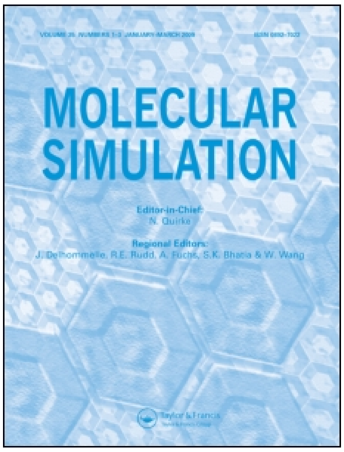

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Rupture Analysis of the Corneal Mucus Layer of the Tear Film

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We investigate the rupture mechanism of a precorneal thin mucus coating sandwiched between the aqueous tear film and the corneal epithelial surface with a monolayer of surfactant overlying the aqueous layer. The Ostwald constitutive relation is employed to model mucus rheology and a linear equation of state describing the relationship between surface tension and surfactant concentration is adopted. Five coupled equations governing the transport of surfactant, mucus and total liquid layer thicknesses, based on lubrication theory, have been derived. The resulting equations are solved numerically in order to explore the effect of system parameters such as mucus rheology, aqueous–mucus thickness ratio, aqueous–mucus interfacial tension and Marangoni number on tear film evolution in the presence of van der Waals forces, which could induce film rupture.

Keywords: Non-Newtonian fluid; Thin film; Van der Waals; Interfaces

INTRODUCTION

The spreading of tear fluids on the occular surface of normal eyes forms a continuously smooth structured cover, the so-called tear film, over the cornea as a consequence of blinking. The integrity of this film is maintained via involuntary periodic blinkings, with a normal interval of 5–10 s. If the eye is held open either voluntarily or by force for 15–40 s, however, the tear film may rupture. Dry eye patients suffer due to a tear film instability, which breaks up much earlier than normally [1]. The tear film is thought to be composed of three main layers, each having a specific function [2]. A mucus layer covers the superficial corneal epithelial cells, which provides a hydrophilic base for even spreading of the aqueous tear film [3]; an aqueous layer overlies the mucus layer. The outermost layer of the tear film corresponds to a lipid–mucin bilayer, containing surfactant phospholipids, which reduce surface tension. Deficiencies in any of the tear film layers as well as defective spreading of the tear film can disturb the tear film and cause dry eye disease [4].

The breakup of the tear film was first explained by assuming that the lipids at the tear film surface transport rapidly to the aqueous–mucus interface due to the Marangoni effect, disrupting the mucin layer function of enhancing the wetting of corneal surface, consequently creating a highly hydrophobic surface [3]. The resulting distribution of the lipids over the aqueous–mucus interface increases aqueous–mucus interfacial tensions as the lipids are much less surface active than the mucus covering the epithelium, which contributes to the stability of tear film [5]. Furthermore, the Marangoni flow induces a convective diffusion, which prevents the molecular diffusion of lipids to the corneal epithelium [6]. Sharma and Ruchenstein [5] argued, however, that the mucus layer ruptures due to long range intermolecular interactions, which exposes the aqueous layer to the hydrophobic cornea, resulting in spontaneous tear film rupture; the predicted rupture times based on this theory are consistent with the range of observed breakup times (BUT). This linear instability criterion was later extended to a bilayer film by incorporating the influence of soluble lipids in the tear film and interfacial tension at

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the aqueous–mucus interface [7]. Recent theoretical and experimental work has further confirmed these findings [8–10].

Although tear films are thought to consist of a shear-thinning non-Newtonian fluid [11], all the aforementioned theoretical investigations have considered Newtonian fluids. In this paper, we develop more realistic models of tear film rupture by incorporating the rheological properties of mucus into the governing equations; this work represents a natural extension of previous work [5,7]. Using these models we determine the effect of relevant system parameters such as the mucus consistency and power law index, ratio of total film thickness to mucus thickness, interfacial tension and Marangoni number on tear film dynamics.

