Author's translation

Hyaluronic acid eye drops

What you should know about their rheological properties

When treating dry eye problems of different origins, eye specialists and patients are spoiled for choice at first, considering the enormous variety of available tear substitute and contact lens wetting solutions containing hyaluronic acid (HA, Hyaluronan, sodium hyaluronate). In order to make a decision, unfortunately it will not be of help either reading information regarding the hyaluronan concentration, or listening to claims in advertising made by the manufacturer. Therefore, we decided to examine the flow properties of common HA tear substitutes and to publish the results here and now.

Since there is neither a standard nor a pharmacopeia procedure for the rheological assessment of tear substitutes, it is reasonable to take the international standard DIN EN ISO 15798:2013 as a landmark, which lays down the criteria and test procedures for viscoelastic substances (OVD) used in cataract surgery. This standard regulates that the manufacturer shall indicate, in addition to their concentrations, also the molar mass of the rheological active components (HA) used. Furthermore, manufacturers are required to measure the viscosity in relation to the shear rate in a range of 0.001 to 1000 s^{-1}, and show the relation between viscosity and shear rates in a diagram on logarithmic scales. What do these terms mean?

Rheological assessment means assessing flow properties (fluidity) under different conditions. If the fluid is located between two surfaces and one of these is moved relatively to the other, the force needed will be proportional to the viscosity of the fluid. The term "shear rate" refers to the velocity of the surface in mm/s divided by the distance of the surfaces in mm. The resulting unit used for shear rate is s^{-1}. Viscosity is generally expressed in mPa·s. A fluid, whose viscosity is the same for all shear rates, is called a Newtonian fluid (e.g. water with a viscosity of 1 mPa·s at 20 °C). In viscoelastic fluids, like hyaluronic acid solutions, the viscosity decreases as the shear rate increases. When shear rates are low, the curve reaches a plateau, whose level approaches the so-called zero shear viscosity (viscosity in absence of shear forces). A shear rate of 1000 s^{-1} approximately matches the conditions under which, in cataract surgery, the viscoelastic substance is injected in the eye through a cannula.

If applied to tear substitutes, the zero shear viscosity (η_0) matches the conditions with open eyelid, and a viscosity at 1000 s^{-1} shear rate, the situation when the rim of the lid glides over the corneal epithelium during blinking. Tear fluid viscosity is about 65 mPa·s when eyes are open, and decreases to 10 mPa·s during blinking (Tiffany 1994). The ideal tear solution should preferably have similar flow properties. The lower the zero shear viscosity, the shorter the residence time on the eye, and thus the lower the effec-

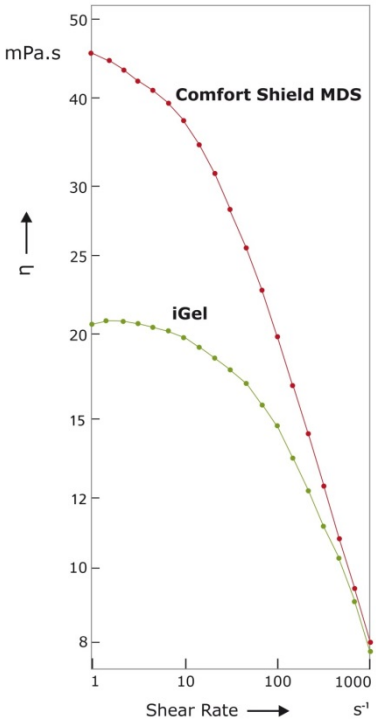

Figure 1: Representation on logarithmic scale of viscosity in relation to the shear rate for Comfort Shield® MDS and iGel HA Eye drops.

