). Non-imprinted gels are prepared in the same manner but without the inclusion of template. As gel structures can have significant flexibility in the polymer chains, the term macromolecular memory or structural plasticity of polymer chains has been used to describe molecular imprinting in gels [15]. In this review,

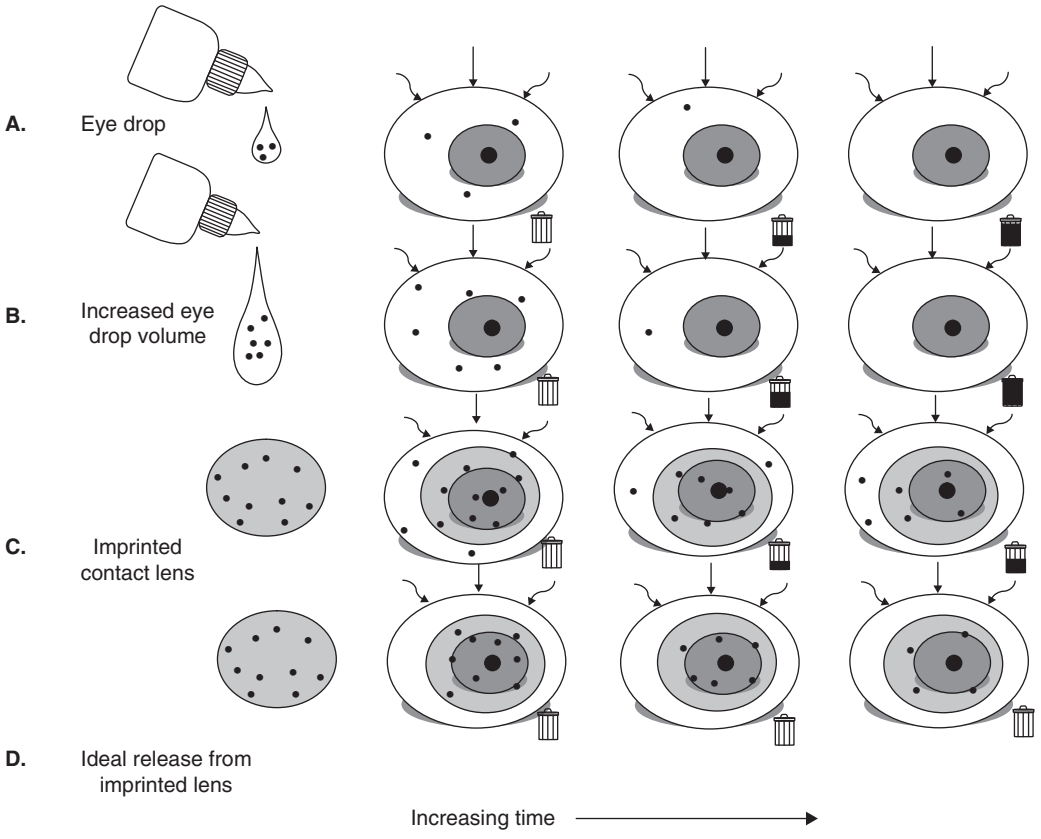

Figure 1. Delivery options and drug loss. A. Drugs delivered through typical tear drop volume are typically removed in 15 min with only 1 – 7% of the drug absorbed productively by the eye. **B.** Increasing drop volume of same drug concentration corresponds to a linear increase in the tear drainage rate, resulting in similar or lower bioavailability with more drug lost reaching systemic circulation (represented by waste cans). **C.** Delivery by means of imprinted contact lenses increases residence time of the drug on the eye surface and extends delivery time, increasing productive absorption and decreasing drug loss. **D.** The ideal imprinted contact with drug release rate correlating with the rate of drug absorption by the eye. The curved arrows represent lacrimation or tear flow rate.

attention was not focused on structures that contain a complex recognition element such as protein, inclusion complex, and so on, unless there were multiple such species on differing polymer chains providing recognition.

Macromolecular memory delays the transport of drug from the polymer matrix by means of interaction of the drug with numerous functional groups organized within the network (**Figure 3**). The drug's heightened interaction with the memory pockets slows its release from the hydrogel despite comparable free volume within the polymer chains for drug transport. This type of network formation can tune the drug loading and release profile with a proper optimization of drug affinity relating to number and strength of functional monomer interactions, crosslinking structure and mobility of polymer chains [15]. It is ideally suited in thin film or 'limited volume' applications and can be applied as a platform application.

Most imprinted polymers produced so far have been highly crosslinked in efforts to limit the flexibility of the associated binding cavities produced between polymer chains. It was assumed that flexibility of polymeric chains would lead to fatal deficiencies in the metrics by which imprinted structures are defined, namely template binding affinity, capacity and selectivity. However, experimental work in the last decade has proved that this is not the case [15]. There have been many excellent reviews on molecular imprinting and the reader is directed to reviews that focus on imprinted hydrogels [15,16], reviews focusing on biomedically relevant areas [15,16,55-61] and traditional imprinting strategy reviews [62-70].

