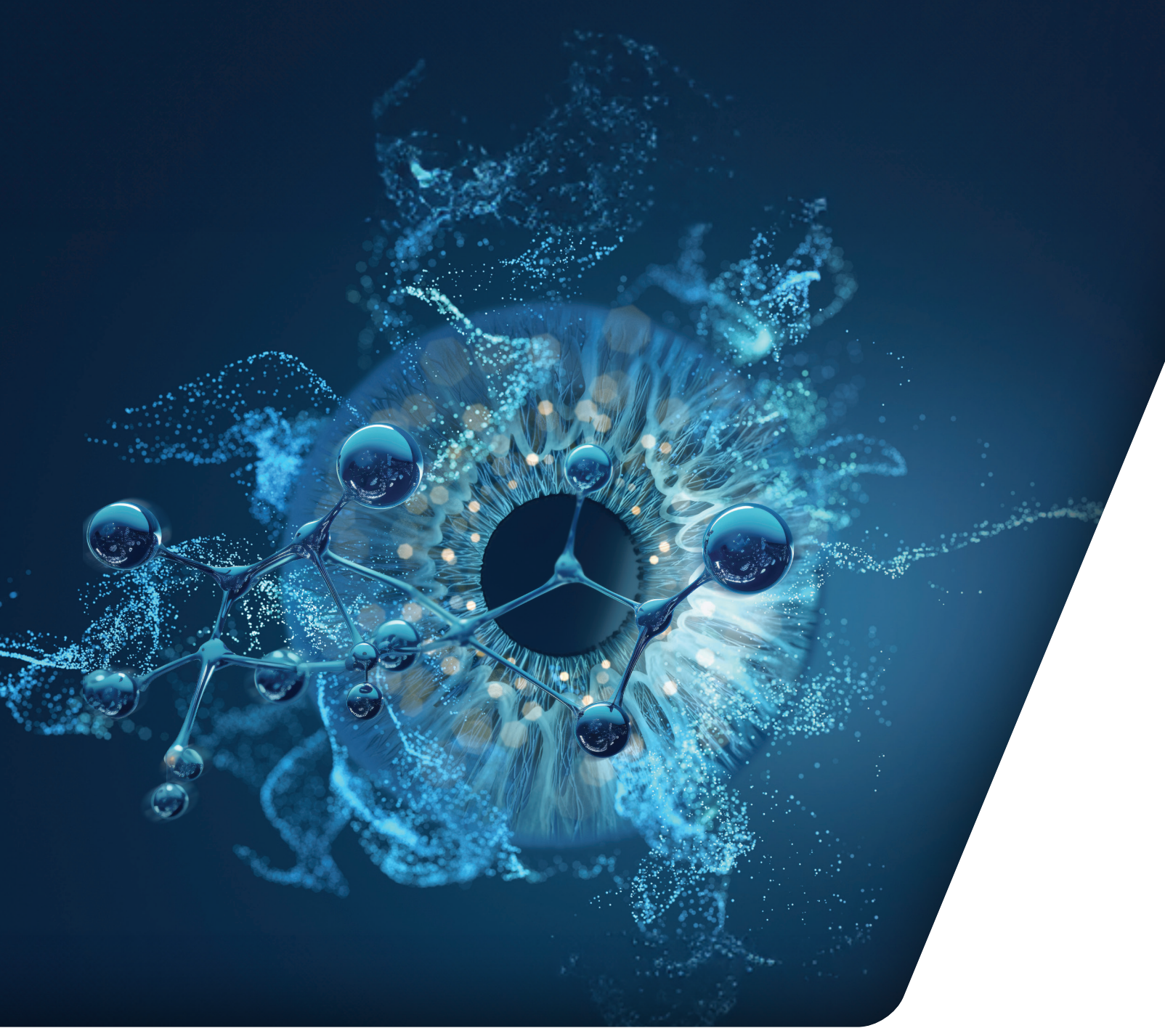


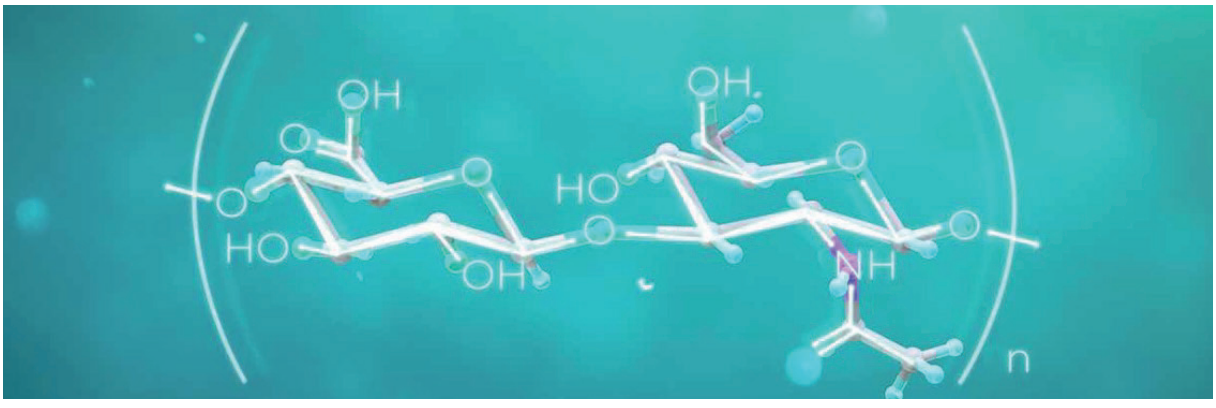
Long Chain High Molecular Weight Hyaluronic Acid

A high performing molecule for Dry Eye Disease

SCOPE

Contents

Background of hyaluronic acid in eyecare



Hyaluronic acid (HA) was discovered in the 1930s by the German physician whose work focused on the composition of the fluid in the vitreous body of the eye (bovine).[1] Since then it has become an important addition in many fields of medicine[2] and serves several crucial purposes in the human body, including joint and tendon lubrication and cell-to-cell communication.[3]

Due to HA's safety profile and physiological effects, it has become an important substance in ophthalmology. HA was first used in ophthalmology in 1978 to stabilise and protect the eye during cataract operations.[4] This was primarily due to its property of having elastic flow behaviour. Since 1982, it has been used for the treatment of dry eyes.[5] However not all HA is the same.

Hyaluronic acid differs in terms of the possible crosslinking, its chain lengths and ultimately the molecular weight. This is why different molecular weights of hyaluronic acid have different applications in medicine. Depending on the area of application, the requirement therefore also varies as to which molecular weight is most suitable:

- **Ophthalmology:** long-chain hyaluronic acid with a high molecular weight that moisturises the surface of the eye for a long time.
- **Dermatology:** short-chain hyaluronic acid that penetrates into deep skin layers and is stored there.
