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Material, immunological and practical perspectives on eye drop formulation

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Abstract:

The most inexpensive, common form of topical drug delivery for the eye is eye drops. Current treatments for common diseases such as glaucoma and dry eye disease rely on aqueous polymeric eye drops that are readily available over the counter. Eye drops offer a non-invasive treatment strategy; however, this can be at the detriment to therapeutic efficacy when compared to more invasive methods such as surgeries, implants and injections. Multiple avenues to improve the efficacy of the topical delivery of drugs to ocular tissues are currently being explored and much of this work centres on investigating improvements to the formulation of eye drops. These improvements focus largely on prolonging the bioavailability of the therapeutic agent, but this is often in preference to improving other patient-focused or clinical factors. In this review, conventional, commercially available polymer eye-drops are explored and the ability for current and future innovations to maintain the existing benefits of eye drops to the patient is assessed. The final form of the drops (liquid, gel or other), the chosen materials in the formulation and the immunological implications for the user are explored. There is currently no consensus for how to most effectively improve the ocular retention and drug-delivery capabilities of eye drops, but key issues are highlighted in the context of current methods under development, and potential questions and considerations for future innovations are raised.

1. Introduction: The barriers to topical ocular drug delivery

Ocular drug delivery is a challenging but rapidly evolving area of research. It is well documented that biological systems that keep the eye free of debris and pathogens and protect the vital posterior structures, present a barrier to topical drug delivery [1]. Usual treatments for ocular diseases include intraocular injections, surgical interventions and/or eye drops [2]. Eye drops are most commonly used for treating conditions affecting the anterior structures of the eye (Figure 1) – the cornea, conjunctiva, sclera and trabecular meshwork – as passage through these structures to the posterior segment of the eye is relatively restricted [3]. The cornea comprises sublayers with different properties; the epithelial and endothelial layers are lipophilic, and the stroma is hydrophilic [3b, 4]. These properties heavily influence which drugs and carriers are effective in passing across the cornea, with positively charged carriers showing higher penetration than neutral or negatively charged carriers [5]. Drugs that are both lipid- and water- soluble (amphiphilic) also show improved penetration [4, 6].

1.1 The anterior ocular immune system

The anterior segment of the eye is considered 'immune privileged', with a higher level of immunological regulation of some immune responses occuring within the cornea and anterior chamber, to limit inflammation that can threaten tissue integrity, and thus compromise vision [7]. So-called 'immune privilege' applies to intraocular tissues, that are protected by a blood-ocular-barrier, developing tolerance to certain stimuli on exposure, rather than inducing the expected inflammatory response that would occur in other peripheral tissue sites such as the skin [8][9]. Mechanisms of immune privilege of the anterior segment have been widely reported, and are largely explained by three major components including formidable physical and cellular barriers, immunological tolerance and a local immunosuppressive microenvironment [7b] This allows for some degree of protection against infection, whilst protecting the delicate, non-regenerative intraocular cells and tissues against the ramifications of repeated inflammatory responses, which can result in the loss of transparency of key tissues and ultimately blindness [3b, 10]. The bias towards tolerance is maintained through the presence of immuno-suppressive factors, such as transforming growth factor-beta-2 (TGF-b2) [11] and alpha-melatonin stimulating hormone [12], which limit or direct the activity of both the resident and infiltrating leukocytes in the cornea and anterior segment . In addition to mechanisms that regulate the nature of the adaptive immune responses, the resilience of the ocular surface in avoiding infection - despite its exposed location - is due to a robust repertoire of anatomical features (including stratified epithelium, apical epithelial tight junctions,) and innate immune components such as tear lysozyme, anti-microbial defensins and secretory IgA. Most non-viral infections that occur in the cornea are usually secondary to mechanical damage to the ocular surface, from injury or contact lens wear [13], or impaired barrier integrity, which compromises the innate ocular defence mechanisms [10a, 14].

When considering the immunological implications of eye drops, it is the anterior tissues that are of particular interest (the conjunctiva, cornea and sclera), as these tissues are both in contact with and treated directly by these topical therapies. The immune cells naturally present in the anterior tissues of the eye can change their phenotype and function depending on the inflammatory environment and the disease state [15]. It is also important to recognise the diverse functions of the tear film, especially if an eye drop is to be designed to aid/replicate those functions.

1.1.1 The tear film

Tears lubricate and smooth the ocular surface and the components of the tear film work to trap debris (mucins), kill pathogens (lysozymes, phospholipase, etc), facilitate the aggregation of the neutralised foreign bodies (sIgA) and assist with the removal of said bodies through blinking [16].

The aqueous content of eye drops plays an important role in lubricating the ocular surface and the osmolarity of the tear film is key to preserving the integrity of the ocular surface barrier. Tear hyperosmolarity is regarded as both one of the most important indicators and primary causes of dry eye

disease [17]. Tear hyperosmolarity, and as a result tear film instability, can lead to the onset of inflammation of the corneal epithelial layer [18].

Mucins act to promote an optimally lubricated ocular surface by supporting the spreading of the bulk of the tear film over the corneal and conjunctival tissues. In particular, secreted, gel-forming MUC5AC and cell adhesive MUC1 facilitate pathogen removal by trapping the pathogen and preventing its adhesion to the underlying epithelial tissue [16b, 19]. The longer, surface adhesive mucins also allow for the formation of reservoirs of oxidative enzymes, defensins, lysozymes and lactoferrin – proteins produced by scavenger cells - neutrophilic granulocytes - that are attracted to inflammation – which work to reduce the adhesion of bacteria and remove damaged host tissue [16b, 20]. Certain molecules are bactericidal: Gram-negative bacteria are killed by lysozymes which split their muramic acid linkages [16a, 21], whereas secretory phospholipase A2 acts against Gram-positive bacteria [16], as do lactoferrin and transferrin which - as the names indicate - bind iron [16a, 20]. Psoriasin, an antimicrobial agent found on the skin, has also been detected at the ocular surface [22].These mucins can also interact with polymers to facilitate the beneficial mucoadhesive properties of some eye drops [23]. In order to stabilise the tear film these mucins are hydrophilic, and the longest (MUC16) have a MW of around 2.5 million D. Polymers exhibit mucoadhesion through a number of possible mucin-polymer interactions which can be electrostatic (hydrogen bonding or electrostatic binding) or through physical entanglement (Figure 9) [19c, 24]. As mucoadhesion therefore requires direct contact between the polymer and the mucosal layer, the wettability of the polymer matrix and the contact angle between the two layers are vitally important [25].

The primary antibody present in tears is secretory immunoglobulin A (sIgA), which is produced in the lacrimal gland and works to prevent bacterial adhesion, aggregate neutralised pathogens and allow clearance of the pathogens from the ocular surface [26] [16b]. It has also been associated with the increased chemotaxis of neutrophils and other immune cells during the prolonged period of eyelid closure during sleep [27]. Tear lipids can also augment the bactericidal properties of tears, as short-chain lipids affect the surface properties of the bacterial cell membrane, and long-chain lipids have a direct effect on bacterial metabolism [20, 28]. It has been shown that tear film lipids can induce cell lysis, distortion and cell wall damage in both Gram-negative and Gram-positive bacteria [28]. These processes all act as part of a wider complex mechanism of ocular surface protection. This system remains virtually impenetrable to pathogens unless there is a physical disruption to the barrier or injury to the tissue.

1.1.2 The cornea, sclera and conjunctiva

Research in both human and murine models has demonstrated, after substantial debate, that bone marrow derived macrophages ($CD45^+$ $CD11b^+$ $CD11c^-$) and dendritic cells ($CD45^+$ $CD11b^+$ $CD11c^+$) reside in the healthy cornea, more specifically in the stroma (Figure 1) [29]. It has also been widely reported that dendritic cells and macrophages become more abundant in ocular tissues as disease severity and inflammation progress, as with elsewhere in the body [29a, 30]. It has been suggested that dendritic cells, in particular, are recruited to the cornea from the limbus [20, 31]. Not all macrophages and

dendritic cells in the cornea are mature and ready to act as antigen presenting cells, as approximately 70% of resident tissue macrophages are negative for the MHC class II complex, which is a molecule critical for activation of T lymphocytes [31-32]. Epithelial tissues elsewhere in the body are associated with a much wider variety of leukocyte subsets, so it is suggested that resident corneal macrophages have the ability to adapt after exposure to certain stimuli (such as trauma) to impart wound-healing functions [29a, 30d, 33]. Previously, the idea was upheld that macrophages act as part of the innate immune system and dendritic cells as part of the adaptive immune system, however in the eye these lines are blurred due to the adaptability of both cell types, and their role in the tolerance and wound healing responses [30d, 34]. Cytokines regulate the recruitment and function of inflammatory cells that play critical roles in epithelial cell regeneration and stromal remodelling [29a, 31].

The limbus, which defines the border between the transparent cornea and the non-transparent sclera, is home to the blood and lymphatic vessels that provide a pathway for the antigen presenting macrophages and dendritic cells to engage with T-lymphocytes [31]. Gamma-delta (γδ) T-cells, which primarily reside in the limbus, have been shown to be pivotal in the regeneration of corneal epithelial tissue after injury [35]. In mice, specific T-helper cells have been shown to gather in the limbus and then spill into the conjunctiva during an inflammatory response, leading to conjunctiva-related allergy symptoms [36].

The activities of the immune cells and the limbal vasculature are influenced by the release of histamines and prostaglandins by immunocompetent cells residing in the conjunctival epithelium [29b]. The conjunctiva is home to the same immune cell types that reside in the cornea (i.e., dendritic cells and macrophages) [20] but also has its own lymphatic drainage, allowing rapid trafficking by the antigen presenting cells and the induction of a rapid response to pathogens and/or injury [26]. The conjunctiva also contains its own collection of immune cells such as T-cells, antibody secreting B-cells and histamine producing mast cells, which are arranged as so-called Conjunctiva Associated Lymphoid Tissue (CALT) [37]. As a result, the conjunctiva is far more prone to inflammatory and allergic responses than tolerance responses compared with the cornea [20].

2. Topical ocular drug delivery: Eye drops

Eye drops are applied directly to the cornea or into the conjunctival sac. Eye drops can be used for therapeutic drug delivery (e.g., corticosteroids, antibiotics, etc.), or for symptom management (e.g., artificial tears for dry eye disease). Eye drops typically include a solvent, electrolytes, a thickening agent (see Table 1), an active agent/drug (see Table 2) and in some cases a preservative (e.g., benzalkonium chloride). In addition, with the intent of mirroring natural tears, eye drops have an optimum pH of approximately 7.4 and are osmo-regulated [7a].