4. Drug delivery and hydrogels: the role of molecular imprinting

Controlled drug release from hydrogels has been studied extensively for the past four decades. Major work has involved structural control over drug release with major variables such as the mesh size, or spaces between the polymer chains, and

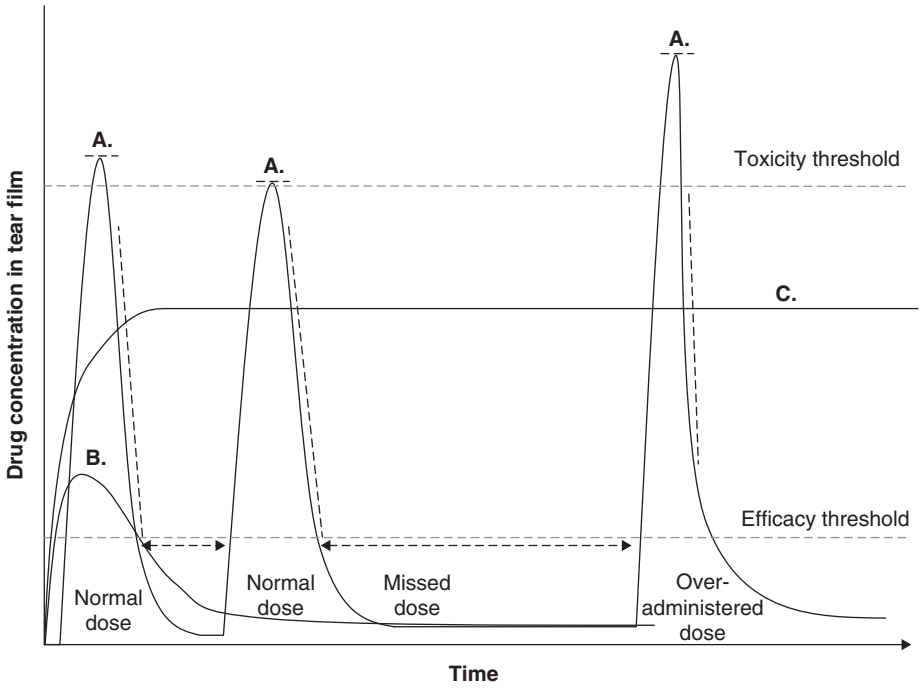

Figure 2. Delivery options and the ocular tear film drug concentration profile. When an eye drop is applied to the eye, the tear film concentration varies with time. **A.** Immediately on application, a maximum concentration is reached, which quickly decreases owing to lacrimation, drainage and absorption, dropping below the efficacy threshold until another drop is applied. If a dose is delayed or missed, the eye will be without therapeutic levels of drug. Relative heights of the eye drop concentration peak and elimination rate depend on factors such as force on the bottle, angle of application, patient administration, lacrimation and drainage rate. **B.** Drug-soaked contact lenses administer small amounts of drug in a very short amount of time, making them virtually ineffective as drug carriers. **C.** Imprinted contact lenses provide a controlled and sustained drug release where a constant concentration of drug can be achieved for an extended period of time.

the drug size. However, the field has done very little to understand the organization of the chemical functionality and orientation of polymer chains when a molecule that is not covalently incorporated into the network is included in the polymerization process. This is exactly where molecular imprinting is gaining a new role in drug delivery. Imprinted network formation can lead to better control over the release profile and further delay release of therapeutic owing to the affinity relating to the number and strength of interactions between the drug and polymer. The crosslinking structure and mobility of polymer chains also play an important role. Thus, molecular design and control of the network architecture are driving new developments in the field [15]. Only recently has molecular imprinting been applied to drug delivery, which is highlighted in [15,16,55,71-74].

It is well known that preparation conditions of hydrogels can lead to significant changes in the network structure and physicochemical properties. Surprisingly, no work has addressed the potential impact of the inclusion of drug and its effect on the organization of polymer chains. This becomes important because two schemes are typically used to load therapeutics into hydrogels. Either the gel is synthesized in the presence of drug or the drug is loaded after synthesis by equilibrium partitioning.

Molecular imprinting has led to the development of extended drug-releasing contact lenses, which cannot use previous strategies to delay drug transport. It is preferred that contact lenses are swollen and in equilibrium for the duration on the surface of the eye. Previous strategies to control drug release from hydrogels have included gel structural changes, including dynamically swelling or swelling-controlled networks (i.e., drug-loaded networks going from a dry to a swollen state), and responsive-swollen networks (i.e., a swollen gel that undergoes a reversible volume transition based on a stimulus such as pH, temperature, ionic strength, etc.). Imprinting can play a role in both of these processes [15], but they are not feasible within the constraints of contact lenses as medical devices because changes in the structure of the lens will alter the fit of the lens on the surface of the eye and the refraction of light within the lens.

For swelling-controlled hydrogels, if there is a constant rate of solvent front penetration that is much smaller than the drug diffusion rate in the swollen gel, a constant drug release rate, or zero-order release, arises [75]. In a Fickian model of