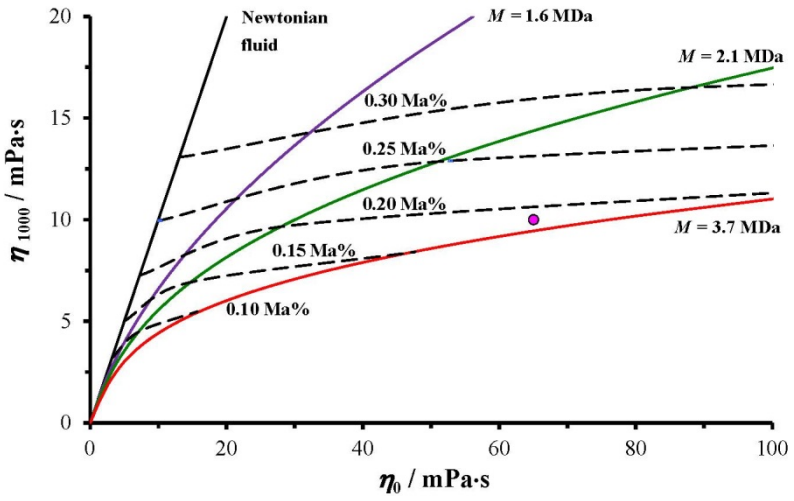

Figure 2: Dependence of zero shear viscosity η_0 and of viscosity η_{1000} at a 1000 s^{-1} shear rate on the molar mass and concentration of HA-solutions. Colored lines refer to HA solutions with same molar mass M, black dashed lines to solutions with same HA concentration. The purple point refers to η_0 and η_{1000} of healthy tear fluid.

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tiveness. A higher viscosity when blinking means that also the shear forces on the epithelium increase, which can lead to undesirable side effects. By measuring the zero shear viscosity and the viscosity at a shear rate of 1000 s^{-1}, it is possible to make a reliable prediction about the flow properties of a tear substitute on the eye.

Figure 1 shows the dependence of viscosity in two HA tear substitutes on the shear rate represented on a logarithmic scale. Since the HA concentration in tear substitutes is significantly lower than in viscoelastic substances used in cataract surgery, it is technically not possible to achieve a reliable measurement of the viscosity in tear substitutes with low shear rates of up to 0,001 s^{-1}, by applying the common methods used for viscoelastic substances. By contrast, with shear rates of 1 s^{-1}, ideal for technical measurements, the viscosity plateau is not yet achieved, and for this reason, the zero shear viscosity (η_0) cannot be assessed. Therefore, we adopted a test procedure that allows determining the zero shear viscosity of tear substitutes by using creep viscosity tests (Master thesis by René Reiss).

With the developed test procedure, it was possible to measure the viscosities η_0 and η_{1000} of hyaluronic acid solutions with different molar masses and concentrations (figure 2). The colored lines stand for HA with the same molar mass, the dashed black ones, for HA with the same concentration. As expected, a lower molar mass results in low viscosity and a higher concentration in high viscosity. Attention should be paid to the fact that the fluidity of natural tears can be simulated only through the combination of high molar mass (ca. 3 MDa) with a respective low concentration (ca. 0.15 % HA).

Figure 3 shows the test results of different tear substitutes (triangles). The horizontal dashed line represents the upper limit of viscosity, at which the shear force (when blinking) does not exceed the respective shear force

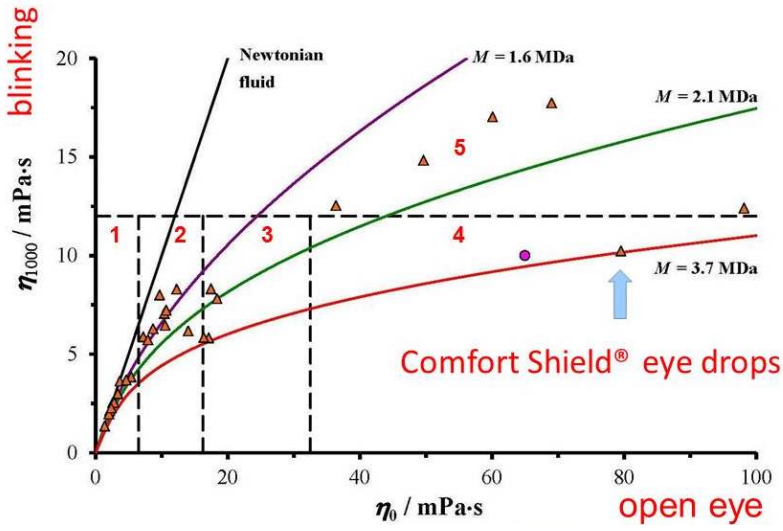

Figure 3: Zero shear viscosity η_0 and viscosity η_{1000} at 1000 s^{-1} shear rate of different HA eye drops (small triangles). The average value of tear fluidity is represented by a dot. Different HA tear solution categories are separated by dashed lines.