Polymers were first used within eye drops to take advantage of their mucoadhesive properties and improve the residence time and resistance to lacrimal clearance of the drops [3a]. Conventional aqueous eye drops are rapidly cleared by blinking and lacrimal drainage, which creates severe limitations to the

bioavailability of any therapeutic agent being delivered. Eye drops are said to provide a bioavailability of around 5% of the delivered drug [38]. Predictions of the average residence time of eye drops on the ocular surface vary greatly, with there being multiple methods of assessing this in both clinical and research settings. Optical Coherence Tomography (OCT) can be used for *in vivo* assessments in clinical settings, and has shown retention times of up to 60 minutes with gel eye drops, and significant differences in the clearance rates for gel and aqueous drop formulations [39]. It is more common for residence time to be measured as a function of tear film break up time (TFBUT) using fluorescein, which provides values ranging from 10 to 90 minutes [40]. The nature of the drug being delivered, the polymer additive, its concentration and the use of preservative can be adapted to create the best possible combination of properties for the desired treatment effect. These changes only have minimal impact on the objectively low efficacy of eye drops compared to more invasive treatments (e.g., such as intraocular injections) for certain diseases [2]. Despite this, eye drops still offer an attractive treatment option, due to their ease of administration, versatility and low cost.

Formulation decisions made purely on the potential therapeutic efficacy can disregard factors such as patient comfort, cost and the ease of manufacture. In order to continue to pursue improvements in topical ocular drug delivery, it is important to understand the reasoning behind the use of eye drops as a treatment, and the choices behind currently available formulations.

2.1 Conventional polymer additives for eye drop formulations

Eye drops formulated for the management of dry eye disease, which involves chronic damage to the ocular surface and leads to eye discomfort and inflammation (particularly in the advanced stages of the disease [17]) typically use polymeric agents to provide ocular lubrication and/or stabilise the tear film [17, 41]. Polymers also increase the ocular retention time of the drops compared to purely aqueous solutions. Certain charged polymers (of which many are listed below) offer the advantage of mucoadhesion – adherence to the mucosal layer of the tear film, which further increases the residence time of the drops on the ocular surface [6, 42]. Currently, commercially available eye drop products will often include one, or more, of the following biocompatible polymeric agents:

2.1.1 *Natural Polymers*

Various ethers of different viscosities and solubilities can be harvested from cellulose, including carboxymethylcellulose (CMC) (Figure 2) and hydroxypropylmethylcellulose (HPMC) (Figure 3) [43]. These inexpensive polymers are found in many commercial eyedrops (see Tables 1 and 2) as mucoadhesive thickening agents. Cellulose alone is poorly soluble, however CMC, as a cellulose ether, overcomes this drawback [44]. Their renewable source qualifies them as sustainable polymers [43].

The viscosities of eyedrops created with CMC are directly proportional to the molecular weight of the CMC chains, and CMC solutions can reach high viscosities without the presence of crosslinks [45]. Viscosity is also influenced by the pH and ions in the solvent/solution as this alters the conformation of the

polymer chains [46]. CMC is polyanionic and the presence of multiple hydroxy groups provides CMC with mucoadhesive, hydrophilic properties [6, 47]. This also enhances swelling in CMC gels, branding them 'superabsorbent', and allows CMC to be pH responsive [43]. The mucoadhesive properties of CMC (and other polymers) are advantageous for drug delivery using eye drops. Compared to medicated non-polymeric (non-viscous) drops, medicated CMC drops have been shown to improve the ocular concentration of the glaucoma drug timolol by 300-900% [48]. CMC is, however, most commonly used in artificial tear eye drops, which are used to provide supportive relief of dry eye symptoms, rather than in other therapeutic drugs. Although CMC is efficacious for the symptomatic treatment of dry eye disease, there are now artificial tear formulations with more advanced components, such as Sodium Hyaluronate [45].

HPMC (Figure 3) is less viscous than CMC but shows superior properties as an emollient – an important factor for treating dry eye disease and promoting epithelial health [45]. HPMC is used both as a thickening agent in medicated drops, and as a mucoadhesive and treating agent in artificial tear drops. HPMC and HPMC-composite microspheres have also been created and tested for drug delivery applications and shown favourable drug delivery profiles in the gut [49].

Hyaluronic acid (HA) (Figure 4) is a naturally occurring polymer formed of linear polysaccharide chains, with sub-units of d-glucuronic acid and N-acetyl-d-glucosamine. These polysaccharide chains form with multiple hydrophilic anionic sites, which attract water molecules and allow HA solutions to become viscous and show beneficial rheological properties [44]. The molecular weight of the HA naturally present in the body elicits different immunological and cellular responses, with shorter chains appearing more conducive to cell growth and repair than long chain forms [44, 50]. This has potential repercussions for the systemic effects of HA use. Chain length has also been found to have a direct influence on the appropriate concentration of HA that should be incorporated into eye drops to allow for improved ocular retention and viscoelasticity. For a given concentration, it was found that, in most cases, commercially available eye drops only reach one third of the optimum chain length value [51].

HA is incorporated into eye drops to manage dry eye (artificial tears) but is not commonly used in medicated drops. HA has a higher ocular retention compared to CMC or HPMC, and has also been shown to have effects on corneal epithelial cell healing in animal models [45] and to improve corneal recovery in patients with superficial punctate keratitis compared to CMC [52]. Larger studies have shown comparable results between CMC and HA with respect to the stabilisation of the tear film after cataract surgery [53], and clinical trials using HA eye drops demonstrate the efficacy of this therapy for improving symptoms and clinical signs in moderate-to-severe dry eye disease over three months [54]. Although HA shows the same, if not improved, benefits with respect to on-eye retention and epithelial health compared to CMC and HPMC in the treatment of dry eye disease, it is infrequently used in medicated drops for other eye conditions. HA does not show a significant detrimental drug binding effect [55]. The exclusion of HA from medicated drops could be due to cellulose based polymers being of lower cost and simpler synthesis.

2.1.2 Synthetic Polymers

Polyethylene-glycol (PEG) (Figure 5) and polypropylene-glycol (PPG) are biocompatible synthetic polymers [56]. PEG and PPG are usually used as a backbone and then modified in various ways to create the desired properties. In comparison to CMC, PPG/PEG eye drops maintain a higher optical clarity after use, which can improve the patient experience and subsequently could improve compliance with treatment regimens [57]. When chain length exceeds a threshold of 200kDA, PEG exhibits mucoadhesive properties, but still shows limited adhesion in comparison to CMC [23f]. Used either separately, or in conjunction as a mixture or co-block polymer, PEG and PPG polymers are relevant to a spectrum of medical and industrial applications. PPG and PEG have been used alongside hydroxymethyl-guar (a naturally occurring gelling agent) to increase the viscosity of eye drops [57-58]. This combination has been shown to be effective as a therapy for dry eye disease [58-59].

PEG is amphiphilic and therefore very versatile and modifiable. These properties render PEG a common choice for testing hybrid lipid-polymer systems and for modifying the surface of difference carriers [60]. PEGylation is the name given to this process. As PEG does not illicit an immune response, it is used to dampen the potential response to an otherwise immunogenic carrier by modifying the surface charge or acting as a bridge for other molecules which illicit the desired immune response [60b]. PEGylation can also modify the solubility of proteins – such modifications could make a vital difference to the penetrability of a carrier through the corneal barrier, for which charge is a vital factor.

Polyacrylic acid (PAA) (Figure 6) is another synthetic hydrophilic polymer used to create superabsorbent gels for nappies and cosmetics under the commercial name 'carbomer' [61]. Carbomers are traditionally synthesised in a benzene solvent, raising issues for medical applications. Other solvents, such as ethyl acetate and cyclohexane [62], can be used as an alternative. Most commercial drops that describe themselves as 'gel' drops use carbomers. Carbomers do gel, however the properties of these gels are heavily influenced by pH, solvents and surfactants; their rheological properties become less favourable and more unpredictable with variations in these factors (pH, solvents and surfactants) in the formulation conditions [63].

Poly-vinyl alcohol (PVA) (Figure 7) is a common synthetic polymer used to enhance the viscosity of eye drops. Synthesis of polyvinyl alcohol involves hydrolysing polyvinyl acetate [64]. Thiolated PVA is mucoadhesive, and even short chain PVA could enhance the viscosity of eye drops beyond the threshold for achieve greater corneal retention [64-65]. It is much more common for PVA to be used in gel form. PVA gels can be formed through physical crosslinking or irradiation, and show favourable degradation profiles for drug delivery [66].

3. Innovations in topical ocular drug delivery

The drawbacks of currently available eye drops are well documented and it is worth noting that alternative forms of topical treatment are being investigated, including ocular devices such as contact

lenses and inserts [10b, 38, 67]. However, eye drops remain a non-invasive and patient friendly approach to ocular disease management and treatment.

Patients have previously reported limitations to their daily activities when eye drop application frequency is increased, as they must accommodate more applications and may not feel comfortable using eye drops outside of their house or a bathroom [68]. The simplest treatment regimens are shown to have better adherence and persistence from patients [68]. The increase in efficacy of drops with higher bioavailability may reduce the necessary frequency of administration and increase patient adherence to the regimes.

A number of reviews have explored the cutting-edge ways in which eye drops are being adapted to overcome their current limitations of bioavailability [1b, 6-7, 23a, 56, 67b, 69]. Each of these routes for innovation either show promising improvements to the bioavailability of the delivered drug, or with artificial tears - the symptoms of dry eye disease. They do, however, each come with their own limitations, both in terms of immunological considerations and also practical, patient focused considerations.

Bioavailability considers the therapeutic efficacy of a treatment in terms of the amount of drug that becomes available to the tissue over the treatment window. When formulating an eye drop with greater bioavailability, there are multiple approaches to consider: i) Ensuring the residence time of the drop is extended to create a larger delivery window (Figure 8), ii) Ensuring the release profile of the delivery vehicle and the dose of the drug being carried allows for the optimum dose to be delivered across that window and iii) enhancing the permeation of the drug through the tissue.

3.1 Bioavailability

3.1.1 Improving the residence time of eye drops

The residence time of eye drops is increased when the drops can overcome the ocular surface's natural clearance mechanisms. Two particular properties that assist in this are mucoadhesion and increased viscosity. It is important to note that these two properties influence each other, and must be balanced for an optimal formulation.