- **Orthopaedics:** cross-linked hyaluronic acid, which acts as a lubricant and 'shock absorber' in joints.

Dry eyes benefit particularly from long-chain high molecular weight HA, as it has a high viscosity and therefore a long residence time on the eye without affecting visual acuity.[6] Long-chain HA is also important in post-operative follow-up care to provide long-lasting moisturisation, which has a favourable effect on the healing process.

Short-chain hyaluronic acid is less suitable in ophthalmology because it can only form low-viscosity solutions. These do not remain on the surface of the eye for long, and drops need to be applied more frequently. Cross-linked hyaluronic acid is also not the first choice in ophthalmology because, due to cross-linking, the gel formation makes it difficult for viscosity to decrease during blinking, which can lead to visual impairment.[7]

The clinical abstracts included in the booklet provide further information on the benefits of long-chain high molecular weight HA in the treatment of Dry Eye Disease.

1 *Meyer K., Palmer J.W., 1934. J Biol Chem, 107: 629-634.*
2 *Kotla N.G., et al., 2021. J Control Release, 336: 598-620.*
3 *Lin W., et al., 2019. Acta Biomater, 83: 314-321.*
4 *Balazs E.A., et al. Proc. Int Congr & First Film Festival on Intraocul Implant, Cannnes, France, May 1979.*
5 *Polack F.M., Mc Niece M., 1982. Cornea, 1: 133-136.*
6 *Hynnekleiv L., et al., 2022 Acta Ophthalmologica, 100(8): 844-860. doi: 10.1111/aos.15159.*
7 *Müller-Lierheim W.G.K., 2020. Diagnostics, 10(8): 511. doi: 10.3390/diagnostics10080511.*