Product name	Manufacturer
eyevice UNIVERSAL wetting solution	OPTOSOL
GenTeal HA solution	Alcon
Hyabak Eye drops	Thea Pharma
Hyalein	Santen
Hylo-Vision HD Eye drops	OmniVision
lacrifresh moisture unidose	Avizor
lens & lid	Laboratorium Dr. G. Bichsel
LipoNit Eye drops	Optima Medical
Thealoz Duo Eye drops	Thea Pharma
TRIUM Eye drops	Santen
Vismed light Eye drops	TRB Chemedica

Table 1: Eye drops of Category 1 with very low zero shear viscosity (η_0 < 6 mPa·s)

Product name	Manufacturer
Artelac Splash Eye drops	Mann / Bausch&Lomb
Artelac Splash EDO Eye drops	Mann / Bausch&Lomb
Piiloset BioDrop	Farmigea
Biolan Eye drops	Santen
Hya-Ophtal system	Winzer
Hylo-Vision HD plus Eye drops	OmniVision
Ocusan Eye drops	AGEPHA

Table 2: HA Eye drops of Category 2 with low zero shear viscosity (6 mPa·s < η_0 < 16 mPa·s)

present in natural tears by more than 20%. Vertical dashed lines indicate 10%, 25% and 50% of zero shear viscosity in natural tear film.

Accordingly it is possible to classify each HA tear substitute solution in one of the following five sectors, or rather categories:

- Category 1: HA eye drops with very low effectiveness (η_0 < 6 mPa·s) and close to Newtonian flow properties (Table 1); in this case, the term "viscoelasticity" should not be used.

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- Category 2: HA eye drops with low effectiveness (6 mPa·s < η_0 < 16 mPa·s) and poorly developed viscoelasticity (Table 2); no "prolonged effect" should be promised.

- Category 3: HA eye drops with good effectiveness (16 mPa·s < η_0 <32 mPa·s); distinct viscoelasticity.

- Category 4: HA eye drops, that simulate tear fluidity (η_0 >32 mPa·s and η_{1000} < 12 mPa·s).

- Category 5: HA eye gels, with high zero shear viscosity (η_0 >32 mPas), but exerting high shear forces on the corneal epithelium during blinking (η_{1000} > 12 mPa·s).

Figure 3 includes only eye drops, whose rheologically active components exclusively consist of HA. Eye drops with combinations of rheologically active components were not taken into consideration. In fact, for instance Blink Intensive Tears Plus contains besides 0.38 % of HA, also 0.25 % of polyethylene glycol 400. The viscosity values measured for Blink Intensive Tears Plus are η_0 = 54.3 mPa·s and η_{1000} = 19.7 mPa·s. Therefore, the fluidity of this product corresponds to that of eye gels listed in Category 5.

Summary: The HA tear substitutes of Categories 1 and 2 (Tables 1 and 2) are suitable for treating light dry eye, also for patients wearing contact lenses. Products in Category 3 (Table 3) have universal application. Caution should be taken when using eye gels of Category 5 (Table 5), especially in patients with sensitive corneal epithelium (for instance, after refractive corneal surgery), when the patient wears contact lenses, as well as when there are chronic inflammatory conditions in case of moderate to severe dry eye. Only the product of Category 4 (Table 4; Comfort Shield®) has universal application, even with patients with recurrent erosions (private communication Tomalla). Thanks to its extremely high HA molar mass, Comfort Shield® simulates human tear fluidity and stabilizes the corneal and conjunctival epithelium, (Müller-Lierheim in "Aktuelle Kontaktologie 2015"). Comfort Shield® thus contributes to restoring balance in chronically irritated eyes. With longer application the dropping frequency decreases. As a result, Comfort Shield® is also extremely cost effective.

Product name	Manufacturer
Bepanthen Eye drops	Bayer Vital
HYLO-CARE Eye drops	Ursapharm
HYLO-COMOD Eye drops	Ursapharm
HYLO-PROTECT Eye drops	Ursapharm
iGel Eye drops	AGEPHA
Vismed multi Eye drops	TRB Chemedica

Table 3: HA Eye drops of Category 3 with medium zero shear viscosity (16 mPa·s < η_0 < 32 mPa·s)

Product name	Manufacturer
Comfort Shield MDS	i.com medicai
Comfort Shield SD	i.com medicai

Table 4: HA Eye drops of Category 4 with high zero shear viscosity and low viscosity when blinking (η_0 > 32 mPa·s and η_{1000} < 12 mPa·s)

Product name	Manufacturer
Biolan Gel	Santen
HYLO-GEL Eye drops	Ursapharm
Hylo-Vision Gel multi Eye drops	OmniVision
Perfect Aqua Plus oK Eye Refresh	MPG&E
Vismed gel multi Eye drops	TRB Chemedica

Table 5: HA Eye gels of Category 5 with high zero shear viscosity (η_0 > 32 mPas), but exerting high shear forces on the corneal epithelium during blinking (η_{1000} > 12 mPa·s)

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