Predictions of eye drop residence time are commonly calculated based on a combination of rheological testing and estimations of tear turnover rate and blinking mechanics. However, blinking mechanics and the rheological properties of the natural tear film are complex and are still being investigated [70]. It generally understood that the natural tear film is shear thinning, a property which could be relatively easily emulated in polymeric eye drops [71]. Assessment of tear film turnover is commonplace in clinical settings in the form of simple fluorescein clearance tests. In order to assess the residence of eye drops in vivo, this same test can be replicated with the fluorescein dye incorporated into the eye drop [72]. This assessment is dependent on the affinity of the eye drop formulation to fluorescein, as a drop that carried fluorescein poorly would appear to remain resident for a shorter time. A number of more sophisticated *in vivo* imaging techniques also rely on the tracking of fluorescent or radio-tracable molecules, which are

again dependant on the nature of the carrier as the release profile and residence profiles may not match up for different carrier chemistries [73]

3.1.2 Mucoadhesion

The mucosa of the ocular surface plays an important role in the protection and function of the eye. Mucins on the ocular surface originate from the conjunctival goblet cells. The glands that produce the aqueous and lipid components of the tear film are also based in the surrounding mucosal tissue. Changes in the amount and the consistency of the ocular mucins can be indicative of inflammation, or in the case of a reduction, can lead to epithelial damage and dry eye disease [24, 74]. Most of the ocular mucin is held to the surface of the eye in a glycocalyx layer, however some secreted mucins float freely in the aqueous portion of the tear film [19c, 74-75]. The glycocalyx forms a protective barrier and an additional layer to penetrate for drug delivery purposes. However, from the perspective of designing artificial tears for the alleviation of dry eye symptoms, the potential for mucosal-polymer interactions may assist in stabilising the tear film and lubricating the ocular surface. Mucoadhesion also creates the possibility of extending the residence time of an eye drop if the correct properties are enhanced. The mucins responsible for the improvement in retention time of mucoadhesive vehicles are the surface adhesive mucins in the glycocalyx [19a, 19c]. For microspheres and nano-particles, their mucoadhesion depends on surface charge.

A number of tests can be deployed to assess the level of mucoadhesion of a polymeric drug delivery vehicle. Depending on the desired application, different tests can be chosen to replicate more realistically the environment *in vivo* [60a, 76]. Similarly, attempts to artificially recreate realistic mucosal tissue have yielded positive results [77]. Different compositions of mucins can be used for testing, either fully or partially hydrated and of different film thickness [78].

Tensile mucoadhesion tests can be done both in vitro and ex vivo to provide a comparative value of mucoadhesion between materials or a value of mucoadhesive force [25]. They rely on creating contact between two surfaces and measuring the force necessary to separate them [25]. One of the most common methods of tensile mucoadhesion analysis is to use a texture analyser and coat the probe in an appropriate mucin [23d, 77, 79]. Alternative tests can also involve peeling one layer away, a vertical gravity resistance test or a shear resistance test [25].

A different approach to investigating mucoadhesion can focus more closely on the nature of the polymer-mucin interactions – for example through Surface Plasmon Resonance [80]. This technique can quantify the strength of molecular interactions between two films by measuring the change in the refractive index [81]. This provides a much more in depth analysis and predication of the level of mucoadhesion that may be expected *in vivo.*

3.1.3 Viscosity

Another innovation investigated for overcoming the eye's natural barriers to drug delivery and improving the bioavailability of the carried drug is to increase the viscosity of the eye drop [7a, 69b, 82]. Tests have shown that more viscous drops show a higher resistance to lacrimal clearance and stay resident on the surface of the eye longer [2, 10b, 38, 51, 61, 76, 83]. As with mucoadhesion, this increases the window available for drug delivery. Rheological assessments that determine viscosity are also frequently used to test the mucoadhesive properties of a polymer solution or gel [76, 79, 84]. This links properties like viscosity and elastic strength to mucoadhesion. However, both cannot be increased indefinitely; as viscosity increases so does the surface tension of the drop. Various studies have examined the contact angle of drops *in vivo* and *in vitro* to assess how changes in viscosity, surface tension and surface chemistry effect the 'wetting' of the drop [85]. Viscosity appears to limit the spreadability of the drop which in turn limits mucoadhesion [25]. This is not necessarily a linear relationship, as for example in viscous hydrogel drops, the crosslinking mechanism in the gel may change the surface chemistry, which can also influence mucoadhesion either positively or negatively [76].

The surface tension of an eye drop formulation has also been highlighted to have an important relationship with the drop size, and its consistency over multiple applications [86]. It was also shown that drop bottle applications produce highly variable results among patients, with drug type (flow characteristics), concentration and drop viscosity affecting drop size [86a]. These factors need to be considered when evaluating the efficacy of eye drops, as if the drop size is not controlled then different dosages of the drug will be administered and the therapeutic efficacy will become variable [86b].

Rheological assessments provide an idea of the theoretically, expected residence time for an eye drop [87]. Although most preparations undergo some form of rheological testing *in vitro* as an assessment of properties, this often does not take into account the complexity of blinking conditions. The natural curvature of the eye, and where the drop sits in relation to the eyelids must be considered and assessed when examining the behaviour of the drops and their efficacy as a treatment [23d, 50b, 63a, 83b, 87-88].

3.1.4 Controlled release

Therapeutic drugs have an upper and lower limit of efficacy – a therapeutic threshold - which is associated with the concentration present in the target tissue. Drug delivery systems need to release their load at a suitable rate to maintain a therapeutically effective dose across the treatment time window, otherwise any improvements in residence time will not translate to improvements in treatment efficacy [83a] . Different drug delivery vehicles offer different levels of tunability of the drug release profile [10b, 56, 82a, 89]. Where the drug delivery relies on the disintegration of the carrier, highly structured vehicles may limit drug release by disintegrating slowly, and diffusion models are influenced by the drug-polymer interactions. Relevant tests which take into account the temperature and pH of the destination tissue can give an idea of the expected in vivo delivery profile.

The release of a drug can also be inhibited by interactions between the drug and the carrier. Many hydrogels are responsive to ionic and pH changes [69p, 82a, 90]. A strong interaction between the drug and the carrier may change the release profile of the delivery device, hindering delivery and preventing the drug from reaching or sustaining the therapeutic threshold [91]. The mechanism of drug loading is also important, as different methods create different release profiles but also involve different solvents [92]. The loading of nanoparticles is also limited by the fact that the encapsulated phase makes up a very small fraction of the overall mixture, and the loading is limited to the equilibrium point between the phases [93]. Encapsulated delivery systems also pose the risk of premature release in storage which can decrease the possible dosage in vivo.

One way to circumvent problems arising from unwanted drug/carrier interactions is to take a prodrug approach and specifically design drugs that work with carriers that have shown promising results. Prodrugs are modified versions of existing drugs, which as a result can carry a different charge or can be non-reactive. Once they reach the host tissue, the environment in that tissue is normally home to an enzyme or other trigger compound, which alters the pro-drug back into its active, therapeutic state [94] This approach can allow drugs which are not normally penetrative or carriable in certain devices to be delivered successfully, but depends heavily on the nature of the tissue being delivered too and the disease state of that tissue. There is also a risk that the full dose may not be released and the therapeutic threshold may not be reached or maintained for a period long enough to see adequate therapeutic effects.

3.1.5 Mechanisms of penetration

Formulating eye drops that overcome the ocular barriers to drug delivery can involve improving resistance to lacrimal clearance through increasing mucoadhesion or viscosity but can also involve facilitating easier passage of the drug through the ocular tissue. The main barrier to transcorneal drug delivery is the epithelial layer, within which there are inter-cellular tight junctions and protein binding sites that work to prevent penetration through the multiple cellular layers (Figure 11). Lipophilic drugs travel through the cornea by passing through the lipid bilayer of the cells themselves. Transport through the stroma is restricted to diffusion, so this is the rate limiting step of the process [38]. For hydrophilic drugs, they must pass through the cellular tight junctions, which present the most significant barrier. It is also common for hydrophilic drugs to accumulate in the stroma, which may limit passage to posterior tissues [38].

The first attempts at improving penetration of drugs through the cornea involved incorporating pharmaceutical permeation enhancers such as ethylenediaminetetraacetic acid (EDTA) to interfere with the epithelial tight junctions to allow for the passage of drugs into the stroma. Both benzalkonium chloride (BAK) – a common preservative used in multi-dosage drops – and EDTA have been shown to improve the penetration of drugs through the cornea *in vitro* [6, 95]. EDTA and similar compounds sequester calcium ions from the epithelial layer, impacting the function of the tight junctions and allowing for the delivery of molecules through the epithelial layer [96]. Although this may appear positive for the

treatment of the primary condition, both types of preservatives can affect the health of the corneal epithelium, which can lead to additional discomfort and secondary ocular damage, such as superficial punctate keratitis and lower sensory nerve density [97]. BAK is even used experimentally to replicate the effects of dry eye disease, as it can cause cell lysis and can be cytotoxic to corneal epithelial cells [98]. The enhanced ocular penetrative effect has also not been replicated in *in vivo* studies, where the contact time of the eye drop preparation is much shorter [99].

There is also evidence to suggest that in drops that use a combination approach of pharmaceutical permeation enhancer and residence prolonging polymers in solution, the polymer/drug/permeation enhancer interactions overall limit the bioavailability of the drug [100]. When this approach was taken with nano-particles, the effects were much more positive, with the permeation enhancers effectively working to enhance the penetration of polymer coated nanoparticles [101]. The surface chemistry of the nano-particles was found to be the deciding factor in the efficacy of the combination approach, which raises an important formulation consideration for permeation enhancing micro and nano-particles [101]. An additional study found again that adjustments to the particles size and charge influenced penetration [9].

In recent years the focus has shifted away from modifying the tissue and towards engineering carriers that can circumvent the eye's natural barriers. One promising innovation has been the development of cell penetrating peptides (CPPs). CPPs are amino-acids containing 5-40 peptides which can pass through cells in a receptor-independent manner[102]. They can be easily specialised and are incredibly versatile, capitalising on their polyanionic nature to navigate a variety of cellular and tissue barriers [102-103]. A variety of CPPs have been developed for topical ocular drug delivery. CPPs can be modified with fluorescent binding agents which allow them to be tracked through the cornea, and through this studies are gaining understanding of how the constituent peptide make-up of the CPPs influences their ability to penetrate the different corneal layers [103]. A recent study found that CPP containing drops could deliver therapeutically effective doses of anti-VEGF drugs to the choroid, potentially allowing an alternative treatment to the current invasive ocular injections [104]. CPPs can also be used to modify polymeric nanocarriers and improve their ocular penetration [103].