Hyaluronic acid for Dry Eye Disease

Hyaluronic acid in the treatment of dry eye disease

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Abstract

Dry eye disease (DED) is a highly prevalent and debilitating condition affecting several hundred million people worldwide. Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan commonly used in the treatment of DED. This review aims to critically evaluate the literature on the safety and efficacy of artificial tears containing HA used in DED treatment. Literature searches were conducted in PubMed, including MEDLINE, and in Embase via Ovid with the search term: "(hyaluronic acid OR hyaluronan OR hyaluronate) AND (dry eye OR sicca)". A total of 53 clinical trials are included in this review, including eight placebo-controlled trials. Hyaluronic acid concentrations ranged from 0.1% to 0.4%. Studies lasted up to 3 months. A broad spectrum of DED types and severities was represented in the reviewed literature. No major complications or adverse events were reported. Artificial tears containing 0.1% to 0.4% HA were effective at improving both signs and symptoms of DED. Two major gaps in the literature have been identified:

1. no study investigated the ideal drop frequency for HA-containing eyedrops, and
2. insufficient evidence was presented to recommend any specific HA formulation over another.

Future investigations assessing the optimal drop frequency for different concentrations and molecular weights of HA, different drop formulations, including tonicity, and accounting for DED severity and aetiology are essential for an evidence-based, individualized approach to DED treatment.

For full online paper, search:
Acta ophthalmologica | Hyaluronic acid in the treatment of dry eye disease (wiley.com)

Accessed May 2023

Hynnekleiv L., Magno M., Vernhardsdottir R.R., Moschowits E., Tønseth K.A., Dartt D.A., Vehof J. and Utheim T.P., 2022. Hyaluronic acid in the treatment of dry eye disease. Acta ophthalmologica, 100(8): pp.844-860.

Why Chain Length of Hyaluronan in Eye Drops Matters

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Abstract

The chain length of hyaluronan (HA) determines its physical as well as its physiological properties. Results of clinical research on HA eye drops are not comparable without this parameter. In this article methods for the assessment of the average molecular weight of HA in eye drops and a terminology for molecular weight ranges are proposed. The classification of HA eye drops according to their zero shear viscosity and viscosity at 1000 s–1 shear rate is presented. Based on the gradient of mucin MUC5AC concentration within the mucoaqueous layer of the tear film a hypothesis on the consequences of this gradient on the rheological properties of the tear film is provided. The mucoadhesive properties of HA and their dependence on chain length are explained. The ability of HA to bind to receptors on the ocular epithelial cells, and in particular the potential consequences of the interaction between HA and the receptor HARE, responsible for HA endocytosis by corneal epithelial cells is discussed. The physiological function of HA in the framework of ocular surface homeostasis and wound healing are outlined, and the influence of the chain length of HA on the clinical performance of HA eye drops is illustrated. The use of very high molecular weight HA (hylan A) eye drops as drug vehicle for the next generation of ophthalmic drugs with minimized side effects is proposed and its advantages elucidated. Consequences of the diagnosis and treatment of ocular surface disease are discussed.

For full online paper, search:
Diagnostics | Free Full-Text | Why Chain Length of Hyaluronan in Eye Drops Matters (mdpi.com)

Accessed May 2023

Müller-Lierheim W.G., 2020. Why chain length of hyaluronan in eye drops matters. Diagnostics, 10(8): p.511.

Physicochemical Properties of Hyaluronic Acid-Based Lubricant Eye Drops

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Abstract

Purpose: To assess the physicochemical properties of hyaluronic acid (HA)-based artificial tears.

Methods: The average molecular weight (MW) and polydispersion index (PDI) of HA in 18 commercially available artificial tears were determined by light scattering/high performance liquid chromatography. Osmolality, pH, viscosity, and sodium concentration were determined using an osmometer, pH meter, rheometer, and inductively coupled plasma mass spectrometer, respectively.

Results: The MW of HA varied considerably between formulations. The PDI was 2.0 in two formulations (2.28 and 4.94), suggesting the presence of a copolymer and/or HA size variability. Three formulations exhibited viscosity exceeding the blur threshold at different shear rates. Viscosity at low shear rates was generally highest in formulations containing high-MW HA. Correlations were found between observed viscosity and a predictive/calculated value, except for four copolymer-containing formulations, and osmolality (range, 154–335 mOsm/kg) and sodium concentration (range, 22–183 mM), with two exceptions. Compared with organic osmolytes, adding sodium decreased viscosity, particularly at lower shear rates.

