Review

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Review

Very High Molecular Weight Hyaluronic Acid as an Enhanced Vehicle in Therapeutic Eye Drops: Application in a Novel Latanoprost Formulation for Glaucoma

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Abstract

The efficacy of topical drug delivery via eye drops is often achieved at the expense of tolerability and consequently, efforts are being made to design strategies that minimize the adverse effects associated with the passage of active pharmaceutical ingredients (APIs) across the ocular surface. Many of these approaches are too complex, costly and challenging to implement on an industrial scale, yet there is increasing evidence that hylan A, a very high molecular weight hyaluronic acid (≥3.0 MDa), may be a promising vehicle for topical drug delivery of ocular therapies. In this review we explore how the mucoadhesive and viscoelastic properties of eye drop formulations based on hylan A help extend the residence time of APIs at the ocular surface, while maintaining patient comfort. Moreover, we examine how hylan A facilitates the dissolution and stabilisation of APIs, as well as their transport across the ocular epithelial barrier without the need to use toxic penetration enhancers, thereby preserving ocular surface health. Finally, we present evidence indicating that the intrinsic biological properties of hylan A, including its anti-inflammatory effects, help mitigate side effects commonly associated with certain APIs. To illustrate these advantages, we examine the pioneering use of a hylan A-based aqueous eye drop formulation as a vehicle to deliver latanoprost, a prostaglandin analogue widely used in the treatment of glaucoma. This case study demonstrates the potential of hylan A-based eye drops to offer safer and more effective topical drug delivery, especially for long-term ocular therapies where tolerability and biocompatibility are critical.

Keywords: hylan A; hyaluronic acid; very high molecular weight; eye drops; ocular drug delivery; ocular surface health; mucoadhesion; viscoelasticity; latanoprost

1. Introduction

The anterior segment of the eye is comprised of the conjunctiva, cornea and anterior chamber, and it is the primary site of several common ocular disorders. The accessibility of this anterior segment makes it well-suited for topical drug delivery, most commonly in the form of eye drops that offer therapeutic opportunities for a range of eye disorders. These approaches offer many advantages, including ease of use, non-invasiveness and lower cost compared to other technologies, establishing eye drops containing active pharmaceutical ingredients (APIs) as first-line therapies for many anterior segment disorders.

However, topical drug delivery via eye drops also faces some limitations due to the anatomy of the eye and tear dynamics. One challenge is the rapid turnover of the tear film, which causes a large proportion of the eye drop to quickly drain into the nasolacrimal duct, reducing the residence time of the API. The API that resists this initial clearance must still then penetrate the most superficial epithelial barrier and consequently, only a small fraction of the dose applied will ultimately reach deeper structures like the anterior chamber (Allyn et al., 2021, Hansen et al., 2024, Ahmed et al., 2023).

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A traditional approach to improving topical drug delivery via eye drops has been to include penetration enhancers in the formulations. These facilitate API penetration in different ways, by enhancing penetration of the glycocalyx of the corneal and conjunctival surface epithelium, by loosening tight junctions to compromise epithelial integrity, and by altering cell membrane properties. For example, metal chelators like ethylene diamine tetraacetic acid (EDTA) may be used as penetration enhancers as they disrupt the tight junctions between epithelial cells by sequestering calcium ions (Moiseev et al., 2019, Ye et al., 2012).

Eye drop formulations often contain additives to enhance the solubility and stability of the API (e.g. surfactants to dissolve lipophilic APIs), prolonging its retention at the ocular surface (e.g. polymers enhancing viscosity), or to maintain sterility during use and storage (i.e. preservatives). Some additives have adverse effects at the ocular surface, producing irritation, dryness and allergic reactions (Kahook et al., 2024, Fineide et al., 2024). This is particularly concerning when treating chronic conditions where long-term daily administration is required, and these adverse effects may reduce patient adherence and persistence (Baudouin et al., 2025). By contrast, adverse effects that are associated with the intrinsic molecular properties of the APIs may be less easy to palliate, although they may be alleviated or exacerbated by additives in the formulation (Hedengran and Kolko, 2023).