3.2 Novel materials approaches

3.2.1 Hydrogels and fluid gels

Hydrogels are now increasingly being investigated for use as biological scaffolds, drug delivery devices and as alternatives to plasters and sutures. Hydrogels show tuneable mechanical properties, drug release profiles and degradation rates. Natural polymers are generally non-toxic and biodegradable and have the added advantage of binding with cells and proteins. However, natural polymer-based hydrogels can have poor mechanical strength, high variability, and can still provoke an immune response despite being non-toxic. Synthetic polymers are more consistent and tuneable in their properties, but do not inherently interact with proteins or cells [69g].

Recently, research efforts have focused on improving the penetrative ability and residence time of eye drops. Much of this research has been directed towards investigating the use of more viscous based materials, primarily hydrogels, for eye drop formulations and several manufacturers advertise commercially available 'gel' eye drops. However, there is a disparity between commercial and academic interpretation of what constitutes a 'gel', with many 'gel' drops simply incorporating viscous polymers to improve the rheological properties instead of creating a true hydrogel. True hydrogels, crosslinked polymer networks that entrap and hold water (Figure 10) [69i], are yet to fully translate into commercial use. This is due to a number of practical factors, including the toxicity of some crosslinking agents to the ocular surface, the rate of lacrimal clearance limiting *in-situ* gelling, pre-formed gels being harder to administer, limitations in pH and temperature sensitivity and patient-focused outcomes (such as comfort and clarity of vision).

As an alternative to pre-formed gels, *in-situ* gels have been tested to allow for simple ocular administration [7a, 69g, 69p, 105]. Harsh chemical gelating agents would be inappropriate for ocular use, so natural variables should be exploited, such as temperature, pH and the presence of electrolytes or proteins [69d]. Carbomer and carbomer/HPMC gels can form spontaneously at a suitable pH when used in combination [69d]. There are gels which can form at certain temperatures such as HPMC [43, 106], however the gelling temperature would need to match the ocular surface temperature closely enough to be effective. The gelling process would also need to occur almost instantaneously in order to take full advantage of the desired effect, or much of the liquid base-material will be lost through lacrimal flow before gelling occurs[19c, 26]. The formed gel then needs to show the appropriate rheological, mucoadhesive and drug release characteristics.

Other considerations for formulations include that the solvent and cross-linking agents that form the gel structure must not have a toxic or damaging effect on ocular cells and tissues. They must also be compatible with the drug being carried [107]. That said, they impact the final structure of the gel and therefore must also produce the desired characteristics in the gel [88a]. Aqueous vs. anhydrous (alcohol) gel formation provides different structures and properties of gel, and these structural changes can inhibit the ability of certain polymer structures to deliver drugs effectively [107-108]. The radiation-initiated cross-linking of some gels has the added benefit of sterilising the gel [43], however pre-formed gels pose a challenge for topical application.

Fluid gels may circumvent issues with administration, allowing for better control of rheological properties and the ability to administer consistent drops [61, 109]. Fluid gels have been explored as a versatile deviation from the traditional hydrogel structure and are formed by shearing hydrogel to produce a complex hydrogel microstructure as opposed to a macrostructure [61]. Fluid gels therefore retain the viscosity and favourable drug delivery profile of a gel, whilst allowing for the necessary flow characteristics for spraying, pouring and drop formation, and they present as a promising medium for eye drops [61, 109-110]. The level of shearing the gels is exposed to can also control the microstructure, which in turn can control the spreadability of the drop. The use of mucoadhesive gels which have been sheared to

provide a fluid gel with the optimum balance of viscosity and wettability may circumvent some of these issues.

3.2.2 Polymeric microspheres and nanocarriers

Microspheres have also been investigated in the context of ocular drug delivery, with respect to resolving potential problems associated with poorly soluble drugs and poor bioavailability, with some showing marked improvements compared to aqueous drops [23b, 69o]. They can increase the penetration of the delivered drug, with some models showing successful delivery to posterior tissues such as the retina and choroid [69n, 105c, 111]. Microspheres show controllable degradation rates, with synthetic polymer composite - PEG/PPG/PAA - microspheres, as with hydrogels, showing much more controllable degradation properties than those made with natural polymers [60c, 112].

On a much smaller scale, nanocarriers have also shown promise for improving the permeability of treatments [1b, 5, 9, 69o, 111, 113]. With regards to the incorporation of microspheres and nanocarriers into eye drops, the potential for phagocytosis by resident corneal and conjunctival immune cells and an associated inflammatory response needs to be considered – both as a drawback and as a potential for immunomodulation [114]. Different shapes, charges and functional groups can influence the immunological response to nano-carriers and the response in inflamed tissue can vary from the response in non-inflamed tissues – an important consideration for treating different pathologies [115].

3.2.3 Lipid based drug delivery systems

Although tailoring mucoadhesive polymers presents one option for improving the efficacy of eye drops, other avenues are also being explored, including emulsions and microemulsions, lipid-based carriers and permeation enhancers [63c, 110b, 116]. Lipid or emulsion-based eye drops show comparable results to conventional polymer-based drops [116-117]. Emulsions also offer the added benefit of being able to carry hydrophobic/poorly soluble drugs [118], however there are concerns with regards to the methods of synthesis relying on a high proportion of surfactants (<10%) which interact with the ocular surface and increase the residence time of the drops, but can be cytotoxic to the corneal cells[119]. There are also concerns as to how well emulsions will last in prolonged storage – if the dispersion of the emulsion becomes uneven and separation occurs, the dosage of each eye drop will become uneven and the therapeutic threshold may not be reached [119b].

As with simple polymeric drugs for dry eye disease, eye drops do not necessarily have to carry a drug to have a beneficial clinical effect. The lipid components of eye drops can assist with supplementing the tear lipid layer, which is often deficient in conditions such as dry eye disease and meibomian gland dysfunction [116, 117b, 120]. The addition of topical lipids or fatty acids can help rebuild the natural lipid film, thus replenishing the protective function of the lipid components of the tears [120a]. Such as with the polymer choice in polymeric drops, the choice of oil in emulsion-based drops significantly changes the properties of the drop. Long chain oils do not interact with the surfactants and emulsify as easily as short

chain oils, but show a higher drug solubility[121]. This means that there needs to be a balance between drug compatibility and emulsion compatibility. The proportion of oil in the eye drop is also dependent on the dose of drug that needs to be carried [119b]. This means the properties of the resulting emulsion are largely dictated by the nature of the drug being delivered.

Liposomes – nanospheres with one or more phospholipid bi-layers – have also been investigated for use in eye drops to increase corneal penetration, with considerable success [114c, 121-122]. However, the use of liposomes elsewhere in the body has been shown to illicit an inflammatory immune response - this has even been harnessed to improve the response to vaccines [122-123]. This raises questions for long-term ocular use, as prolonged inflammation can be detrimental to ocular surface health.

Solid lipid nanoparticles (SLNs) offer similar advantages to polymeric nanoparticles in terms of permeation of the natural barriers of the eye, whilst also presenting the option to carry drugs that may not be transportable in a polymeric system. SLNs can be optimised to target specific pathologies as different combinations of lipid structures (triglycerides, fatty acids, waxes etc) can be used [124]. Solid lipid nanoparticles are less likely to be made with harsh solvents, which may be beneficial for conditions where the ocular surface is already damaged or inflamed. However, they do normally incorporate surfactants to stabilise the emulsion, and despite these measures can still carry a lot of water and undergo structure changes during storage which can lead to a reduced drug carrying capacity [124]. SLN drops do however typically contain less surfactant than emulsion drops [118]. Similarly, smaller liposomes can be designed and optimized to carry and deliver both hydrophilic and hydrophobic drugs by adjusting the lamellar structure [125]. Both SLNs and liposomes can be designed as polymer-lipid composites to draw on the advantageous properties of both and allow for various synthesis methods [125b].

3.2.4 Hybrid approaches

There is no single simple or ideal answer to how to most effectively improve the formulation of topical eye drops. A combination of approaches can benefit from a multitude of advantages, for example microspheres incorporated into gels to allow for a much more consistent and controllable drug delivery profile [126]. The question of which material or structure will be most effective ultimately depends on the nature of the disease being treated and its influence on the physiology and function of the eye's anterior tissues.

Emulsion based eye drops can incorporate polymers to allow for mucoadhesion, whilst using lipids to transport the hydrophobic drug [127]. This approach can be carried across into nano-carriers, with the synthesis of lipid-polymer hybrid nanoparticles (LPHN). These nano-carriers can deliver a hydrophobic drug in a polymer core, which is surrounded by a lipid layer. This lipid layer acts to ensure the hydrophobic drug remains encapsulated whilst also enhancing permeability through lipophilic tissues [125b].

3.3 Preservatives, surfactants, ease of sterilisation and storage

Eye drops designed for multiple usages contain preservatives to maintain the sterility of the product. Phosphate-based preservatives have been found to induce rapid corneal calcification and temporary loss of sight when applied to an already injured ocular surface, which has ultimately led them to be phased out of use [128]. BAK is a common preservative, but has also been found to interact with carbomers and influence their viscosity, to the detriment of the desired improvement in bioavailability [88a, 129]. Due to the interference of preservatives with gel structures [63a, 87-88, 108] and also the potential side-effects of common preservatives [99, 129-130], the manufacture of eye drops (especially multi-dose formulations and gels) must be performed under sterile conditions to prevent the entrapment of pathogens in the drops that could be later released *in vivo*. Many preservatives, although useful for maintaining sterility, interact with the polymers and influence the structure of the gel [88a, 131]. When incorporating preservatives or other additives, it must be prioritised that the structure and function of the eye drops are maintained over a reasonable window of storage (~ 12 months). Multi-use drops in particular need to remain sterile over a window of use which may span a number of weeks. If this cannot be achieved, then a simple process for creating an appropriate, sterile formulation at the point of use needs to be considered. Alternative preservatives and preservative-free options have therefore been explored as a result.

The storage temperature of different polymer solutions can impact their osmolarity over time [132]. Osmolarity is a key formulation criterion for eye drops, and thus needs to be measured accurately and maintained well over the storage period. Modelling and *in vitro* testing are needed to predict the 'worst-case storage scenario' and allow for the formulation to accommodate any associated osmolarity changes. This is critical, as a large difference from the natural tear osmolarity will affect the integrity of the tear film [132].

