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Ocular Hydrogel Materials and Corresponding Methods of Anterior Segment Drug Delivery: A Review

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ABSTRACT
Ocular conditions have historically proven difficult to treat. Topical eye drops are the primary method of anterior ocular drug delivery but have demonstrated low effectiveness as they require perpetual administration to achieve adequate doses of drug in the target tissue. This can lower patient compliance and increase the risk of side effects, such as systemic toxicity as most of the drug is absorbed through the eye's natural clearance pathways. Considering this, further development of alternate anterior delivery methods has the potential to improve drug effectiveness, residence times, and bioavailability, as well as reduce systemic toxicity. To this end, the ongoing development of contact lenses, thermogels, nanoparticle delivery systems, as well as mucoadhesive and mucopenetrative properties are being explored. This paper will discuss these developments, as well as their implications in ocular treatment.
Keywords: Contact lens, thermogel, nanoparticle, mucoadhesion, mucopenetration

1 INTRODUCTION
The structure of the eye can be broken down into two segments: the anterior segment, or the front of the eye, and the posterior segment, or the back of the eye. The structure of the anterior segment includes many structures that aid in vision and ocular health. These structures include the conjunctiva, cornea, sclera, anterior chamber (which contains the aqueous humour), trabecular meshwork, iris, and ciliary body (Fig. 1). The structures in the anterior segment are largely responsible for the focusing of an image, with auxiliary structures that aid in nutrient maintenance and structural support. The ability for the eye to function is an integral aspect of life, with visual impairment greatly limiting the ability for quality of life to be maintained. According to the World Health Organization, as of 2019, more than 2.2 billion individuals suffered from visual impairment in some capacity, and of that number, 1 billion cases could have been prevented. The economic draw of visual impairment is massive, with $16.5 billion USD spent annually in the United States alone (World Health Organization, 2019). Research into combatting vision impairment has been continuously evolving, with many avenues explored and many more that continue to develop. One advancing technology in vision research is the use of delivery methods to administer ophthalmic drugs to the eye, with aims to reduce toxicity, increase efficacy, or prolong delivery of drugs to the ophthalmic tissues.

Conditions pertaining to the anterior segment of the eye, such as allergic conjunctivitis, are typically treated with topical drug applications, though it is possible to administer drugs through more invasive methods, such as ocular injections (Dave et al., 2021). While topical administration of a drug via eye drops is the most common method, as it is easy to facilitate and is accepted by patients due to its non-invasive nature, it suffers from many drawbacks as an ideal delivery method. Due to clearance mechanisms on the eye to protect the eye from foreign substances and provide waste removal from ophthalmic cells, eye drops have a limited residence time on the surface of the eye. Due to tearing, blinking and drainage mechanisms, only 5% of the administered drug remains on the eye after roughly five minutes. Because of this, the administration of a drug must be frequent and requires a high dose to remain within the therapeutic window. As a result of the frequent high doses of administered drugs, there is an increased risk of complications, which can include systemic toxicity and limited patient compliance related to the inconvenience of frequent dosing (Mangiacotte et al., 2020).

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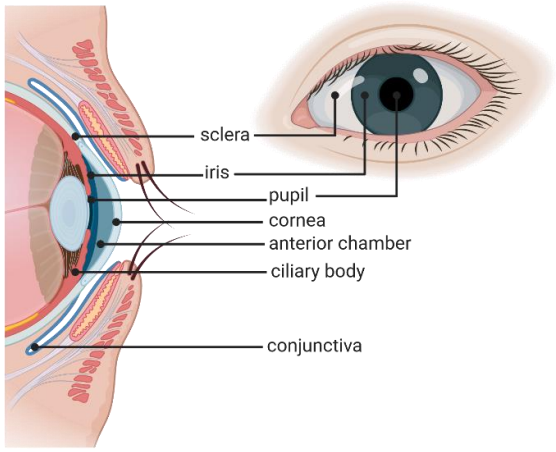

Figure 1: Overview of anatomy of the anterior segment of the eye

Alternative methods of anterior segment drug delivery suffer from unique complications that limit their widespread usefulness in most applications. Injection-based ophthalmic drug delivery in the anterior segment can be achieved through intracameral or subconjunctival injections (Gaudana et al., 2010), though due to the invasive nature of these administration methods, they prove to have low patient acceptance (Heimes et al., 2016)(Okada et al., 2021). Additionally, potential complications are associated with anterior segment injections, as this administration route requires application by healthcare professionals and carries the risk of endothelial toxicity and toxic anterior segment syndrome should the ophthalmologist fail to deliver the correct dose or make a mistake in preparation (Janagam et al., 2017). Further, the skill required to deliver anterior segment injections is substantial, as is the training involved, which limits the availability of using injections as a widespread method of delivering drugs to the anterior segment of the eye. Alternatively, delivery can, to an extent, be achieved through systemic administration. Systemic delivery is substantially limited by the avascular nature of most ophthalmic tissues, which limits the diffusion of the drug from the blood to the ocular tissues, thus requiring a high concentration of drug, which greatly increases the risk of organ toxicity (Gaudana et al., 2010). As a result of the drawbacks associated with both systemic delivery and injections, the most widely accepted method of delivering drugs to the anterior segment of the eye remains via eye drop. While it is a widely accepted route of delivery, patient compliance remains an issue, especially in patients with impaired vision who may struggle with the administration process. As an alternative to the conventional eye drop delivery method, contact lenses (CLs) have been explored, as they have the potential to provide a sustained delivery system due to their polymeric structure and long duration in contact with the corneal surface (Dave et al., 2021). While CLs may be a promising avenue for drug delivery applications, this method of drug delivery has challenges that must be overcome before acceptance as a method for effectively delivering drugs to patients with ocular conditions. Obstacles that must be overcome when developing CLs drug delivery systems include the necessity for the visual transparency of the lens and the requirement for oxygen permeation, specifically due to the avascular nature of the eye and the need for direct application to the eye, requiring comfort from shear forces and limiting fouling properties of the lens itself while still dosing a therapeutic concentration of drug for a sustained period. These factors must be considered as the lens must be wearable for a prolonged duration to become accepted as a viable alternative to traditional eye drops (Maulvi et al., 2021).