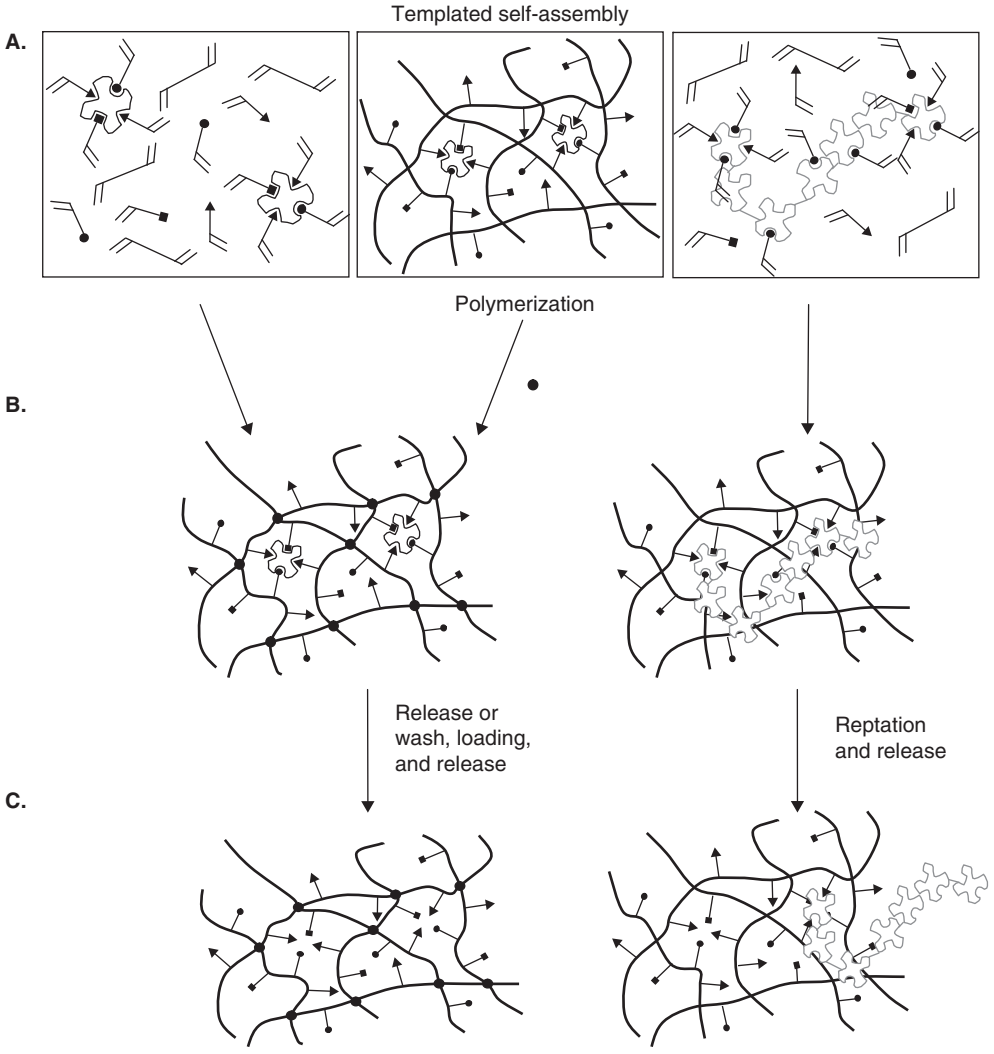

Figure 3. Creation of macromolecular memory in hydrogels through molecular imprinting. A. Non-covalent self-assembly of the functional monomer drug complexes within the pre-polymerization solution. This can be in the form of monomeric species (left box) or oligomers/polymers that have pendant double bonds or are reacted to other chains by other molecules (•) (middle box) with small or large molecular weight templates (right box, macromolecule). **B.** Formation of an idealized macromolecuar network with recognition sites consisting of functional chemistry on differing polymer chains. **C.** Release of drug with or without wash steps. The transport of long molecular weight molecules (ocular comfort molecules) can also be controlled by imprinting mechanisms. Whereas the size of the macromolecule and conformation as well as the polymer mesh size will influence release, imprinting leads to an extra level of control to delay release or turn release on and off [97,98].

release kinetics within swelling gels, the polymer relaxation rate is high and the diffusion processes are rate-limiting, resulting in the release rate of the drug being proportional to the concentration gradient between the drug source and the surroundings. To achieve constant drug release, several strategies have been attempted, such as bioerodible and biodegradable systems with solvent penetration fronts [76], hydrogels with rate-controlling barriers such as higher crosslinked outer edges [77], and non-uniform drug distribution [78].

Drug diffusion through a drug-imprinted polymer network can be influenced by three main variables: average mesh size, template size and drug–polymer chain interactions (i.e., the imprinting effect). Manipulation of one or more of these variables can alter the drug diffusion coefficient. Also, the degree of drug–polymer chain interactions or the degree of memory for the drug by means of multiple polymer chains is intrinsically linked to the polymer mesh size. An increase in polymer mesh size while holding template size and template–polymer chain interactions relatively constant would lead to an increase in drug diffusion. An increase in drug size while holding mesh size and drug–polymer chain interactions constant would lead to a decrease in the drug diffusion coefficient. An increase in

drug–polymer chain interactions while holding drug size and mesh size constant would correspond to a decrease in the drug diffusion coefficient.

5. Imprinted contact lens combination devices: the current state of the field

Successfully controlling the loading and transport of drugs from a contact lens depends on several factors. It depends on how much the polymer structure changes post synthesis, the number and diversity of the functional species within the polymer that interact with the template, the functionality of the template and molecular size, the relative strength of the polymer–template interactions, and the polymer structure dictated by polymerization reaction. As it is a medical device, and the inclusion of drug release is independent of its role to provide corrective vision, it is classified as a combination device. Relevant loading and transport parameters of various imprinted lenses are compared in **Table 1**. All papers presented below have adequate mechanical and optical properties for use as contact lenses. For further background, a general review of contact lens drug delivery is recommended [79].

One of the most important considerations in effective imprinting is to maintain the binding cavity produced via differing polymer chains close to the state when the original imprint was formed (i.e., close to the relaxed state of the polymer). In other words, the swollen or collapsed polymer volume at equilibrium must not be too different from the relaxed polymer volume fraction. This has always been important in the synthesis and production of lenses. Size and curvature are essential for a good fit on the surface of the eye as well as for precise optical power. If the polymer swells isotropically or anisotropically, problems in both of these areas can occur, and if the lenses are imprinted there will be a significant loss of control over the release. The expansion of polymer chains will increase the free volume available for template transport, but it decreases the effectiveness of the imprinting site created by multiple polymer chains. Therefore, solvent and polymer architecture are also important to imprinted contact lenses.