3.4 Novel polymers and polymer combinations

There are hundreds of possible polymer combinations that could be used to formulate hydrogels, with each different pairing creating different properties and advantages [43, 56, 61, 69b, 69c, 69f, 69g, 69j, 90, 133]. Novel processing and characterisation techniques have highlighted a number of new synthetic, naturally occurring and hybrid polymers which show advantageous properties for ocular drug delivery (Table 3).

4. **The immunological response to polymeric materials**

The relationship between the immune system and several classes of medical materials are well established. Implantation in the body can induce a foreign body response, with the severity of the response dependent partly on the material properties of the implant. Materials are generally classed as toxic/harmful, bio-inert or bio-compatible. The first stage of an immune response to implantation of an exogenous component results in neutrophil migration to the site and subsequently, macrophage

recruitment. Implantation may result in chronic inflammation and fibrous encapsulation rather than integration into the tissue, which can cause the implant to fail [30c].

Synthetic and natural polymers are well established in the field of medical devices and are used in implants and drug delivery devices [67b]. More recently, hydrogels have been investigated as a means of delivering or attracting immune cells for immunotherapy. They have successfully been used for the delivery of dendritic cells [134] or agents to improve the chemotaxis of dendritic cells, such as granulocyte-macrophage colony-stimulating factor [135] and MIP3-beta [136] for the treatment of or vaccination against cancer. Also, to deliver antigens to induce tolerance in T-cells [137] and prevent auto-immunity. The optimal combination of base-polymers to form the gel, as well as the desired final properties of the gel, depends on the types of cells and chemokines being delivered [138].

It has also been shown that the properties of the materials used in biomedical applications themselves, rather than the drugs or cells they carry, can regulate immune responses [139]. The innate immunogenic properties of Hyaluronic Acid have been harnessed to target specific tumour cells. Specific chain lengths of the HA on a coating of nanoparticles were found to have an affinity for CD44+ cells, opening up opportunities for targeted drug delivery and immune activation [140].

Macrophages switch polarisation depending on their environment [30c, 35, 114b, 114c, 135, 141]. Hydrophilic versus hydrophobic surfaces produce different macrophage profiles in culture, with hydrophilic surfaces inducing the M1 (proinflammatory) phenotype and hydrophobic surfaces eliciting an anti-inflammatory M2 phenotype that encourages wound healing and tissue remodelling [141f, 142]. It was found that different processing methods during manufacturing of the same implant induced different macrophage responses in rodents [141c]. It has also been shown that a surface topography that encourages cellular elongation may facilitate M2 polarisation and therefore wound remodelling [30b].

With regard to microspheres and nanoparticles for general drug delivery, the likelihood and consequences of phagocytosis needs to be considered [114c, 141e, 142-143]. Immunomodulatory effects are achievable through either releasing immunomodulatory drugs or inducing macrophage polarisation by targeting phagocytotic activity or surface adhesion. Again, surface chemistry is important for modulating the immune response, with hydrophobic microspheres phagocytosed by macrophages to a greater degree than their hydrophilic counterparts [141f]. This may be due to differing protein adsorption on the surface, which is the primary cue for macrophage activity [143]. Surface modification of synthetic polymer microspheres may be advisable to allow for mucoadhesion and better tissue retention [111, 141e] however the influence on the subsequent phagocytosis or inflammatory response would need to be monitored. The response is also likely to differ depending on the existing level of inflammation in the target tissue.

4.1 Biomaterials in the eye

The response of immune cells to the presence of biomaterials on the ocular surface will likely differ from examples of implantation elsewhere in the body, due to the plasticity and tolerance of ocular immune

cells, and the consistent exposure of the ocular surface to the external environment. One example of regular, prolonged contact of polymers to the ocular surface (as opposed to the current minimal contact of aqueous eye drops) is with contact lenses. An increase in dendritic cell numbers in the central cornea has been observed to occur in silicone-hydrogel contact lens wear [144], as has an increase in tear inflammatory markers [145]. Contact lens wearers can also experience a range of conditions linked to ocular surface inflammation, including dry eye disease [146], Contact Lens Associated Red Eye (CLARE) [147] and contact lens intolerance [148]. The use of non-aqueous eye drops is unlikely to illicit a similar response, as even with a prolonged residence time, overall the contact with the ocular surface and any mechanical disruption will be minimal in comparison.

There may be potential to harness the properties of the polymers used to induce biomaterials-based immunomodulation in relation to ocular surface diseases. This is particularly worth exploring in dry eye disease, which is often associated with ocular surface inflammation and is one of the conditions for which eye drops are currently most commonly prescribed.

Many current topical therapies for dry eye disease, which often incorporate the polymers listed Table 1, provide some relief of dry eye symptoms but generally do not treat the underlying aetiology of the condition. The use of pharmaceutical components that promote the production of mucins and lipids are being investigated [17], as are components targeting lymphocytes to reduce the inflammatory response that triggers epithelial damage [18a, 149]. For example, by interfering with the antigen receptors on T-cells, Lifitegrast attenuates the immune response by reducing the secretion of pro-inflammatory cytokines [150]. Immunomodulation, both intentional and unintentional (as a result of interaction between immune cells and drug delivery devices), needs to be considered when formulating eye drops.

Concerns for the use of materials with longer residence times in the eye have arisen around the potential for incomplete breakdown of devices designed to biodegrade in order to release their drug load, and the uncertainty of responses to the by-products of different materials decomposition. In a repeated dosing situation, as with eye drops, there is a risk of material build up and an associated inflammatory response [115]. Material may build in the conjunctival sac, which poses a potential risk as the conjunctiva is more prone to inflammatory responses than the cornea [20]. This could also lead to a foreign body response and a feeling of discomfort, which will not aid adherence to a treatment regime.

5. Patient focused considerations for eye drop formulations:

In order to design an optimised eye drop that can make the full transition from benchtop to effective clinical use, considerations beyond just the achievable bioavailibility in controlled conditions need to be made. Like any biomedical device, the interaction between the patient and their eye drops – practically, physiologically and psychologically – needs to be assessed to achieve the optimum outcome, and each decision influences another (Figure 12). There are also formulation considerations that influence eachother, and in turn influence the experience of use for the patient.

5.1 Comfort

The performance of an eye drop after instillation is only one of the important clinical factors to consider. Eye drops can be administered at home and with minimal discomfort and relative ease. With a trend for eye drops to have increased viscosity, the eye drop still needs to be dispensable from a bottle and produce drops of the desired size and drug concentration. The surface tension and viscosity of a drop also has important implications for the sensation of the drop on the cornea [151].

A shift towards more viscous eye drops, which are more resistant to lacrimal clearance and blinking may increase bioavailability in theory, however in practice they will be more uncomfortable for the patient, increasing blinking and clearance, and creating blurred vision [151]. The potential for longer residence times also raises questions around the use of other ocular devices, such as contact lenses.

Depending on the longevity and severity of the eye condition being treated, patients may inappropriately stop using their eye drops if they find the formulation uncomfortable or hard to administer, or if their symptoms subside too rapidly or insufficiently. Some researchers suggest semi-permanent devices would be a preferable alternative, as they do not rely on adherence from the patient [67a, 67b]. However, eye drops are still preferable for conditions where the anterior tissues are damaged or inflamed, as semi-permanent devices can aggravate these conditions. Where more viscous drops may also be an advantage is in reducing the administration frequency, which may balance out the unpleasant patient experience.

5.2 Personalisation of treatment regimes

Dry eye disease is one of the most common conditions for which eye drops are used. Patients who present with symptoms of dry eye often purchase over-the-counter artificial tears (see Table 1) with the intent of reducing ocular surface irritation. With this method of self-selection, there is no assurance that the formulation they choose will be the most effective for their particular manifestation of the condition [18a, 41a, 59, 117a, 152]. A key feature of dry eye disease is the presence of elevated tear film osmolarity (i.e., tear hyperosmolarity), which occurs ubiquitously in all subtypes of the disease [153]. There are two primary forms of dry eye disease, characterised by either insufficient lacrimal secretion (aqueous-deficient dry eye) or lipid layer deficiency (evaporative dry eye) [17, 152a]. Although patient symptoms for each disease subtype are similar, different subtypes may respond better to different formulations of eye drops [117a, 154]. There is also large within-patient variability in the rate of lacrimal flow and clearance of an eye drop from the target tissues. Patients with a high lacrimal flow will potentially dilute the drug and clear it faster than those with a low or inhibited lacrimal flow, and thus may have a poorer treatment outcome with the same concentration of drug [6]. There are also different lifestyle factors that can affect the expression of dry eye disease, and which will affect the treatment regime, for example prolonged computer use reduces the blink rate and can exacerbate the dry eye [155].

As well as individual differences in lacrimal flow and tear osmolarity, the health and thickness of the mucin layer on the ocular surface may also play a key role in influencing how well mucoadhesive polymers and gels work to improve the bioavailability of a therapeutic agent. An investigation into the mucoadhesive capacity of carbomer gels found that it was the concentration of mucins naturally available on the ocular surface that was the major determining factor, rather than factors related to the gel itself [88b]. These differences in tear composition can also be exaggerated by diurnal patterns and environmental cues, and an approach which incorporates multiple drop types is advocated for by some clinicians [156].

5.3 Patient adherence

Investigations into methods of improving the efficacy of eye drops often rely on the assumption that there is already good adherence to treatment regimes in the patient population, which unfortunately is not necessarily the case. Studies in clinical populations have reported non-adherence rates between 27% and 80% [157].

Self-efficacy and difficulty administering eye drops are two of the most important barriers to adherence to glaucoma medications [157a]. A study in elderly patients showed that 56% of patients required two or more attempts to accurately administer an eye drop, and 28% of attempts missed the eye completely [158]. It has also been shown that even after education, patients can still unknowingly administer eye drops incorrectly [159].

However, there are practical methods which can be enlisted to improve technique, efficacy and as a result - adherence. Aids have been shown to be effective in improving eye drop administration in some cases [86b, 160], however the instructions for the guide must be clear also [161]. Where consistent positive communication is combined with reminders and education, significant improvements to adherence have been shown [162]. Where access is a barrier or where patients have negative connotations with clinical settings, education can take place in a more relaxed environment or at home through short educational videos [163].

