Role of rheology in tears and artificial tears

Steve A. Arshinoff, MD, FRCSC, Ilan Hofmann, PhD, Hemi Nae, PhD

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.

OVD use in ophthalmic surgery is different with respect to our interest here in the rheological properties of tears. OVDs are used primarily as space occupiers (eg, to deepen, pressurize, and stabilize a shallow anterior chamber) and protect the corneal endothelial cells from fluid turbulence, and facilitate surgery. Shortly after their introduction, publications appeared, showing that their rheological properties were beneficial in artificial tear solutions and in surgery.

The study of the rheological properties of OVDs used during anterior segment surgery has provided extensive information, which allows the ophthalmic surgeon to better understand and predict the value of various OVDs in different surgical situations. OVDs currently available to surgeons are generally classified as viscoadaptive, higher-viscosity cohesive, viscous-cohesive, viscous-dispersive, medium viscosity-dispersive, or lower viscosity-dispersive. The classification of these OVDs, based on their rheological behavior, has demonstrated that behavior of 2 OVDs may be different despite similar generic constituent concentrations because the molecular structural nature of the rheologically active polymer, usually hyaluronic acid (hyaluronan [HA]), in different manufacturer’s solutions may be very different, usually with respect to its molecular mass average and polydispersion of the molecular weight (MW). The classification of OVDs has proven to be useful in understanding the optimal clinical utility of each type and to predict the performance characteristics of any given OVD during specific surgical procedures.

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fter many years of study, polymeric solutions with specific rheological properties and sterile non-inflammatory source were first approved for use in ophthalmology, in 1980, as surgical viscoelastics, now referred to as ophthalmic viscosurgical devices (OVDs). OVDs can create and preserve surgical space, pressurize the anterior chamber in the presence of an open wound, partition spaces, protect the corneal endothelial cells from fluid turbulence, and facilitate surgery. Shortly after their introduction, publications appeared, showing that their rheological properties were beneficial in artificial tear solutions and in surgery.

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There are 2 primary rheological profiles of various OVDs. Pseudoplasticity is indicative of its degree of non-Newtonian behavior, with flatter curves being more Newtonian. The varying rheological properties of different OVD types are used to perform different functions during ophthalmic anterior segment surgery. mPas = millipascal seconds; s = seconds.

Figure 1. Rheological profiles of various OVDs. Pseudoplasticity curves illustrate the effect of increasing shear rate on the viscosity of various OVDs plotted as the log of viscosity vs log of shear rate. In this figure, examples of viscoadaptive (I-Visc Phaco and Healon5), superviscous-cohesive (Healon GV), viscous-cohesive (Healon), medium viscosity-dispersive (Viscoat), and lower viscosity-dispersive (Ocucoat) OVDs are compared. The steepness of each curve is indicative of its degree of non-Newtonian behavior, with flatter curves being more Newtonian. The varying rheological properties of different OVD types are used to perform different functions during ophthalmic anterior segment surgery. mPas = millipascal seconds; s = seconds.

Figure 2: Newtonian, plastic, pseudoplastic, and dilatant. All materials that have been found to be useful as OVDs exhibit pseudoplastic behavior, as illustrated in Figure 1.

Tear film integrity is an integral component of the visual refractive system, which has a direct effect on the patient’s comfort and quality of vision. DED has been defined by the Dry Eye Workshop subcommittee for definition and classification (DEWS I and DEWS II) as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, in which its instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles and together induce ocular symptoms. There are 2 primary categories of DED, aqueous deficient and evaporative. Treatment of both these broad categories of DED typically starts with artificial tears for tear replacement therapy.

Numerous over-the-counter (OTC) products are available, which attempt to stabilize or supplement the natural tear film. All these treatments are symptomatic and palliative in that they often allow the patient to live fairly comfortably and function normally, but generally do not resolve the underlying pathophysiology of DED. Artificial tears are formulated to create a stable lubricating complex to mimic the properties of human tears and provide corneal protection, prolonged residence time, moistening, relief from symptoms, and comfort. The most common ingredients found in artificial tears are demulcients and emollients. Demulcents, such as cellulose derivatives and liquid polyols, are substances that relieve the irritation of the mucous membranes by forming a protective film, reducing friction, and aiding in water retention. Emollients, such as fats and oils, may stabilize or increase the lipid layer thickness and potentially reduce evaporation. Other additives, with a physical effect on the artificial tears, include hyaluronan (hyaluronic acid, HA, or sodium hyaluronate), hydroxypropyl guar (HPG, a derivative of the galactomannan polysaccharide extracted from guar beans), sodium carboxymethyl cellulose (CMC), and lightly crosslinked acrylic polymers (carbomer), which are generally referred to as rheological additives, viscosity enhancers, thickeners, or gelling agents and are used either individually or in combinations.