The first paper to describe the synthesis and characterization of imprinted hydrogels for potential use as soft contact lenses was published in 2002 [80]. Imprinted hydrogel thin films were produced for timolol, a non-selective beta-andrenergic blocker, used to treat glaucoma. Glaucoma is the gradual loss of sight over a long period of time as a result of damage to the optic nerve, affecting ~ 0.5% of people under the age of 50 and 8 – 10% of people over the age of 80 [81,82]. Timolol has been shown to be effective in the treatment of certain types of glaucoma by reducing increased ocular pressure inside the eye, preventing damage to the optic nerve. The dosage regimen is typically one eye drop twice daily [83]. Poly(hydroxyethylmethacrylate) hydrogels were produced with either methacrylic acid (MAA) or methyl methacrylate comonomers. Release from imprinted swollen films in artificial lacrimal solution resulted in 6 – 10 h release that was Fickian. The main emphasis was on loading, and MAA-imprinted gels containing 100 mM MAA had the highest loading levels of 12 mg timolol/g dry hydrogel and were the only gels with significantly higher loading (threefold) than non-imprinted gels [80]. Film thickness directly after synthesis was ~ 700 µm, with further swelling taking place, increasing the size. Conventional contact lenses on the market today have thicknesses < 100 µm, and the thickness of the lens influences corneal oxygen transport and lens fit/comfort. A thicker lens decreases oxygen transport and drug transport (release scales to the reciprocal of thickness squared). Thus, in terms of delivery it is better to have a thicker lens, but imprinted lenses have been produced in the thickness range of conventional lenses and demonstrate significantly delayed release.

Work published by many of the same authors also involved imprinting timolol using MAA as functional monomer with emphasis on varying crosslinker concentration [84] as well as altering the backbone monomers within similar formulations [85]. The focus was in the determination of a minimum crosslinking concentration for imprinting to be effective as well as the influence of the backbone polymer and gel swelling on recognition. Release from 300 µm or greater thick films in a salt solution was again Fickian, with 90% of timolol being released in ~ 16 h [84] and in ~ 4 h [85]. No differences in the shape of the imprinted release curves compared with non-imprinted films were demonstrated, and no significant differences in timolol diffusion coefficient were found between corresponding imprinted and control gels. In 2005, release rate was correlated to affinity with release rate decreasing by increasing the functional monomer/template (M/T) ratio within the formulation [86]. This work was encouraging, demonstrating a slower *in vitro* release rate, with 50% of drug being released in 3 days. The extension of release, which is a vital metric in the design of imprinted contact lenses, was starting to be reached.

The functional M/T ratio is a major variable in an effective design. There is considerable evidence of an optimal M/T ratio within highly crosslinked imprinted structures. There is also an optimum in weakly crosslinked structures, and the work of Alvarez-Lorenzo and co-workers has been at the forefront [86,87]. In non-covalent systems, an excess of functional monomer is needed to push the reversible template–functional monomer interaction to the complexed state. Therefore, M/T ratios are usually much higher than unity and are not commonly in stoichiometric amounts based on the functionality of the template. This optimum can be seen distinctively by looking at two extreme cases. At a very large M/T ratio, the memorized configuration of monomer within the polymer chains is very small compared with the randomly incorporated monomer and there is no difference between the non-imprinted and imprinted gels. At very small M/T ratios, there are not effective multiple monomer interactions with the template, resulting in no recognition.

Table 1. Composition, loading and release/transport data of imprinted contact lenses*.

Functional monomers (crosslinker)	Crosslinking (%), template, solvent, mold thickness (mm)	Classification of therapeutic	Characterization of binding parameters	Characterization of template release/transport	IP structural/ swelling analysis	Ref.
HEMA/MAA (EGDMA) HEMA/MMA (EGDMA)	Low (0.128%), timolol, no solvent, 0.7	Anti-glaucoma	HEMA/MAA IPs bind 12 mg/g at pH 5.5, NIPs bind 4 mg/g. HEMA MMA IPs demonstrate poor binding	90 – 100% released in 9 h	Swelling	[80]
HEMA/AA/AM/NVP (PEG200DMA)	Low (5%), ketotifen fumarate, no solvent, 0.4 and 0.7	Antihistamine	Most biomimetic IP (AA/AM/NVP/ HEMA functional monomers) bound 21.3 mg/g, with NIP binding 3.4 mg/g (~ 8 × greater than single functional monomer IP)	IP demonstrated delayed release compared with NIP. Most biomimetic or more functionalized gels showed more delayed release compared with less functionalized gels. Most diverse network released 65% of template in 3.5 days and 100% in 5 days	Swelling	[88,89]
DEAA/MAA (EGDMA)	Low – high (7 – 67%), timolol, no solvent, 0.3	Anti-glaucoma	Most IPs demonstrated improved binding compared with NIP (~ 2.5 × NIP)	IP did not demonstrate delayed release compared with NIP. Release completed in 8 – 24 h for both NIP and IP lenses	Swelling	[84]
HEMA (EGDMA) SiMA-DMAA (EGDMA) MMA-DMAA (EGDMA) DEAA (EGDMA)	Timolol, no solvent Low (2%), 0.3 Low (1.7%). 0.3 Low (1.5%), 0.3 Low (2.35%), 0.3	Anti-glaucoma	First 3 IPs bind 6.5 – 7 mmol/l gel. DEAA IP bind 3 mmol/l gel IPs demonstrated best bind by small margin (~ 1.2 × NIP) Greatest Increase in bind between IP/NIP (~ 2 × NIP) IP bind ~ 1.5 × NIP Lowest binding by large margin (~ 2 × NIP)	NIP release in 7 h, IP release in ~ 10 h 90 – 100% released in 3 h for 3 IPs and 1.5 h in IP for DEAA, SiMA-DMAA and MMA-DMAA	Swelling	[85]
MAA (EGDMA)	Low (variable), timolol, no solvent, 0.3	Anti-glaucoma	IP demonstrated higher affinity than NIP	Template diffusion coefficients were calculated from template release studies. The diffusion coefficient from IP at certain M/T ratios (16/1, 32/1) 2 orders of magnitude lower than NIP. Lowest IP diffusion coefficient approaching 10^{-10} cm^2/s)	Swelling	[86]
AA or NVP (EGDMA)	Low (1%), norfloxacin, no solvent, 0.4 and 0.9	Antibiotic	IP loaded more than NIP. Highest loading at M/T of 3:1 and 4:1	IP polymer release extended compared with NIP. IP at M/T 4/1 released 40% template in 24 h	Swelling	[87]