An alternative area of development in ophthalmic drug delivery methods involves increasing the efficiency and efficacy of eyedrops themselves. If this can be accomplished, it has the potential to substantially increase patient compliance while simultaneously decreasing the need for more invasive drug administration techniques. To this end, the epithelial and mucosal layers of the cornea are a potential target for increasing the efficacy of ophthalmic drug delivery (Dave et al., 2021).

2 OVERVIEW OF THE ANATOMY OF THE ANTERIOR SEGMENT

The majority of the eye is considered avascular, as it has limited blood nutrient transport. The anterior and posterior segments have distinct structures that allow the eye to function, as well as allow visual stimuli to be processed before being delivered to the brain. The structure of the anterior segment of the eye consists of many layers, with more structures surrounding the ocular space that function in conjunction with the eye to provide nutrients to the ocular tissues. The iris

acts as an aperture, changing the amount of light that can reach the back of the eye to be processed. The ciliary body pulls on the iris to dilate or constrict the iris, allowing more or less light to enter the eye as needed. The space between the eyelid and the eye is known as the conjunctiva, which is responsible for production of the lipid layer, via the meibomian glands, and the aqueous layer of the tear film (Sridhar, 2018). The tear film itself is responsible for protecting the eye from the exterior environment and covers the surface of the eye. The tear film is comprised of three layers; a surface lipid layer that prevents evaporation and creates a smooth outer surface to provide clear vision, an aqueous layer that allows oxygen and nutrient transport and an inner immobilised mucosal layer, providing a wettable surface for the hydrophobic corneal surface (Fig. 2)(Chang & Purt, 2023). Tears are produced by the conjunctiva and are cleared through either evaporation from the ocular surface, or by nasolacrimal drainage via the nasolacrimal duct (Bachu et al., 2018).

The cornea, responsible for 80% of the visual processing power of the eye, can be broken into five layers; the outermost of which is a cellular layer known as the corneal epithelium, followed by an acellular layer known as Bowman's membrane, the stroma, which consists of tightly packed visually transparent cells, followed by Descemet's membrane, which is a collagenous barrier between the stroma and the corneal endothelium, which is a monolayer of cells (Fig. 3)(Naylor et al., 2019).

The corneal epithelium is responsible for the production of the mucosal layer that exists within the tear film. Tight junctions exist within the corneal epithelium and form the outer blood retinal barrier (OBRB). Due to the combination of the OBRB and the surface bound mucin, transport of nutrients and clearance of waste is limited through the corneal structure (Naylor et al., 2019). To reach interior structures, active nutrient transport occurs through Schlemm's canal through a layer of cells called the trabecular meshwork and into the aqueous humour. Due to the avascular nature of the eye, these pathways are integral for intraocular cells to receive the nutrients they require to sustain themselves (Karpinich & Caron, 2014).