Various other additives have an intended chemical effect, such as trehalose, ectoine, glycerin and L-carnitine, that perform functions such as osmoprotection, bioprotection, anti-inflammatory activity, and free radical scavenging. Still other ingredients include buffers, electrolytes, emulsifiers, and preservatives, which altogether make artificial tears multicomponent complex systems.

RHEOLOGY AND TEARS

The tear film is the interface of the ocular system with the outer environment, continuously transforming during the blinking cycle to effectively coat the ocular surface, keeping it moist, providing protection against dust and bacteria, and washing away waste. Rheology, the science that studies how
materials deform and flow under the influence of external forces, has been instrumental in understanding the changes to the tear film of natural and artificial tears during the blink cycle. To understand the flow of tears, it is important to understand the changes the tear layer experiences due to the movement of the eyelid and therefore the basics of fluid rheology:

If an external force $F$ is applied to an area $A$ of a material, the shear stress $\sigma$ is defined as

$$\sigma = \frac{F}{A}$$

The units of the shear stress $\sigma$ are newtons per square meter (N/m$^2$) or pascals (Pa).

If the application of an external force results in the elongation of the system, the material experiences shear strain $\gamma$. The shear strain $\gamma$ is defined as the change in length $\Delta L = (L - L_0)$ relative to the initial, undeformed length $L_0$ of the material:

$$\gamma = \frac{(L - L_0)}{L_0}$$

The strain $\gamma$ is dimensionless.

We may visualize the tear film as a uniform 3-dimensional system that is made of layers, occupying the space between the ocular surface and the eyelid, and the movement of the eyelid is forcing the layers to move in a certain direction (Figure 3). Unlike human trilayer tears, in which the 3 layers are different from each other, when making an artificial tear, it is helpful, mathematically, to look at the tear film as a homogeneous fluid, so we will use that model herein. At rest, the material has a thickness $X_0$, length $L_0$, and width $W_0$. Assuming that flow is laminar, the upper layer would be displaced by $dL$ and the thickness by $dX$ when the system is moving at speed $V$ (velocity).

The shear rate, $\dot{\gamma}$, is defined as the ratio between the change in velocity $dV$ and the change in thickness $dX$:

$$\dot{\gamma} = \frac{dV}{dX}$$

The units of the shear rate are (meters/second)/meter = 1/second or reciprocal seconds (s$^{-1}$).

Newton defined the viscosity ($\eta$) of a fluid as the ratio between the shear stress, $\sigma$, and the shear rate, the velocity gradient, $\dot{\gamma}$, where ($\dot{\gamma} = \frac{dV}{dX}$).20

Hence, $\eta = \sigma / \dot{\gamma}$

Newton determined that this ratio is constant for a given fluid, which implies that the viscosity of the fluid remains constant with increasing shear rate. Therefore, fluids that follow this relationship have the same viscosity at low and high shear rates and are referred to as Newtonian fluids. In reality, few fluids are truly Newtonian; many complex fluid systems and polymer solutions are plastic or pseudoplastic and do not exhibit Newtonian behavior as their viscosity decreases with increasing shear rate. Many mathematical models have been proposed to describe the changes in the viscosity of non-Newtonian fluids.21-25

Rheological measurements may be performed with a capillary viscometer, determining the viscosity by measuring how long it takes for a defined volume of liquid to flow through a capillary tube of a specific length and width. This measurement can determine the kinematic viscosity of the system (a measure of a fluid’s internal resistance to flow under gravitational forces, usually used to measure the viscosity of Newtonian systems, and equal to dynamic viscosity/density). Another type of rheological measurement may be performed with a rotational rheometer, which measures the force (or torque) required to turn a spindle of known geometry in a fluid while varying the speed. This measurement assesses dynamic viscosity (or absolute viscosity), measuring the force needed by a fluid to overcome its own internal molecular friction so that the fluid will flow over a range of shear rates. This type of measurement is independent of density and is usually used to measure the viscosity of non-Newtonian systems.26 The rheology of the natural tear film has been studied rheologically and is relatively well understood. Artificial tears are designed to mimic, replace, or supplement a deficiency of the natural tear film and augment or enhance any remaining tear film. The rheology of both the natural tear film and artificial tears will affect their ability to hydrate, lubricate, and maintain the desired physical and chemical conditions on the corneal surface. The rheology of these solutions will also affect their ability to withstand repeated blinking cycles without being eliminated too rapidly, necessary to provide comfort and relief from symptoms of DED. Rheological additives, sometimes referred to thixotropic or viscoelastic substances, have been playing an increasingly important role in artificial tear formulations over the past 2 decades.27