6. General discussion

Polymers were originally incorporated into eye drops to improve the residence time and bioavailability of a carried drug. They achieve this through mucoadhesion and small increases in viscosity, which allow for better resistance of the drop to the clearance mechanisms of the ocular surface. There still may be benefits to be had from optimising the formulations of these eyedrops, for example ensuring the optimum chain length and viscosity is reached.

Innovations in eye drop formulations are moving towards creating highly viscous hydrogels or micro/nano encapsulated drug delivery systems, with the ability to provide controlled release of the

required drug. Although this may in theory provide greater bioavailability and improve treatment outcomes, patient comfort and its implication on the adherence to treatment regimens need to be considered.

The response of the ocular immune systems to long term use of these carriers is not well understood and needs to be further investigated, as it will likely differ from the response to polymeric materials elsewhere in the body. Although the response to contact lenses can be used as a point of comparison it cannot be assumed that the responses would be the same at such low contact times. A particular point of interest would be the risk of immune cells engulfing nanocarriers and the associated risks of increased inflammation or the opportunity to use this process for immunomodulatory purposes. The potential for a build-up of 'waste' material needs to be investigated, as does a systemic absorption of micro/nano carriers.

Mucoadhesion plays an important role in increasing in the resistance of the drops to the eye's natural clearing mechanisms. The polymers investigated show a range of tuneable properties, and versatility and adaptability are clearly important properties to look for in choosing the polymers for eyedrop formulation. This should come alongside testing that replicates the application scenario, with the drop size and application ease given due consideration.

The impact of the disease on the ocular environment needs to also be considered, as tear formulation, glycocalyx health and pre-existing inflammation may influence the efficacy of the treatment. Particularly for dry eye, but also for carrying non-charged drugs for other conditions, lipid and hybrid drops offer similar benefits to polymeric drops.

Where the material properties of the delivery vehicle can create increases in mucoadhesion and viscosity and in theory increase bioavailability of the delivered drug, these advances can be compromised by interference of the drug with the carrier if not selected with this in mind. The delivery mechanism therefore becomes important to consider in light of the nature of the drug to be delivered.

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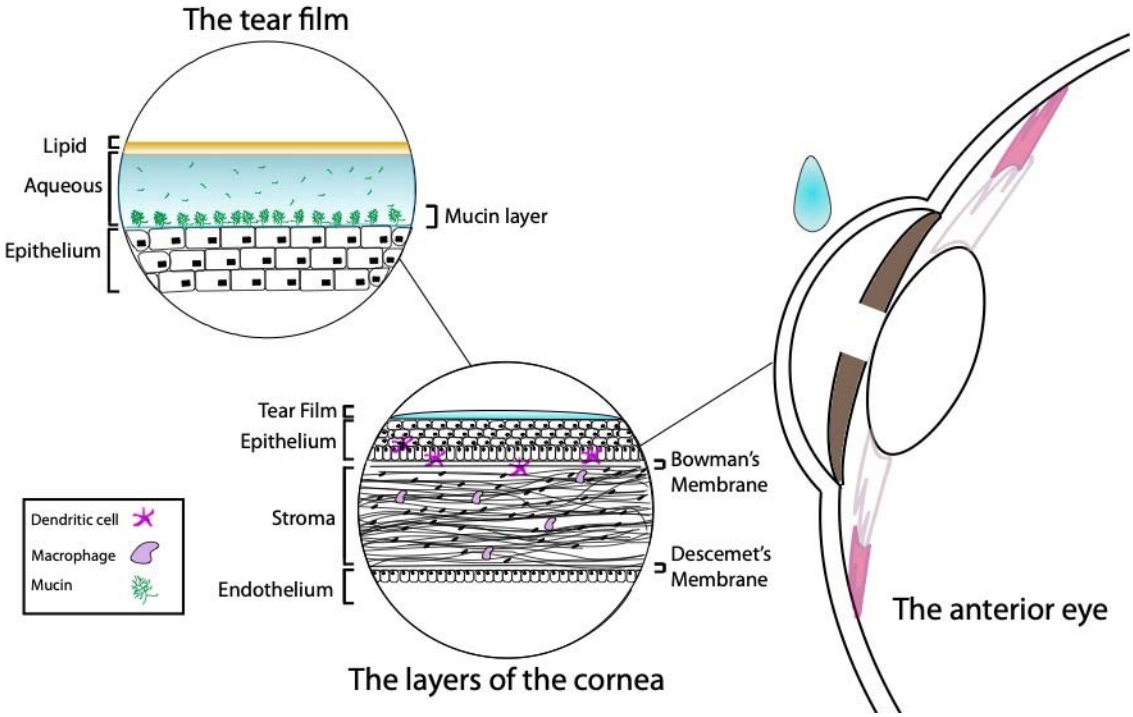


Figure 1: The structure of the cornea and the tear film

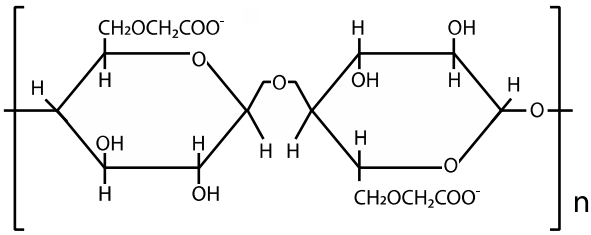


Figure 2: Carboxymethylcellulose structure

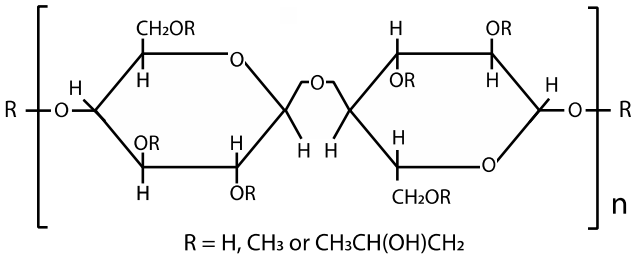


Figure 3: Hydroxypropylmethylcelllulose structure

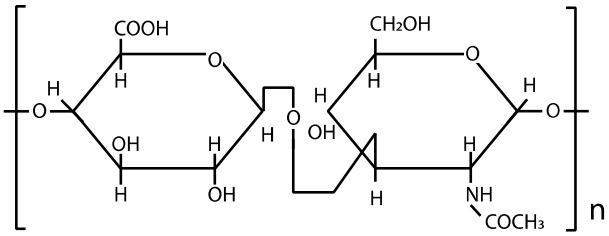


Figure 4: Structure of Hyaluronic Acid

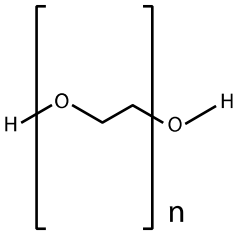


Figure 5: Polyethylene Glycol structure

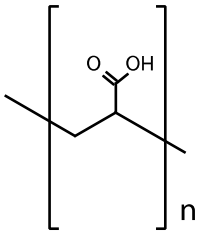


Figure 6: Polyacrylic Acid monomer structure

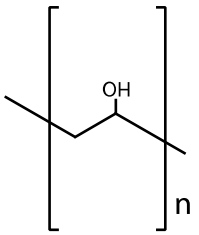


Figure 7: Polyvinyl alcohol monomer structure

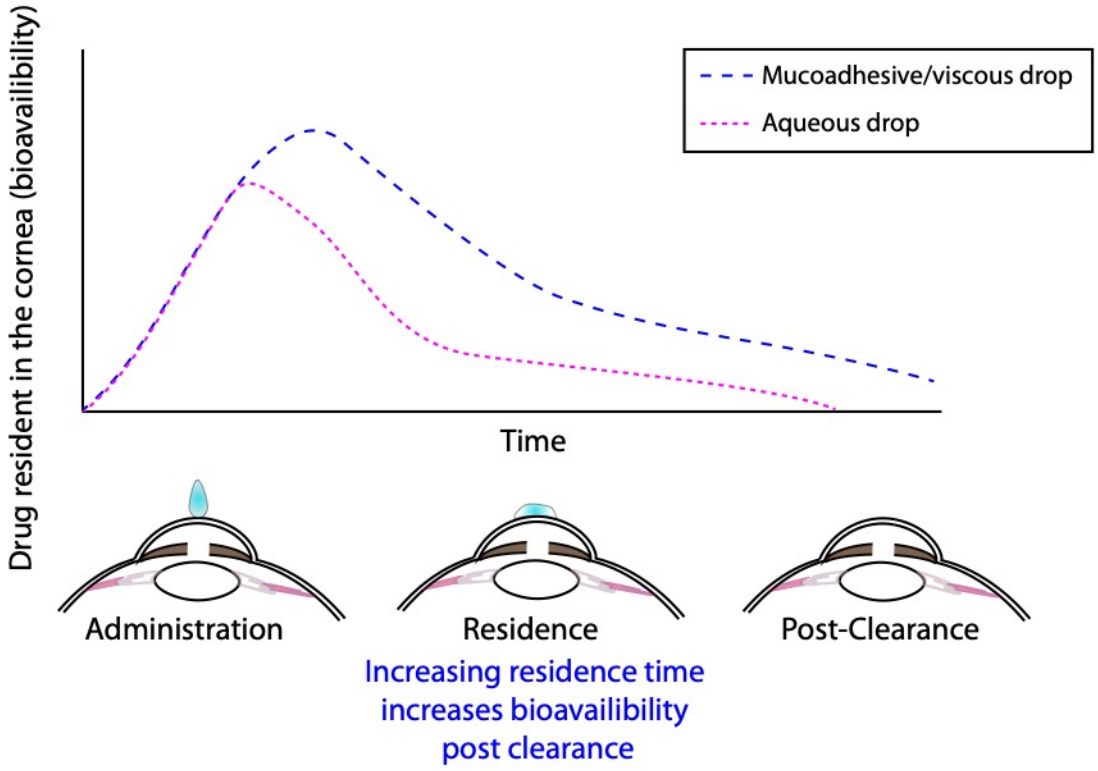


Figure 8: Schematic representation of the effects of increased residence on bioavailibility