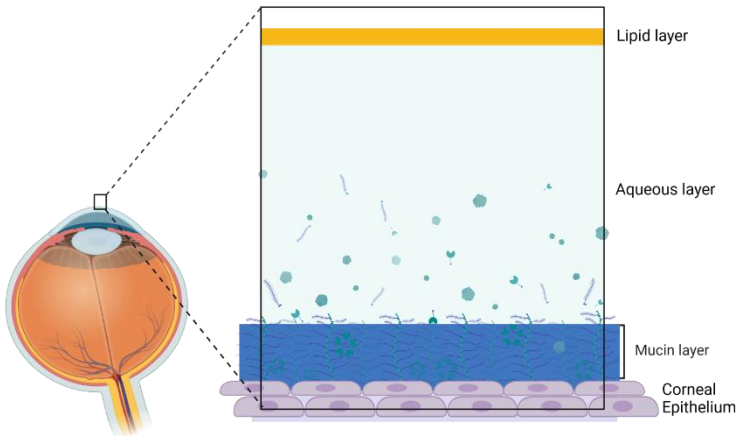

Figure 2: Overview of the anatomy of the tear film

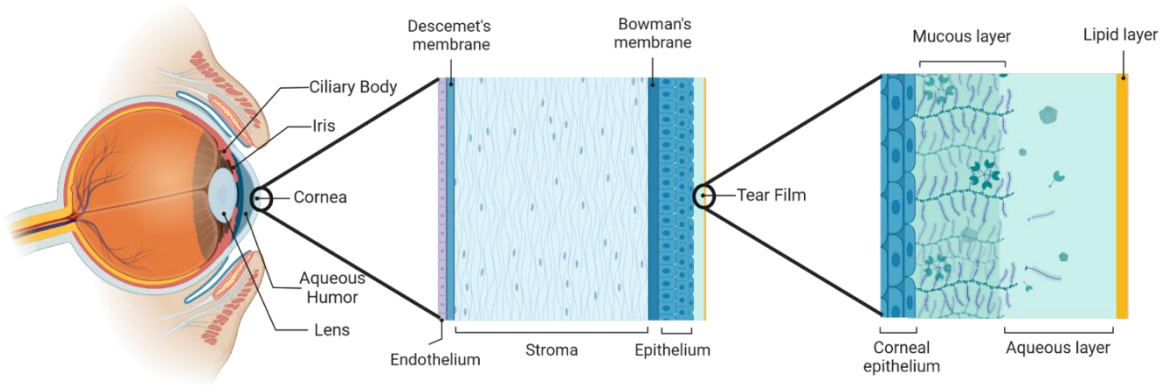

Figure 3: Overview of the anatomy of the cornea and tear film

3 OVERVIEW OF EYE DROPS

Eye drops remain the most common method of topical drug administration to date, with approximately 95% of all marketed ophthalmic drug formulations being applied as eye drops (Ahmed et al., 2023). The mucin within the tear film that is generated by the corneal epithelium creates a hydrophilic layer that traps debris and pathogens. Every 2-3 minutes the tear film restores itself, washing away this debris (Mangiacotte et al., 2020). This turnover, as well as the contained drug's inability to permeate the layers of the cornea, and the rapid tear drainage through the nasolacrimal pathway, are all factors involved in the drugs inability to reach targeted tissues. There are also other more niche factors, such as frequency of blinking, position of patient when applying the drops (standing or laying down), varying lacrimation, and so on (Naylor et al., 2019). Due to this low bioavailability, frequent dosing is required, which can lead to issues regarding patient compliance and may be difficult for mobility-impaired patients to conduct. Furthermore, as only roughly 5% of the drug reaches the target tissue, as much as 95% of the administered drug can be absorbed systemically through the eye's natural clearance pathways (Mangiacotte et al., 2020). This indicates that frequent dosing is required to have a desired effect on the target tissue. Furthermore, high concentrations of active ingredients must exist within the drops to achieve these effects, which may lead to complications such as organ toxicity as they are absorbed through the other means, such as the conjunctiva or through lacrimal drainage. These side effects could occur in greater magnitude in children, as the doses that exist in eye-drops are not adjusted for their physiology (Naylor et al., 2019).

4 OVERVIEW OF CONTACT LENSES

4.1 Materials of contact lenses

As eye drops are largely known to be an inefficient modality of drug delivery, alternative methods have been stipulated. One alternative delivery approach is through the use of ocular CLs. As of 2018, the estimated global market size for CLs was estimated to be worth $7.5 billion USD worldwide (PentaVision, 2017). These lenses could prove to enable more sustained drug delivery, as they maintain prolonged contact with the ocular surface and are not susceptible to run-off. As such, the concentration and volume of dosage required would be smaller as opposed to eye drops. CLs consist of both hydrophilic and hydrophobic components and can be made from a variety of different materials. Modern CLs are primarily made of both synthetic and non-synthetic hydrogels, but other materials such as polymethylmethacrylate (pMMA) have been used previously (Nicolson & Vogt, 2001). As of 2021, roughly 75% of all prescribed CLs are made with soft, silicone-based hydrogels (PentaVision, 2021).

Since transparency, oxygen permeability, and comfort remain issues for the design of a contact lens, choosing the correct material for the contact lens is of greatest importance. For instance, pMMA lenses are not frequently used for modern CLs due to their lack of oxygen permeability, meaning that they could only be worn for very finite periods of time before they had to be removed. Further development of CLs led to hydrogels in the 1960s as they had demonstrated greater oxygen permeability and flexibility, with the first hydrogel-based CLs being predominantly made from hydroxyethyl methacrylate (HEMA). While the oxygen permeability of HEMA proved to be greater than that of pMMA, it did not prove sufficient for the lenses to be worn for any periods longer than 24 hours. In the 70s, rigid gas permeable (RGP) materials were introduced as a more oxygen permeable alternative to HEMA, as RGP materials contained more hydrophobic silicone components which allowed lenses to be worn for periods as long as one month. However, the increase in hydrophobicity from the silicone components resulted in decreased compliance as the lenses were uncomfortable, in addition to poor wettability on the surface of the eye. In 1998, another adaptation of the contact lens was developed using purely silicone-based hydrogels, which were found to have high oxygen permeability, as well as increased wearing comfort (Musgrave & Fang, 2019). Currently, HEMA is the most used polymer in the creation of CLs. While HEMA itself is a water-soluble monomer, when polymerized it becomes poly-HEMA, a water insoluble and bio-inert material, with a high resistance to degradation and high chemical stability. Furthermore, it is not damaged by heat or pressure, and shares a similar density and water content to living tissue, making it an ideal hydrogel for CL production. Poly-HEMA hydrogels have an average water content of 40%, but this value can be manipulated through the alteration of polymeric crosslinking density (Mangiacotte et al., 2020).

Comfortability and ease of use are large factors in increasing compliance. High stiffness is undesirable, as it can lead to complications such as contact lens associated papillary conjunctivitis (CLAPC), which is caused by conjunctival irritation induced by the stiffness and edge profiles of a contact lens, or superior epithelial arcuate lesions (SEALs). To this end, the elastic modulus of the materials being used is of great consideration. The elastic modulus (or Young's modulus) is defined as the ratio of applied stress (σ) over the resulting strain (ϵ), and is defined by equation (1). A low elastic modulus indicates a material that is more rubber-like, meaning it has a more gradual slope in its elastic deformation region. Materials with a low elastic modulus will deform quickly but return to their original form easily (Alasfar et al., 2022). In terms of CLs, a low modulus value indicates a CL that will better deform on the eye. Conversely, a higher modulus value indicates a CL that is stiffer and therefore more easily handled and applied (Shihab Id et al., 2021).

$$E = \frac{\sigma}{\epsilon} \tag{1}$$

Early iterations of silicone hydrogel lenses are considered to have a high modulus, with estimates of up to five times that of conventional hydrogels, while more modern iterations are considered to have approximately two to three times higher than that of conventional hydrogels. The earlier iterations of CLs were recorded to have a 6% prevalence of CLAPC, and a 7% prevalence of SEALs, but has since been reduced to 3.6% and 4%, respectively, as the elastic modulus was reduced in newer iterations. Furthermore, rates of complications such as conjunctival flaps have been demonstrated to be much greater with overnight wear, as opposed to strictly during the day, with 37% and 3%, respectively. This complication is caused by a non-rounded lens edge profile, which causes splitting in the conjunctiva during extended wear (Young et al., 2010).