Hyaluronan, a naturally occurring glycosaminoglycan, distributed widely throughout connective, epithelial, and neural tissues, is viscoelastic or elastoviscous (with the first syllable of the descriptor indicating which property dominates in a particular solution) and has high water retention capacity.28 Hyaluronan is known to bind with fibronectin and CD44, a cell surface adhesion molecule, which has been found on corneal epithelial cells and contributes to longer residence time.29-32 The first hyaluronan solution found to

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**Figure 3.** Basic model for the flow of tears between the ocular surface and the eyelid. The tear film is visualized as a homogeneous 3D system, applicable more to artificial than natural tears, made of layers between the stationary ocular surface and the moving eyelid. The moving eyelid is forcing the tear film layers to flow, sliding on top of each other (laminar flow). The upper layer is displaced by $dL$, whereas the thickness is displaced by $dX$ as the system is moving at a speed (velocity). The shear rate is defined as the ratio between the change in velocity $dV$ and the change in thickness: $\dot{\gamma} = dV/dX$. The units of shear rate are 1/second or reciprocal seconds (s$^{-1}$). $A =$ eyelid surface of the tear film; $X_0 =$ initial thickness of the tear film.
be effective in alleviating the discomfort of dry-eye syndrome was a dilution of Healon, a viscoelastic OVD, tested for tear replacement in the early 1980s in several clinical trials.\textsuperscript{3,33} Hyaluronan is not naturally present in tears; however, its usefulness, partially due to its water-binding capacity (hydration), as a superior lubricant and as a barrier to prevent irritation from environmental irritants, makes it uniquely desirable as an additive in the development of an optimal elastoviscous tear solution.\textsuperscript{34} The first commercially available hyaluronan-containing eyedrops, Hylashield and HylashieldNite (Biomatrix Inc.), containing 0.15% and 0.4% HA and manufactured specifically as tear replacements, for patients with severe keratoconjunctivitis sicca, were used by author S.A.A. in a double-masked crossover study of 39 patients, which demonstrated significantly increased efficacy, compared with placebo, in relieving symptoms of ocular burning, itching, and grittiness of patients with dry eye.\textsuperscript{35,36} Although Hylashield is no longer commercially available, interest in the rheology of artificial tears has led to the development of various artificial tears based on hyaluronic acid. We continue to believe that rheologically designing better artificial tears should greatly benefit patients. Non-Newtonian HA solutions are perceived as more comfortable, cause less blurring, have a longer residence time, provide superior hydration, and reduce surface friction. As a result, such solutions are effective in relieving the symptoms of DED.\textsuperscript{37} It has been shown that HA enhances corneal epithelial wound healing and cell proliferation, while reducing inflammation.\textsuperscript{38–40} Hyaluronan is now added into multiple brands of artificial tears to treat DED.

Our experience with Hylashield convinced us that an important feature of artificial tears is their ability to stay on the corneal surface for prolonged periods of time, as a function of the properties of the elastoviscous film they form in the presence of repeated blinking. Estimates of tear film thickness (TFT) from actual measurements and mathematical models, some of which include the effect of the blink cycle, taking into account gravitational and evaporative effects, range from 3 to 46 μm.\textsuperscript{41–47} The duration of a single blink has been estimated at 100 to 400 ms.\textsuperscript{48} Most artificial tears form a thicker film initially on instillation, which becomes progressively thinner with repeated blink cycles, but remains, in many cases, thicker when compared with the normal tear film (1.5 to 5 μm), and that of patients with DED.\textsuperscript{49–51} In a study by Wang et al., using Refresh Liquigel, TFT was measured with optical coherence tomography (OCT) at 0, 5, 20, 40, and 60 minutes following installation. The preinstallation TFT was 3.2 μm, increased to 35.6 μm at instillation, 10.3 μm at 5 minutes, 6.0 μm at 20 minutes, and back to baseline at 60 minutes. Only at times 0 and 5 minutes was TFT statistically significantly greater than preinstillation, and the authors concluded that the artificial tear retention time was between 5 and 20 minutes.\textsuperscript{52} In a similar OCT study by Kaya et al., using 0.15% HA eyedrops, the preinstallation TFT was 4.8 μm, increased to 13.9 μm at 10 minutes, 13.7 μm at 20 minutes, 13.0 μm at 30 minutes, all statistically significantly higher than baseline, and returned to baseline at 60 minutes, hence lasting longer than non–HA-containing solutions.\textsuperscript{53} Some clinicians believe that more viscous solutions are more effective because they feel that they provide longer-lasting relief from symptoms.\textsuperscript{54} In support of this opinion, increasing the HA concentration from 0.1% to 0.3% was demonstrated to provide longer-lasting relief of symptoms as measured with noninvasive break-up time (NIBUT).\textsuperscript{55} These studies, taken together, suggest that using HA not only provides longer-lasting increased TFT but by increasing HA concentration NIBUT also increases.

