The Role of Lipid Abnormalities, Aqueous and Mucus Deficiencies in the Tear Film Breakup, and Implications for Tear Substitutes and Contact Lens Tolerance

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We had earlier proposed a "two-step, double-film" mechanism of tear film rupture, which traces the instability of the tear film in the van der Waals interaction mediated rupture of the thin mucus coating of the corneal epithelium. A transport model is now formulated for investigating the instability of the mucus layer in the presence of naturally occurring solutes of the tear film. It is shown that the normal lipids of the tear film play a dual role in stabilizing the mucus layer: (1) they augment the mucous-aqueous interfacial tension and (2) they induce an interfacial tension driven Marangoni convection. Both of these oppose the growing interfacial perturbations and consequently, the thinning of the mucus layer which is caused by the van der Waals interactions. An increased surface activity of lipids, due to numerous pathological conditions of the eyes, is shown to affect the tear film breakup time (BUT) adversely. The observed deleterious effects of highly surface active ingredients of tear substitutes, clinical stains, and anesthetics on BUT are also explained within the framework of the proposed mechanism. The aqueous tear deficiency which is reflected in the reduced thickness of the tear film, is shown to facilitate a rapid redistribution of solutes and thus undermines the stabilizing effect of the Marangoni convection. A marginally healthy eye may thus develop dry eye syndromes because of the aqueous tear deficiency. The proposed mechanism is in agreement with clinical observations of the factors causing the dry eyes and numerous other experimental and clinical findings related to the phenomenon of tear film rupture. The role of tear substitutes in prolonging the time of rupture as well as the implications of the present mechanism for the formulation of tear substitutes are delineated. The factors affecting the contact lens tolerance due to the altered physiology of the tear film are discussed. A particular emphasis is, however, placed on the possible adhesion of the contact lens to the cornea. Finally, it is emphasized that the clinical measurements of BUT are an overall outward manifestation of several factors discussed above and their synergisms thereof. © 1986 Academic Press, Inc.

INTRODUCTION

A rational understanding of the factors affecting the rupture of the tear film, which covers the conjunctival and corneal surfaces, is important in various pathological conditions associated with a dry eye, their diagnosis and treatment. A widespread use of contact lenses has catalyzed research on the contact lens-tear film interactions, inasmuch as the instability and premature rupture of the tear film manifests itself in poor contact lens tolerance. The formulation of wetting and cushioning solutions, which are used to coat the surface of the contact lens before its insertion into eye, is another area which may benefit from a fundamental understanding of the rupture of the tear film.

To this day, one of the single most important treatment of a dry eye is the use of tear substitutes. The tear substitutes are aqueous based formulations which, when periodically instilled in a pathological eye, increase the time of the tear film rupture and consequently, alleviate discomfort and epithelial damage. It is hoped that a basic understanding of the tear film breakup and of the various factors affecting it, would also result in delineating the role

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of the tear substitutes and guidelines for the selection of their ingredients.

A normal tear film completely covers the corneal and conjunctival surfaces and keeps them in the proper conditions of lubrication and hydration. The structural continuity of this tear film is maintained by involuntary periodic blinking, with a typical interblink period ranging from 5 to 10 s (1). It is, however, observed that if either the eyelids are held open for a longer time period or if the eye is pathological, the tear film breaks (usually first over the corneal surface), resulting in the appearance of increasingly dewetting areas on the epithelial surface. The time elapsed between a blink and the first hole to appear is defined as the breakup time (BUT) and is found to be in the range of 15–45 s for a normal adult eye (2a). This estimate of BUT is, however, based on a conventional technique that requires the instillation of fluorescein in the tear film. Some recent in vivo tests of tear film stability have employed a noninvasive technique, the Toposcope, and have concluded that the instillation of fluorescein reduces the actual BUT by as much as a factor of 30 (2b). A tear film breakup time of less than 10 s (more precisely, a BUT less than the interblink period) is considered abnormal and may result in epithelial tissue damage and corneal ulceration (1). The adhesion of contact lens to cornea (3, 4) and the rapid buildup of deposits on the lens surface (5) have also been observed to be related to a premature rupture of the tear film. It is in view of these considerations that the clinical measurements of BUT, although statistical (6), serve as a useful yardstick for differentiating a normal eye from a pathological one. The tear film is, in reality, composed of at least three distinct layers, which are: (a) a thin (200–400 Å) (7a) mucus coating of the epithelial surface, (b) an aqueous layer which rests on the mucus-coated epithelium and which is about 4–10 μm thick, and (c) a 1000-Å-thick lipid layer that makes the tear-air interface. For a more elaborate discussion of the physiology of the eye, the structure of the precorneal tear film and other related issues, the reader is referred to reviews (1, 7a).

