1040-5488/08/8508-0715/0 VOL. 85, NO. 8, PP. E715–E725
OPTOMETRY AND VISION SCIENCE

ORIGINAL ARTICLE

Effect of Viscosity on Tear Drainage and Ocular Residence Time

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ABSTRACT

Purpose. An increase in residence time of dry eye medications including artificial tears will likely enhance therapeutic benefits. The drainage rates and the residence time of eye drops depend on the viscosity of the instilled fluids. However, a quantitative understanding of the dependence of drainage rates and the residence time on viscosity is lacking. The current study aims to develop a mathematical model for the drainage of Newtonian fluids and also for power-law non-Newtonian fluids of different viscosities.

Methods. This study is an extension of our previous study on the mathematical model of tear drainage. The tear drainage model is modified to describe the drainage of Newtonian fluids with viscosities higher than the tear viscosity and power-law non-Newtonian fluids with rheological parameters obtained from fitting experimental data in literature. The drainage rate through canaliculi was derived from the modified drainage model and was incorporated into a tear mass balance to calculate the transients of total solute quantity in ocular fluids and the bioavailability of instilled drugs.

Results. For Newtonian fluids, increasing the viscosity does not affect the drainage rate unless the viscosity exceeds a critical value of about 4.4 cp. The viscosity has a maximum impact on drainage rate around a value of about 100 cp. The trends are similar for shear thinning power law fluids. The transients of total solute quantity, and the residence time agrees at least qualitatively with experimental studies.

Conclusions. A mathematical model has been developed for the drainage of Newtonian fluids and power-law fluids through canaliculi. The model can quantitatively explain different experimental observations on the effect of viscosity on the residence of instilled fluids on the ocular surface. The current study is helpful for understanding the mechanism of fluid drainage from the ocular surface and for improving the design of dry eye treatments.

(Optom Vis Sci 2008;85:E715–E725)

Key Words: canaliculi, model, tear balance, tear drainage, viscosity, shear-thinning

Eye drops are commonly instilled to treat a variety of ocular problems, such as dry eyes, glaucoma, infections, allergies, etc. The fluid instillation results in an increase in tear volume, and it slowly returns to its steady value due to tear drainage through canaliculi, and also fluid loss through other means such as evaporation or transport across the ocular epithelia.[1] In fact, if the instilled fluid has a viscosity similar to that of tears, which is about 1.5 mPa · s, the instilled fluids or solutes are eliminated from the tears in a few minutes.[2–4] As a result, the fluids or solutes have a short contact time with the eye surface, which results in reduced effects for artificial tears or low bioavailability for ophthalmic drugs. To increase the duration of comfort after drop instillation and to increase the bioavailability of the drugs delivered via eye drops, it is desirable to prolong the residence time for the instilled fluid. It has been suggested and also shown in a number of clinical and animal studies that increasing the viscosity of the instilled fluid leads to an increase in the retention time. Zaki et al.[5] studied the clearance of solutions with viscosities from 10 to 100 mPa · s from the precorneal surface. These experiments showed a rather interesting effect of viscosity: the retention began to increase only after the fluid viscosity exceeded a critical value of about 10 mPa · s and also the relative increase in retention became smaller at very high viscosities. Although increasing fluid viscosity increases the residence time, it may also cause discomfort and damage to ocular epithelia due to an increase in the shear stresses during blinking. Shear thinning fluids such as sodium hyaluronate (NaHA) solutions can be used to obtain the beneficial effect of an increase in retention and yet avoid excessive stresses during blinking.[2] The likely reason is that the shear rates during blinking are very high and at such high shear rates these shear-thinning fluids exhibit low viscosity but during the interblink which is the period during which tear drainage occurs, these fluids act as high viscosity fluids

leading to reduced drainage rates and a concurrent increase in residence time.

