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The viscosity of human tears

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Abstract

Blinking involves high rates of shear within the tear film, requiring a low tear viscosity to avoid damage to epithelial surfaces. Conversely, in the open eye, a higher viscosity is desirable to resist drainage and film break-up. Samples of human tears were collected with moderate stimulation from 5 adult males, 3 with normal and 2 with marginally-dry eyes. The apparent viscosity at 22° C was found using a Couette-type rheometer over the range of shear rate 2–160 sec^{-1}. Marked shear-thinning was apparent in all samples, with little apparent difference between normal and dry-eye tears. Although a power-law equation could be fitted over part of the range, analyses according to either the Casson plastic model as used for rabbit tears (with a low yield-point indicative of some very loose initial gel-like structure) or the Steiger-Ory model (a true pseudoplastic model with no initial yield point) were inconclusive over the range of shear rate studied. The descriptive model of Cross gave zero-shear viscosity values of 4.4, 7.1 and 8.3 mPa.sec for normal tears, and 27.1 and 31.1 mPa.sec for dry-eye tears; the corresponding time constants were 0.13, 0.27 and 0.38 sec for normal tears, and 2.7 and 2.9 sec for dry-eye tears. These time-constants can be considered as an approximate relaxation time, indicating the time taken for the tear film to stabilise after a blink.

Introduction

There is great interest in the formulation of tear replacement solutions for supplementation of insufficient lacrimal volume or treatment of inadequate lubrication of the eye. It has long been recognised that the contact time of such solutions is prolonged by increasing their viscosity, but that if the viscosity is too high rapid eye movements will produce dragging sensations and possibly epithelial damage. The range of shear rates experienced during relative movements of the lids and globe is extremely wide (Table 1; refs. 1–5). Ideally a tear replacement solution will be able, in the same way as natural tears, to cope with both the low-shear region of the open eye and minor movements, and the high-shear region of rapid pursuit and blinking. This is best achieved by a visco-elastic fluid whose viscosity is high under conditions of low shear-rate and low under conditions of high shear-rate (a non-Newtonian fluid exhibiting shear-thinning) rather than a fluid whose viscosity is independent of shear-rate (a Newtonian fluid). It is known that human tears, due to their content of soluble mucous glycoprotein, have this property [6].

Although a number of values have been reported for the viscosity of human tears, they were all obtained essentially under uncontrolled conditions of shear-rate, so that it cannot be inferred whether their behaviour is Newtonian or not. Hamano and Mitsunaga [7] studied rabbit tears in a variable shear-rate rheometer, and analysed the results according to a model of plastic rheological behaviour. The method used a relatively large volume of tears collected over several days and pooled from several animals. A similar study has not up to now been performed on human tears, possibly because of the volume required.

A recent comparison has been made of the viscosity as a function of shear rate of human tears collected from normal and dry eyes [8]. Unfortunately this involved the application of a shear rate ramp with time, so that equilibrium values of viscosity were not obtained. The effect is that viscosity is very seriously under-estimated at shear rates below about 20 sec^{-1}, although as expected the results for dry eyes were always less than for normal tears.

Several studies have been reported on the rheological behaviour of tear substitutes [9, 10] and have referred to the desirability of matching as closely as possible the performance of real and artificial tears [10], yet the absence of any reliable published figures on the actual *in vitro* rheological performance of human tears seems to be overlooked. The need for exact matching of *in vitro* performance of tears and tear replacements has indeed been questioned [11], on the grounds that the *in vivo* performance of the substitute, allowing for mixture and gradual dilution by natural tears, is more important.

This paper describes equilibrium measurements on freshly-collected individual samples of human tears from both normal and marginally-dry eyes, and attempts to fit the data to commonly-used rheological models.

Materials and methods

Viscometer

The instrument used was a Contraves Low-shear 30 Couette-type rheometer. The sample is held in the annular space between an outer cylindrical cup which can be rotated at a series of fixed speeds to give steps of constant shear rate, and an inner cylinder or bob suspended from a torsion wire. The restoring force which must be supplied electrically to prevent rotation of the bob due to viscous drag is converted by instrument calibration tables to values of apparent viscosity at constant rate of shear strain. An averaged value is used for the rate of shear since it is not constant across the annular gap by this method. Other methods such as the cone and plate rheometer give a uniform rate of shear throughout the fluid sample, but require a significantly larger sample volume. With the present instrument a sample of 70 μl is adequate. The range of the instrument with this small-volume cup and bob combination is 6.3×10^{-2} to 2.9×10^{6} mPa.sec (or cP) for viscosity over 5 ranges of sensitivity, and 2.2×10^{-2} to 1.6×10^{2} sec^{-1} for shear rate in 30 steps.