Conclusions: In the context of the literature, our findings suggest that for most patients with dry eye disease, the ideal HA-based artificial tear should include high MW HA with a low PDI and exhibit enhanced viscosity at low shear rate (without exceeding the blur threshold). The inclusion of synergistic copolymers and a low sodium concentration may increase viscosity, but whether any of these physicochemical properties or correlations can predict clinical efficacy will require further investigation.

Translational Relevance: Understanding the properties of HA-based artificial tears will support the development of unique formulations that target specific ocular surface conditions.

For full online paper, search:
TVST | JournalsPhysicochemical Properties of Hyaluronic Acid–Based Lubricant Eye Drops (arvojournals.org)

Accessed May 2023

Aragona P., Simmons P.A., Wang H. and Wang T., 2019. Physicochemical properties of hyaluronic acid–based lubricant eye drops. Translational Vision Science & Technology, 8(6), pp.2-2.

Test Product	[HA][a] (%)	Average MW[b] (kDa)	Standard Viscosity[c] (cP)	PDI	pH	Osmolality (mOsm/kg)	Sodium (mM)
High-MW HA (>1000 kDa)							
Hylo-Comod	*0.10*	*2026*	*13.2*	*2.28*	*7.21*	*280*	*149*
Hylo-Forte	*0.20*	*1748*	*80.6*	*1.79*	*7.20*	*280*	*132*
Hylo-Parin	*0.10*	*1428*	*9.1*	*1.12*	*7.13*	*280*	*155*
Optive Fusion (multidose)	*0.10*	*318 (201 post-H'ase)[d]*	*15.5*	*3.49*	*7.37*	*335*	*57*
HA component		*1178*		*1.10*			
Optive Fusion (unit dose)	*0.10*	*318 (201 post-H'ase)[d]*	*14.8*	*3.49*	*7.37*	*276*	*52*
HA component		*1178*		*1.10*			
Medium-MW HA (500–1000 kDa)							
Vismed Multi	0.18	918	11.5	1.20	7.16	154	88
Xailin HA	0.20	914	11.1	1.20	6.94	240	157
Artelac Rebalance	0.15	902 (<100 post-H'ase)[e]	7.8	1.13	7.30	279	128
Hylo-Vision HD	0.10	851	3.3	1.16	6.95	294	183
Blink Intensive Tears	0.20	772 (<100 post-H'ase)[e]	10.0	1.06	7.29	178	22
BLUyal OSD	0.15	694	5.1	1.05	6.99	286	178
Hyalistil Bio	0.20	650	9.2	1.13	7.16	230	146
Artelac Splash	0.24	533	7.2	1.11	7.10	288	145
Low-MW HA (<500 kDa)							
Zolag	*NA*	*327*	*9.9*	*1.11*	*7.29*	*287*	*142*
Hyabak	*0.15*	*248*	*2.5*	*1.07*	*7.12*	*211*	*117*
Systane Hydration	*0.15*	*1334 (2233 post-H'ase)[f]*	*4.7*	*1.44*	*7.90*	*280*	*121*
Thealoz Duo	*0.15*	*220*	*2.8*	*4.94*	*7.09*	*209*	*56*
Thealoz Duo Gel	*0.15*	*204 (193 post-H'ase)[g]*	*2034.4*	*1.64*	*7.07*	*210*	*28*

Benefits of high molecular weight HA

The Effects of High Molecular Weight Hyaluronic Acid Eye Drop Application in Environmental Dry Eye Stress Model Mice