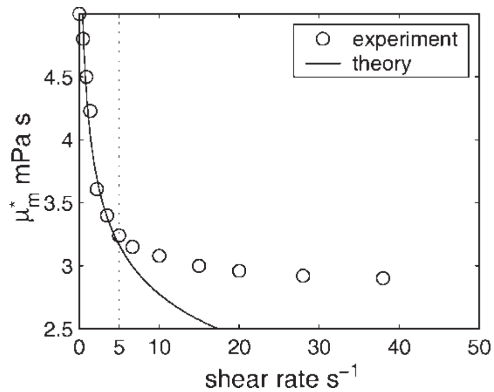

FIGURE 1 Variation of the viscosity with the shear rate: Ostwald model ($\mu^* = \mu_0^* \dot{\gamma}^{*(1-n)}$ in which $n = 0.81$ and $\mu_0^* = 4.3\,\mathrm{mPa\,s}^{n-2}$) (solid line); experiment [11] (circle). Good agreement is observed between experiment and theory based on the Ostwald equation for $\dot{\gamma} < 5\,\mathrm{s}^{-1}$ (dotted line).

GOVERNING EQUATIONS

We consider a tear film bilayer of initially uniform thickness composed of incompressible fluids lying on a flat, impermeable plane, the epithelium surface, which is located at $z^* = 0$; the asterisk denotes dimensional quantities. The deviation of the tear film from the vertical plane is small; hence the curvature of the corneal epithelium is neglected. The upper layer is an aqueous film of constant viscosity μ_a^*, whereas the lower mucus layer has a shear rate dependent viscosity μ_m^*; an insoluble surfactant monolayer overlies the aqueous layer. Only attractive intermolecular forces [12], described by the potential ϕ^* and incorporated as a body force within the momentum conservation equations, are considered, while the shorter range repulsive forces are neglected here:

$$\phi_m^* = \frac{A_1^*}{6\pi h_m^{*c}} + \frac{A_2^*}{6\pi h_a^{*c}},$$
$$\phi_a^* = \frac{A_3^*}{6\pi h_a^{*c}} + \frac{A_4^*}{6\pi (h_a^* - h_m^*)^c}. \tag{1}$$

Here, $c = 3, 4$ for the unretarded and retarded cases, respectively, while A_i^* ($i = 1, 2, 3, 4$) are the respective unretarded and retarded Hamaker constants, which correspond to $c = 3$ and 4, respectively. In order to model mucus rheology, data of human mucus, obtained by Tiffany [13] and Pandit *et al.* [11], were fitted using the Ostwald equation, which is given by:

$$\mu_m^*(\dot{\gamma}_{ij}^{*m}) = \mu_0^* \left[(\dot{\gamma}_{ij}^{*m})^2\right]^{\frac{(n-1)}{2}}, \tag{2}$$

where n and μ_0^* are the power law exponent and consistency index ($\mathrm{kg\,m^{-1}s^{n-2}}$), respectively. As shown in Fig. 1, Eq. (2) is fairly representative of human mucus for $\dot{\gamma} < 5\,\mathrm{s}^{-1}$, which is the range of interest. In all the cases examined, shear rates, $\dot{\gamma} = \mathscr{V}^*/\mathscr{H}^*$ in which $\mathscr{V}^*$ and $\mathscr{H}^*$ are the characteristic velocity and thickness, respectively, during film rupture are less than $1\,\mathrm{s}^{-1}$. It is then reasonable to adopt Eq. (2) as a model of mucus rheology.

