Review

Very High Molecular Weight Hyaluronic Acid: A Superior Transport Vehicle for Ocular Therapeutics

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Very High Molecular Weight Hyaluronic Acid: A Superior Transport Vehicle for Ocular Therapeutics

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Abstract: Topical drug delivery via eye drops often achieves efficacy at the expense of tolerability. Recent efforts have focused on developing strategies to allow active pharmaceutical ingredients (APIs) to cross ocular surface barriers while minimising adverse effects. However, many of these remain complex, costly and challenging to implement at scale in industrial settings. We highlight here emerging evidence supporting the potential of hylan A, a very high molecular weight hyaluronic acid, as a promising vehicle for topical drug delivery in ocular therapeutics. We explore how the mucoadhesive and viscoelastic properties of a hylan A-based eye drop formulation contribute to extending residence time of APIs on the ocular surface while maintaining patient comfort. Additionally, we examine the role of hylan A in facilitating the dissolution and stabilisation of APIs, as well as in transport across the ocular epithelial barrier without the need for 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 all these advantages, we examine the pioneering use of a hylan A-based aqueous eye drop formulation as a delivery vehicle for latanoprost, a prostaglandin analogue widely used in the treatment of glaucoma. This case demonstrates the potential of hylan A-based eye drops to support safer and more effective topical drug delivery systems, 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, comprising the conjunctiva, cornea and anterior chamber, is the primary site of several common ocular disorders. Due to its external accessibility, the anterior segment of the eye is particularly well-suited for therapeutic options using topical drug delivery, most commonly in the form of eye drops. This together with advantages such as ease of use, non-invasiveness and lower cost compared to other technologies, have established active pharmaceutical ingredient (API)-containing eye drops as the first-line treatment for numerous anterior segment disorders.

Despite its widespread use, topical drug delivery via eye drops faces limitations due to the eye anatomy and tear dynamics. One of the challenges is the rapid turnover of the tear film, which causes a large portion of the eye drop volume to drain quickly into the nasolacrimal duct. API molecules that escape this initial clearance must still penetrate the most superficial epithelial barrier and only a small fraction of them ultimately reach deeper structures such as the anterior chamber (Allyn et al., 2021, Hansen et al., 2024, Ahmed et al., 2023). A traditional approach to improving topical drug delivery via eye drops has been to include in the formulation substances known as penetration enhancers. These facilitate the penetration of the API via several mechanisms, such as penetrating the glycocalyx of the surface epithelia of cornea and conjunctiva, loosening tight junctions to compromise

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epithelial integrity, and altering cell membrane properties. Examples of penetration enhancers are metal chelators such as disodium edetate (EDTA), which disrupts tight junctions between epithelial cells by sequestering calcium ions (Moiseev et al., 2019).

Moreover, eye drop formulations often contain additives to enhance the solubility and stability of the API (e.g., surfactants to dissolve lipophilic APIs), prolong its retention time on the ocular surface (e.g., polymers enhancing viscosity), and maintain sterility during use and storage (i.e., preservatives). Many of these additives are associated with ocular surface adverse effects, including irritation, dryness, and allergic reactions (Kahook et al., 2024, Fineide et al., 2024). This is particularly concerning in the treatment of chronic conditions, where long-term daily administration is required and can reduce patient adherence and persistence (Baudouin et al., 2025). Adverse effects associated with topical ophthalmic treatments may result not only from the additives in the formulation but also from the intrinsic molecular properties of the API (Hedengran and Kolko, 2023).

Improved eye drop formulations for topical drug delivery are a very active area of development (Wang and Wang, 2022), with various additives employed to enhance parameters such as API solubility, retention time and transport into the eye. However, identifying an optimal combination remains a challenge, as improvements in a single aspect are often insufficient or may come at the expense of another. For example, preservative-free eye drops are associated with reduced ocular surface symptoms, yet clinical studies have not consistently shown improved patient adherence with these formulations in certain therapeutic areas, such as glaucoma treatment (Jayaram et al., 2023). This may be attributed to adverse effects associated with other additives or to the intrinsic properties of the APIs themselves. Further innovations are therefore necessary, particularly to enhance API bioavailability while avoiding side effects, and ideally providing additional benefits to the ocular surface.