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Abstract

Hyaluronic acid (HA) ophthalmic solution is widely used in dry eye treatment worldwide. However, there are no reports comparing the dry eye treatment effects of high molecular weight HA with low molecular weight HA. Sixty eight-week-old C57BL/6 mice were assigned to the following 6 groups and exposed to environmental dry eye stress (EDES) that mimics office work environment: (1) 0.1% low molecular weight HA (LMWHA) eye drops, (2) 0.3% LMWHA eye drops, (3) 3% diquafosol sodium (DQ) eye drops, (4) 0.15% high molecular weight HA (HMWHA) eye drops, (5) no treatment with exposure to EDES (EDES+/Treatment−), and (6) no treatment without exposure to EDES (EDES−/Treatment−). After EDES, the HMWHA group had significantly longer break-up time (BUT) than the 0.1%, 0.3% LMWHA groups and the DQ group. After EDES, the HMWHA group had significantly lower lissamine green staining scores than the LMWHA and DQ groups. Subepithelial presumed dendritic cell density in the HMWHA group was significantly lower than the EDES+/Treatment− group. After EDES exposure, Conjunctival Muc5AC mRNA expression in the HMWHA group was significantly higher than the 0.1 and 0.3% LMWHA groups. Ophthalmic HMWHA solution may have a better dry eye treatment effect than LMWHA or DQ solution, owing to its anti-inflammatory effect.

For full online paper, search:
IJMS | The Effects of High Molecular Weight Hyaluronic Acid Eye Drop Application in Environmental Dry Eye Stress Model Mice (mdpi.com)

Accessed May 2023

Kojima T., Nagata T., Kudo H., Müller-Lierheim W.G., van Setten G.B., Dogru M. and Tsubota K, 2020. The effects of high molecular weight hyaluronic acid eye drop application in environmental dry eye stress model mice. International journal of molecular sciences, 21(10): p.3516.

The role of high molecular weight hyaluronic acid in mucoadhesion on an ocular surface model

Cristian Guarise[1], Laura Acquasaliente[2], Gianfranco Pasut[2], Mauro Pavan[1], Matteo Soato[1], Giacomo Garofolin[1], Riccardo Beninatto[1], Elena Giacomel[1], Eleonora Sartori[1], and Devis Galesso[1]

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Abstract

Hyaluronic acid (HA) is frequently formulated in eye drops to improve the stability of the tear film by hydration and lubrication. Mucoadhesion is related to the ocular residence time and therefore to the effectiveness of the eye drops. The ocular residence time of the HA formulation is correlated with the ability of HA to create specific strong interactions in the ocular surface with the mucus layer, mainly composed of a mixture of secreted mucins (MUC; gel forming MUC5AC and MUC2) and shed membrane-bound soluble mucins (MUC1, MUC4, and MUC16). Dry eye disease (DED) is a multifactorial pathology of the preocular tear film with possible damage to the ocular surface classified in two types: (1) aqueous-deficient dry eye and (2) evaporative dry eye, caused by a decrease in goblet cell density that reduces MUC expression and/or by meibomian gland dysfunction, that results in a drop in the lipidic fraction of the tear film. In this work, the binding affinity between HA and MUC2 has been evaluated with three complementary approaches because the secreted MUCs play a pivotal role in the viscoelastic properties of the tear film:

1. Rheological analysis, measuring the mucoadhesive index and the complex viscosity in relation to MM (Molecular Mass) and concentration;
2. Fluorescence analysis, using a fluorescent hydrophobic probe, to investigate the conformational change of MUC2 during the interaction with the HA polymer;
3. Surface plasmon resonance analysis, used to measure the affinity between MUC2 (immobilized on the surface of a sensor chip) and the HA polymers that flowed on it at the molecular level.

For all these tests, the mucoadhesive performance of the natural HA linearly increases with the MM, whereas cross-linked HA and other emollient and gelling agents (formulated in artificial tears) do not show the same mucoadhesive properties (with the exception of xanthan gum). The mucoadhesive performance of high MM HA has also been confirmed in conditions that simulate the pathological condition of the tear film during DED by decreasing the MUC2 or oleic acid concentration. Physico-chemical analysis of a series of marketed artificial tears confirms the linear correlation between the MM of the HA used in the products and the mucoadhesive index measured on the ocular surface model.

For full online paper, search:
jmbbm | The role of high molecular weight hyaluronic acid in mucoadhesion on an ocular surface model (sciencedirect.com)

Accessed January 2024

Guarise C., Acquasaliente L., Pasut G., Pavan M., Soato M., Garofolin G., Beninatto R., Giacomel E., Sartori E. and Galesso D., 2023. The role of high molecular weight hyaluronic acid in mucoadhesion on an ocular surface model. Journal of the Mechanical Behavior of Biomedical Materials, 143: p.105908.