Flow is described by the velocity field $\{w_k^*(x^*, z^*, t^*), u_k^*(x^*, z^*, t^*)\}$, where x^* and z^* denote the horizontal and vertical coordinates, respectively, t^* is the time, u_k^* and w_k^* represent the horizontal and vertical components of the flow velocity, respectively. The origin is coincident with that of the centre of eye, while the total and mucus film thickness are denoted by h_a^* and h_m^*, respectively; gravitational forces are neglected. The governing equations are rendered dimensionless using the following scalings:

$$x = \frac{x^*}{\mathscr{L}^*}, \quad z = \frac{z^*}{\mathscr{H}^*}, \quad h_k = \frac{h_k^*}{\mathscr{H}^*}, \quad u_k = \frac{u_k^*}{\mathscr{V}^*},$$
$$w_k = \frac{\mathscr{L}^* w_k^*}{\mathscr{H}^* \mathscr{V}^*}, \quad t = \frac{\mathscr{V}^* t^*}{\mathscr{L}^*}, \quad p_k = \frac{p_k^*}{\mathscr{P}^*}, \tag{3}$$

$$\Gamma = \frac{\Gamma^*}{\Gamma^{\max *}}, \quad \sigma_k = \frac{\sigma_k^* - \sigma_k^{\min *}}{\mathscr{S}^*}, \quad \tau_{ij}^k = \frac{\mathscr{H}^* \tau_{ij}^{*k}}{\mu_a^* \mathscr{V}^*},$$
$$A_i = \frac{A_i^*}{\mathscr{A}^* \mathscr{H}^{*c-3}}, \quad \mu = \frac{\mathscr{V}^{*n-1} \mu_0^*}{\mu_a^* \mathscr{H}^{*n-1}}, \quad \rho_k = \frac{\rho_k^*}{\rho_a^*}, \tag{4}$$

where $\mathscr{L}^*$ is the characteristic length; p^* is the pressure; $\mathscr{P}^*$ is the characteristic pressure; ρ^* is the fluid density; Γ^* is the surfactant concentration; σ^* is the interfacial tension; $\Gamma^{\max *}$ and $\sigma_k^{\min *}$ are the surfactant concentration and interfacial tension of the most contaminated part, respectively; τ_{ij}^* ($i, j = x^*, z^*$) is the stress tensor; $\mathscr{S}^*$ is the spreading pressure; $\mathscr{A}^*$ is a typical Hamaker constant; $\phi_m = A_1 h_m^{-c} + A_2 h_a^{-c}$; $\phi_a = A_3 h_a^{-c} + A_4 (h_a - h_m)^{-c}$; the index $k = a$ and m in which a and m are the lipid–aqueous layer and mucus layer, respectively.

We select the characteristic velocity and pressure scale as $\mathscr{P}^* = \mathscr{A}^*/(6\pi\mathscr{H}^{*3})$ and $\mathscr{V}^* = \mathscr{A}^*/(6\pi\mu_a^*\mathscr{H}^*\mathscr{L}^*)$ in order to balance pressure with van der Waals forces, and viscous retardation with the pressure and van der Waals forces, respectively [14].

Tear film dynamics are governed by the following dimensionless evolution equations [15]

$$h_{m,t} + \left(\int_0^{h_m} u_m \, dz\right)_{,x} = 0,$$
$$h_{a,t} + \left(\int_0^{h_m} u_m \, dz + \int_{h_m}^{h_a} u_a \, dz\right)_{,x} = 0, \tag{5}$$

$$\Gamma_{,t} + (u_a\Gamma)_{,x} = (1/Pe)\Gamma_{,xx}, \tag{6}$$

where u_m and u_a are given by

$$u_m = \frac{e_1}{a_m}\left[\left|a_m z - a_m h_m - a_a(h_a - h_m) - \mathscr{M}\Gamma_{,x}\right|^{\frac{1+n}{n}} - \left|-a_m h_m - a_a(h_a - h_m) - \mathscr{M}\Gamma_{,x}\right|^{\frac{1+n}{n}}\right], \tag{7}$$