Although the mechanisms of the impact of viscosity on residence time are qualitatively understood for both Newtonian and non-Newtonian fluids, no quantitative model has been yet proposed that can explain the detailed physics and predict the effect of viscosity on drainage rates and on retention time of eye drops. Such a model is likely to lead to an improved quantitative understanding of the effect of viscosity on tear dynamics, and also aid as a tool in development of better dry eye treatments and drug delivery vehicles. The goal of this study is to develop a mathematical model to predict the effect of viscosity on drainage rates and the residence time for both Newtonian and non-Newtonian fluids. The current study is an extension of our previous study that focused on modeling drainage of tears, which were considered to be Newtonian fluids with a viscosity of 1.5 mPa · s. Both the previous and the current models are based on the physiological description of canalicular tear drainage proposed by Doane,[6] which is described in detail elsewhere,[7] and are briefly presented below. According to Doane, the drainage of tears through lacrimal canaliculi is driven by the cyclic action of blinking. The entire blink cycle is divided into two phases, the blink phase and the interblink phase. During the blink phase, the eyelids move towards each other and meet, the puncta are closed and lacrimal canaliculi are squeezed by the surrounding muscles. The squeezing of canaliculi, along with puncta closure causes tear flow towards the nose. During the interblink phase, the eyelids separate leading to opening of puncta and a valve-like mechanism prevents any flow at the nasal end of canaliculi. Additionally, the muscles do not squeeze the canaliculi and this leads to a vacuum inside the canaliculi that sucks fluids from the ocular tear film. As a result of this cyclic process, tears are drained from the ocular tear film into the nose.

The tear drainage model developed by Zhu and Chauhan[7] showed that for tears with a viscosity of 1.5 mPa · s, the canaliculus radius will reach steady states during both the blink and the interblink phase. The canaliculus reaches a steady state in the blink phase when the stresses generated by the deformation of canaliculi balance the pressure applied by the muscles. The steady state is reached in the interblink when canaliculi have relaxed to an extent at which the pressure in the canaliculi equals that in the tear film. Achieving steady state both in the blink and the interblink implies that if the duration of the interblink and the blink are further increased, there will be no changes in total tear drainage per blink. However, the drainage rates will decrease due to the reduction in the number of blinks per unit time. The canaliculus radius was shown to reach a steady state in a time $\tau = \frac{16\mu L^2}{\pi^2 bER_0}$, where L, b, and R_0 are the length, thickness, and the undeformed radius of canaliculi, E is the elastic modulus of canaliculi, and μ is the viscosity of the instilled Newtonian fluid. As the viscosity of the fluid increases, the time to achieve steady state increases, but as long as the canaliculus reaches a steady state in both the blink and the interblink, there is no change in the total amount of fluid drained in a blink, and so there is also no change in the drainage rates. This explains the observation of Zaki et al.[5] that below a critical viscosity, increasing viscosity does not lead to enhanced retention. However, as the viscosity increases to a critical value at which the time to achieve steady state (τ_s) becomes larger than the duration of the blink phase, the canaliculus does not deform to the fullest extend possible, and so the amount of tears that drain into the nose during the interblink decreases. In the current study, the drainage model will be modified to calculate the drainage rate of instilled Newtonian fluids with viscosities that are larger than the critical viscosity, and so the system does not reach steady state in the blink phase. Additionally, the drainage rates will be calculated for power-law fluid, which is a reasonable approximation under physiological shear rates for typical non-Newtonian fluids used for ocular instillation. Finally, the modified tear drainage model will be incorporated into a tear balance model to predict the effect of viscosity on residence time of eye drops.

METHODS

Below we will first develop the models for the drainage of Newtonian and non-Newtonian fluids, respectively. The models are used to predict the drainage rates, residence time and bioavailability, and these predictions are compared with the experimental measurements[2,8–10] reported in literature. In our mathematical models, the canaliculus is simplified as a straight pipe of length L with an undeformed radius R_0, wall thickness b, and modulus E. The canaliculus is considered to be a thin shell, i.e., its thickness is much smaller than the radius and thus axial deformation is neglected and the length of canaliculi L is assumed to be constant. Each of these assumptions is an approximation, and the impact of each of these on the model predictions are discussed elsewhere.[7]

Drainage of a Newtonian Fluid

It has been shown by Zhu and Chauhan[7] that for a Newtonian fluid, the time and position dependent radius of the canaliculus can be predicted by solving the following equation:

$$\frac{bER_0}{16\mu}\frac{\partial^2 R}{\partial x^2} = \frac{\partial R}{\partial t} \tag{1}$$

where R is the radius of canaliculi that depends on axial position and time, x is the position along the canaliculus, with x = 0 for the puncta side and x = L (length of canaliculi) for the nasal side. The details of the derivation of Eq. 1 are described elsewhere.[7] The boundary conditions and the initial conditions for Eq. 1 are:

For the blink phase ($0 < t < t_b$)

$$\begin{aligned} q = 0 &\Rightarrow \frac{\partial R}{\partial x}(x = 0, t) = 0 \\ p\,(x = L, t) &= 0 \\ R\,(x, t = 0) &= R_{ib} \end{aligned} \tag{2}$$

For the interblink phase ($t_b < t < t_c$)

$$\begin{aligned} p\,(x = 0, t) &= -\frac{\sigma}{R_m} \\ q\,(x = L, t) &= 0 \\ R\,(x, t = t_b) &= R_b \end{aligned} \tag{3}$$

where t_b is the duration of the blink phase, t_c is the duration of one blink-interblink cycle, q is the flow rate of instilled fluids or tears through the canaliculus, L is the length of the canaliculus, p is the

pressure inside the canaliculus, σ is the surface tension of the instilled fluids or tears, R_m is the radius of curvature of the tear meniscus, and R_b and R_{ib} are the steady state canaliculus radii in the blink and the interblink, respectively, and these are given by the following expressions:

$$R_b = \frac{R_0}{1 + \frac{(p_0 - p_{sac})R_0}{bE}} \tag{4}$$

$$R_{ib} = \frac{R_0}{1 + \frac{\frac{\sigma}{R_m}R_0}{bE}} \tag{5}$$

where p_0 and p_{sac} are the pressure applied by the surrounding muscles to the canaliculus during blinking and the pressure in the lacrimal sac. The pressure p in Eq. 3 can be written as a function of the canaliculus radius R through the following equation:

$$p = p_0 + \frac{bE}{R_0}\frac{R - R_0}{R} \tag{6}$$

The details of the above model development are described earlier by Zhu and Chauhan.[7] The radius of the canaliculus can be solved analytically as a function of axial position and time from Eq. 1, 2, and 3. The volume of fluid contained in the canaliculus at any instant in time can be computed by using the following equation:

$$V_{canaliculus} = \int_0^L \pi R^2(x)dx \tag{7}$$

The volume of fluid drained in one blink-interblink cycle can then be computed as the difference between the volume at the end of an interblink ($V_{interblink}$) and that at the end of the blink (V_{blink}), and then the drainage rate through the canaliculus can be computed as

$$q_{drainage} = \frac{V_{interblink} - V_{blink}}{t_c} \tag{8}$$

The above procedure can be used to calculate the effect of viscosity on tear drainage. To determine the effect of tear viscosity on the residence time of eye drops, the tear drainage rates are incorporated in a tear mass balance.

Incorporation of Tear Drainage into Tear Balance

A mass balance for the fluids on the ocular surface yields

$$\frac{dV}{dt} = q_{production} - q_{evaporation} - q_{drainage} \tag{9}$$

where V is the total volume of the fluids on the ocular surface, including tears and the instilled fluids, $q_{production}$ is the combined tear production rate from the lacrimal gland and conjunctiva secretion, $q_{evaporation}$ is the tear evaporation rate, and both of these are assumed to be constant. In the above equation, tear transport across the cornea is neglected because the area of cornea is much smaller than that of conjunctiva. The effects of such approximations are discussed elsewhere.[7]

A mass balance for the solutes in the instilled fluid, such as radioactive tracers or fluorescent dye molecules, can be written as

$$\frac{d(cV)}{dt} = -cq_{drainage} \tag{10}$$

where c is the concentration of the solutes and V is the total volume of ocular fluids. The above equation is only valid for solutes that do not permeate the ocular epithelia such as fluorescent dextran. The drainage rate $q_{drainage}$ depends on viscosity, and this dependence leads to the dependence of dynamic concentration profiles on viscosity. The normal viscosity of tears is about 1.5 mPa · s and after instillation, it increases to a value μ_i that is close to the viscosity of the eye drops μ_{drop}. Immediately after instillation, due to the dilution by the tears μ_i will be smaller than μ_{drop}, but here for simplicity μ_i is assumed to be equal to μ_{drop}. Subsequently, the viscosity of the ocular fluid begins to decrease due to changes in the polymer concentration c. The viscosity of a polymer solution can be a complex function of concentration, and here for simplicity, the viscosity is assumed to be a linear function of concentration, i.e.,