Intense efforts are being made to enhance eye drop formulations for topical drug delivery (Wang and Wang, 2022), testing the incorporation of various additives to enhance parameters like API solubility, retention time and penetration into the eye. However, identifying optimal combinations is still largely considered a challenge, as improvements in one aspect are often either insufficient or may come at the expense of another. For example, preservative-free eye drops produce fewer ocular surface symptoms but they do not appear to be associated with consistently improved patient adherence, for example in the treatment of glaucoma (Jayaram et al., 2023). This may be due to adverse effects associated with other additives or to the intrinsic properties of the APIs themselves. Hence, there is still a need to develop formulations that enhance API bioavailability while avoiding side effects, and that ideally provide additional benefits to the ocular surface.

Here we focus on a novel vehicle for topical drug delivery via eye drops, a buffered saline solution containing 0.15% of a linear, very high molecular weight (MW) hyaluronic acid (HA; hylan A, ≥3.0 MDa) (Müller-Lierheim, 2020, Bron et al., 2022). We will provide evidence of the promise this aqueous hylan A formulation offers to address several key challenges, enhancing ocular surface retention, API solubilisation and stabilisation, and API transport, while maintaining a healthy ocular surface. To illustrate these benefits, we will examine the pioneering use of this aqueous hylan A formulation as a vehicle for latanoprost, a prostaglandin analogue and a frontline approach to treat glaucoma.

2. An Aqueous Hylan A Formulation with Optimal Viscoelastic Properties Enhances Ocular Surface Retention of APIs

Achieving increased ocular surface retention by adjusting the formulation of eye drops is desirable as it means the API will stay at the ocular surface longer, thereby enhancing its therapeutic efficacy and drug delivery to the eye. One approach often used to extend ocular surface retention is to increase the viscosity of the eye drop, which hinders drainage from the ocular surface. This can be achieved with synthetic polymers like polyvinyl alcohols (PVAs), natural polymers like HA, or with derivatives of natural polymers such as hypromellose (HPMC) (Grassiri et al., 2021). However, excessively high viscosity can cause problems, like increased reflex tearing, which can accelerate API clearance, exacerbate discomfort and cause temporary visual blurring (Grassiri et al., 2021, Giri et al., 2024). To avoid these issues, eye drops can be formulated with a polymeric solution that exhibits viscoelastic properties closely mimicking the flow of healthy human tears. Ideally, such formulations maintain the high viscosity of natural tears when the eye is open, promoting prolonged residence times, while they respect the low viscosity of natural tears during blinking, thereby limiting the friction between eyelid and epithelial surface to ensure comfort and avoid altered vision (Arshinoff et al., 2021b, Tiffany, 1994, Müller-Lierheim, 2020).

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The flow of dissolved polymers is determined by their ability to entangle (Graessley, 2005). HA is a linear, naturally occurring polysaccharide and an essential component of the vertebrate extracellular matrix (Almond, 2007). HA can be produced through fermentation, adopting a wide range of MWs (i.e. chain lengths) up to several million Daltons (MDa) (Fallacara et al., 2018). Longer HA chains in solution become more easily entangled, which enhances their viscoelasticity. Accordingly, an aqueous solution with 0.15% hylan A (≥3.0 MDa) exhibits flow behaviour mimicking that of natural tears, whereas an aqueous solution containing 0.15% lower MW HA does not produce this effect (Arshinoff et al., 2021a, Müller-Lierheim, 2020). This is primarily attributed to the very high MW of hylan A without the need for additional viscosity-enhancing agents. A comprehensive examination of this topic has been presented in a previous article (Müller-Lierheim, 2020).

Mucoadhesion is an even more critical factor than viscosity in determining the retention of APIs at the ocular surface. This feature refers to the interaction with mucus, which is mainly composed of water (>95%) and mucins, a family of large, highly glycosylated hydrophilic proteins (Andrews et al., 2009, Grassiri et al., 2021). Mucins are secreted into the mucoaqueous layer of the tear film at the ocular surface, and they also exist as cell membrane-bound proteins within the glycocalyx formed by the superficial corneal and conjunctival epithelial cells (Baudouin et al., 2019). The flexibility of polymer chains drives their entanglement with mucin chains and the formation of hydrogen bonds (Andrews et al., 2009, Smart, 2005). In aqueous solution, HA is a very flexible polyanion able to entangle intimately with and adhere to the mucin molecules at the ocular surface. The mucoadhesive properties of aqueous HA are influenced strongly by its MW, with high MW but not low MW HA binding readily to membrane-bound mucins, enhancing the cellular barrier against pathogens and prolonging local drug retention (Hansen et al., 2017). Indeed, the mucoadhesive performance of linear HA increases in direct proportion with its MW, with crosslinked HA and other polymers commonly used in eye drops exhibiting lower mucoadhesion (except for xanthan gum) (Guarise et al., 2023). Accordingly, an aqueous hylan A formulation would be expected to exhibit superior mucoadhesiveness at the ocular surface given its very high MW. Together with its viscoelastic properties comparable to natural tears, an aqueous 0.15% hylan A formulation is therefore likely to be a suitable vehicle for ocular drug delivery, producing adequate ocular surface retention and patient comfort.