We will focus here on a novel vehicle for topical drug delivery via eye drops consisting of a buffered saline solution with 0.15% linear, very high molecular weight hyaluronic acid (hylan A; ≥3.0 MDa) (Müller-Lierheim, 2020, Bron et al., 2022). We will provide evidence supporting why this hylan A aqueous formulation offers a promising approach with the potential to simultaneously address several key challenges, including improved ocular surface retention, enhanced API solubilization and stabilization, facilitation of API transport, and support of ocular surface health. To illustrate these benefits, we will examine the pioneering use of this hylan A aqueous formulation as a vehicle for latanoprost, a prostaglandin analogue and a frontline approach to glaucoma treatment.

2. Hylan A aqueous Formulation: Enhanced Ocular Surface Retention with Optimal Viscoelastic Properties

Eye drop formulations with increased ocular surface retention are highly desirable for many treatments, as they keep the API on the ocular surface longer, thereby enhancing drug delivery into the eye and therapeutic efficacy. One of the most employed approaches to extend ocular surface retention is to increase viscosity, which helps reduce rapid drainage from the ocular surface. This can be achieved with synthetic polymers such as polyvinyl alcohols (PVA), natural polymers such as hyaluronic acid (HA), and derivatives of natural polymers such as hypromellose (HPMC) (Grassiri et al., 2021). However, a formulation with excessively high or constant high viscosity can cause problems such as increased reflex tearing, leading to faster API clearance, as well as discomfort and temporary visual blurring (Grassiri et al., 2021, Giri et al., 2024). To avoid these issues, an eye drop formulated with a polymeric solution that exhibits viscoelastic properties closely mimicking the flow behaviour of healthy human tears is preferred. Ideally, such formulation maintains the high viscosity of natural tears when the eye is open (promoting prolonged residence time), while exhibits the low viscosity of natural tears during blinking (promoting low friction between eyelid and epithelial surface, high comfort and absence of visual disturbances) (Arshinoff et al., 2021b, Tiffany, 1994, Müller-Lierheim, 2020).

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The flow behaviour 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 methods in a wide range of molecular weights (i.e., chain lengths) up to several million Daltons (MDa) (Fallacara et al., 2018). Longer HA chains entangle more easily, resulting in increased viscoelasticity of the solution. An aqueous solution with 0.15% hylan A (very high molecular weight hyaluronic acid; ≥3.0 MDa) has been shown to exhibit flow behaviour mimicking that of natural tears (Müller-Lierheim, 2020). An aqueous solution containing 0.15% HA of lower molecular weight does not produce this effect (Arshinoff et al., 2021a, Müller-Lierheim, 2020).

Mucoadhesion is an even more critical factor than viscosity in determining the retention of formulations on the ocular surface. It refers to the interaction with mucus, which is composed mainly of water (>95%) and mucins, a family of large, highly glycosylated, hydrophilic proteins (Andrews et al., 2009, Grassiri et al., 2021). On the ocular surface, mucins are present both as secreted form in the mucoaqueous layer of the tear film and as cell membrane-bound form within the glycocalyx formed by the superficial epithelial cells of the cornea and conjunctiva (Baudouin et al., 2019). The flexibility of a polymer chains is important for interpenetration and entanglement with the mucin chains to allow the formation of hydrogen bonds (Andrews et al., 2009, Smart, 2005).

HA in aqueous solution is a highly flexible polyanion able to intimately entangle with and adhere to the mucin molecules at the ocular surface. The mucoadhesive properties of aqueous HA solutions are significantly influenced by the HA molecular weight. High molecular weight HA, unlike low molecular weight HA, has been shown to bind to membrane-bound mucins on cells, enhancing the cellular barrier against pathogens and prolonging local drug retention time (Hansen et al., 2017). Guarise and colleagues have more recently showed that the mucoadhesive performance of linear HA increases linearly with molecular weight. Crosslinked HA and other polymers commonly used in eye drops exhibit lower mucoadhesive properties (except for xanthan gum). A physico-chemical analysis of a series of eye drops containing low to high molecular weight HA showed, as expected from these results, a linear correlation between HA molecular weight and mucoadhesiveness (Guarise et al., 2023). Based on these results, a hylan A aqueous formulation is expected to exhibit superior mucoadhesiveness on the ocular surface, owing to the very high molecular weight of hylan A. Together with viscoelastic properties comparable to natural tears, this makes a 0.15% hylan A aqueous formulation a suitable vehicle for ocular drug delivery in terms of ocular surface retention and patient comfort.