*When appropriate, crosslinking % was calculated and is equivalent to (100% × (mole crosslinking monomer/(mole crosslinking monomer and all other monomers))).

AA: Acrylic acid; AM: Acrylamide; DEAA: Diethyl acrylamide; DEAEM: Diethylaminoethyl methacrylate; DMAA: Dimethyl acrylamide; EGDMA: Ethylene glycol dimethacrylate; HEMA: 2-Hydroxyethylmethacrylate; IP: Imprinted polymer; LCP: Living-controlled polymerization; MAA: Methacrylic acid; MMA: Methyl methacrylate; M/T: Monomer template ratio; NIP: Non-imprinted polymer; NVP: N-vinyl 2-pyrrolidinone; PEG200DMA: Poly(ethylene glycol)200 dimethacrylate; PVA: Poly(vinyl alcohol); SiMA: Silicone methacrylate.

Table 1. Composition, loading and release/transport data of imprinted contact lenses* (continued).

Functional monomers (crosslinker)	Crosslinking (%), template, solvent, mold thickness (mm)	Classification of therapeutic	Characterization of binding parameters	Characterization of template release/transport	IP structural/ swelling analysis	Ref.
HEMA/AA/AM/NVP (PEG200DMA)	Low (5%), ketotifen fumarate, no solvent, 0.4 and 0.7	Antihistamine	Partitioning of template into IP gels composed of multiple functional monomer was ~ 8 × greater than less diverse IPs. Each IP bound more template than corresponding NIP	One-dimensional transport studies show template diffusion coefficient 2 orders of magnitude lower (7×10^{-10} cm^2/s) in most diverse IP with comparable gel mesh sizes and equilibrium polymer volume fractions. All IP gels had lower template diffusion coefficients than corresponding NIP with comparable mesh sizes	Swelling and structural analysis	[92]
HEMA/AA/AM/NVP (PEG200DMA)	Low (5%), ketotifen fumarate, no solvent, 0.4 and 0.7	Antihistamine	Partitioning of template into IP gels composed of multiple functional monomer was ~ 8 × greater than less diverse IPs. Each IP bound more template than corresponding NIP ~ 200 μg loaded/lens	Best release duration in sink was ~ 7 days. Release in physiological flow was 3.5 days	Swelling	[96]
PVA/NVP/AM/ DEAEM	Hyaluronic acid, no solvent, 0.127	Therapeutic agent, comfort agent, epithelial cell migration promoter, corneal healing aid		Diffusion coefficient IP for multiple monomers was 1.6 × lower than NIP and 1.5 × lower than single monomers. Release therapeutic rate of 6 μg/h for 24 h, complete release in 40 h	Swelling and structural analysis	[97,98]
DEAEM/HEMA (PEG200DMA)	Low (5%), Diclofenac sodium, no solvent, 0.25	Anti-inflammatory	LCP IP gels bound 1.5 × the IP gels and 3.6 × NIP gels	LCP IP: More zero-order release (2 × extension of release compared with conventional IP and 4 × over NIP); 70% released over 24 h for LCP IP, 70% over 11 h for IP, 70% over 5 h for NIP)	Swelling and structural analysis	[99]
DEAA/MAA (EGDMA)	High (61%), timolol, no solvent, 0.08	Anti-glaucoma	IP bind: 35 μg/lens NIP bind: 21 μg/lens	*In vitro* release: IP and NIP release 90 – 100% in 24 h *In vivo* release: Release of NIP-IP complete in 30 min – 1 h	Swelling	[101]

*When appropriate, crosslinking % was calculated and is equivalent to (100% × (mole crosslinking monomer/(mole crosslinking monomer and all other monomers))).

AA: Acrylic acid; AM: Acrylamide; DEAA: Diethyl acrylamide; DEAEM: Diethylaminoethyl methacrylate; DMAA: Dimethyl acrylamide; EGDMA: Ethylene glycol dimethacrylate; HEMA: 2-Hydroxyethylmethacrylate; IP: Imprinted polymer; LCP: Living-controlled polymerization; MAA: Methacrylic acid; MMA: Methyl methacrylate; M/T: Monomer template ratio; NIP: Non-imprinted polymer; NVP: N-vinyl 2-pyrrolidinone; PEG200DMA: Poly(ethylene glycol)200 dimethacrylate; PVA: Poly(vinyl alcohol); SiMA: Silicone methacrylate.