3. An Aqueous Hylan A Formulation Improves API Solubilisation, Stability and Ocular Transport

A major challenge when using eye drops for topical drug delivery is the poor aqueous solubility and stability of many APIs, which restricts their bioavailability. While advanced solutions have been developed to address this issue (Ahmed et al., 2023, Giri et al., 2024), they are often complex, costly, and may face lengthy evaluation and regulatory approval processes before reaching the market and patients (Giri et al., 2024, Tenpattinam et al., 2025). A simpler alternative, supported by extensive biocompatibility and clinical data, is the use of linear, natural HA in aqueous solution. This approach differs from the use of HA/drug chemical conjugates or HA modified nanoparticles or micelles, although all these strategies exploit similar properties of HA (Jiang and Xu, 2023, Zhang et al., 2018, Fallacara et al., 2018, Guter and Breunig, 2017, Buckley et al., 2022).

At physiological pH in aqueous solution, HA is a negatively charged polyanion and it forms salts generally referred to as hyaluronan or hyaluronate (e.g. sodium hyaluronate), which are very hydrophilic and consequently, surrounded by water molecules. More precisely, water molecules link the HA hydrophilic functional groups (e.g. carboxyl, COOH) to hydrogen bonds that stabilize the secondary structure of the biopolymer, i.e. a two-fold helix. In this extended conformation, HA chains also form hydrophobic domains within their secondary structure that can interact non-covalently with other hydrophobic molecules in an aqueous environment (Rouse et al., 2007, Ghosh et al., 1994). This feature can improve the solubility of APIs in aqueous solutions, enhancing their chemical stability by decreasing water accessibility and inhibiting hydrolysis, or by reducing the access of enzymes to the API. When the secondary structure of HA molecules provokes entanglement, an

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extended three-dimensional network can form (i.e. a tertiary structure) in which the strong intermolecular interactions between HA chains reduce the availability of these hydrophobic domains and the ability of HA to interact with hydrophobic molecules (Rouse et al., 2007). Both the concentration and MW of HA influence the transition from secondary to tertiary structures in aqueous solutions (Fallacara et al., 2018). Indeed, based on the properties of HA studied previously (Rouse et al., 2007, Ghosh et al., 1994), it is plausible that a 0.15% hylan A aqueous solution contains enough HA molecules in conformations that can interact with hydrophobic molecules to improve the solubility and stability of the latter.

There is some evidence as to how hylan A might facilitate the transport of other molecules into the eye. In vertebrates, several cell surface receptors for HA exist, the best studied being cluster-determined 44 (CD44) (Aruffo et al., 1990, Wang et al., 2025). The binding of HA molecules to CD44 involves its engagement with multiple CD44 receptor sites (Ruppert et al., 2014), such that the avidity of HA increases with its MW and high MW HA binds much more strongly to this receptor than low MW forms (Lee-Sayer et al., 2015). Among the known functions of the CD44 receptor is its role in facilitating HA internalization and its subsequent degradation (Knudson et al., 2002). When high MW HA binds to CD44 it can be cleaved into intermediate-sized fragments by cell surface enzymes (membrane-bound hyaluronidases), which can then be internalized by and directed to intracellular compartments where they are further degraded (Wang et al., 2025, Garantziotis and Savani, 2019). CD44 receptors have been identified in both corneal and conjunctival epithelial cells (Lardner and van Setten, 2020, Zhu et al., 1997, Lerner et al., 1998), such that this pathway is a potential route for API delivery to deeper ocular regions without compromising cell membrane integrity when these molecules interact with HA. Receptors involved in alternative uptake pathways include the HA receptor for endocytosis (HARE) (Zhou et al., 2000, Harris and Baker, 2020), which is also found on corneal epithelial cells (Falkowski et al., 2003) and might facilitate the delivery of molecules that interact with HA (Müller-Lierheim, 2020).