3. Improvement of API Solubilization, Stability, and Ocular Transport by Hylan A aqueous Formulation

A major challenge in topical drug delivery via eye drops is the poor aqueous solubility and stability of many APIs, which limits their bioavailability. While sophisticated solutions have been developed to address this issue, they are often complex, costly, and involve molecules with potential toxicity under certain conditions, requiring extensive additional testing. A simpler and safer alternative is the use of linear, natural HA in aqueous solution. This approach differs from the use of HA-drug chemical conjugates and HA-modified nanoparticles or micelles, although all these strategies exploit similar HA properties (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 negatively charged (polyanion) and forms salts generally referred to as hyaluronan or hyaluronate (e.g., sodium hyaluronate), which are highly hydrophilic and, consequently, surrounded by water molecules. More precisely, water molecules link HA hydrophilic functional groups, such as carboxyl (COOH), with hydrogen bonds that stabilize the secondary structure of the biopolymer, i.e., two-fold helix. In this extended conformation, HA chains also present extensive hydrophobic faces within their secondary structure (Fallacara et al., 2018). These hydrophobic patches can interact with hydrophobic molecules (Rouse et al., 2007, Ghosh et al.,

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1994). This can improve API solubility in aqueous media as well as enhance chemical stability, for instance by decreasing water accessibility and inhibiting hydrolysis or by delaying enzyme access to the API. When secondary-structure HA molecules entangle to form an extended three-dimensional network, i.e., the tertiary structure, the strong intermolecular interactions between HA chains reduce the availability of these hydrophobic domains. As a result, the ability of HA to interact with hydrophobic molecules is diminished (Rouse et al., 2007). Both the concentration and molecular weight of HA influence the transition from secondary to tertiary structure in aqueous solutions (Fallacara et al., 2018). Based on the HA properties previously studied (Rouse et al., 2007, Ghosh et al., 1994), it is plausible that a 0.15% hylan A aqueous solution contains enough HA molecules in a conformation that still permits interactions with hydrophobic molecules, improving their solubility and stability.

How might hylan A further facilitate the transport of interacting molecules across the ocular surface? In vertebrates, several cell surface receptors for HA exist, with the most well studied being cluster-determined 44 (CD44) (Aruffo et al., 1990, Wang et al., 2025). The binding of HA molecules to CD44 depends on engagement with multiple CD44 receptor sites (Ruppert et al., 2014). As a result, the binding avidity of HA increases with its molecular weight, with high molecular weight HA showing significantly stronger receptor binding than low molecular weight forms (Lee-Sayer et al., 2015). Among the known functions of CD44 receptor is its role in facilitating the internalization of HA and its subsequent degradation (Knudson et al., 2002). When high molecular weight HA binds to CD44, it can be cleaved by cell surface enzymes (membrane-bound hyaluronidases) into intermediate-sized fragments. These fragments are then internalized by the cell and directed to intracellular compartments, where they undergo further enzymatic degradation (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). This pathway, therefore, is a potential route for delivering APIs that interact with HA across the ocular surface without compromising cell membrane integrity. Additionally, alternative uptake pathways involving other receptors such as the HA receptor for endocytosis (HARE) (Zhou et al., 2000, Harris and Baker, 2020), which is also present on corneal epithelial cells (Falkowski et al., 2003), may additionally serve as delivery routes (Müller-Lierheim, 2020).

4. Benefits of Hylan A aqueous Formulation for Ocular Surface Health

When adverse effects in topical eye drop therapies arise from the inherent properties of the API, it becomes important to formulate these eye drops including substances that counteract these effects and support ocular surface health. Beyond the formulation benefits outlined above, hylan A has been extensively demonstrated to promote ocular surface health showing superior effects compared to HA of lower molecular weight. This superiority is attributed to its unique very high molecular weight (Müller-Lierheim, 2020).

The biological activities of HA in both healthy and diseased states vary depending on its molecular weight (Bohaumilitzky et al., 2017, Cyphert et al., 2015). In homeostasis, HA predominantly exists as a high molecular weight polymer. Due to its biophysical properties, high molecular weight HA serves as lubricant, space-filler, and shock absorber in joints and connective tissues. Moreover, it promotes anti-inflammatory, anti-proliferative, and anti-angiogenic effects, and multiple studies have highlighted its role as a tissue protector and homeostasis promoter after injury and inflammation. By contrast, pathological stages are characterized by increased HA fragmentation, resulting in elevated levels of low molecular weight HA linked to inflammation (Bohaumilitzky et al., 2017, Cyphert et al., 2015, Monslow et al., 2015, Garantziotis and Savani, 2019). Furthermore, high molecular weight HA, unlike low molecular weight HA, has been shown to reduce 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.