In 2006, a diversity of functional monomers was demonstrated by the authors' group to increase binding parameters and delay release of antihistamine-imprinted hydrogels for use as imprinted contact lenses [88,89]. A major impact of this work was that drug loading was significantly higher than other imprinted gels in the literature (~double). Single non-covalent bond energies are much less than single covalent bond energies, and they are slightly higher than the average kinetic energy of molecules at room temperature. Thus, many molecules almost possess sufficient kinetic energy to break their non-covalent bonds. However, when multiple non-covalent bonds exist, they produce very stable binding complexes, such as those found in proteins and receptor ligand binding pockets [90,91]. The authors' group has demonstrated that at a fixed M/T ratio loading of drug into networks synthesized from multiple functional monomers (four different monomers) was eight times greater than networks synthesized from single monomers [88,89]. Gels of multiple complexation points with varying functionalities outperformed gels formed with less diverse functional monomers and showed superior loading of ketotifen fumarate, with a sixfold difference over control gels. Also, in this work a biomimetic approach was used by incorporating a natural receptor-based rational design strategy in the synthesis. A therapeutically relevant release was demonstrated *in vitro* in a controlled fashion for 5 days in lacrimal solution from 400 μm imprinted films, with an even further extension in the presence of protein. The highest functionalized imprinted gels showed diffusion coefficients 10 times smaller than less functionalized gels [92]. Ketotifen fumarate is a second generation H1-antihistamine and mast cell stabilizer that is prescribed over the counter (OTC) to treat ocular allergic conjunctitivis and relieve inflammation and pruritus. The recommended dosage regimen is one drop twice daily [93,94], with most other OTC allergy eye drops being 1 – 2 drops every 4 – 6 h [93,94]. Seasonal and perennial allergies affect ~ 25% of the population [95].

The best performing lenses from the author's work [88,89] were studied using a new microfluidic device that simulated the volumetric flow rate, tear volume and composition of the eye and resulted in a constant, zero-order release [96]. Release could potentially be achieved for at least 150 days from these imprinted films (by extrapolating to the total loaded amount), which would translate to > 10 – 15 day release from lenses with a maximum center thickness of 100 μm. This work also presented the equilibrium volume swelling ratio, which showed all gels swelling to the same extent, which was verified furthered by structural analysis [92]. Imprinting delays transport from the polymer chains, and a tumbling hypothesis was proposed analyzing one-dimensional template transport [92]. One-dimensional template permeation studies were conducted by means of diffusion cells and all imprinted networks had significantly lower diffusion coefficients than non-imprinted networks, in spite of comparable mesh sizes and equilibrium polymer volume fractions in the swollen state. This analysis significantly strengthened the argument of multiple, organized functionalities and an appropriate mesh size, experienced heightened interactions with memory sites, and showed delayed transport kinetics. The phenomena are not a result of differing mesh structures or porosity, and this was the first time that this was demonstrated in the field [92].

Work with imprinted lenses has included other ocular therapeutics such as norfloxacin [87], hyaluronic acid (HA) [97,98] and diclofenac sodium [99]. For HA, this work was the first demonstration of imprinting a high-molecular-mass polymer within a hydrogel and the effect of imprinting on the reptation of the long chain macromolecule from the structure. Hydrogel films and contact lenses (~ 120 μm thickness) composed of nelfilcon A, acrylamide (AM), N-vinyl pyrrolidone (NVP) and 2-(diethylamino) ethyl methacrylate (DEAEM) were biomimetically imprinted in the presence of HA, for the controlled release of HA over 24 h. The lenses were designed for the therapeutic delivery of HA to the eye surface, to improve the comfort and wettability of contact lenses and to treat symptoms of dry eye [97,98]. Current dry eye treatment includes delivering comfort agents to the eye by means of drops, but low bioavailability and multiple administrations continue to be barriers to effective treatment.

The diffusion coefficient of 1.2 million dalton HA was controlled by varying the number and variety of functional monomers (increasing the variety lowered the HA diffusion coefficient 1.5 times more than single functional monomers, and 1.6 times more than nelfilcon A alone) [98,99]. The variations resulted from the biomimetic imprinting process, not structural changes in the hydrogel as gels had similar swelling and calculated structural parameters. HA was delivered from a daily disposable lens at a therapeutic rate of ~ 6 μg/h for 24 h. Interestingly, at a limiting amount of functional monomer that led to a crucial number of complexation points between HA and the network, HA release was turned off and did not occur until the ionic bonds between HA and DEAEM were disrupted by altering the pH. Thus, immobilizing comfort molecules within lenses that are partially outside the lens emanating from the surface may be very beneficial with or without release of comfort molecule. Also, the lenses produced in this work could serve dual roles as a comfort and therapeutic contact lenses, as HA has been shown to have therapeutic properties in corneal wound healing and epithelial cell migration [100].

More recently, anti-inflammatory, diclofenac sodium, imprinted hydrogels were produced exploring living polymerization mechanisms [99]. Poly(DEAEM-*co*-HEMA-*co*-PEG200DMA)-imprinted gels prepared by means of 'living/controlled' polymerization techniques showed a 54% increase in loading capacity over poly(DEAEM-*co*-HEMA-*co*-PEG200DMA)-imprinted gels prepared using conventional free-radical polymerization. Both imprinted gels bound more diclofenac sodium compared with non-imprinted gels, and the conventionally imprinted gel

had a 140% increase in template loading over that of the non-imprinted network. The imprinted gel prepared by means of 'living/controlled' polymerization had a 269% increase over that of the non-imprinted gel. Release data showed that imprinting via 'living' polymerization extends or delays the template release profile by twofold over that of imprinting via conventional free-radical polymerization techniques and fourfold over that of the control network. It also shifted the release towards more zero-order release with a duration of ~ 5 days. Living/controlled polymerization with a reversible termination reaction can provide more control over the network structure. It increased the potential for the growing polymer network and template binding complexes to reach a global energy minimum and led to further memorization of the chain conformation [99].