$$\mu = \mu_{tears} + \frac{c}{c_0}(\mu_i - \mu_{tears}) \tag{11}$$

where c_0 is the solute concentration immediately after instillation. Since experimental studies on the residence time of instilled fluids often measure the transient of total quantity of radioactive tracers or dye molecules in the ocular fluids, we combine Eq. 9 and 10 to yield the following equation for the total quantity of solutes

$$\frac{I}{I_0} = \frac{V}{V_0}\exp\int_0^t\left(-\frac{q_{production} - q_{evaporation}}{V}\right)dt \tag{12}$$

where I (=cV) is the total quantity of solutes, and I_0 and V_0 are the values of I and V immediately after instillation. It is noted that the drainage rate calculations are coupled to the tear balance because the radius of curvature of the meniscus depends on the total tear volume, and the drainage rate is affected by the curvature through boundary condition (3). By geometric considerations, the tear volume can be related to the meniscus curvature by the following equation[11]:

$$V(R_m) = V_{film} + (1 - \frac{1}{4}\pi)R_m^2 L_{lid} \tag{13}$$

where the second term accounts for the fluid in the meniscus and V_{film} accounts for the remaining tear volume, i.e., fluid in the exposed and the unexposed tear film. In the above equation L_{lid} is the perimeter of the lid margin. The volume V_{film} depends on the tear film thickness (h), which in turn is related to viscosity through $h = 2.12R_m(\mu U/\sigma)^{2/3}$, where U is the velocity of the upper lid; and σ is the tear surface tension.[12] The relationship yields unrealistically large value of film thickness for large viscosities and therefore is likely invalid. Therefore in this study V_{film} is assumed to be independent of viscosity and based on our earlier calculations[11] and the measurements by other researchers,[13] its value is fixed at 5.37 μl. This yields a total normal tear volume of 7 μl for a

meniscus radius value of 0.365 mm.[14] It is noted that the instillation of extra fluids may cause large variations of the radius of curvature, changes of the geometry of the tear menisci, and even overflow of the ocular fluids onto the cheeks, which may render Eq. 13 invalid. However, such factors may vary across different subjects and there is no quantitative expression to account for these factors. Therefore in this study, Eq. 13 will be used, while noting that it is only an approximation, and a more accurate expression can be used instead if more detailed physiological information is available. By solving Eq. 1, 7, 8, 9 and 12 simultaneously using finite difference method, the transient quantity of the solutes in the ocular fluids can be obtained as a function of time.

In Eq. 10 above, it is assumed that the tracers do not permeate into the ocular surface, which is a reasonable assumption for some commonly used tracers. However it is not a reasonable assumption for ocular drugs delivered via drops. For such solutes, the mass balance needs to be modified to include drug transport through the ocular tissue. The modified mass balance is

$$\frac{d(cV)}{dt} = -c(K_{conj}A_{conj} + K_{cornea}A_{cornea}) - cq_{drainage} \tag{14}$$

where the constants K_{cornea} and K_{conj} are the permeabilities of cornea and conjunctiva to timolol, respectively, and A_{cornea} and A_{conj} are the areas of cornea and conjunctiva, respectively. By combining the above mass balance with Eq. 9, bioavailability (β), i.e., the fraction of the instilled drug that permeates into cornea can be calculated as

$$\beta = \frac{K_{cornea}A_{cornea}}{V_0} \int_0^\infty \exp\left[-\int_0^\tau \frac{(K_{conj}A_{conj} + K_{cornea}A_{cornea}) + (q_{production} - q_{evaporation})}{V(t)}dt\right]d\tau \tag{15}$$

where V_0 is the sum of the tear volume and the volume of the instilled fluid immediately after the instillation. In Eq. 15 the transient total ocular fluid volume (V(t)) can be calculated using Eq. 1, 7, 8 and 9. It is assumed that all the drug that is absorbed into the conjunctiva or drained in the canaliculi goes to the systemic circulation. The derivation and the details of Eq. 15 are given elsewhere.[11]