The temperature within the Couette cup could be controlled, but evaporation was found to be high when measurements were made at 37° C. It was considered undesirable to cover the surface of the sample in the cup with silicone oil to reduce evaporation, since this might disturb the distribu-

Table 1. Velocities of eye movements and shear rates in the human eye.

Movement			
Type	Angular (°/sec)[a]	Linear (mm/sec)[b]	Shear rate (sec^{-1})[c]
Blink[d]	—	170–200	4250–28500
Saccade	≤ 700	164	4100–23500
Smooth pursuit	80–160	20–40	475–5400
Microsaccades	3.3	0.8	20–115
Tremor	0.006	0.001	0.03–0.14

[a] Ref. 1.
[b] Taking distance from corneal surface to centre of rotation as 13.45 mm (ref. 2).
[c] Range taking limits of tear film thickness as 7–40 μm (refs. 3, 4).
[d] Ref. 5.

tion of the strongly surface-active tear macromolecules. For limited samples, therefore, measurements were made only at room temperature (22 ± 1° C).

Tear collection

Ideally tears should be collected with essentially no stimulation of reflex secretion. This may be possible when collecting volumes of, say, 1–5 μl for other purposes. However, where volumes as large as 70 μl are required from individual subjects, some degree of stimulation is unavoidable if collection is to take place within a reasonable space of time. Excessively long storage gives time for degradative processes to commence in the sample if held at room temperature, while refrigeration is known to affect measurements of tear surface tension, which also depends on the macromolecular content [12]. Mild stimulation was therefore used, by blowing a jet of air onto the cornea. Tear fluid was collected from the lower conjunctival sac in precleaned 10 μl disposable glass capillary tubes with flamepolished tips, and transferred to 1.5 ml plastic micro-centrifuge tubes. After centrifugation to remove any particulate material, the tears were transferred to the rheometer cup by Hamilton microlitre syringe.

Viscosity measurement

The rotational speed of the cup was increased stepwise, starting with the lowest. At each speed, the motion was allowed to become steady, and the torsional force response was then read from the digital display. After reaching the maximum speed, the process was reversed and readings were taken in descending order of speeds. No hysteresis was seen. Use of tables provided with the instrument for this combination of cup and bob, rotational velocity and sensitivity scale then gave the viscosity at each value of shear rate.

Results

Samples

Five samples of tears, each of 65–90 μl, were collected from individual adult human male subjects aged 22–48 years. Three of these (samples A–C) were from normal eyes, but two (samples D and E) were from marginally dry eyes as judged by slightly low (ca. 20 sec) values for non-invasive tear film break-up time [13] and occasional sub-clinical complaints of 'scratchy' or 'smarting' sensations (see Table 2). In practice only figures in the shear rate range of 2–160 sec^{-1} were recorded, as torsional force figures at lower speeds were very small with large errors.

Table 2. Cross equation constants for tears.

Sample	Age of subject	η_0 (mPa . sec)	$D_{1/2}$ (sec^{-1})	$t_{1/2}$ (sec)
Human normal tears				
A	22	8.30	3.76	0.27
B	23	7.14	2.64	0.38
C	47	4.44	7.87	0.13
Human dry-eye tears				
D	47	27.09	0.34	2.94
E	48	31.13	0.37	2.70
Mean of A, B and C		5.95	6.02	0.17
Rabbit tears[a]		90.9	0.24	4.22

[a] From ref. 7.

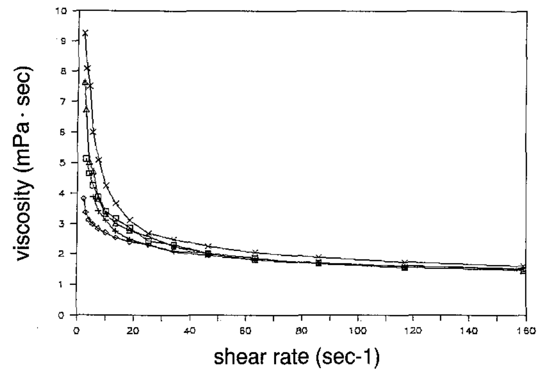

Fig. 1. Apparent viscosity as a function of shear rate for five individual human tear samples: A, □; B, +; C, ◇; D, △; E, ×