$$u_a = \frac{e_1}{a_m}\left[\left|a_a h_m - a_a h_a - \mathscr{M}\Gamma_{,x}\right|^{\frac{1+n}{n}} - \left|-a_m h_m - a_a(h_a - h_m) - \mathscr{M}\Gamma_{,x}\right|^{\frac{1+n}{n}}\right] - \mathscr{M}\Gamma_{,x}(z - h_m) + \frac{1}{2}a_a(z - h_m)(z + h_m) - a_a(z - h_m)h_a, \tag{8}$$

in which $a_a = \phi_{a,x} - \mathscr{C}_a h_{a,xxx}$; $a_m = \phi_{m,x} - \mathscr{C}_a h_{a,xxx} - \mathscr{C}_m h_{a,xxx}$; $e_1 = n/(1+n)\mu^{(1/n)}$. Here, $Pe = \mathscr{L}^*\mathscr{V}^*/\mathscr{D}^*$ is the surface Peclet number, in which $\mathscr{D}^*$ is the Surface diffusivity; $\mathscr{M} = \mathscr{H}^*\mathscr{S}^*/\mu_a^*\mathscr{L}^*\mathscr{V}^* \equiv 6\pi\mathscr{H}^{*2}\mathscr{S}^*/\mathscr{A}^*$ is the Marangoni number; $\mathscr{C}_k\,(k = a, m)$ is a capillary parameter: $\mathscr{C}_k = \epsilon^3\mathrm{Ca}_k^{-1}$ where $\mathrm{Ca}_a = \mu_a^*\mathscr{V}^*/\sigma_a^{\min *}$ and $\mathrm{Ca}_m = \mu_a^*\mathscr{V}^*/\sigma_m^{\min *}$, while $\epsilon = \mathscr{H}^*/\mathscr{L}^*$. For a typical tear film, $\mu_a^* = 10^{-2}\,\mathrm{g\,cm^{-1}\,s^{-1}}$ ($\sim$water), $\mu_0^* = 10^{-2} - 10^{-1}\,\mathrm{g\,cm^{-1}s^{n-2}}$ [10,11,13], $n = 0.6$–1 [11,13], $h_a^*(x^*, t^* = 0) = 4$–$8\,\mu\mathrm{m}$ [16,17], $h_m^*(x^*, t^* = 0) = 20$–$50\,\mathrm{nm}$ [3,18], $\rho_a^* = 1\,\mathrm{g\,cm^{-3}}$ [6], $\rho_m^* = 1\,\mathrm{g\,cm^{-3}}$ ($\sim$Water), $\sigma_a^*(x^*, t^* = 0) = 42$–$46\,\mathrm{dyn\,cm^{-1}}$ [19], $\sigma_m^*(x^*, t^* = 0) = 10^{-3} - 5\,\mathrm{dyn\,cm^{-1}}$ [7], unretarded Hamaker constant $A^* = 10^{-21}$–10^{-20} J [5], retarded Hamaker constant $A^* = 10^{-28}\,\mathrm{J\,m}$ [5], $\mathscr{D}^* = 10^{-5}\,\mathrm{cm^2\,s^{-1}}$ [7], $\mathscr{A}^* = 10^{-20}\,\mathrm{J}$, $\mathscr{S}^* = 7.5\times10^{-5}\,\mathrm{dyn\,cm^{-1}}$ [20], $\mathscr{H}^* = 40\,\mathrm{nm}$, so that $\epsilon = 10^{-4}$, $Re = 10^{-7}$–10^{-9}, $\mathrm{Ca}_a = 10^{-10}$, $\mathrm{Ca}_m = 10^{-8}$, $\mathscr{M} = 10^{-3}$–10^{-2}, $Pe = 0.1$–10. The capillary effect for the evolution of mucus thickness cannot be uniformly neglected and has been retained in our model for its smoothing effect [15]. Note finally that a linear equation of state has been adopted to model the dependence of surface tension on surfactant concentration [15].