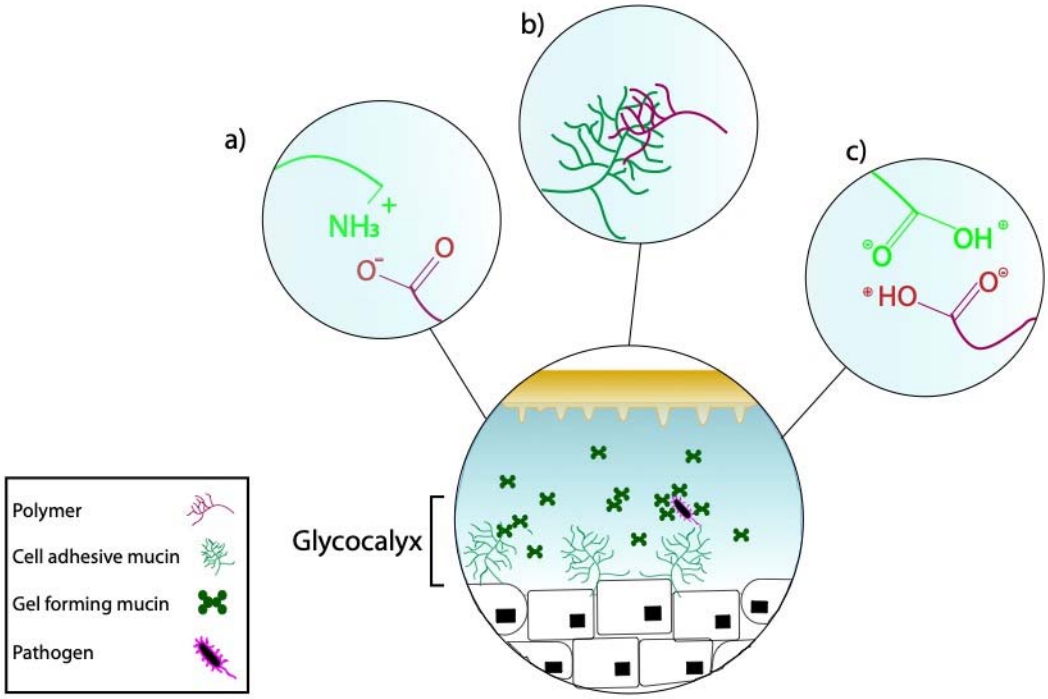


Figure 9: The anatomical elements of mucoadhesion and the mechanisms of adhesion including a) Strong electrostatic attraction, b) Physical entanglement and c) Hydrostatic bonding

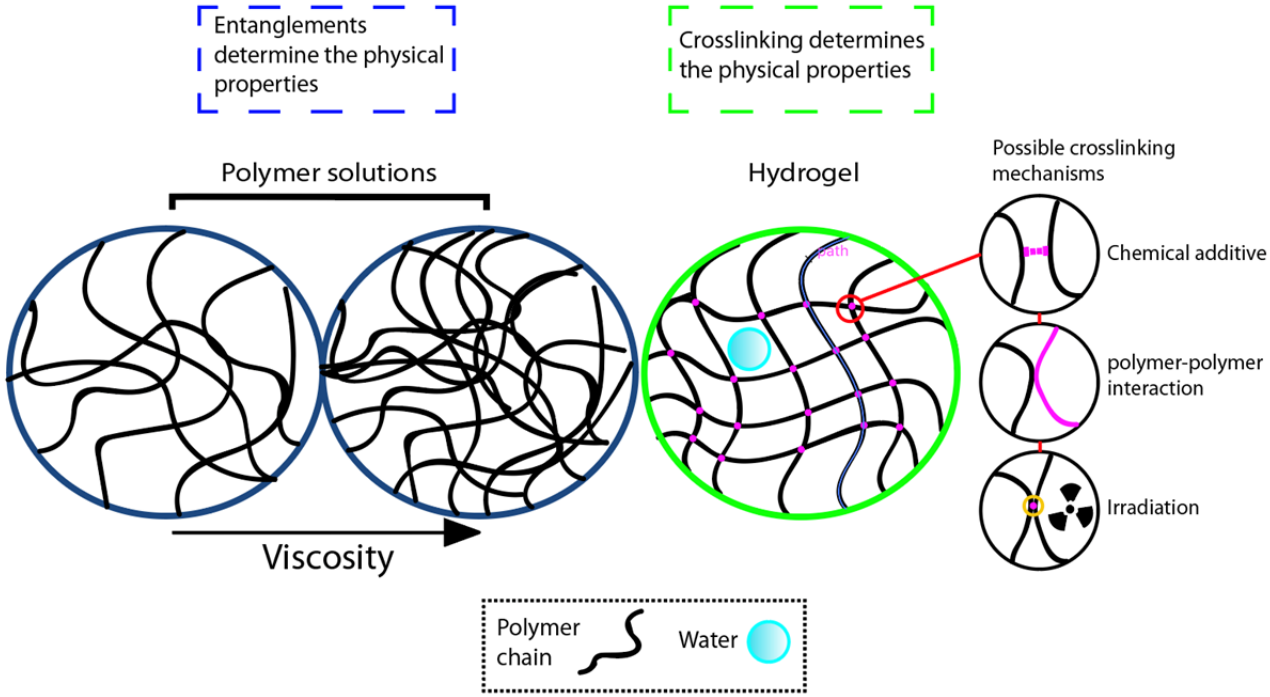


Figure 10: A comparison of the structure of polymer solutions and hydrogels

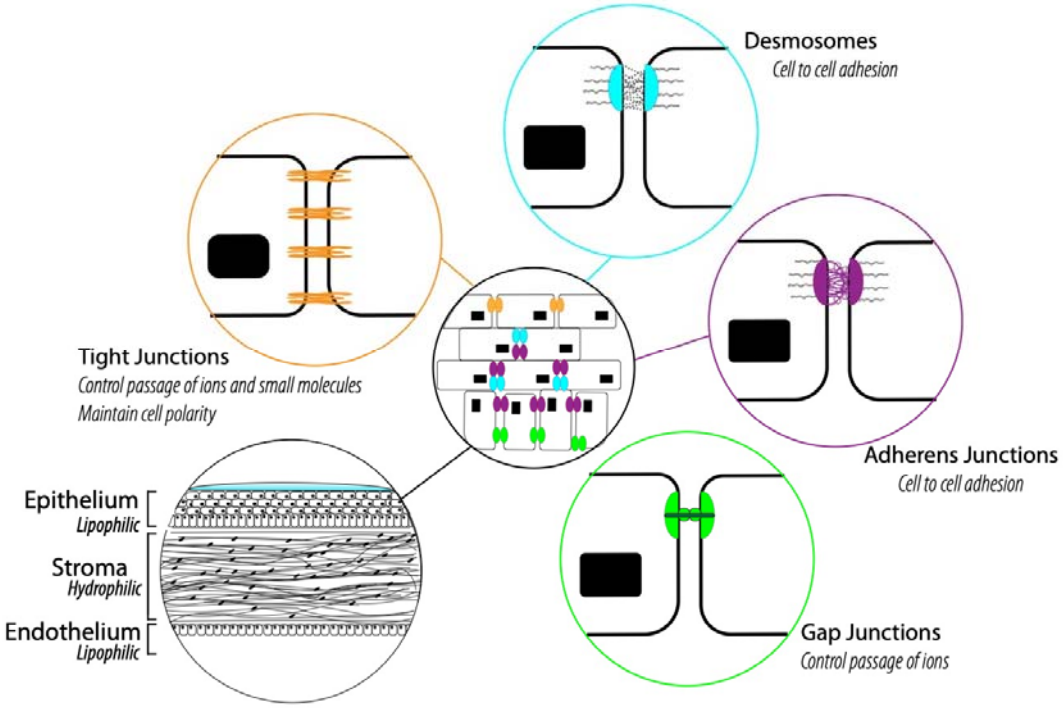


Figure 11: The wider structural and epithelial intra-cellular barriers to drug penetration in the cornea [164]

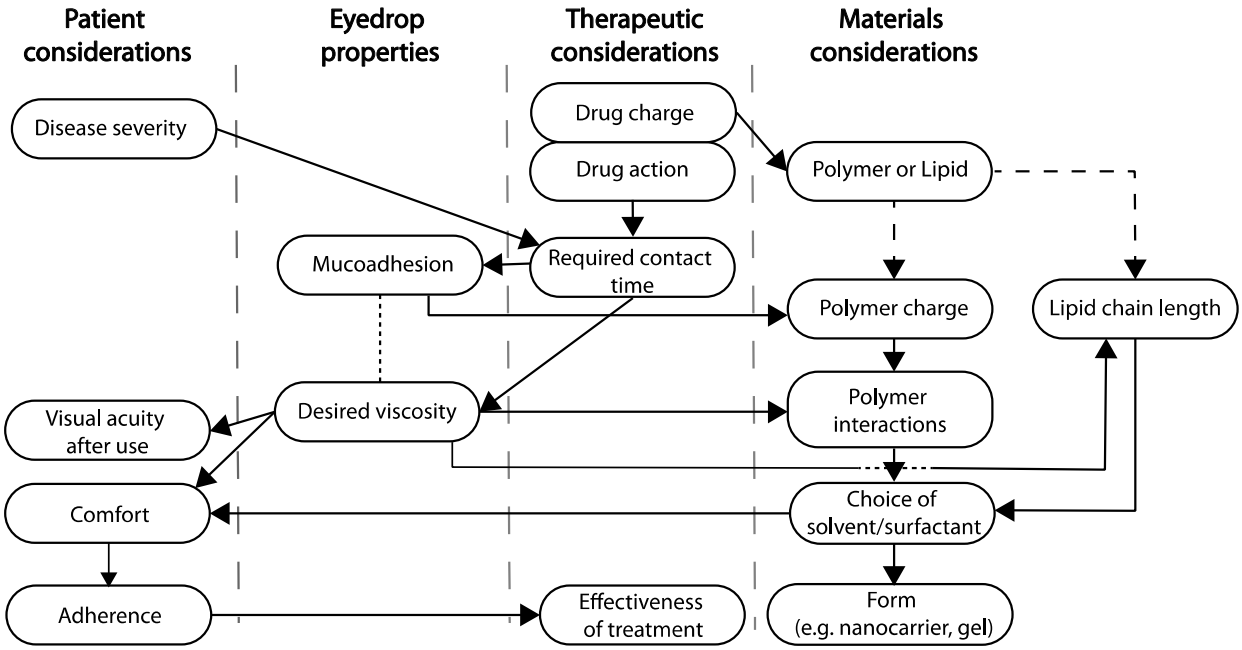


Figure 12: The relationship between various formulation decisions

Table 1. Examples of over-the-counter (United Kingdom) non-medicated artificial tear eye drops and their thickening agents