4. The Benefits of Using an Aqueous Hylan A Formulation for Ocular Surface Health

When the inherent properties of the API in a therapeutic eye drop produce adverse effects, it is important to include substances in these formulations that counteract such effects and that favour ocular surface health. Beyond the benefits outlined above, hylan A has consistently been demonstrated to promote better ocular surface health than lower MW HA, primarily due to its unique very high MW (Müller-Lierheim, 2020).

The MW of HA affects its biological activity in both healthy and diseased states (Bohaumilitzky et al., 2017, Cyphert et al., 2015). In homeostatic conditions, HA predominantly exists as a high MW polymer with biophysical properties consistent with its activity as a lubricant, space-filler and shock absorber in joints and connective tissues. Moreover, it has anti-inflammatory, anti-proliferative and anti-angiogenic effects, and multiple studies have highlighted its role as a tissue protectant and promoter of homeostasis after injury and inflammation. By contrast, in pathological circumstances HA fragmentation is enhanced and produces more low MW HA that is linked to inflammation (Bohaumilitzky et al., 2017, Cyphert et al., 2015, Monslow et al., 2015, Garantziotis and Savani, 2019). Furthermore, unlike low MW HA, high MW HA reduces peripheral nociceptor activity (Gomis et al., 2004, Caires et al., 2015) as well as inflammatory and neuropathic pain (Bonet et al., 2020, Ferrari et al., 2018), including pain induced by chemotherapy (Bonet et al., 2022) or surgery (Zhang et al., 2024) in preclinical models. Elsewhere, tear film stability was improved when eye drops with 0.15% aqueous hylan A (Comfort Shield, i.com medical, Munich, Germany) were evaluated in a preclinical model of environmental dry eye stress (Table 1), reducing ocular surface damage and inflammation when compared to the use of low MW HA or secretagogues (secretion stimulating drugs) (Kojima et al., 2020).

Clinical data suggest that the physiological activity of very high MW 0.15% hylan A eye drops is effective to treat severe ocular disease and that they may even be superior to autologous serum eye

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drops (Table 1) (Beck et al., 2019). These benefits were backed up in the HYLAN M clinical study, where switching from optimized artificial tear treatments to 0.15% hylan A eye drops significantly improved symptoms in severe dry eye patients (within four weeks), including visual stability, discomfort and pain (Table 1) (Medic et al., 2024, van Setten et al., 2020a, Alsheikh et al., 2021). Moreover, 0.15% hylan A eye drops appeared to increase the length of corneal nerves (van Setten et al., 2020b), which are typically compromised in this population (Benitez-Del-Castillo et al., 2007, Shetty et al., 2023, Galor et al., 2025). The benefits of hylan A for corneal nerves were further demonstrated in patients who underwent corneal surgery, procedures known to cause unavoidable corneal nerve damage. In this context, daily 0.15% hylan A eye drop application after surgery accelerated the recovery of corneal nerve structure and sensitivity relative to eye drops containing low MW HA, while also improving ocular surface symptoms (Özkan et al., 2025). In addition, hylan A treatment helped prevent the increase in inflammation-related immune cells observed three months after surgery when low MW HA was used (Table 1) (Özkan et al., 2025).

Table 1. Summary of the studies demonstrating the benefits of the 0.15% hylan A eye drop formulations in ocular surface health.

Study	Study type	Model/ Patients	Comparisons	Conclusions
Kojima et al., 2020	Preclinical	Mouse model of environmental dry eye disease	Low MW HA eye drops, secretagogue eye drops	Improved tear film stability. Reduced ocular surface damage. Less inflammation with 0.15% hylan A eye drops.
Beck et al., 2019	Clinical	11 patients treated with autologous serum eye drops	Autologous serum eye drops	Eye drops containing 0.15% hylan A effectively treat severe ocular disease. These 0.15% hylan A eye drops may replace eye drops of autologous serum.
van Setten et al., 2020a	Clinical **HYLAN M study**	84 patients with severe dry eye disease	Optimized artificial tear treatments	Symptoms rapidly improved by switching to 0.15% hylan A eye drops include: visual stability, discomfort and pain.
van Setten et al., 2020b	Clinical. Subgroup analysis of the HYLAN M study	16 patients	Optimized artificial tear treatments	Switching to 0.15% hylan A eye drops promotes corneal nerve growth.
Medic et al., 2024	Clinical Subgroup analysis of the HYLAN M study	47 patients	HA containing artificial tears (15 commercial brands with HA of diverse MWs)	Fewer 0.15% hylan A eye drops required than those with lower MW HA. Eye drops containing 0.15% hylan A have better clinical effects.
Özkan et al., 2025	Clinical	63 eyes from 55 patients with keratoconus following corneal crosslinking (CXL)	Low MW HA eye drops	After CXL, 0.15% hylan A eye drops produce: faster corneal nerve regeneration; faster recovery of sensitivity; improved ocular symptoms; and fewer inflammation related immune cells than low MW HA eye drops.