Application frequency – key indicator for the efficiency of severe dry eye disease treatment – evidence for the importance of molecular weight of hyaluronan in lubricating agents

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Abstract

Purpose: Lubricant eye drops are the main therapeutic resource for dry eye disease (DED), with each drop representing the equivalent of ocular surface disease treatment. Thus, any reduction in the frequency of eye drop application reflects a degree of therapeutic success. Considering also the socioeconomic burden of DED, we investigated eye drop application frequency (DF) as a parameter to potentially track the success of therapy in severe DED. Hyaluronan (HA)-containing eye drops have become the first choice for tear substitution in many countries, and recent data indicate that the average molecular weight (Mw) of HA determines the therapeutic efficacy of such eye drops. This posthoc subgroup analysis of a previously published multicentre prospective randomized open-label study, HYLAN M, is set out to compare the effects of very high Mw HA (hylan A) eye drops to comparator eye drops, containing lower Mw HA (control).

Methods: Patients with severe DED (n=47), recruited as part of the larger HYLAN M prospective, multicentre, open-label study, were randomized into two groups: hylan A and control group. In the hylan A group, 24 patients replaced their HA-containing eye drops with eye drops containing 0.15% hylan A, whereas the 23 control patients continued to use comparator HA eye drops. The DF was recorded daily by all participants over 8 weeks, and other subjective and objective parameters of DED were assessed at the time of inclusion (baseline), as well as at week 4 and 8.

Results: There was a significant decrease in DF in the hylan A users between the baseline and week 4 (p=0.004), remaining stable until week 8. Indeed, in contrast to the baseline, the hylan A group had a significantly lower DF than the control group at weeks 4 (p=0.018) and 8 (p=0.008). Likewise, the ocular surface disease index (OSDI) improved significantly between the time of inclusion and week 4 (p<0.001) in hylan A users, remaining stable until week 8. The OSDI was similar in both groups at the baseline but it was significantly lower in the hylan A group than in the control group at week 4 (p=0.002), remaining lower at week 8. Such a decrease in the DF and OSDI was not witnessed in the control group at any time point. The objective parameters assessed did not differ significantly within or between the two groups.

Conclusion: When treating severe DED, the DF can be significantly reduced by using very high Mw HA (3MDa) lubricant eye drops, which better alleviate DED symptoms and decrease the OSDI scores. These drops not only provide an attractive and comfortable alternative for patients with severe DED but also offer the possibility of reducing the disease's socioeconomic burden, both for affected individuals and society as a whole.

For full online paper, search:
Acta Ophthalmologica | Application frequency – key indicator for the efficiency of severe dry eye disease treatment (wiley.com)

Accessed January 2024

Medic N., Boldin I., Berisha B., Matijak-Kronschachner B., Aminfar H., Schwantzer G., Müller-Lierheim W.G., van Setten, G.B. and Horwath-Winter J., 2023. Application frequency – key indicator for the efficiency of severe dry eye disease treatment – evidence for the importance of molecular weight of hyaluronan in lubricating agents. Acta Ophthalmologica of the Mechanical Behavior of Biomedical Materials, 143: p.105908.

The clinical efficacy of higher molecular weight sodium hyaluronate in artificial tears: A randomised clinical trial

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Abstract

Purpose: To ascertain whether the molecular weight of sodium hyaluronate in artificial tears, affects its clinical efficacy.

Methods: The rheology of HydraMed, Evolve and Hylo-Forte eye drops, which all contain 0.2% hyaluronic acid as the principal component, was assessed using a research rheometer fitted with a 60mm aluminium flat plate measuring system at 31°C. Shear rate profiling was performed on each artificial tear. A total of 25 participants diagnosed with dry eye disease (TFOS DEWS II criteria), aged 23.6±9.2 years, were randomly allocated to receive each drop, on different days. Comfort, non-invasive breakup time, tear meniscus height and ocular redness was assessed at baseline and then 5, 15, 30, 45, 60 and 90 minutes after application.