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Regarding ocular surface health, a preclinical study using a model of environmental dry eye stress showed that eye drops with 0.15% hylan A in aqueous solution (Comfort Shield, i.com medical, Munich, Germany) improved tear film stability, reduced ocular surface damage, and lowered inflammation compared to low molecular weight HA or secretagogues (secretion-stimulating drugs) (Kojima et al., 2020). Clinical data have suggested that, due to the molecular weight dependent physiological functions of HA, 0.15% hylan A eye drops are effective for severe ocular disease and may even replace autologous serum eye drops in some cases (Beck et al., 2019). These benefits were supported in the HYLAN M clinical study, which found that switching from optimized artificial tear treatments to 0.15% hylan A eye drops significantly improved symptoms, including visual stability, discomfort and pain, in severe dry eye patients within four weeks (Medic et al., 2024, van Setten et al., 2020a, Alsheikh et al., 2021). Moreover, a subgroup analysis from the study revealed that 0.15% hylan A eye drops support the increase in length of corneal nerves (van Setten et al., 2020b), which are typically compromised in this patient population (Benitez-Del-Castillo et al., 2007, Shetty et al., 2023, Galor et al., 2025). Hylan A benefits for corneal nerves were further demonstrated in patients who underwent corneal surgery known to cause unavoidable corneal nerve damage. In this context, the daily application of 0.15% hylan A eye drops after surgery accelerated the recovery of corneal nerve structure and sensitivity compared to the application of eye drops containing low molecular weight HA, while also improving ocular surface symptoms (Özkan et al., 2025). In addition, the hylan A treatment regime helped prevent the rise in inflammation-related immune cells observed three months after surgery in the group treated with low molecular weight HA (Özkan et al., 2025).

5. Hylan A Aqueous Formulation as New Vehicle for Latanoprost in the Management of Elevated Intraocular Pressure

Alterations in components of the anterior segment can contribute to the development of severe diseases that affect structures of the posterior segment of the eye like the retina and optic nerve. A prominent example is glaucoma, one of the most common causes of irreversible blindness on a global scale. Glaucoma often develops when the aqueous humour fluid drainage systems of the anterior chamber become impaired or imbalanced, leading to elevated intraocular pressure (IOP), which in turn can cause 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 progression of glaucoma (Weinreb et al., 2014, Jayaram et al., 2023).

IOP reduction via eye drops containing APIs remains the primary strategy in the treatment of glaucoma (Jayaram et al., 2023). Prostaglandin analogues that increase outflow via the unconventional pathway such as latanoprost are most frequently used (Jayaram et al., 2023) and among the most effective APIs contained in eye drops for lowering the IOP to slow disease progression (Li et al., 2016). Adverse effects on the ocular surface are well documented for such APIs (Kolko et al., 2023). Topical latanoprost at therapeutic concentrations, for instance, was shown to cause ocular surface damage resembling dry eye disease in a mice model, primarily through inflammatory mechanisms (Yang et al., 2018). Moreover, many commercial IOP lowering eye drops still contain the quaternary ammonium cationic detergent benzalkonium chloride (BAK) as a preservative and penetration enhancer (Kahook et al., 2024). The negative long-term effects of BAK on the ocular surface have been well-documented for a long time (Baudouin et al., 2010) and preservative-free IOP lowering eye drops have become available in the recent years (Konstas et al., 2021, Hollo et al., 2018, Kim et al., 2021, Kahook et al., 2024). Although less problematic to the ocular surface, more recent formulations still include penetration enhancers such as EDTA, which potentially cause long-term ocular surface damage (Villani et al., 2016, Halder and Khopade, 2020). Other additives such us Polyethylene glycol (PEG) and propylene glycol (PG), which act as lubricants, surfactants and co-solubilizers, have been also identified as potential contributors to dry eye disease (Gomes et al., 2017).