5. An Aqueous Hylan A Formulation as New Vehicle for Latanoprost to Manage Elevated Intraocular Pressure

Alterations to the anterior segment may influence the development of diseases that affect structures in the posterior eye segment, such as the retina and optic nerve. One prominent example is glaucoma, one of the most common worldwide causes of irreversible blindness. Glaucoma often develops when aqueous humour drainage from the anterior chamber is impaired or unbalanced, leading to an elevation in intraocular pressure (IOP) that can provoke structural changes in the posterior segment of the eye and optic nerve injury. Currently, IOP is the only risk factor that can be modulated to prevent glaucoma progression (Weinreb et al., 2014, Jayaram et al., 2023). Thus, reducing IOP via eye drops containing APIs is the primary strategy to treat glaucoma (Jayaram et al., 2023).

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Prostaglandin analogues increase aqueous humour outflow via the unconventional pathway, such that latanoprost has become a frequently used treatment (Jayaram et al., 2023) and one of the most effective APIs used in eye drops to lower IOP and slow glaucoma progression (Li et al., 2016). Prostaglandin analogues produce well documented adverse effects at the ocular surface (Kolko et al., 2023) and at therapeutic concentrations, topical latanoprost can cause ocular surface damage in a mouse model that resembles dry eye disease, primarily through inflammatory mechanisms (Yang et al., 2018). Moreover, many commercial IOP lowering eye drops contain the quaternary ammonium cationic detergent benzalkonium chloride (BAK) as a preservative and penetration enhancer (Kahook et al., 2024), although long-term BAK use has negative effects at the ocular surface (Baudouin et al., 2010) and an emergence of preservative-free IOP lowering eye drops has occurred in recent years (Konstas et al., 2021, Hollo et al., 2018, Kim et al., 2021, Kahook et al., 2024). These formulations may include other penetration enhancers like EDTA, which while less problematic can potentially cause long-term ocular surface damage (Villani et al., 2016, Halder and Khopade, 2020, Ye et al., 2012). Other additives like polyethylene glycol (PEG) and propylene glycol (PG) act as lubricants, surfactants and co-solubilisers, yet they may also contribute to dry eye disease (Gomes et al., 2017).

The prevalence of ocular surface disease is very high in individuals with glaucoma, particularly in those with uncontrolled glaucoma and those who use multiple topical medications (Fechtner et al., 2010, Skalicky et al., 2012, Baudouin et al., 2012b). A large-scale study found a higher IOP in glaucoma patients with severe ocular surface disease than in those with no or mild disease (Baudouin et al., 2012b). Moreover, there is evidence that chronic ocular surface inflammation increases outflow resistance, further favouring IOP elevation (Baudouin et al., 2012a, Batra et al., 2014, Baudouin et al., 2021). Therefore, adopting a management strategy for ocular surface problems, particularly inflammation, is key to improving the effectiveness of IOP control. This can be achieved by reducing the toxicity of glaucoma medications and incorporating supportive therapies (e.g. ocular surface lubrication and anti-inflammatory treatment) (Dubrulle et al., 2018, Messmer et al., 2024, Kemer et al., 2024).