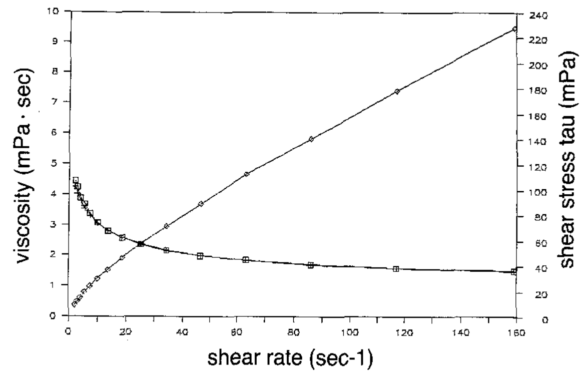

Fig. 2. Apparent viscosity and shear stress as a function of shear rate for mean normal human tears: Experimentally-determined viscosity, □; viscosity calculated from values of shear rate using the Cross equation with constants from Table 2, +; shear stress (τ), ◇.

Viscosity results

Figure 1 gives the apparent viscosity η as a function of rate of shear for each of the samples over the range 2–160 sec^{-1}. Marked shear-thinning is shown by all the samples, with viscosity falling from about 5 mPa.sec at the lowest shear rate to about 1.5 mPa.sec at the highest shear rate for normals, and from about 9 down to 1.5 mPa.sec for samples D and E.

Figure 2 shows the viscosity/shear rate curve for an averaged normal sample: each point is the mean of the corresponding viscosity values for samples A–C at the same shear rate. The form of the curve is similar to that of each individual sample, and the error limits shown are no wider than the variation found for consecutive samples of a standard viscoelastic test fluid. This average curve is used in further investigations on possible rheological models for tears (see Discussion). Figure 2 also shows the corresponding shear stress (τ) values. Unlike the results of Hamano and Mitsunaga [7], this curve tends smoothly towards zero at low shear rates, with no yield-point.

Discussion

Human tears, both normal and from marginally-dry eyes, show marked shear-thinning over the range of shear rates studied. This covers many of the ‘open-eye’ rates of shear estimated in Table 1. Unlike the results of Bron and Mengher [8], dry-eye tears have somewhat higher viscosity throughout the range, and markedly higher at values of shear rate below 5 sec^{-1}.

Shear-thinning is a property of solutions containing long polymeric macromolecules which are not strongly bonded into a globular form. At rest, such molecules are loosely tangled together; when a shearing force is applied, they tend to be disentangled and to stretch out parallel to the lines of shearing force. At the same time, Brownian motion tends to re-entangle the chains, so the degree of entanglement during shear, and hence the apparent viscosity, is greater at low than at high rates.

It had previously been found [6] that human tears had characteristics in common with dilute solutions of mucous glycoproteins; also that, at concentrations likely to be found in tears, the contribution of mucus is considerably greater than that of proteins. Stimulated tears will contain less soluble conjunctival mucus than unstimulated, since their rate of production gives less opportunity for equilibration within the conjunctival sac. Our present results suggest that sufficient mucus is present in the sample, despite stimulation prior to collection, to give the characteristic shear-thinning.

It seems possible that the overall slower rate of production of tears from dry-eye subjects (even the mild sub-clinical cases used here), and the consequent longer collection time, might allow greater mixing of lacrimal gland fluid with conjunctival secretions and hence a slightly higher mucus content. Paradoxically, therefore, the dry-eye tears may more closely resemble normal tears collected without stimulation than do the normal samples tested here. No conclusions can be drawn from these studies about the concentration or chemical nature of normal or dry-eye mucus in tears.

Rheological models

Many equations have been proposed to express the relationship between shear stress τ and rate of shear strain D for the fluid motion of various materials, with varying degrees of success. Often one part of the τ vs. D curve can be fitted by a particular model, but not the whole. Viscous behaviour can be divided into plastic (where a yield-point must be exceeded before the material flows), and pseudoplastic (where the τ vs. D graph is non-Newtonian or curved, but passes through the origin without a yield-point).

In their study of rabbit tears, Hamano and Mitsunaga [7] found a yield-point and hence fitted Casson's plastic model to the data. Human tears show no yield-point so pseudoplastic models seem appropriate. Among the simplest of these are the Ostwald and the Steiger-Ory equations.

(a) Ostwald equation

This has the power-law form $D = c\tau^n$, where c is a constant and $n > 1$. Since $\eta = \tau/D$, this can be expressed as $\eta = c'D^{-(1-1/n)}$, where $c' = 1/c^{1/n}$. Taking logarithms, $\log\eta = \log c' - (1 - 1/n)\log D$. Hence the intercept at ($\log D = 0$) and the slope of the linear portion of the graph of $\log\eta$ vs $\log D$ (Fig. 3) can give both c and n.