RESULTS AND DISCUSSION

Equations (5)–(8) are solved using the finite element method. Convergence was achieved upon mesh refinement with a typical computation utilizing 1000 grid points. The computations were halted at the instant immediately prior to rupture when the spatial derivative could no longer be determined accurately.

A monolayer of surfactant with an initial uniform distribution, $\Gamma(x, t = 0) = \Gamma_0$, placed on the free surface of a bilayer of liquid, evolves under the action of small periodic disturbances of wave length λ in the film thicknesses, which are given by $h_a(x, t = 0) = c_h + \bar{h}_m\cos((2\pi/\lambda)x)$ and $h_m(x, t = 0) = 1 + \bar{h}_m\cos((2\pi/\lambda)x)$ for $0 \le x \le \lambda$ in which $\bar{h}_m$ is the disturbance amplitude in the mucus layer, and c_h is the ratio of the initial film thickness to the initial mucus layer thickness, viz. $c_h = h_a^*(x^*, t^* = 0)/h_m^*(x^*, t^* = 0)$. The boundary conditions imposed on $x = 0$ and λ are $\Gamma_{,x} = 0$, $h_{a,x} = 0$ and $h_{m,x} = 0$. The following physical and geometric properties are used throughout this study except where quantities are stated: $\mathscr{H}^* = h_m^*(x^*, t^* = 0) = 40\,\mathrm{nm}$, $\mu_a^* = 1\,\mathrm{g\,cm^{-1}s^{-1}}$, $\sigma_a^{\min *} = 45\,\mathrm{dyn\,cm^{-1}}$, $\sigma_m^{\min *} = 1\,\mathrm{dyn\,cm^{-1}}$, $\Gamma_0 = 0.5$, $A_2 = A_3 = A_4 = 0.25$, $\mathrm{Pe} = 10$, $\mathscr{M} = 10^{-2}$, $\epsilon = 10^{-4}$, $\bar{h}_m = 10^{-2}$.

In the absence of modelling results on the influence of mucus rheology on tear film breakup, the present nonlinear results have been validated against the predictions of linear stability theory: agreement is achieved in terms of growth rates at early times, before nonlinearities become significant [15]. Having validated our numerical procedure, we now examine typical profiles of the tear film undergoing rupture. Figure 2 shows the evolution of the total height and mucus layer thickness as well as surfactant concentration, starting from an initially small amplitude disturbance to the air–aqueous interface and an initially uniform surfactant concentration. Van der Waals forces grow beneath the depression in h_a and h_m and drive motion of fluid and surfactant to neighbouring regions. These forces then become even larger in the thinned region, causing further rapid thinning and, eventually, rupture. The increase in concentration in the elevated regions in relation to the thinned region gives rise to a Marangoni flow, which retards the van der Waals-driven thinning. In all cases considered, however, this Marangoni-driven reverse flow succeeds in retarding rupture, but not in preventing it [14,15,21]. Note that in Fig. 3a we have plotted, h_m and $c_h^{-1}h_a$, rather than h_a, for clarity.

In order to examine the influence of van der Waals forces on tear film rupture, a wide range of Hamaker constants $A_1 = 0.3$–3 is chosen, which is within the relevant physical range [7]. Rupture time increases with decreasing A_1, as shown in Fig. 3a.