**Ideal Rheology**

The ideal rheology of artificial tears should mimic human tears. Human tears exhibit non-Newtonian shear-thinning viscoelastic behavior that prolongs the contact time on open eyes and protects the ocular surface by decreasing viscosity during the blink cycle.\textsuperscript{56} It has also been stated that thin multilayered films, such as human tears, will intrinsically be more resistant to dewetting if the outermost constituent exposed to air has increased viscosity.\textsuperscript{57}

As stated above, it is clear that the rheological demands for artificial tears are very different from the rheological behavior of surgical OVDs, with which we are primarily concerned about the behavior of OVDs just before they begin to move in the eye. In contrast, the tear film is in almost continuous motion, going through cycles of accelerating and decelerating shear resulting from the blinking action of the eyelids, so we are concerned with the tear film’s rheology when it is in motion at continuously changing speeds from stationary to very fast. We may classify artificial tear solutions into 2 major rheological categories, Newtonian and non-Newtonian, with the non-Newtonian solutions behaving in a pattern similar to pseudoplastic OVDs but encompassing the entire vertically shrunk curve instead of just the left (Figure 1). Plastic and dilatant behaviors are not seen in artificial tears and will be omitted from further discussion below.

A recent study examined the rheological behaviors of 18 artificial tear solutions, which contained HA. In this study, the authors concentrated mainly on the effect that MW and the polydispersion index (PDI) of the constituent HAs MW had on the rheological behavior of these solutions. They divided their products into 3 groups based on the MW of the HA, with the highest group having an MW > 1000 kDa and the lowest group with an MW of <500 kDa. They conclude that the highest MW HA solutions with the lowest PDI show the best shear-thinning behaviors and that these solutions will probably result in the optimal formulation for providing the longest duration of relief and best comfort for the patient. In addition, they define a blur threshold for their solutions to be a viscosity between 20 and 30 cP [20–30 centipoise (CGS units) = 20–30 mPa s (SI units)].\textsuperscript{58}

Typical Newtonian and non-Newtonian behaviors, as applied to tears, are shown in Figure 4. Although Newtonian
behavior is manifested by a constant viscosity as a function of shear rate, non-Newtonian behavior exhibits 3 phases: The first phase is one of Newtonian behavior at very low shear rates where viscosity, $\eta = \eta_0$ (zero-shear viscosity). In artificial and human tears, this phase is present in the open eye, between blinking cycles, when the tear film is at rest. The high viscosity of the tears in this phase is desirable to resist drainage and tear film break-up. The second phase, shear thinning, is seen with the changing speed of lid movement as the blink progresses across the cornea, which applies increasing stress on the tear film as the blink accelerates, progressively reducing viscosity of the tear film to allow the tears to spread over the ocular surface, thereby avoiding damage to the epithelial surface. Ideally, this shear thinning should be significant to allow the tears to have low viscosity at high shear rates, similar to the behavior of natural human tears. Finally, the third phase, which is a second Newtonian plateau at high shear rates, where viscosity, $\eta = \eta_\infty$, is the viscosity of the thin film formed at peak blink acceleration (note that this zone is not relevant to OVDs—Figure 2). The minimum shear viscosity of eyedrops required to maintain precorneal residence in man has been reported to be 10 mPa.s. Prior to the current study in our companion article this issue, earlier reports of the rheology of artificial tears were often limited to 1 point or very narrow range of viscosity measurements and were focused on 1 certain type of artificial tear or a limited number of artificial tears.

As with OVDs, measuring the rheological properties of artificial tears over a broad range of shear rates should shed more light on their behavior in the complex system of tears in the natural setting.

Shear rates ($\dot{\gamma}$) for the blinking forces may be estimated by using the following equation:

$$\dot{\gamma} = \frac{dv}{dy} = \frac{v(lid)}{h}$$

Where $v(lid)$ is the velocity of the eyelid, and $h$ is the film thickness. Assuming that the eyelid is traveling a maximum distance of 1 to 2 cm (down and up), and taking into account the range of eyelid blink duration and the range of TFT, the estimated maximum high shear rate related to the blink cycle is in the range of about 2,000 s$^{-1}$ to 20,000 s$^{-1}$, with some studies estimating the high shear rate ranges from 4,000 s$^{-1}$ to 100,000 s$^{-1}$, depending on the film thickness. We can use mathematical models to help us determine the second Newtonian plateau, making it unnecessary for us to continue to remeasure viscosity at extremely high shear rates (our companion article this issue illustrates how this is done).