To address these challenges, a novel latanoprost ophthalmic formulation has been developed using an aqueous hylan A solution as the vehicle, leveraging the advantages outlined in the previous sections (Figure 1). The formulation is a preservative-free 0.15% hylan A solution prepared in isotonic phosphate buffered saline at pH 7.4, a stable vehicle to which 20 µg/ml of latanoprost is added (Müller-Lierheim, 2021). Notably, this concentration exceeds the normal solubility of latanoprost in water by approximately 8 µg/ml (Table 2), probably facilitated by an interaction between latanoprost and hylan A. In one subject with ocular hypertension, this new formulation lowered the IOP more than a commercial latanoprost eye drop (Table 2), despite the higher concentration in the latter (50 µg/ml latanoprost) (Müller-Lierheim, 2021). This effect further suggests that hylan A may facilitate the transport of latanoprost into the eye (Müller-Lierheim, 2020, Bron et al., 2022), as seen in a rat model where the therapeutic concentration of latanoprost in the animals' aqueous humour was similar after the administration of a hylan A-based eye drop containing 14 µg/ml latanoprost to that achieved with a commercial formulation containing 50 µg/ml latanoprost (Table 2). Indeed, this commercial formulation not only contained around 3.5 times more latanoprost but it also included the penetration enhancer EDTA (Higa et al., 2024). The same formulations were also tested in a mouse model in which the novel hylan A-based formulation induced less inflammation, caused fewer ocular surface alterations and retained better corneal epithelial barrier integrity than the commercial formulation, while controlling IOP better. Significantly, all the ocular surface parameters analysed in animals treated with the hylan A-based latanoprost formulation were indistinguishable from those of the untreated wild-type controls (Table 2) (Dogru et al., 2023).

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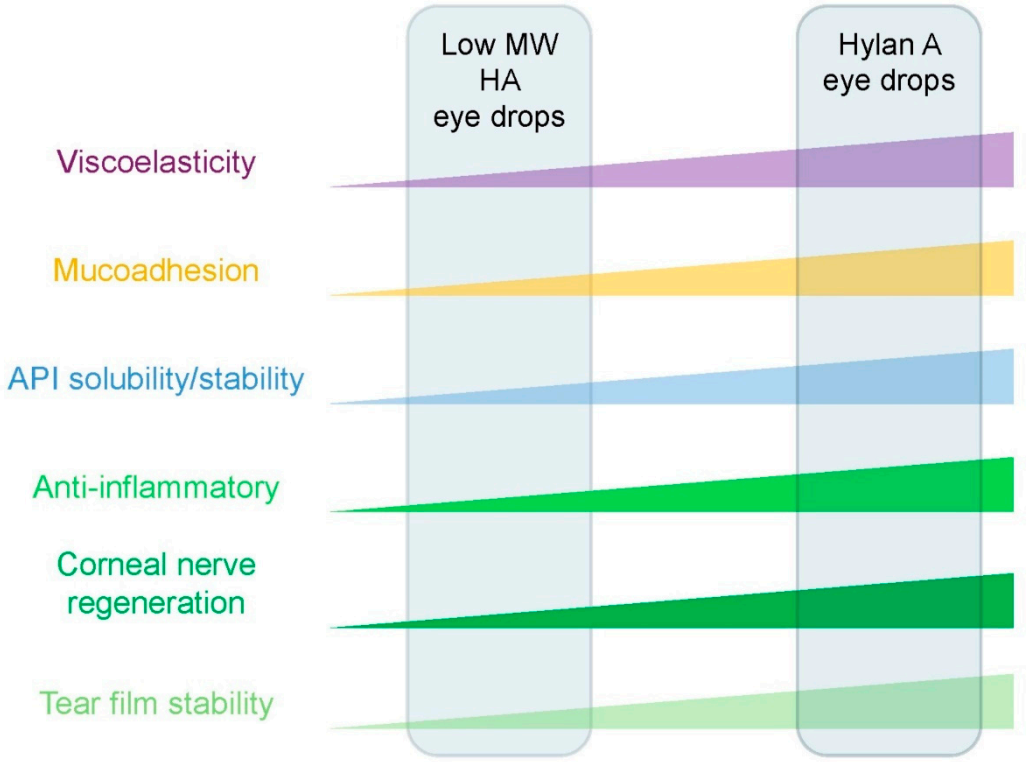

Figure 1. Qualitative comparison of physicochemical and physiological properties of two aqueous eye drop formulations containing 0.15% HA: one with low MW HA and the other with hylan A, a very high MW HA.

Table 2. Summary of the studies demonstrating the benefits of a novel 0.15% hylan A eye drop formulation as a vehicle for latanoprost.