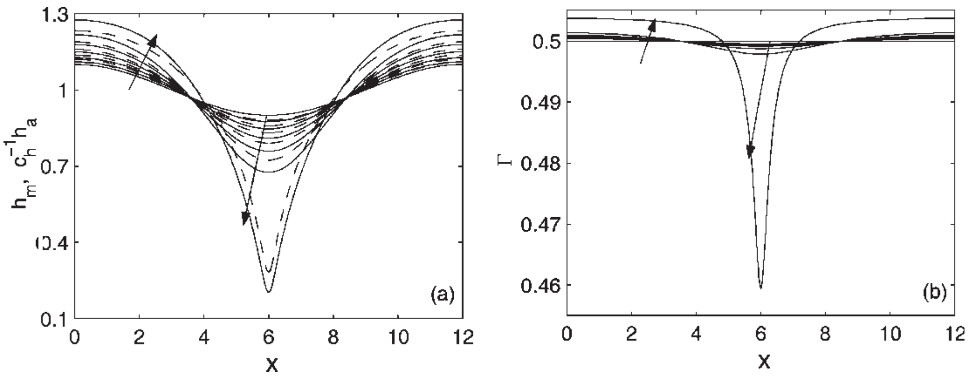

FIGURE 2 Evolution profile of the total liquid thickness and mucus layer thicknesses (h_m and $c_h^{-1}h_a$) as well as surfactant concentration (Γ) shown at equal time intervals over a period of 7.36 for $c_h = 200$, $A_1 = 1$, $n = 1$, $\mu = 1$. (a): h_m, (solid line) and $c_h^{-1}h_a$ (dashed line) and (b): Γ; the arrows show increasing time.

In fact, the rupture time for $n = 0.8$, $\mu = 4.11$ and $A_1 = 1–0.5$ is found to be in the physical range of 20–50 s for normal subjects [1]. Note that the minimum rupture time obtained here signifies the minimum time taken for the mucus layer thickness to reach a value of order (10^{-3}) in our computations, for perturbations of different wavelength and a fixed set of system parameters. More precise predictions of rupture time could be made provided more accurate measurements of the effective Hamaker constant for the epithelium–mucus–aqueous layer system are made.

The effect of aqueous–mucus interfacial tension ($\sigma_m^{\min *}$) on rupture time has also been examined in detail [15] by chosing a wide range of $\sigma_m^{\min *}$, $10^{-3} - 5\,\mathrm{dyn\,cm^{-1}}$. As shown in Fig. 3b, the minimum rupture time, t^*_{rup}, increases almost linearly with increasing interfacial tension, as does the difference between the predictions of linear and nonlinear theory. From the clinical viewpoint,