The structure of the tear film and various plausible physicochemical interactions occurring therein form a complex and delicately balanced system. It is therefore not surprising that a systematic investigation of certain aspects of the hydrodynamics of the tear film is of very recent origin. Based on a linear stability analysis, Lin and Brenner (8) showed that the temperature or mucin concentration gradient driven Marangoni convection in the aqueous tears appears unlikely under the normal circumstances. They also proposed the possibility of the rupture of micron-sized aqueous tear film due to retarded van der Waals dispersion interactions (9). An evaluation of the time of rupture based on their mechanism, however, showed that this rupture would take at least tens of days (10).

In our earlier papers (10, 11), we proposed a “two-step, double film” mechanism of the tear film rupture. Briefly, the mechanism consisted of the following two events in succession:

Step 1: the rupture of the mucus layer. Immediately after blinking, the shear created by rapid lid motion restores the structural integrity of a thin (~200- to 400-Å-thick) mucus

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2 Contrary to the consensus so far regarding to the thickness of the mucus layer (7a), a recent study conducted on the exercised guinea pig cornea has concluded that the maximum thickness of the mucus layer covering the corneal epithelium is about 0.4–0.8 μm (7b). The corneal mucus layer thickness, however, was not observed to be uniform in this study because of the presence of epithelial protrusions, the so-called microvilli. These microvilli have a characteristic dimension of about 0.2–0.5 μm over the corneal epithelium. The thickness of the mucus layer thus typically varies from about 0.05 to 0.2 μm over the tip of the microvilli to the maximum thickness cited above. Although much of the computations illustrated in the paper are carried out for a mucus layer of thickness 400 Å, we show in Appendix B that the proposed mechanism of the tear film rupture is consistent with the thickness reported in Ref. (7b) for the feasible range of physicochemical parameters. Also, it is to be noted that various conclusions drawn from calculations based on the mucus layer thickness of 400 Å remain valid when instead a different set of feasible parameters is used for computations.
layer on the corneal epithelium. The overlying aqueous tear film completely wets this mucus-coated epithelium because of a low interfacial tension at the mucous–aqueous interface and because of the surface tension depression at the tear–air interface due to surface active mucin and lipids (12). The underlying thin mucus layer, however, begins to thin because of the van der Waals interactions and eventually, ruptures in a time period consistent with the observed range of breakup time (~15–100 s). The linear stability analysis showed that the time of rupture is directly proportional to the mucous–aqueous interfacial tension and is proportional to the fifth power of the mucus layer thickness.

Step 2: wetting instability. The rupture of the mucus layer exposes the corneal epithelium to the aqueous tears at various places. There is ample experimental and clinical evidence which suggests that the mucus free corneal epithelium is a low energy surface and is nonwettable by aqueous tears (12–14). This wetting to nonwetting transition of the support of the aqueous layer is thus responsible for effectuating the rupture of the overlying aqueous film. Although the equilibrium considerations related to the stability or instability of a liquid layer on a solid support are known for a long time (15), the dynamics of this rupture is not well understood. However, clinical observations suggest that in the absence of mucus-secreting goblet cells, the tear film ruptures in about 3–5 s following a blink (16). This time, which may be referred to as the “dewetting time,” is short compared to the time taken for the rupture of the mucus layer in a normal eye and it may be assumed to be constant, pending the development of an appropriate theory. In certain pathological conditions, most notably, in the event of an altered morphology of the epithelium (epitheliopathies such as dellen, erosion, and bullae), the tear film may break immediately following a blink (17). This is referred to as a permanent discontinuity, wetting time zero, or alternately, a permanent dry spot. In such cases and perhaps also in the case of an absolute deficiency of the aqueous tears, when a continuous aqueous film does not form following a blink, the dewetting time is close to zero.