The logarithmic plot in Figure 3 shows curvature both below $D \approx 5.4$ and above $D \approx 47\,\text{sec}^{-1}$. The linear portion fits the Ostwald relationship $D = 0.0804\tau^{1.408}$, or $\eta = 5.99\,D^{-0.29}$, but this does not hold for shear rates experienced in either the 'open eye' or blinking situations. The data for rabbit tears at 30° C [7] show an upward curvature deviating from the linear relationship above about $75\,\text{sec}^{-1}$. The conclusion by these authors of a 'point of change', indicated as the point of intersection of two linear sections at about $200\,\text{sec}^{-1}$, seems unjustified from the results presented. The corresponding Ostwald equation from the linear region of the logarithmic graph for rabbit tears at 30° C is $\eta = 34.6\,D^{-0.62}$.

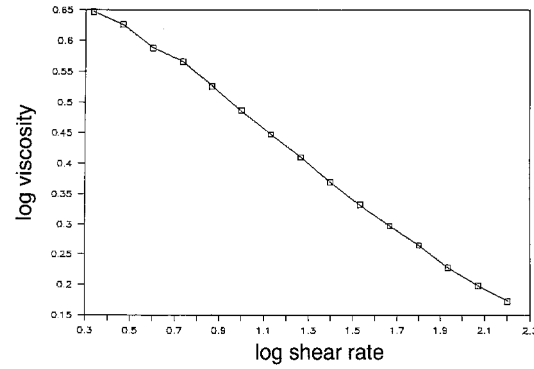

Fig. 3. Logarithmic plot of viscosity against shear rate for mean normal human tears.

(b) Steiger-Ory equation

The major drawback of the Ostwald equation is that the slope of the D-τ graph is zero at zero shear, implying that the zero-shear viscosity is infinite. The Steiger-Ory equation $D = a\tau^3 + c\tau$, where a and c are constants, aims to overcome this, since it has a slope of c at low shear, and hence $\eta_0 = 1/c$. However, attempts to derive unique values over a wide range of shear rates for the constants a and c using a curve-fitting computer program have proved unsuccessful.

(c) Cross equation

Cross [14] has derived the descriptive equation

$$\eta = \eta_\infty + (\eta_0 - \eta_\infty)/[1 + (D/D_{1/2})^{2/3}]$$

where η_0 and η_∞ are the apparent viscosity at zero and infinite shear rate, respectively, and $D_{1/2}$ is the value of shear rate at which viscosity is the mean of its two limiting values. A graph of $1/\eta$ vs. $D^{-2/3}$ is linear at low shear rates, with intercept $1/\eta_0$, and a graph of η vs. $(\eta_0 - \eta)/D^{2/3}$ is linear over most of the range, but especially at high shear rates, and has a gradient of $(D_{1/2})^{-2/3}$. Hence the two characteristic values η_0 and $D_{1/2}$ can be found. Figure 2 also shows the very close correspondence between values of η

calculated using η_0 and $D_{1/2}$ derived from the mean viscosity of normal tears, and the experimental data. The ranges of these factors calculated for samples A–E, and for rabbit tears, are given in Table 2.

The Cross equation has been found to hold for a wide variety of polymer solutions, disperse systems and polymer melts, and has already been used to compare the performance of human tears and tear replacements [15]. $D_{1/2}$ effectively defines the shear rate at which substantial disentanglement of the polymer chains has taken place. Since the units of $D_{1/2}$ are sec^{-1}, its reciprocal $t_{1/2}$ is a characteristic time in seconds; although not a true relaxation time, $t_{1/2}$ can be taken as a measure of the time required to re-establish the high-viscosity 'open-eye' condition in the precorneal tear film following a blink. The values of $D_{1/2}$ and $t_{1/2}$ in Table 2 thus indicate the degree of non-linearity of the viscosity/shear rate curves; if, as suggested above, the 'dry-eye' tears actually contain more mucus than the 'normal' tears, we should expect their $t_{1/2}$ to be longer since re-entangling of the macromolecules will take longer. If, in addition, tear film stability depends upon the amount of soluble mucus present, $t_{1/2}$ should be related in some way to break-up time. The value of 4.22 sec for $t_{1/2}$ in the rabbit therefore reflects its long inter-blink period and high tear-film stability, and implies that the tear film undergoes a prolonged settling period after each blink. Unfortunately it is not possible to draw any conclusion of this type from the human results presented here, since it is not clear which of them more accurately reflect the performance of normal unstimulated tears *in vivo*.

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