Results: Hylo-Forte showed a more non-Newtonian relationship between viscosity and sheer force (r2=0.295) compared to HydraMed (r2=0.485) and Evolve (r2=0.521). Comfort and tear stability improved with drop instillation ($p>0.05$), declining with time ($p<0.001$), with all drops following a similar profile ($p>0.05$). Hylo-Forte demonstrated the highest comfort and tear stability retention effect. Tear volume increased with drop instillation and then declined with time ($F=18.643$, $p<0.001$). Evolve had a reduced initial effect compared to HydraMed and Hylo-Forte ($F=4.045$, $p<0.001$). Average bulbar redness was low (0.63±0.44 Efron grade) and did not change with drop application ($F=1.721$, $p=0.120$).

Conclusions: The molecular weight and rheology of sodium hyaluronate in artificial tears leads to differences in clinical effectiveness. The intra-blink viscosity reduces (which may reduce frictional effects) compared to the inter-blink viscosity, increasing in-eye retention and comfort.

For full online paper, search:
IOVS | The clinical efficacy of higher molecular weight sodium hyaluronate in artificial tears (arvojournals.org)

Accessed April 2023

Semp D., Dutta D. and Wolffsohn J.S., 2023. The clinical efficacy of higher molecular weight sodium hyaluronate in artificial tears: A randomised clinical trial. Investigative Ophthalmology & Visual Science, 64(8): pp.3970-3970.

Importance of rheology for artificial tears

Role of rheology in tears and artificial tears

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Abstract

The study of viscoelastic fluids as artificial tears dates back to the late 1970s. Healon, the first ophthalmic viscosurgical device, was approved in 1980, but studied extensively before then, exhibits very interesting shear-thinning properties that were found to be beneficial in both ophthalmic surgery and somewhat later as a tear replacement solution. Unlike the previous tear film replacements, which were mainly viscous in nature, viscoelastic solutions, particularly those based on hyaluronan, exhibited very interesting, potentially beneficial, rheological properties, especially when slightly altered to become elastoviscous. This review examines the rheological properties that are significant in artificial tear solutions. We define herein the necessary parameters that need to be further studied to design and formulate rheologically better artificial tears, which should provide enhanced efficacy compared with their predecessors.

For full online paper, search:
JCRS | Role of rheology in tears and artificial tears (lww.com)

Accessed April 2023

Arshinoff S.A., Hofmann I. and Nae H., 2021. Role of rheology in tears and artificial tears. Journal of Cataract & Refractive Surgery, 47(5): pp.655-661.

Rheological behaviour of commercial artificial tear solutions

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Abstract

Purpose: To measure the rheological behaviour of artificial tears to gain insight into the potential role of rheology in predicting the efficacy of artificial tear solutions for the treatment of dry-eye disease (DED).

Setting: Research laboratories of I-MED Pharma, Canada, Rohn and Associates, Inc., New Jersey, and Hydan Technologies, New Jersey.

Design: Laboratory investigation.

Methods: Twenty commercially available artificial tear drops were purchased in Canada and the United Kingdom. Rheological measurements of viscosity and normal stress as a function of shear rate were performed at 25°C.

Results: For comparison of the rheological behaviour, the various artificial tears were sorted into 3 groups: group A, which exhibit significant non-Newtonian shear-thinning behaviour; group B, which exhibit moderate non-Newtonian shear-thinning behaviour; and group C, which exhibit Newtonian behaviour throughout the shear rate range. Results of normal stress difference, N1, as a function of shear rate were concordant with the rheological testing, indicated the viscoelastic nature of the samples in groups A and B, whereas members of group C did not exhibit any elasticity.

Conclusions: The various artificial tear solutions were sorted into groups based on their Newtonian or non-Newtonian behaviours. The results suggest that non-Newtonian solutions should provide better comfort and longer-lasting symptomatic relief for DED. It remains to be confirmed clinically if there is a direct correlation between the rheological behaviour of artificial tears and their ability to provide prolonged relief in DED, or if other factors are more important.

For full online paper, search:
JCRS | Rheological behaviour of commercial artificial tear solutions (lww.com)

Accessed April 2023

Arshinoff S., Hofmann I. and Nae H., 2021. Rheological behaviour of commercial artificial tear solutions. Journal of Cataract & Refractive Surgery, 47(5): pp.649-654.

Additional clinical benefits for Dry Eye Disease

Impact of Hyaluronic Acid-Containing Artificial Tear Products on Reepithelialization in an In Vivo Corneal Wound Model

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Abstract

Purpose: To evaluate the effect of 6 commercially available hyaluronic acid (HA)-containing topical artificial tear products on corneal reepithelialization following injury, in an in vivo mouse model.