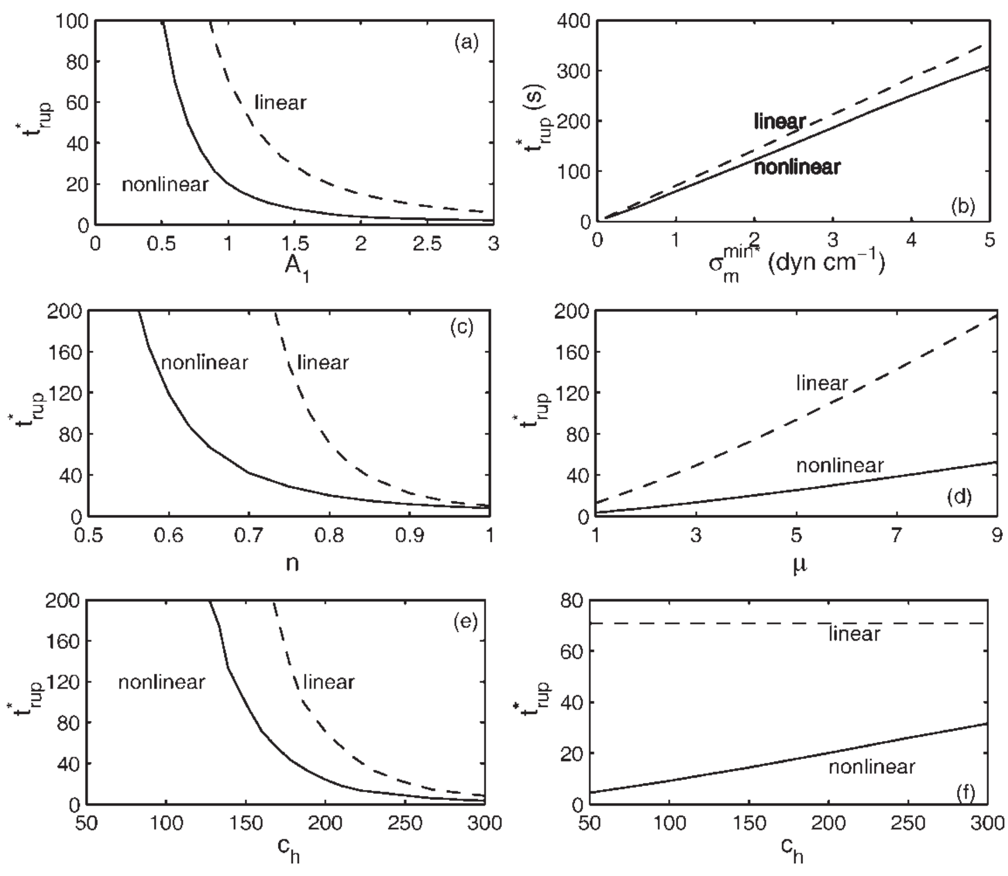

FIGURE 3 Variation of rupture time with Hamaker constant (A_1), interfacial tension ($\sigma_m^{\min *}$), power law exponent (n), viscosity ratio (μ) and the ratio of initial film thickness to initial mucus layer thickness (c_h) generated using the following parameter values: $A_1 = 1$, $n = 0.8$, $\mu = 4.11$ and $c_h = 200$ except we vary (a) A_1; (b) $\sigma_m^{\min *}$; (c) n; (d) μ; (e) c_h for fixed $h_a^*(x^*, t^* = 0) = 8\,\mu\mathrm{m}$; (f) c_h for fixed $h_m^*(x^*, t^* = 0) = 40\,\mathrm{nm}$. Nonlinear theory (solid line); linear theory (dashed line).

incorporation of a less surface active material, such as antisurfactant, which increases $\sigma_m^{\min *}$, in the eye would increase the rupture time; tear substitutes would then be even more effective.

Next we examine the effect of the power law exponent, n, which is dependent on the mucus content [13,22]. As shown in Fig. 3c, decreasing n significantly increases t^*_{rup}, which is a similar finding to that for a pseudoplastic airway liquid film within the lung [23]; the discrepancy between linear and nonlinear theory follows a similar trend. Models based on Newtonian rheology, therefore, provide an underestimate of the tear film rupture time. This is due to the small values of the shear rate observed during rupture (typically less than $1\,\text{s}^{-1}$) for which mucus viscosity increases with decreasing n for a fixed consistency; this exerts a stabilizing influence on the rupture process. Note that the influence of n on the rupture time for such a pseudoplastic fluid obtained using our model is opposite to those obtained using other models [24]. This is related to the fact that the magnitude of the shear rate in those cases is larger than $1\,\text{s}^{-1}$ whereas shear rate in our case is less than $1\,\text{s}^{-1}$. For marginally dry eyes, the value of n seems to be smaller than that for normal eyes [13]. According to the results shown in Fig. 3c, the tear film therefore ruptures slower for the marginally dry eye with all other parameters remaining fixed. The mucus deficiency for such dry eyes, however, would, in fact, decrease the thickness of the mucus coating of the corneal epithelium [7], possibly offsetting the effect of n on rupture time. Our results also suggest that t^*_{rup} increases quasi-linearly with increasing viscosity ratio (μ), as shown in Fig. 3d, as does the difference in prediction between linear and nonlinear theory.