Study	Study type	Model/ Patients	Comparators	Conclusions
Müller-Lierheim, 2021	Formulation solubility and stability	N/A	N/A	A preservative-free 0.15% hylan A solution in isotonic phosphate buffered saline (pH 7.4) enhances latanoprost solubility by 75%
Dogru et al., 2023	Preclinical	Standard mouse strain	Commercial eye drops with 50 µg/mL latanoprost	A hylan A-based eye drop with 14 µg/mL latanoprost preserves ocular surface parameters while effectively lowering IOP
Higa et al., 2024	Preclinical	Standard strain rat	Commercial eye drops with 50 µg/mL latanoprost	A hylan A-based eye drop with 14 µg/mL latanoprost achieves comparable therapeutic latanoprost levels in aqueous humour as a 50 µg/mL commercial formulation
Müller-Lierheim, 2021	Proof-of-concept	One subject with ocular hypertension	Commercial eye drops with 50 µg/mL latanoprost	A hylan A-based eye drop with 20 µg/mL latanoprost lowers IOP better than a commercial latanoprost eye drop with a higher API concentration

Taken together, these findings support the potential of this novel latanoprost formulation, which is free of toxic additives, that uses a lower amount of the API, and that takes advantage of the lubricating and anti-inflammatory properties of hylan A. By promoting ocular surface health, this formulation may enhance the reduction of IOP by chronic treatments, as preclinical results indicate. Further clinical studies are being prepared to confirm these potential benefits.

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6. Hylan A-Based Eye Drops as Next Generation Vehicles for Therapeutic API Delivery

A variety of new delivery systems for topical drugs are being developed that offer promise to advance ocular therapy, such as hydrogels, nanoparticles carriers, contact lenses and ocular inserts (Zeppieri et al., 2025). However, they pose significant challenges related to implantation, removal, long-term biocompatibility and patient acceptance. Many of these new technologies are also costly and difficult to scale-up for industrial production. In the case of glaucoma, which affects around 100 million people worldwide across a wide range of socioeconomic and healthcare settings (Kolko et al., 2023), it is essential to establish a range of treatment options. Thus, eye drops continue to represent a practical, accessible and widely accepted option.

There are many ongoing efforts to improve eye drop formulations for topical drug delivery, with different additives being tested to enhance critical parameters like mucoadhesiveness, viscoelasticity and API solubility, stability and ocular transport, as well as to favour ocular surface health. While optimizing one parameter in many new formulations compromises another, the hylan A-based eye drops presented here seem to represent a promising solution to simultaneously address all these critical aspects (Figure 1). Indeed, the evidence supports the efficacy of hylan A-based eye drops to treat various ocular surface conditions (Table 1), also representing a useful vehicle for latanoprost (Table 2). Although the benefits observed can mostly be attributed to the unique properties of hylan A, other physicochemical properties of the formulation also contribute positively, such as pH, osmolarity and the buffer employed (Hedengran and Kolko, 2023, Higa et al., 2024).

We envisage that hylan A-based eye drops will represent a platform that could support a wide range of ocular therapies. A further promising application is the topical delivery of cyclosporine A (CsA), an immunosuppressive drug commonly used to manage the inflammatory component of chronic dry eye disease (Patil et al., 2025, Craig et al., 2017). This is a condition where effectively overcoming ocular drug delivery barriers while avoiding adverse effects remains a challenge, mainly due to the large MW and hydrophobic nature of CsA (Nagai and Otake, 2022, Periman et al., 2020). Hylan A-based eye drops could address these limitations, as already seen with latanoprost (Müller-Lierheim, 2021, Higa et al., 2024, Dogru et al., 2023). Beyond its use as a vehicle, hylan A itself produces anti-inflammatory effects (Kojima et al., 2020, Bron et al., 2022) that may act synergistically with CsA to more effectively treat chronic dry eye disease. Moreover, given the involvement of neurosensory abnormalities in dry eye disease (Craig et al., 2017), the neurotrophic effects of hylan A (Özkan et al., 2025, van Setten et al., 2020b) may offer further therapeutic benefits. Interestingly, recent findings *in vitro* showed that CsA can alter HA metabolism in orbital fibroblasts (Galgoczi et al., 2024). If similar effects occur *in vivo*, this could have negative effects on ocular surface health. In such a case, co-formulation of CsA with hylan A may help maintain physiological HA homeostasis and mitigate potential adverse effects.

In summary, the use of hylan A as a vehicle represents a promising step towards a new generation of eye drops for topical ocular drug delivery, designed to improve API bioavailability, reduce adverse effects and support long-term ocular surface health in a range of therapeutic indications.

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