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To tackle these issues, a novel latanoprost eye drop formulation employing as the vehicle the hylan A aqueous solution described in the previous sections has recently undergone development and preclinical testing. In particular, the formulation is a preservative-free solution comprised of 0.15% hylan A dissolved in isotonic phosphate buffered saline solution with pH 7.4. Using this solution as a vehicle resulted in a stable formulation containing 20 μg/ml of latanoprost (Müller-Lierheim, 2021). Notably, this concentration exceeds the typical solubility of latanoprost in water by approximately 8 μg/ml, which is likely due to an interaction between latanoprost and hylan A. In one subject with ocular hypertension, the new formulation showed a superior IOP-lowering effect compared to a commercial latanoprost eye drop, despite the latter having a higher API concentration (50 μg/ml latanoprost) (Müller-Lierheim, 2021). This finding strongly supports the hypothesis that hylan A may facilitate the transport of latanoprost into the eye (Müller-Lierheim, 2020, Bron et al., 2022). A preclinical study in a rat model further supported this hypothesis. Following administration of a hylan A-based eye drop containing 14 μg/ml latanoprost, the therapeutic concentration of latanoprost in the animals' aqueous humour reached levels comparable to those achieved with a commercial formulation containing 50 μg/ml latanoprost. This occurred despite the commercial formulation containing approximately 3.5 times more latanoprost and including the penetration enhancer EDTA (Higa et al., 2024). In a parallel preclinical study using a mouse model, the same formulations were tested. The results showed that the novel hylan A-based formulation induces less inflammation, caused fewer ocular surface alterations, and better corneal epithelial barrier integrity than the commercial formulation, while maintaining an IOP-lowering effect comparable to the commercial formulation. Notably, all ocular surface parameters analysed in animals treated with the hylan A-based latanoprost formulation were indistinguishable from those in the untreated wild-type control group (Dogru et al., 2023).

6. Towards a New Generation of Hylan A-Based Eye Drops as API Delivery Vehicles for Ocular Therapeutics

New topical drug delivery systems, such as hydrogels, nanoparticulate carriers, contact lenses, and ocular inserts, hold promise for advancing ocular therapy (Zeppieri et al., 2025). However, challenges related to implantation, removal, long-term biocompatibility and patient acceptance remain significant. Many of the new technologies are also costly and difficult to scale 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), a wide range of treatment options is essential. Therefore, eye drops continue to represent a practical, accessible, and widely accepted option.

Efforts to improve eye drop formulations for topical drug delivery are ongoing, with various additives employed to enhance critical parameters such as mucoadhesiveness, viscoelasticity, API solubilization, stability and ocular transport, and benefits for ocular surface health. In many new formulations, optimizing one parameter compromises another. We presented here hylan A-based eye drops as a promising solution that simultaneously addresses all these critical aspects (**Figure 1**). This is supported by evidence demonstrating the efficacy of hylan A-based eye drops in the treatment of various ocular surface conditions (**Table 1**), as well as data showing the successful use of this formulation as a vehicle for latanoprost (**Table 2**). Although the observed benefits can be mostly attributed to the unique properties of hylan A compared to lower molecular weight HA, other physicochemical properties of the formulation, such as pH, osmolarity and the buffer employed, also contribute positively (Hedengran and Kolko, 2023, Higa et al., 2024).

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

Study	Study type	Model / Patients	Comparators	Conclusions

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Kojima et al., 2020	Preclinical	Mice model of environmental dry eye disease	Low molecular weight HA eye drops, secretagogue eye drops	Improved tear film stability, reduced ocular surface damage, and less inflammation with 0.15% hylan A eye drops
Beck et al., 2019	Clinical	11 patients on treatment with autologous serum eye drops	Autologous serum eye drops	0.15% hylan A eye drops are effective for severe ocular severe disease and may even replace autologous serum eye drops
van Setten et al., 2020a	Clinical **HYLAN M study**	84 patients with severe dry eye disease	Optimized artificial tear treatments	Switching from optimized artificial tear treatments to 0.15% hylan A eye drops significantly improved symptoms, including visual stability, discomfort and pain, already after 4 weeks
van Setten et al., 2020b	Clinical Subgroup analysis from the HYLAN M study	16 patients	Optimized artificial tear treatments	Switching from optimized artificial tear treatments to 0.15% hylan A eye drops promoted corneal nerve growth after 8 weeks
Medic et al., 2024	Clinical Subgroup analysis from the HYLAN M study	47 patients	HA-containing artificial tears (15 commercial brands with diverse HA molecular weight)	0.15% hylan A eye drops have a superior clinical effect as compared to other eye drops containing HA with a lower molecular weight, both in terms of dropping frequency and symptoms
Özkan et al., 2025	Clinical	63 eyes of 55 patients with keratoconus following corneal crosslinking (CXL)	Low molecular weight HA eye drops	Faster regeneration of corneal nerves and sensitivity after CXL with 0.15% hylan A eye drops and improvement of ocular symptoms Three months after CXL, the group treated with 0.15% hylan A eye drops showed a lower presence of inflammation-related immune cells compared to the group receiving low molecular weight HA eye drops