While flexibility in CLs is important to ensure comfort and maintain the integrity of the ocular surface and conjunctiva, higher flexibility can result in more deformation of the CL on the eye, possibly altering the dimensions of the lens. This could lead to a poorer performance of the lens to properly correct the vision of the wearer (Shihab Id et al., 2021). Furthermore, high flexibility in CLs can lead to decentration of the lens on the eye as it moves, which can cause increased eye strain and lead to further complications such as astigmatism or vertical coma (Remón et al., 2020). Considering this, the water content of the lens is of importance when considering the flexibility of a CL, as the water content of the CL is directly related to both its flexibility and refractive index, where a higher water content will increase its flexibility and lower its refractive index (Lira et al., 2020).

Finally, oxygen permeability is of great importance for prolonged CL wear, as prolonged wearing durations of CLs restricts oxygen flow to the intraocular space and can lead to hypoxia, which can further lead to oedema (corneal swelling)(Sulley & Dumbleton, 2020). Considering this, the value of oxygen transmissibility (Dk/t) is a useful measure. Dk/t is a quantification of the amount of oxygen that can diffuse through a lens at a given temperature and pressure, typically measured in Barrers/cm, where D is the oxygen diffusion coefficient in a given lens material, k is the oxygen solubility constant, and t is the thickness of the lens. Together, the product of Dk makes up the oxygen permeability coefficient of the CL, in Barrers. The higher the Dk/t value, the more oxygen permeable the lens (Ehrmann, 2024). In hydrogel-based CLs, the value of Dk is determined by the water content of the material, where an increase in water content will result in a higher Dk value (Sulley & Dumbleton, 2020). As such, Dk/t values must be taken into consideration in the materials used in creating CLs.

4.2 Methods of drug loading in contact lenses

As CLs offer a method of more sustained anterior ocular drug delivery, they are of great interest. A more controlled delivery of the drug would infer that less drug concentration would be required, and less systemic absorption would occur as the drug wouldn't be subject to conjunctival or nasal absorption, or nasolacrimal drainage. Considering this, there are several methods available to load drugs into a CL, such as soaking, molecular imprinting, or more recently, through the use of various nanoparticle delivery methods (Maulvi et al., 2016).

4.2.1 Soaking method

Most early CL drug release studies incorporated the soaking method. It is considered the simplest and most cost-effective method of anterior CL drug delivery, as it simply involves soaking a CL in a drug solution, utilising the hydrogel's water retention properties to absorb the drug. When a CL is placed on the eye, it is enveloped by the tear film, allowing diffusion on all surfaces of the CL (Fig. 4.)(Bengani et al., 2013).

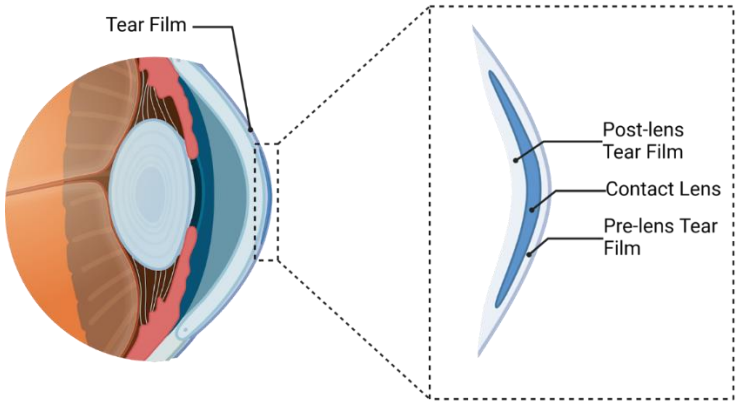

Figure 4: Contact lens in relation to the surrounding tear film

As the drug capacity in the CL relies on the specific composition of each material's absorbing properties, this method of drug delivery is strongly dependent on the material that the CL is composed of (Maulvi et al., 2016). This method has proven quite effective in administering ketotifen, an antihistamine used to treat allergic conjunctivitis, to the eye with minimal loss of the drug (Pall et al., 2023). However, this method comes with several limiting factors when being used with other drugs. It has been shown that higher molecular weight drugs such as hyaluronic acid cannot penetrate the aqueous channels of the CLs and typically are only adsorbed on the surface, limiting the efficacy and volume of drug delivered to the eye. Furthermore, increasing the concentration for soaking was found to have negligible impact on the sustained release of hyaluronic acid (Maulvi et al., 2015).

4.2.2 Molecular Imprinting

Molecular imprinting involves the creation of networks of cavities, called macromolecular memory sites, within the CL hydrogel material through the polymerization of functional monomers with a specific drug as a template. Once the monomers and drug molecules have polymerized, the template drug is removed, leaving behind a 3D network of well organised monomers that create molecular sites with an increased affinity for the specified drug molecule as well as loading capacity, allowing for a more prolonged sustained drug release period (Fig. 6.)(Maulvi et al., 2016).