Methods: Ninety-six C57Bl/6 mice (16 per treatment group; male to female ratio, 1:1 per group) were anesthetized. Epithelial debridement was performed on 1 cornea per animal, and the debrided eye was imaged. A 30 mL masked test solution containing 1 of 6 artificial tear products was instilled, immediately on debridement, and subsequently, every 2 h, for a total of 4 administrations. At 24 h post debridement, corneas were stained with fluorescein and imaged to calculate corneal healing rate (number of fluorescein-negative corneas).

Results: All 6 artificial tear products used in this study permitted the initial process of corneal wound healing. However, the corneal reepithelialization rate after 24 h was higher with Hydroxypropyl guar (HPG)/HA (53.33%) compared with other HA-containing artificial tear products [HA1 (12.5%), HA2 (26.67%), HA3 (31.25%), HA4 (6.25%), and HA5 (43.75%)]. The average area and percentage area of reepithelialization after 24 h were also higher with HPG/HA compared with other treatment groups.

Conclusions: Percentage of eyes with complete corneal reepithelialization 24 h post debridement was highest with HPG/HA compared with other HA-containing artificial tear products tested. The results of this study provide additional evidence on the potential benefits of HPG/HA in the management of dry eye and its role in the rapid restoration of a healthy ocular epithelium. However, further studies are required to confirm the effects on human corneal wounds.

For full online paper, search:
Journal of Ocular Pharmacology and Therapeutics | Impact of Hyaluronic Acid-Containing Artificial Tear Products on Reepithelialization in an In Vivo Corneal Wound Model (liebertpub.com)

Accessed May 2023

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Hyaluronic Acid in Inflammation and Tissue Regeneration

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Abstract

Hyaluronic acid (HA), the main component of extracellular matrix, is considered one of the key players in the tissue regeneration process. It has been proven to modulate via specific HA receptors, inflammation, cellular migration, and angiogenesis, which are the main phases of wound healing. Studies have revealed that most HA properties depend on its molecular size. High molecular weight HA displays anti-inflammatory and immunosuppressive properties, whereas low molecular weight HA is a potent proinflammatory molecule. In this review, the authors summarize the role of HA polymers of different molecular weight in tissue regeneration and provide a short overview of main cellular receptors involved in HA signalling. In addition, the role of HA in 2 major steps of wound healing is examined: inflammation and the angiogenesis process. Finally, the antioxidative properties of HA are discussed and its possible clinical implication presented.

For full online paper, search:
Wounds | Hyaluronic-Acid-in-Inflammation-and-Tissue-Regeneration.pdf (researchgate.net)

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In vitro modulation of preservative toxicity: High molecular weight hyaluronan decreases apoptosis and oxidative stress induced by benzalkonium chloride

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Abstract

Objective: Benzalkonium chloride (BAK) is one of the most often used preservative in pharmaceutical products and it is known to induce toxic effects. Hyaluronan (HA), a linear biopolymer, is involved in several biological processes. The aim of this work is to *in vitro* investigate if HA is able to decrease BAK toxicity.

Methods: Two human epithelial cell lines were treated with different incubation time protocol with BAK and three different molecular weights HA (HA 20 kDa, HA 100 kDa and HA 1000 kDa, 0.2%, w/v). Flow cytometry, fluorescence microscopy, microplate cytofluorometry and confocal microscopy were performed to evaluate expression of CD44 receptor, cell viability, oxidative stress, mitochondrial mass, chromatin condensation, plasma-membrane permeability, DNA fragmentation and cytoskeleton morphology.

Results: The three HAs studied induce neither oxidative stress nor apoptosis. HA 1000 kDa significantly decreases oxidative stress, apoptosis and necrosis induced by BAK. Experiments with HA 20 kDa or HA 100 kDa did not show the same effects. For instance, the more molecular weight decreases, the more protection decreases. Moreover, we suggest that HA interacts with cell plasma-membrane and inhibits cell death receptors.

Conclusion: High molecular weight HA (1000 kDa, 0.2%) is an effective protective agent against BAK.

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EJPS | In vitro modulation of preservative toxicity: High molecular weight hyaluronan decreases apoptosis and oxidative stress induced by benzalkonium chloride (sciencedirect.com)

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