The change in c_h, the ratio of the total initial film thickness to the initial mucus layer thickness, is achieved by varying the thickness of either the aqueous or the mucus layer. We examine the effect of the mucus layer thickness on the rupture time for a fixed initial total film thickness first. Figure 3e shows the variation of t^*_{rup} with c_h for an initial total film thickness fixed at 8 μm. In this case, an increase in c_h can be interpreted as being due to a decrease in the thickness of the mucus layer and *vice versa*. It can be seen that t^*_{rup} decreases significantly when c_h increases, which in this case corresponds to a decrease in the mucus layer thickness. Figure 3f shows the dependence of t^*_{rup} on c_h with the initial mucus layer thickness held constant at 40 nm; c_h is varied by varying the initial total film thickness. Here, t^*_{rup} increases quasi-linearly with c_h, in contrast to the results shown in Fig. 3e. Note also that the difference in prediction between linear and nonlinear theory in terms of t^*_{rup} decreases with increasing c_h for a fixed initial mucus layer thickness; this is qualitatively similar to the results shown in Fig. 3e.

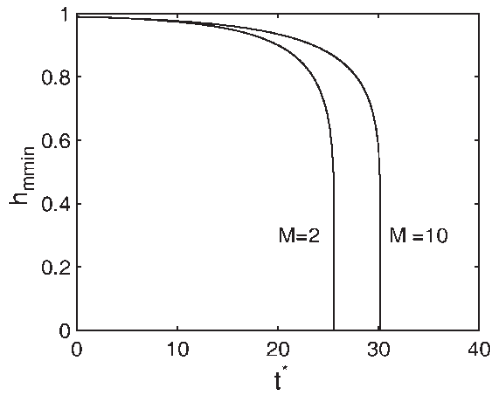

FIGURE 4 The effect of Marangoni number, $\mathscr{M}$, for $\mu = 4.15$ $A_1 = 1$, $n = 0.8$, $c_h = 200$.

Clinical implications of such variations of c_h represent the mucus and/or aqueous deficiency. Deficiency of the aqueous layer is the most common cause of dry eye and is usually caused by decreased tear secretion from the lacrimal glands [4], and is also associated with many factors, such as goblet cell population. Although increased evaporation of tears may also be involved, evaporative effects on tear film rupture is small and have been neglected in this study. Our results suggest that rupture occurs faster as the deficiency of the aqueous layer becomes more pronounced.

We also study the effect of having an insoluble surfactant at the air–aqueous interface on film rupture. For $\mathscr{M}$ in the physical range $\mathscr{M} = 10^{-3} - 10^{-2}$ [15], Marangoni effects appear to be so weak as not to influence appreciably the rupture process. Recent evidence, however, has shown that strong Marangoni effects may in fact be present [25]. We explore this possibility by considering a wider range of $\mathscr{M}$. Inspection of Fig. 4 reveals that the Marangoni effect retards the rapid thinning driven by van der Waals forces. This stabilizing Marangoni effect ultimately leads to a delay in film rupture but not to its prevention.

CONCLUDING REMARKS

In this paper, we have investigated the rupture of a precorneal thin mucus coating lying between the corneal epithelial surface and the aqueous tear film over which surfactant spreads. The Ostwald constitutive relation is employed to model mucus rheology and a linear equation of state describing the relationship between surface tension and surfactant concentration is used. Lubrication theory is used to derive coupled evolution equations for the surfactant concentration, mucus and aqueous layer thicknesses. Numerical solutions of these equations are obtained for a wide range of Hamaker constants, rheological properties of mucus (power law exponent and viscosity ratio), ratio of total initial film thickness to initial mucus layer thickness, aqueous–mucus interfacial tension and Marangoni number [15].

Our results show the van der Waals-driven rupture is retarded by decreasing the power law exponent, or by increasing the mucus viscosity and Marangoni number. We have also shown that as the initial mucus layer (20–50 nm) is much thinner than the total initial tear film (4–8 μm), van der Waals forces act more significantly to destabilize this layer, despite its higher viscosity and smaller power law exponent. The time of rupture obtained using our model is in good agreement with the clinically observed breakup time of about 15–50 s for healthy eyes, and of about 1–7 s for dry eyes [1].

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