Earlier studies in molecular imprinting by Alvarez-Lorenzo et al. have tested the effects of weakly cross-linked HEMA-based hydrogels with the addition of methacrylic acid (MAA) and methyl methacrylate (MMA) on drug-loading capacity and drug release capabilities for the release of timolol, a medication used to treat open-angle glaucoma and ocular hypertension (Barnes & Moshirfar, 2023)(Alvarez-Lorenzo et al., 2002). It was found that the incorporation of 100-400mM of MMA had negligible effects on the properties of the hydrogels, while the incorporation of 100mM of MAA into the hydrogels increased the loading capacity of timolol to therapeutically beneficial levels while retaining acceptable rates of release (Alvarez-Lorenzo et al., 2002). Other studies have suggested using acrylic acid as a functional monomer for molecular imprinting in CLs, as it does not alter the vision correcting properties of the lens, if required (Malakooti et al., 2015). Furthermore, the addition of small amounts of polymyxin B, a polypeptide antibiotic used in the treatment of infections (Scholar, 2007), during the developmental process of the molecular imprinting enabled better modulation of the loading and release profiles of the CL. However, the addition of too much polymyxin B can cause translucency in CLs, which could have adverse effects on their ability to correct vision (Malakooti et al., 2015).

While molecular imprinting proves a promising route for anterior ophthalmic drug delivery, there are several limitations that must be considered. While most molecular imprinting methods have no adverse effect on lens transparency or oxygen permeability, imprinting systems become sub-optimal if more than one drug needs to be loaded into the CL at a time. Additionally, higher concentrations of cross-linking monomers can increase rigidity of the CL, and the drug cost of the templates can be high. The final challenge this administration method faces is maintaining an appropriate therapeutic release window, as burst releases of a drug can be an issue (Zhang et al., 2020).

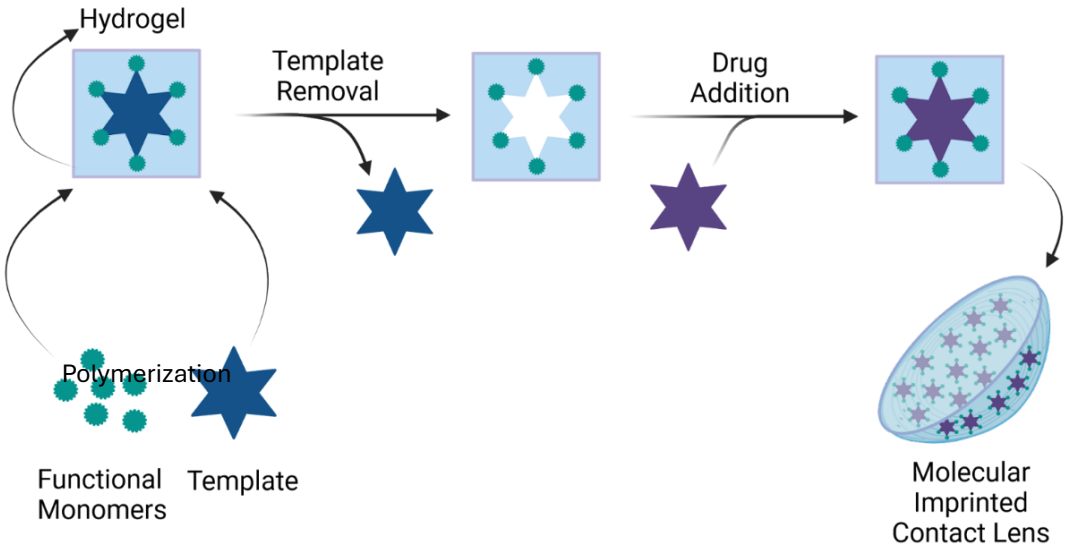

Figure 5: Molecular imprinting for specific drug loading in a hydrogel contact lens

5 METHODS OF NANOPARTICLE DRUG DELIVERY

Nanoparticles (also referred to as nanocarriers in a drug delivery context) are the most recent form of drug delivery system, offering a more precise delivery of drugs to a specified area (Patra et al., 2018). There currently exist several types of nanoparticle delivery (polymeric nanoparticles, liposomes, niosomes, micelles, etc.). In terms of CLs, these nanoparticles can be loaded in various ways, including soaking, during or before polymerization, or surface coating. Typically, the nanoparticles are incorporated into the monomers of the CL before polymerization (Choi & Kim, 2018). For anterior ophthalmic drug delivery, the method in which the nanoparticles are loaded into the CL will influence its ability to release, and each method faces its own challenges. However, each type of nanoparticle can be designed to be released in various ways such as diffusion, erosion, or triggered to release by external stimuli, such as changes in pH or temperature (Maulvi et al., 2021). This section will focus on a few of the more prevalent nanoparticle types of nanoparticles, in addition to the methods of anterior delivery currently being researched.

5.1 Polymeric nanoparticles

Polymeric nanoparticles are currently one of the most common forms of nanoparticle delivery. They are typically composed of various biodegradable polymeric materials such as polymethylmethacrylate (pMMA), poly(ϵ-caprolactone) (PCL), poly (D,L-lactide-co-glycolide) (PLGA), or polycyanoacrylate (PCA), in addition to naturally occurring polymers such as gelatin, chitosan, albumin, and sodium alginate (Vaneev et al., 2021). These nanoparticles have previously been loaded with timolol and incorporated into a methacryloxypropyl-based CL prior to polymerization, with no effect on water content and transparency. They further demonstrated a constant release of the drug over a period of 1 month due to timolol's hydrophilic nature. Conversely, with hydrophobic drugs such as those used in the treatment of allergic conjunctivitis, loading of nanoparticles into CLs proves more of a challenge. However, there are modalities that allow for a sustained drug release despite the hydrophobic nature of these drugs. A nanocarrier system composed of polycaprolactone (PCL), a hydrophobic polymer, was loaded with Loteprednol etabonate (LPE), an anti-inflammatory used in the treatment of allergic conjunctivitis, allowed for a sustained transmittance over the course of 12 days when tested in-vitro (Choi & Kim, 2018).