NORMAL STRESS

The rheological information above concerns the changing viscosity of tears throughout the blink cycle. However, elasticity is also critically important in tears so that they rapidly return to their preblink physical status prior to the next blink, thereby increasing comfort and prolonging residence time. An ideal artificial tear should be highly elastoviscous, allowing it to spread across the cornea in a thin clear layer with each blink and then rapidly return to its preblink status to be ready for the next blink. In a polymer solution or emulsion at rest, polymer chains occupy an approximately spherical-shaped volume to minimize enthalpy and entropy. When the microstructure is deformed due to applied shear force, such as with blinking, the spherical structured units deform into ellipsoids, which have their major axes tilted toward the direction of flow. The deformed spherules exert restoring forces to counteract the external force, giving rise to normal stress components perpendicular to the direction of flow. Normal stress may develop when a material is being mixed, and as a result, it climbs the mixing rod (known as the Weissenberg effect) or when a material is being forced through a die (known as the die swell effect). These normal forces are evidence of the elasticity in the fluid and are not constant, but rather depend on the applied shear rate. Measuring normal forces may shed light on the viscoelasticity of system. The first normal stress difference, $N_1$, is defined as the difference between the stress tensors along the x (\(\sigma_{xx}\)) and y (\(\sigma_{yy}\)) directions, where $\sigma_{xx}$ is the stress that is applied in the direction of the shearing forces, and $\sigma_{yy}$ is the resulting normal stress in the direction perpendicular to the plane of the shearing forces. For Newtonian liquids, there is no perpendicular stress, and therefore, $N_1 = 0$. It is important to measure $N_1$, the first normal stress difference, in human and artificial tears to get a good understanding of the elastic component of the viscoelasticity of the non-Newtonian fluid being assessed (see our companion article this issue).

The various components of artificial tears form a 3D structure that dictates the rheological properties of the fluid. Measuring both the viscosity of the system and the normal stress difference, $N_1$ over a large range of shear rates may provide insight to the behavior of artificial tears from instillation, through the blink cycle and back to rest. In the companion article this issue, we have sought to measure the viscous behavior of 20 commercial artificial tears and their normal stress ($N_1$) values, thereby enabling us to divide them into rheological groups.
CONCLUSIONS

The natural tear film is a highly complex multidimensional fluid gel solution. There are many factors such as constituent rheological polymer nature and concentration, specific demulcents and emollients, thickeners, gelling agents, pH, osmolarity, temperature, electrolyte concentrations, oxygen permeability, clarity, and others that can affect its performance. The discussion in this review is limited to defining and explaining the values of the rheological properties of natural and artificial tears in the context of the blinking cycle with likely implications on the importance of rheology in artificial tears in helping determine their ability to provide the desired properties of comfort, hydration, lubrication, bio- and osmoprotection, and a clear and unobstructed refractive field of view. We have discussed the assessment methods and areas of significance (compared with OVDs) of the Newtonian or non-Newtonian viscous behavior of tears and the importance of determining elastic behavior through measurement of normal stress values. This combined viscous and elastic assessment across broad ranges of shear rates should demonstrate, through laboratory measurements, strong indicators of how a specific tear formulation will behave clinically. When formulating a new artificial tear substitute, it is important to understand the role of rheology of these solutions to assist in designing an artificial tear film that provides the patient with the highest levels of comfort and relief from symptoms of DED and the longest duration of action with no deleterious effects. Our companion article article this issue assesses the parameters presented above in 20 commercial artificial tears.66

REFERENCES

20. Newton IS, Philosophiae Naturalis Principia Mathematica. 1st ed; 1687; Book 2, Section IX.
36. Larsen NE, Balazs EA, Hylashield (2.0 Pa elastoviscous hylan fluid 0.15%) protective corneal shield: evaluation of biological and physical properties. Ophthalmic Pract 1994;12:137-140.
44. Berke A, Mueller S. The kinetics of lid motion and its effects on the tear film. In: Sullivan DA, Darrt DA, Menear MA, eds. Lacrimal Gland, Tear Film, and

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First author:
Steve A. Arshinoff, MD, FRCSC
York Finch Eye Associates, Toronto, Ontario, Canada

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