Non-Newtonian Fluid

The residence time of non-Newtonian fluids can also be calculated by following the same approach as outlined above for Newtonian fluid except that Eq. 1 needs to be modified. Unlike Newtonian fluids, which have a linear relationship between the shear stress and the shear rate, non-Newtonian fluids have more complicated relation between the shear stress and the shear rate. One of the most common non-Newtonian fluids for dry eye treatment is sodium hyaluronate solution. Rheological measurements have shown that at the concentration used for ocular instillation, it can be approximated as power-law (shear-thinning) fluid, i.e., the relation between the shear stress τ and the shear rate γ can be written as

$$\tau = K\gamma^n \tag{16}$$

where K and n are rheological parameters that can be obtained by fitting the viscosity vs. shear rate data. Here, the constant K is assumed to be related linearly to the instantaneous polymer concentration in the tear film by using a linear relationship as given by Eq. 11. Using Eq. 16 the equation for the deformation of canaliculi as a result of blinking can be derived as

$$\frac{\partial R}{\partial t} = a\left(-\frac{\partial R}{\partial x}\right)^{\left(\frac{1}{n}-1\right)}\frac{\partial^2 R}{\partial x^2} \tag{17}$$

where a is a constant that is defined as

$$a \equiv \frac{1}{2}\left(\frac{bE}{2KR_0^2}\right)^{\frac{1}{n}}\frac{R_0^{\frac{2n+1}{n}}}{3n+1} \tag{18}$$

The derivation of Eq. 17 is described in the appendix (available online at www.optvissci.com.). It is noted that Newtonian fluid is a special case of a power-law fluid with n = 1 and Eq. 17 correctly reduces to Eq. 1 for this case. By solving Eq. 17, 7, 8, 9, and 12 simultaneously using finite difference method, the transient quantity of the solutes in the ocular fluids can be obtained as a function of time. Similar to the Newtonian fluid case, the bioavailability can be also calculated using Eq. 15.

Model Parameters

Most of the parameters needed in the model are available in literature and these are listed in Table 1.[6,7,15–23]

The rheological parameters K and n were obtained by fitting the viscosity vs. shear rate data, and these are listed in Table 2 for a variety of fluids that are commonly used in ocular studies. The non-linear least square fitting was applied to the original data points shown on the respective plots in the references, and was conducted using the curvefitting toolbox in Matlab and the nonlinear equation given in the caption of Table 2. In Table 2, "$R_{fitting}$" represents the correlation coefficient.

TABLE 1.
Physiological parameters used for the model

Parameter	Value	Source (reference #)
L	1.2×10^{-2} m	15
t_c	6 s	7
t_b	0.04 s	6
R_0	2.5×10^{-4} m	16
σ	43.0×10^{-3} N/m	17
p_0	400 Pa	18
p_{sac}	0 (atmospheric)	7
μ_{tear}	1.5×10^{-3} Pa · s	19
L_{lid}	57×10^{-3} m	20
K_{cornea}	1.5×10^{-7} m/s	21
K_{conj}	5.2×10^{-7} m/s	21
A_{cornea}	1.04×10^{-4} m^2	22
A_{conj}	17.65×10^{-4} m^2	22

TABLE 2.
Rheological parameters of typical fluids used in ocular studies. The parameters were obtained by fitting the rheological data in literature to the constitutive equation for a power law fluid, i.e., $\mu = K\gamma^{n-1}$

Solution	K (mPa · s^n)	n − 1	$R_{fitting}^2$
0.2% NaHA[2]	323.3	−0.329	0.973
0.3% NaHA[2]	884.2	−0.3913	0.9788
CMC (low MW)[10]	194.8	−0.09201	0.9285
CMC (high MW)[10]	194.4	−0.2943	0.933
Human tears[19]	5.578	−0.264	0.9963

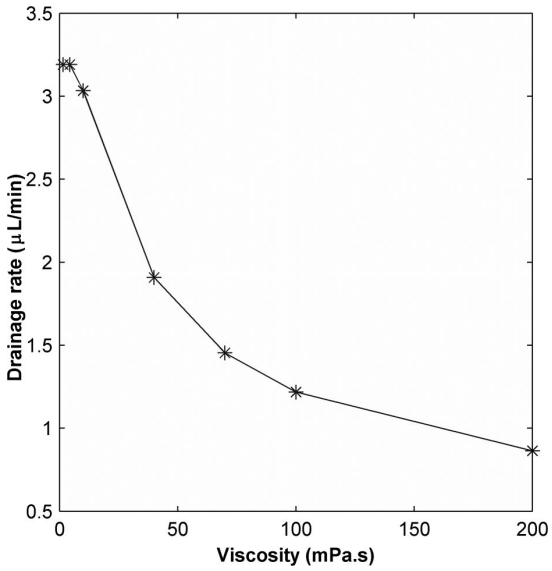

FIGURE 1.
The effect of viscosity on the drainage rate through canaliculi for Newtonian fluids.