While these nanocarriers show promise in the delivery of hydrophilic drugs, there remain additional steps that must be taken in the administration of hydrophobic drugs. As such, the addition of various polymers, such as the case with PCL must be considered. Furthermore, the addition of naturally occurring polymers such as chitosan have previously demonstrated effective delivery of hydrophobic drugs such as indomethacin, another anti-inflammatory drug (Vaneev et al., 2021). Furthermore, chitosan has mucoadhesive and mucopenetrative properties which aid in the sustained delivery of drugs. This will be further discussed in section 6 of this review.

5.2 Polymeric Micelles

Micelles describe a sphere-shaped vessel made of amphiphilic monomers. When these monomers are introduced to aqueous media exceeding their critical micellar concentration (CMC), they self-organise into a core/shell structure with the shell being composed of hydrophilic heads and the core being composed of hydrophobic tails (Fig. 6.). These hydrophobic cores can then be crosslinked with hydrophobic drugs to facilitate their release at the target site (Mandal et al., 2017).

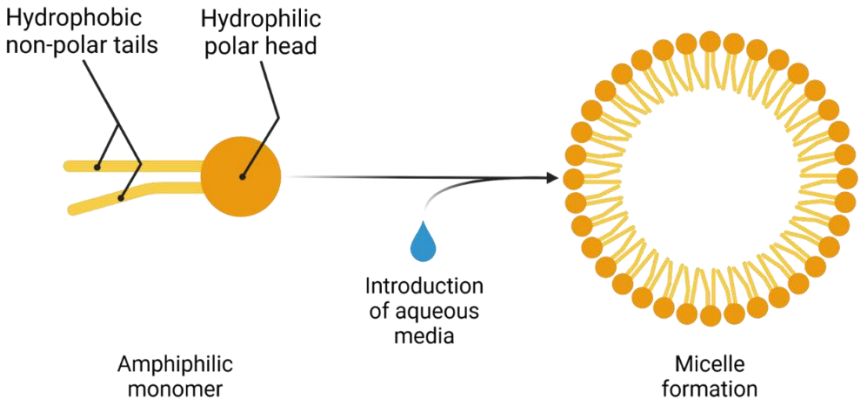

Figure 6: Assembly of amphiphilic monomers into a micelle structure when introduced to aqueous media exceeding their CMC

Polymeric micelle delivery vehicles are typically made up of a hydrophilic polyethylene glycol (PEG) shell and a hydrophobic Pluronic-composed core, such as polylactide (PLA), PLGA, or PCL (Vaneev et al., 2021). A study by Sun et al. utilised a micelle system composed polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymers (PVCL-PVA-PEG) as a delivery system to carry Myricetin (Myr), a hydrophobic drug used for its versatile array of medical applications, including as an anti-inflammatory, to the eye via eye drop. This system demonstrated greater aqueous solubility and stability of Myr, overcoming some of the administration limitations typically associated with topical eye drop application (Sun et al., 2019).

Inclusion of polymeric micelles in CLs share the same variety of techniques as polymeric nanoparticles and can be further utilised for the delivery of antifungal agents (Mandal et al., 2017). Through the utilization of a hydrogel delivery system rather than topical eye drops, micelle delivery could be further sustained.

6 MUCOADHESION AND MUCOPENETRATION FOR INCREASED EFFECTIVENESS IN NANOCARRIERS

Mucoadhesion describes a delivery system's ability to bind or adhere with the mucosal membranes that exist within the human body, increasing the amount of time a drug will remain at the target site, and thereby increasing the efficacy of the delivered drug. Mucopenetration describes a material's ability to permeate the mucus layer to reach the underlying epithelial layer, and is directly affected by the drug carrier's size, charge, and hydrophobicity. An increase in mucopenetrative properties would allow for more efficient transport of a drug to the ocular tissue (Dave et al., 2021)(Schattling et al., 2017). In terms of drug delivery, mucoadhesion and mucopenetration are of great interest when considering the delivery of drugs via nanocarriers. Increasing the mucoadhesive and mucopenetrative capabilities of nanocarriers has the potential to increase the residence time of the drug on the eye and thereby improve the overall effectiveness of the drug delivered (Sosnik et al., 2014). In the anterior segment of the eye, there are two mucus layers of interest. The first is the mucus layer produced by the corneal epithelium that exists within the tear film, and the second is the mucus layer that exists on the surface of the conjunctiva (Shumway et al., 2023).

6.1 An overview of mucus

Mucus is defined as a protective layer of fluid that acts as a barrier against foreign debris or pathogens that may cause harm and provides lubrication against shearing forces. Furthermore, mucus is important to homeostatic functions, such as ion transport and water balance. Within mucus exists hydrophilic, negatively charged (anionic) molecules known as mucins. Different forms of mucoadhesive interactions can occur within mucin when a nanocarrier is introduced. Polymeric nanocarriers are propagated by covalent or non-covalent diffusion through entanglement with mucin fibres. Furthermore, due to their anionic nature, mucins that exist within the cornea and conjunctiva are the driving factor and primary target of cationic mucoadhesive agents (Sosnik et al., 2014).

6.2 Mucoadhesive and mucopenetrative nanocarriers

Several types of nanocarriers have demonstrated mucoadhesive properties with varying degrees of effectiveness. Particular mucoadhesive nanocarrier types of note are: hydrogen-bonding, cationic, thiolated, and boronic acid based (Dave et al., 2021). This paper will focus primarily on cationic nanocarriers and their mucoadhesive properties. Cationic nanocarriers work by forming a positive charge on the surface of the nanoparticles; the cationic (positively charged) surface of the nanocarrier forms an ionic interaction with the mucus layer within the cornea, which is anionic (Nirbhavane et al., 2020).