Type	**Product name/***Brand*	**Thickening agent**	**Concentration (%)**
Artificial tears	Carmize 0.5% *Aspire Pharma* (PF), Cellusan 1% *Farmigea* (PF), Evolve Carmellose *Lumecare* 0.5% (PF), Melopthal, PF Drops Carmellose *Martindale*, Xailin Fresh *Nicox*	Carboxymethycellulose	0.5-1.0%
	Optive *Allergan*	Carboxymethycellulose	0.5%
	Optive Plus *Allergan*	Carboxymethycellulose Castor Oil	0.5% 0.25%
	Systane, Systane Gel Drops, Systane Ultra *Alcon (Novartis)*	Polypropylene Glycol PEG 400	0.3% 0.4%
	Systane Balance *Alcon (Novartis)*	Polypropylene Glycol	0.6%

Evolve Hypromellose *Lumecare*, Hydromoor *Rayner*, Hypromellose *FDC*, Hypromol *Ennogen*, Lumecare Hypromellose, Lumecare Tear drops, Ocu-lube Sai-Med, PF Drops Hypromellose *Moorfields*, SoftDrops eye drops *Ajanta*, Vizulize Hypromellose, Xailin Hydrate *Nicox*	Hydroxypropylmethylcellulose	0.3-0.5%
Liquifilm Tears *Allergan*, Sno tears *Chavvin*	Polyvinyl Alcohol	1.4%
Refresh Opthalmic *Allergan*	Polyvinyl Alcohol Povidone	1.4% 0.6%
Artelac Rebalance *Bausch + Lomb*, Clinitas, Evolve HA *Lumecare*, Hy-Opti *Alissa*, Hyabak *Thea pharmaceuticals*, Hylo-fresh *URSAPHARM*, Hylo-forte *URSAPHARM*	Sodium Hyaluronate	0.1-0.4%
Blink Intensive Tears *Abbot*	Sodium Hyaluronate PEG	0.2% 0.25%
HydraMed *Farmigea*	Sodium Hyaluronate Tamarind Seed polysaccharide	0.2% 0.2%
Hylo-care *URSAPHARM*	Sodium Hyaluronate Dexpanthanol	0.1% 2%
Hylo-Dual *URSAPHARM*	Sodium Hyaluronate Ectoin	0.05% 2%
Lubristil Gel *Moorfields*	Sodium Hyaluronate Xanthan Gum	0.15% 1%
Optive Fusion *Allergan*	Sodium Hyaluronate Carboxymethylcellulose Glycerol	0.1% 0.5% 0.9%
Thealoz Duo *Thea*	Sodium Hyaluronate Trehalose	0.15% 3%
Thealoz Duo Gel Thea	Sodium Hyaluronate Trehalose	0.15% 3%

		Carbomer	0.25%
	Emustil *Rayner*	Soy bean oil	7%
		Natural Phospholipids	3%
	Artelac Nighttime gel *Bausch + Lomb*, Clinitas Carbomer gel *Altacor*, Evolve carbomer 980 eyegel *Lumecare*, Lumecare carbomer eye gel, Xailin gel *VISU pharma*	Carbomer (Polyacryclic acid)	0.2%

Table 2: Active ingredients and main thickening agents of different types of medicated eye drops (United Kingdom)

Purpose	Product name/*Brand*	Active ingredient	Thickening agent
Artificial tear	Ilube *Rayner*	Acetlycysteine 5%	Hydroxypropylmethylcellulose
Antiviral treatment	Virgan *Thea pharmaceuticals*	ganciclovir 0.15%	Carbomer 974P
Allergy relief	Otrivine-Antistin *Thea pharmaceuticals*	Xylometazoline 0.05% Antazoline 0.5%	-
	Optilast *Mylan*	Azelastine hydrochloride 0.05%	Hydroxypropylmethylcellulose
	Emadine *Alcon*	emedastine 0.5 mg/ml	Hydroxypropylmethylcellulose
	Relestat *Allergan*	0.5 mg/ml epinastine hydrochloride	-
	Zaditen *Thea Pharmaceuticals*	0.345 mg/ml ketotifen fumarate	Glycerol
	Alomide *Novartis*	Lodoxamide 0.1%	Hydroxypropylmethylcellulose
Glaucoma treatment	Iopidine *Novartis*	Apraclonidine 5mg/ml	-
	Lumigan *Allergan*	0.3mg/ml bimatoprost	-
	Alphagan/ Brymont *Allergan*	2mg/ml Brimonidine	Polyvinyl Alcohol
	Azopt *Novartis*	10mg/ml Brinzolamide	Carbomer 974P
	Trusopt *Santen*	22.26 mg/ml dorzolamide hydrochloride	Hydroxyethyl cellulose
	Monopost *Thea Pharmaceuticals*	50 µg/ml latanoprost	Carbomer 974P PEG (macrogol 4000)
	Betagan *Allergan*	levobunolol hydrochloride 0.5%	Polyvinyl Alcohol
	Oftaquix *Santen*	5.12 mg/ml levofloxacin hemihydrate	-
	Saflutan *Santen*	15 micrograms/ml tafluprost	Glycerol
	Travatan *Novartis*	40 micrograms/ml travoprost	Polypropylene glycol

	Betoptic *Novartis*	Betaxolol 0.5%	Carbomer 974P
	Tiopex gel *Thea Pharmaceuticals*	1mg/g timolol	Polyvinyl alcohol
Bacterial eye infections	Azyter *Thea*	azithromycin dihydrate 15mg/g	Medium chain triglycerides
	Golden Eye	Chloramphenicol 0.5%	-
	Fucithalmic Viscous eye drops *Advanz pharma*	10mg/g Fusidic acid	Carbomer
	Gentamicin eye/ear *FDC International*	0.3% gentamicin	-
	Ciloxan *Novartis*	Ciprofloxacin 0.3%	-
Eye inflammation (e.g., post-cataract surgery)	Betnesol *RPH Pharmaceuticals AB*	Betamethasone 0.1% Neomycin 0.385%	PEG 300
	Vistamethasone *Martindale Pharma*	Betamethasone Sodium Phosphate 0.1%	-
	Yellox *Bausch + Lomb*	0.9mg/ml sodium sesquihydrate/Bromfenac	-
	Maxidex *Novartis*	Dexamethasone 0.1%	Hydroxypropylmethylcellulose
	FML *Allergan*	1 mg/ml Fluorometholone	Polyvinyl Alcohol
	Ocufen *Allergan*	Flurbiprofen sodium 0.03%	Polyvinyl Alcohol
	Acular *Allergan*	Ketorolac trometamol 5 mg/ml	-
	Lotemax *Bausch + Lomb*	0.5%w/v loteprednol etabonate	Glycerol
	Nevanac *Novartis*	3 mg/ml nepafenac	Polypropylene Glycol Carbomer Carboxymethylcellulose galactomannan polysaccharide
	Pred forte *Allergan*	1% prednisolone acetate	hydroxypropylmethylcellulose
	Vexol *Alcon*	1% Rimexolone	Carbomer
	Tobradex *Novartis*	Tobramycin 3mg/ml Dexamethasone 1mg/ml	Hydroxyethylcellulose
	Voltarol Optha *Thea Pharmaceuticals*	Diclofenac sodium 1mg/ml	Polypropylene glycol

Table 3: A brief overview of polymers showing promising results in research, which are not yet available in over the counter eye drop formulations

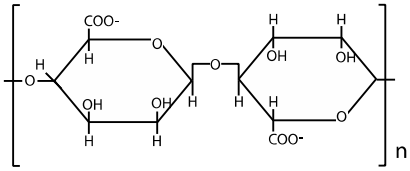
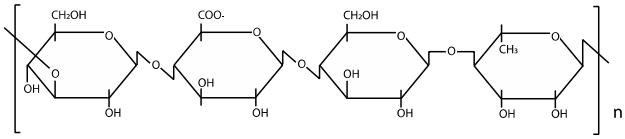
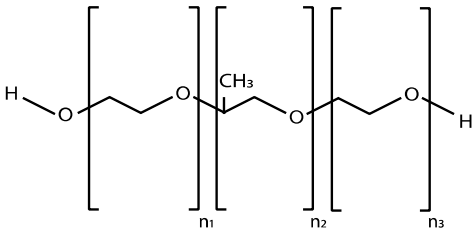
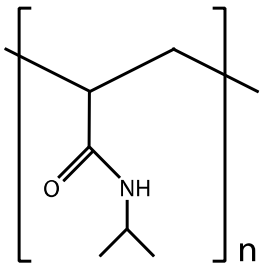
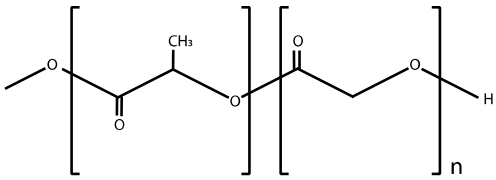
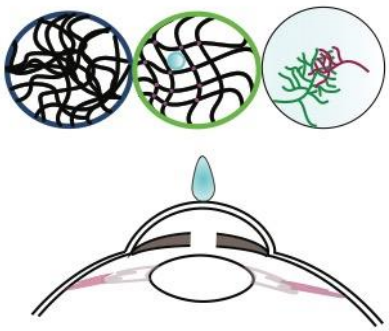
Name	Structure	Natural/ Synthetic	Charge	Properties
Sodium Alginate		Natural	Anionic (Hydrophilic)	Mucoadhesive [25, 42] Gels in the presence of Ca[69h]
Gellan		Natural	Anionic (Hydrophilic)	Gels in the presence of Na+, Ca+ or Mg+ ions [69p] Mucoadhesion [25] Property enhancement through shearing [61]
Poloxamer		Synthetic	Amphiphilic	Thermal gelation [82b, 83c, 165]
Poly-NIPAAM		Synthetic	Amphiphilic	Thermal responsiveness [166]
PLGA		Synthetic (Natural co-polymers)	Hydrophilic	Tunable biodegradation into metabolizable by-products [167]

Table of contents text:

This progress report considers recent innovations in the formulation of eye drops and assesses these innovations from both a materials engineering and immunological perspective. The principles of materials engineering are linked to the specific needs of topical ocular drug delivery and the relevant immunological considerations. Various drug-carriers are compared based on their materials, tunability, drug affinity and compatibility with common ocular pathologies.



Biographies:

Naomi Bennett is currently a PhD student within the School of Chemical Engineering TRAILab at the University of Birmingham. She is investigating novel topical treatments for corneal mineralisation and is supervised by Dr Lisa Hill and Professor Liam Grover. She received her undergraduate degree in Sport and Materials Science (Joint Honours) BSc from the University of Birmingham in 2018.