RESULTS

Effect of Viscosity on Tear Drainage

The effect of viscosity on tear drainage rate $q_{drainage}$ immediately after instilling 25 μl of fluids is shown in Fig. 1 for a Newtonian fluid. The drainage rates for shear-thinning fluids depend on K and n, and the results for shear thinning fluids are shown in Fig. 2. The drainage rates depend on the tear volume, and the results reported in Figs. 1, 2 correspond to a tear volume immediately after instillation, which is taken to be 32 μl.

Effect of Viscosity on Residence Time of Instilled Fluids

The effect of viscosity on residence time in eyes is typically measured by instilling the high viscosity fluid laden with tracers such as radioactive or fluorescent compounds, and then following the total amount of tracer present in the tear volume by measuring the radioactivity or fluorescence. The transients of the total signal from the tracer I(t), which is a measure of the total solute quantity are plotted in Fig. 3 for Newtonian fluids for a range of viscosities.

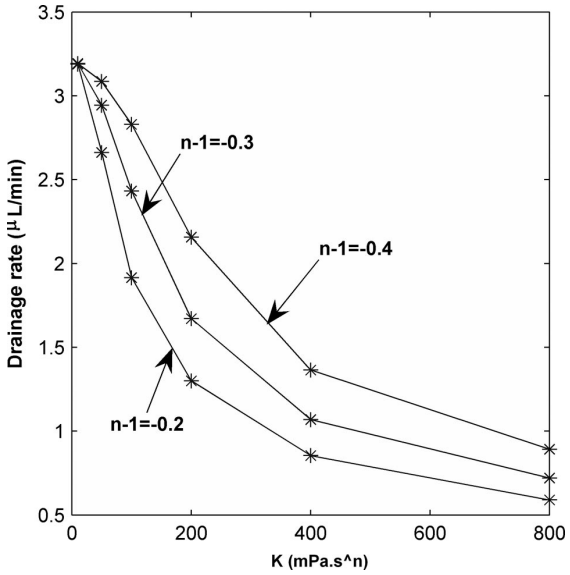

FIGURE 2.
The effect of rheological parameters (K and n) on the drainage rate through canaliculi for power-law shear thinning fluids.

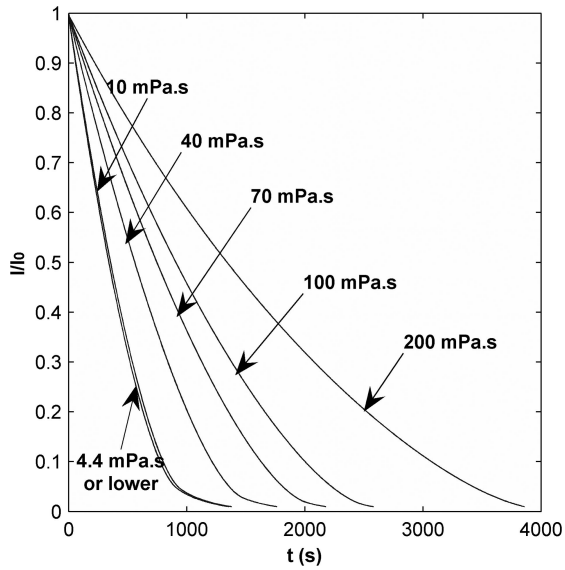

FIGURE 3.
The transients of solute quantity (I) after the instillation of Newtonian fluids with different viscosities.

Similar data is compared with experiments in Fig. 4, 5. It is noted that for fluids with viscosities lower than 4.4 mPa · s, the transients of I(t) overlap. In these and all other calculations reported below, the volume of all the instilled drops is set to be 25 μl.

For non-Newtonian fluids, the transients of I are calculated for sodium hyaluronate acid of 0.2 and 0.3% w/v concentrations, which are commonly used for ocular instillation. The initial values of K and n for these and all other shear-thinning fluids that are discussed in this paper are listed in Table 2. The solute quantity transients I(t) are plotted in Fig. 6a to c for these two fluids in solid

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