Cationic nanocarriers are of particular interest, specifically cationic chitosan polymers, have been largely explored due to their naturally strong inherent mucoadhesive properties (Dave et al., 2021)(Albarqi et al., 2023). Chitosan is a natural polymer produced from the exoskeletons of crustaceans, making it easy and relatively cheap to obtain, as well as giving it a low ecological impact. In addition to its mucoadhesive properties, it is biodegradable and carries a natural positive charge with high biocompatibility, giving it a high retention time. Furthermore, chitosan has been observed to increase the mucopenetrative capabilities of nanocarriers, as well as the ability to loosen the tight junctions that exist within the corneal epithelium (Katiyar et al., 2014)(Albarqi et al., 2023). Chitosan can be crosslinked using its existing free amino group (Fig. 7.) with the aldehyde group of a crosslinking agent, such as dialdehydes (Jóźwiak et al., 2017)(Albarqi et al., 2023).

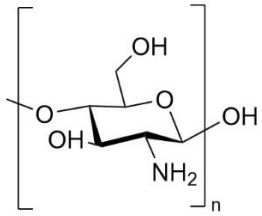

Figure 7: Molecular structure of chitosan, showing its free amino (NH_2) group.

These chitosan-based nanocarriers, when administered to the eye, require specific properties to ensure adequate mucin binding, and are largely dependent factors within the interaction environment. Too high concentration causes the polymeric chitosan chains to entangle, limiting its capability to interact with the surrounding mucins. Similarly, too high concentrations of mucin can lead to the same type of entanglement, as well as the formation of gel networks. This indicates that a proper ratio of chitosan to mucin must be maintained. Furthermore, the pH of the surrounding environment must be taken into consideration, as an ideal pH value of 5.2 must be maintained in order to prevent electrostatic repulsion forces between the chitosan and mucin (Collado-González et al., 2019).

Overall, if these conditions can be met, chitosan-based nanocarriers can prove to enhance ocular drug delivery through the loosening of tight junctions, improving residence and therefore prolonging the release of the contained drug through improved mucoadhesive and mucopenetrative properties. However, several steps must be taken to ensure proper drug administration can occur, as prolonged nanocarrier residence times could potentially facilitate the over-accumulation of the released drug within ocular tissues, which potentially increase the risk of therapeutic effects (Albarqi et al., 2023).

7 ALTERNATIVE APPLICATIONS OF HYDROGELS IN ANTERIOR SEGMENT DRUG DELIVERY

While the most commonly explored method of hydrogel-based anterior segment drug delivery is via CLs applied directly to the cornea, other avenues of treatment are possible. A recently emerging application in the field of hydrogels is that of thermogels. Thermogels are hydrogels that are liquid at room temperature, and change to gel after exposure to physical stimuli, such as changes in temperature (temperature triggered), pH (pH triggered), or ionic strength (ion triggered). Temperature triggered thermogels exist in solution, as hydrogen bonds between water molecules and hydrophilic polymer groups continuously facilitate the dissolution of the polymer chains. They continuously exist in this state until triggered by what is known as the lower critical solution temperature (LCST). Once the temperature of the solution rises above the LCST, these hydrogen bonds are broken, and the transition from liquid to gel occurs (Irimia et al., 2018)(Ross & Sheardown, 2023). In terms of the eye, these state-changing properties allow for easy administration of the thermogel via eyedropper, which will then transition to a gel when the liquid drops are exposed to the ambient temperature within the inferior fornix (Fig. 8.)

Several recent studies conducted by Ross et al. have explored the possibility of applying these temperature triggered thermogels to the inferior fornix in the treatment of several conditions as simple as allergic conjunctivitis, to more complex conditions such as cystinosis, a genetic condition that causes an accumulation of crystals composed of the amino acid cysteine in various tissues throughout the body, including the conjunctiva and iris (Ross, Mofford, et al., 2023). For treatment of allergic conjunctivitis, the hydrogels were utilised chitosan as a crosslinking agent, as chitosan-based hydrogels have proven to have biodegradable, biocompatible, and muco-adhesive properties, as well as antifungal and antimicrobial effects. Similar to CLs, these hydrogels offer a more sustained drug delivery when compared to conventional eye drops (Ross et al., 2022). Furthermore, chitosan's biodegradable properties allow for an application that can be degraded by lysozyme, an enzyme found in very high concentrations in tear fluid. This means that the thermogel would naturally dissolve over a controlled period (typically 1-4 days) and be cleared by the eye's own mechanisms. With the addition of a disulfide monomer, the mucoadhesion properties of these thermogels could be controlled to required specifications (Ross & Sheardown, 2023)(Ross et al., 2023). Finally, as these particular thermogels are not applied to the cornea, they do not obstruct vision or directly affect the oxygen permeability of the cornea. As such, transparency is not a factor that needs to be considered in their production.

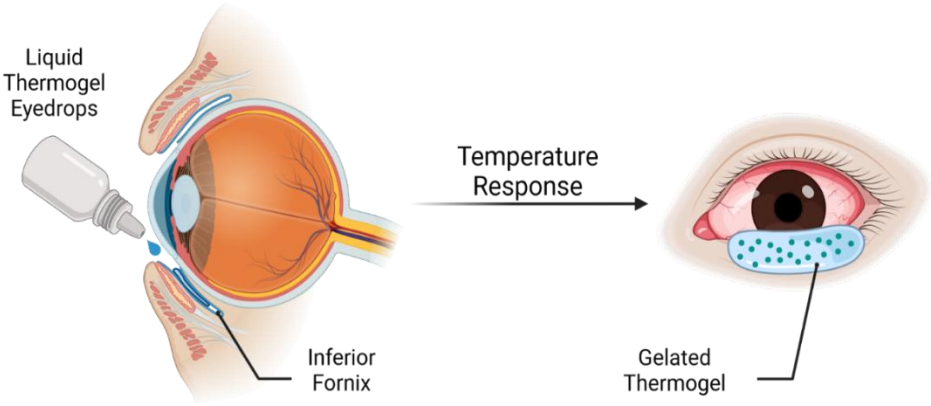

Figure 8: Application of liquid thermogel, and its transition to gel when exposed to a change in temperature within the inferior fornix.