Anti-inflammatory medications are applied directly to the eye in the treatment of corneal abrasions and the post-operation treatment of LASIK and cataract surgeries. After cataract surgery, the treatment regimen requires 2 drops of anti-inflammatory medication 4 times a day for ~ 2 weeks. Corneal refractive surgery treatment requires 1 drop of anti-inflammatory every hour for the first day, 1 drop every 2 h for the second day, and 1 drop 4 times a day for up to 7 days [104-105]. Anti-inflammatory releasing lenses would be very beneficial in this area.

In terms of *in vivo* release from imprinted lenses, only one study has been published so far. In 2005, the first *in vivo* study of imprinted contact lenses was published [101]. Poly(MAA-*co*-DEAA-*co*-EGDMA) lenses imprinted for timolol were produced with a diameter of 14 mm and a center thickness of 80 µm. Timolol tear fluid concentration profiles in rabbits were highest for the imprinted lens compared with non-imprinted and eye drops, but they did not extend release past 90 min. It is important to note that much progress and extension of release *in vitro* has been demonstrated since then.

6. Conclusion

Molecular imprinting has been experimentally verified as a successful method for producing contact lenses with high drug loading and controllable release. Progress in the field has mostly included low-molecular-weight therapeutics in the middle of the hydrophilic/lipophilic spectrum used to treat anterior eye disorders. Control in loading and delay of release has been established with careful attention to the functional monomer/template ratio, the diversity of functional monomers, and the polymer backbone and crosslinking structure. Experimental work has also demonstrated that macromolecular memory, not structural phenomena, is responsible for delayed template release kinetics. Current methods can produce lenses of suitable thickness, water content, and mechanical and optical properties compared with lenses on the market today. In comparison with topical alternatives, imprinted lenses provide an increased residence time of therapeutic at the surface of the eye leading to increased bioavailability and more convenient and efficacious therapy.

7. Expert opinion

There has been exciting progress in the field since the first experimental evidence appeared in 2002, but clearly this field is in its infancy, with only a handful of researchers demonstrating success with increased therapeutic loading and delayed transport *in vitro*. *In vivo* success and validation of therapeutic contact lenses has not been sufficiently demonstrated so far and is a significant aim of the field. This primarily concerns matching release duration with the wear time of the lens and maintaining suitable drug concentration. Also, a wide spectrum of therapeutics has not been experimentally demonstrated; however, it is expected to be a platform technology for most ocular hydrophilic drugs, hydrophilic comfort molecules and drugs of slight to moderate lipophilicity. For more lipophilic molecules, modification or inclusion complexes may be incorporated to increase the applicability of the imprinting approach. Constraints on optical clarity, oxygen transfer and mechanical properties add some hurdles to network design in some systems, but these issues can be overcome. It is important to note for all the drugs that have been experimentally demonstrated, the presence or release of drug did not affect lens optical clarity or mechanical properties. Considering the timeframe of drug release from lenses and that large concentrations of drug are not needed, it is expected that lens clarity, modulus, or surface properties such as wettability will not be adversely affected by drug in the lens. Imprinted lenses can be produced by means of UV free-radical polymerization in molds and sterilized post-synthesis with no degradation or reaction of drug during the process. In the HA-imprinted lenses, the steam sterilization protocol decreased HA degradation when in the lens compared with HA in solution [97,98]. Sterilization is not expected to be a significant problem for most drugs, but post-sterilization aseptic loading is an alternative.

Drug loading was the first major issue to be studied using imprinted lenses, and groundbreaking work has been conducted. For example, it is interesting to note that the earliest produced imprinted gels were much thicker than contact lenses on the market today and contained marginal concentrations of water. Contemporary imprinted lenses are an order of magnitude thinner and equivalent to lenses in the market, contain copious amounts of water, and drug loading has increased substantially. In early systems, drug loading was moderately higher for the imprinted lenses over non-imprinted lenses, but because the duration of release was, low on the order of hours, high loading was not needed. Increased drug loading became crucial to success as the duration of the release challenge increased. Thus, the rate of drug needed and the duration of release are important design parameters. It is now evident that a therapeutically relevant amount of drug can be loaded for release to occur over

multiple days, which allows the technique to be applied to extended-wear lenses on the market. This is predominantly owing to using a diversity of non-covalent interactions to provide imprinting control. So far, these systems have shown the highest loading levels [89,92].

Current trends in the contact lens market divide soft contact lens wear into three major categories: extended, continuous-wear; daily-wear; and daily-disposable lens wear. In the US, daily-wear lenses account for three-quarters of lens fittings, making daily-wear the dominant product in the market. Daily-disposable and extended-wear lenses account for 8 and 7% of lens fittings, respectively [102]. However, contact lenses capable of drug delivery may cause daily-disposable and extended-wear lenses to grow into a more substantial share of the market. All imprinted lenses in the literature fall into the daily-wear category.

The advent of silicone hydrogel lenses to the lens market in the 1990s has made extended, continuous-wear lenses practical and safe. Silicone hydrogels provide extremely high levels of oxygen permeability and movement of the lens on the eye surface, allowing continuous wear for up to 30 days. No imprinted lenses of this type have been experimentally demonstrated, and this is a natural progression of the field along with integrating the technique into existing manufacturing techniques. Silicone hydrogels may require more understanding of the partitioning of the drug, but they can be imprinted with drug. For all lens types, the flux of drug from the imprinted lens must be controlled so the reservoir of drug inside the lens is not depleted before the lens is removed. Thus, it is expected that extended delivery of a wide variety of drugs will increase in all modalities of contact lens wear.