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Table 2. Summary of studies demonstrating the benefits of a novel eye drop formulation based on 0.15% hylan A 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) provides a stable vehicle for 20 µg/mL latanoprost, enhancing latanoprost solubility by 75%
Dogru et al., 2023	Preclinical	Standard strain mice	Commercial eye drops with 50µg/mL latanoprost	Unlike the commercial latanoprost eye drops, a hylan A-based eye drop formulation with 14 µg/mL latanoprost preserved ocular surface parameters comparable to untreated controls, while achieving a similar IOP-lowering effect as the commercial product
Higa et al., 2024	Preclinical	Standard strain rat	Commercial eye drops with 50µg/mL latanoprost	A hylan A-based eye drop formulation with 14 µg/mL latanoprost achieved therapeutic levels of latanoprost in the animal's aqueous humour comparable to the 50 µg/mL commercial formulation
Müller-Lierheim, 2021	Proof-of-concept	One subject with ocular hypertension	Commercial eye drops with 50µg/mL latanoprost	A hylan A-based eye drop formulation with 20 µg/mL latanoprost showed a superior IOP-lowering effect compared to a commercial latanoprost eye drop, despite the latter having a higher API concentration

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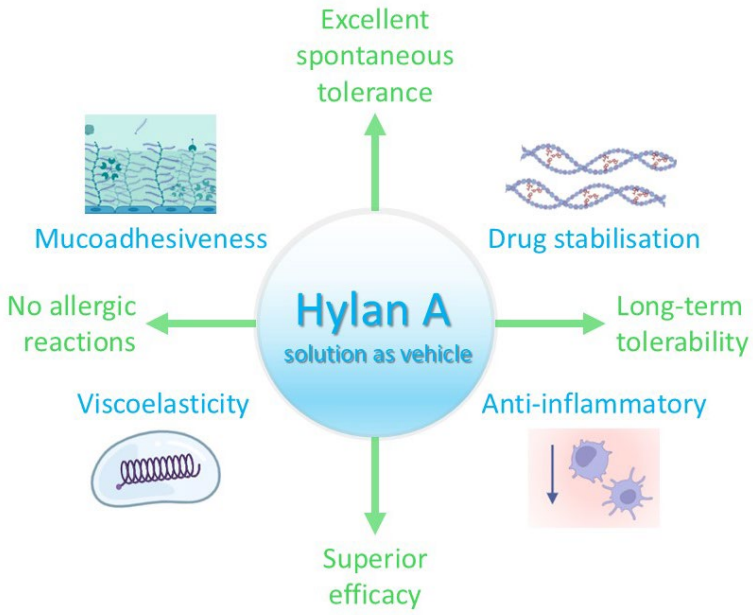

Figure 1. Overview of the properties of the hylan A-based aqueous eye drop formulation (blue) and its advantages as a vehicle for APIs in ocular therapies (green).

We envision hylan A-based eye drops as a formulation platform that can be extended to support a broad range of ocular therapies. A particularly promising further 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 an area where effectively overcoming ocular drug delivery barriers while avoiding adverse effects remains a challenge, mainly due to the large molecular weight and hydrophobic nature of CsA (Nagai and Otake, 2022, Periman et al., 2020). Hylan A-based eye drops could address these limitations as already shown in the case of latanoprost (Müller-Lierheim, 2021, Higa et al., 2024, Dogru et al., 2023). Beyond its vehicle properties, hylan A itself possess anti-inflammatory effects (Kojima et al., 2020, Bron et al., 2022) that may act synergistically with CsA for a more effective treatment of chronic dry eye disease. Additionally, 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 benefit. Interestingly, recent in vitro findings 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 for ocular surface health. In such 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 toward a new generation of API-containing eye drops for topical ocular drug delivery, designed to improve bioavailability, reduce adverse effects, and support long-term ocular surface health across a range of therapeutic indications.

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Conflicts of Interest: The author Wolfgang G. K. Müller-Lierheim is Chief Executive Officer of i.com medical GmbH, a company developing and manufacturing hyaluronan containing eye drops. The author Jesús Pujol-Martí is Chief Scientific Officer of i.com medical GmbH.

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