8 COMPARISON OF METHODS AND ADDITIONAL CONSIDERATIONS

Each of the drug delivery methods described have their respective advantaged and drawbacks. As such, the method in which a drug is administered must be carefully considered when deciding treatment for a patient, such as compliance and quality of life for the patient. As topical eye drops still dominate the market due to their ease of use and wide availability, future research into mucadhesive nanoparticle delivery systems would allow for minimal disruption to the existing market, as patients are already accustomed to eyedrops. Further research in this regard would lead to an increase in drug retention times and thereby increasing patient compliance as drops would need to be administered less frequently (Sosnik et al., 2014). While CLs remain a good alternative to topical eye drops, the properties of oxygen permeability and opacity remain a drawback that must be considered for prolonged CL wear. Furthermore, there are other factors that need to be considered by patients when using CLs, such as maintaining proper CL hygiene to avoid infections (Center for Disease Control, 2024). Additionally, according to the Center for Disease Control (CDC), as of 2024 approximately 45 million US citizens actively wear CLs (Center for Disease Control, 2024). This accounts for approximately 13.5% of the current US population, which indicates that the number of patients who are accustomed to wearing and caring for CLs is relatively low. Considering this, it is imperative that patients are properly informed of the risks associated with CL wear, as well as how to properly care for them to reduce risk of infection. Comparing the use of CLs to eye drops, it is evident that eye drops are easier to use, and carry less potential risk to wearers, however, the prolonged contact of CLs with the eye, as well as their efficient drug loading options continue to make them strong options for drug delivery. Finally, thermogels prove a promising alternative to CLs for anterior drug delivery, however, several limits remain. Thermogels have poor inherent mucoadhesive ability which necessitated the addition of a disulfide monomer. Additionally, they require chemical alteration of their mechanical properties to compensate for the weak hydrophilic/hydrophobic interactions that drive the gelation process. Finally, thermogels are opaque. While this is not an issue when they are applied to the inferior fornix, it does limit their ability to be applied directly to the cornea, thereby restricting the available topical applications available to it (Ross & Sheardown, 2023).

Another point of consideration for developing drug delivery methods is their potential commercial prospects. Ocular drug delivery research is expanding rapidly as the global demand for more methods of delivery grows. As of 2022, the global ocular drug delivery market is estimated to be $67.7 billion USD and is projected to increase to $115.5 billion by 2032 with a compound growth rate of 5.5% (Allied Market Research, 2023). Considering this, there is great incentive for researchers to develop more efficient, safer, and more desirable ocular drug delivery methods that will improve patient compliance and lower drug costs through increased efficiency, such as increased drug retention times.

9 CONCLUSIONS

Based on the collected information, the following conclusions can be made:

1) While eye drops remain the most common form of topical drug delivery for the anterior segment of the eye because of its easy administration, hydrogel delivery mechanisms promise a much more consistent and versatile delivery mechanism.
2) Hydrogel delivery systems in the form of CLs offer a convenient method of treatment for all, but particularly in those who already require them for vision correction purposes, as these individuals are already accustomed to their application and removal.
3) Thermogels demonstrate promise in a wide range of treatment options as they are easily administered, dissolvable, and naturally cleared from the eye, eliminating the need for manual removal.
4) Hydrogel structures make available a wide array of administration techniques that can be tailored as needed for many applications. In CLs, the challenge of opacity and oxygen permeability remain a limitation that must be consistently monitored and addressed as different drug formulations and polymeric materials are used in their creation. Similarly, dissolvable thermogels suffer from issues with opacity that must be overcome for corneal applications that must be overcome for clinical acceptance.
5) Nanoparticle delivery systems are of great interest, as they allow for increased residence time, more consistent therapeutic windows, and better customizability of delivery with tailorable triggers for release via external stimuli.
6) The inclusion of mucoadhesive and mucopenetrative capabilities to nanoparticle carriers offers many possible advantages, such as better sustained drug delivery.
7) Improving mucoadhesion and mucopenetration properties of drug delivery systems also provides a method to increase the efficacy of topical eye drops. However, for any application, steps must be taken to ensure that over-accumulation of the released drug does not occur to avoid unforeseen therapeutic effects.
8) There is a large potential market for the ongoing development of ocular drug delivery methods, with the global market estimated to value $115.5 billion by 2032.

10 FUTURE CONSIDERATIONS

Future research into mucoadhesion and mucopenetration has the potential to yield increasingly long residence times, thus substantially improving patient compliance as the need for consistent direct application of topical products would be drastically reduced. Furthermore, the mucopenetrative capabilities of micelles, as well as the tight junction loosening properties of chitosan yield the potential for topically applied drugs to reach the posterior segment of the eye via corneal or scleral channels, considerably improving patient acceptance and compliance in posterior drug delivery. This is of great interest as the primary delivery method for posterior segment treatment remains via injection. Finally, further research into hydrogel materials for CLs to ensure adequate oxygen permeability and tensile resistance qualities would allow CLs to remain on the eye for more prolonged periods of time, increasing the effectiveness of CL-based drug delivery systems, as well as improving the compliance of those who require them.

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Note:

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