The ideal situation is not having to reload drug or lose drug in a wash/disinfecting medium. Thus, daily-disposable imprinted lenses would be inserted, deliver the drug, and then be discarded. For the extended-wear category, imagine a patient receiving a drug-releasing lens in the doctor's office and having it removed on a follow-up visit 2 weeks later. The lens could release drug in a controlled manner during the period between visits. This type of lens and delivery may be better suited for the elderly or for patients who need continuous delivery. Daily-wear lenses that are taken out before sleeping require disinfection and cleaning, which would lead to small amounts of drug lost to the cleaning solution and potential for adverse interactions with the drug.

Considerable attention has also been given to controlling the rate of therapeutic release from contact lenses. Release profiles from drug-soaked lenses, the first generation of drug-eluting contact lenses, were Fickian in nature (i.e., concentration dependent) and very short in duration, with all drug being released in less than an hour. Release profiles from the first reported imprinted lenses were also Fickian, with most drug being released in ~ 9 h. This led to discussion on reloadable contact lenses, but the contact lens market and progress in the field made this type of lens obsolete before it was even developed. Thus, the only significant advantage to imprinted lenses was that drug release rates were higher, but the shape of the drug release curve was the same for the non-imprinted lenses. In the last few years, differences in the release curves have been obtained by our group with imprinting delaying release [88, 89, 92, 99]. Thus, the therapeutic release can be controlled and the shape of the release curve moved from Fickian release closer to more constant, zero-order release, compared with the non-imprinted systems. This was a significant accomplishment of the field, demonstrating that imprinting was directly related to delayed template release when comparing imprinted and non-imprinted lenses with similar network structures and free volume. In an ocular flow rate, with limited tear turnover, release rates will decrease owing to significant drug concentration boundary layers.

Given the control demonstrated over release rate, there is enormous potential for ideal release rates to be designed considering specific ocular drug absorption rates (**Figure 1D**). This is also a significant challenge of the field, and it would result in the best possible ocular delivery with the least amount of drug entering the systemic circulation. Such achievements may only be possible with imprinted lenses and inserts, which can specifically control the rate that the drug is delivered into the eye. Although there will also be some variation in drug release from imprinted lenses based on a person's tear volumetric flow rate and volume, it is not a limitation of the technology. This variation exists in other forms of topical delivery, including eye drops, and a faster tear flow rate would lead to higher levels of drug released.

It is apparent that imprinted lenses are ideally suited to treating anterior diseases of the eye. All experimental work so far has included these types of therapeutic, and future progress will begin to target posterior delivery. It is difficult to deliver medications to these regions without systemic delivery or invasive procedures, which have many drawbacks [17]. Topical posterior eye delivery is hampered by low penetration of the drug into the eye owing to transport barriers and removal of drug from the eye, which reduce the amount of drug available. This limitation can be overcome in theory by the addition of permeation enhancers to ease transport temporarily. Work demonstrating the versatility of multiple monomer systems, high drug loading levels and the effectiveness in controlling drug release has potential to aid this direction of work. Lenses designed to release two or more molecules at specified rates could allow a molecule to aid the transport of a second molecule and deliver it to the desired area.

Loading levels are now high enough that multiple therapeutics could be delivered from the same lens, mimicking some successful dual-therapeutic eye drop formulations. Also, it is important to note that imprinted lenses can be produced as corrective or non-corrective drug delivery devices and several variations of cosmetic, non-refractive contacts and bandage lenses are now being sold. Thus, bandage lenses or non-vision-altering lenses would be significantly improved by using imprinted methods.

The value proposition of imprinted, drug-releasing contact lenses targets consumers, ophthalmologists and optometrists, contact lens manufacturers and pharmaceutical companies. For consumers, it has the potential to deliver over-the-counter or prescription eye medication more effectively, delivering a more constant and optimal therapeutic concentration. It will be more convenient, eliminating multiple daily drops with less systemic absorption, fewer side effects and adverse reactions, and less toxicity. Thus, ophthalmologists and optometrists will be able to provide better care for their patients. For contact lens manufacturers, there is more opportunity to enhance existing product lines as well as create new contact lens products. Significant opportunities exist for pharmaceutical companies to address more consumer needs in an integrated solution. There is also potential to protect or extend existing patent rights on existing drugs close to patent expiration exploiting imprinted drug delivery systems. Thus, the future is indeed bright for the field, which will see a sharp increase in the number of ocular therapeutics imprinted within lenses as well as *in vivo* studies. *In vivo* validation will take center stage, which will significantly increase the commercialization and clinical translation of these systems.

Declaration of interest

ME Byrne is a professor of chemical engineering and chief technical officer of OcuMedic, Inc. and is named on pending US patent US20060177483A1. This work was supported by a grant from the National Science Foundation (NSF-CBET-0730903, Grant G00003191) and the US Department of Education (GAANN grant P200A060184; CJ White is a US Department of Education GAANN fellow).

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Affiliation

Charles J White & Mark E Byrne[†]
[†]Author for correspondence
Auburn University,
Department of Chemical Engineering,
Biomimetic and Biohybrid Materials,
Biomedical Devices and Drug Delivery Laboratories,
Auburn, AL 36849, USA
Tel: +1 334 844 2862; Fax: +1 334 844 2063;
E-mail: byrneme@eng.auburn.edu