This mechanism is shown to be in accord with several clinical and experimental observations related to the phenomenon of tear film rupture (10, 11). It clarified as to why a decreased amount of mucus production leads to a pathologically short BUT.

It is well known that apart from the mucus deficiency, the lipid abnormalities and the aqueous tear deficiency also cause a rapid rupture of the tear film and the dry eye syndromes (see, for instance, Ref. (7a)). One of the purposes of this work is to elucidate the role of normal lipids in the stability of the thin mucus layer and consequently, the effect of various types of lipid abnormalities on BUT. The effect of the aqueous tear deficiency and the action of the tear substitutes is also considered within this unified framework. For this purpose, we first discuss (albeit briefly) some of the relevant clinical observations which we wish to explain and then examine the instability of the mucus layer in the presence of lipids and aqueous tears. An estimate for the time of rupture is obtained and the parametric dependence of BUT on various factors involved is discussed. We also explain numerous clinical observations within this framework and discuss various implications of this analysis for the diagnosis and treatment of dry eyes and for the tolerance of contact lenses.

DEFICIENCIES OF A PATHOLOGICAL EYE

Numerous clinical observations accumulated so far indicate the following eye deficiencies to be primarily responsible for a rapid tear film breakup and various dry eye syndromes. The classification of dysfunctions of a dry eye as mucus deficiency, aqueous tear deficiency and lipid abnormalities follows that of Holly and Lemp (7a).

A. Mucus Deficiency

The corneal and conjunctival surfaces are coated by a thin film of mucus, which is about
LIPID ABNORMALITIES

200 to 400 Å thick in a normal eye (7a). The maximum thickness is reported to be an order of magnitude higher recently (7b). About 2.2 μl mucus per day is secreted by the goblet cells (18), of which about 1.5 million are distributed over the conjunctival epithelial surface (1). An even distribution of the mucus on the corneal surface is most probably facilitated by the shear created during the lid motion. A small amount of mucus is removed from the eye during each blink. Several conditions such as hypovitaminosis A (vitamin A deficiency), ocular pemphigoid, Stevens–Johnson syndrome, trachoma, and chemical burns affect the goblet cell density adversely and consequently reduce the epithelial mucus production (19–21). A reduced goblet cell count has been correlated with a short BUT (21) and corneal desiccation is sometimes observed in such instances, despite the presence of the normal amount of aqueous tears (16).

B. Aqueous Tear Deficiency

The aqueous tear film sandwiched between the mucus-coated epithelium and the superficial lipid layer is about 7–10 μm thick immediately after blinking, in a normal eye (1, 7a). The thickness then decreases in an almost linear manner with time due to the evaporation, drainage, and sometimes, the osmotic transfer across the cornea. Normal tear film is observed to break rather suddenly when its thickness is reduced to about 4 μm within the breakup time (6). The aqueous tears contain dissolved proteins, glycoproteins, carbohydrates, inorganic salts, lipids, and bactericidal agents (lysozyme, etc.) (1, 7a, 22). Some of the glycoprotein fractions (mucin) are highly surface active for the aqueous-air interface. A common cause of decreased BUT is identified to be an absolute or partial deficiency of aqueous tears (1, 7a) as determined from Schirmer (1, 7a) or fluorescein dilution (23) tests.

C. Lipid Abnormalities

The outermost layer of the tear film (located at the tear–air interface) is made up of low polarity waxy and cholesteryl esters (24). This superficial lipid layer is about 1000 Å thick in a normal eye (7a). The amount of high polarity lipids like triglycerides, free fatty acids and phospholipids is negligible in a normal eye (25). The following two distinct types of lipid abnormalities are identified to affect the BUT adversely:

1. A complete absence of the lipid layer may occur if either the lipid-secreting meibomian gland openings are absent or these glands are destroyed. The occurrence of this condition is, however, very rare (7a).

2. An alteration in the chemical composition and the consequent high surface activity of the eye lipids, such as that seen in the case of chronic blepharitis and facial skin infections like acne rosacea, leads to a marked decrease in BUT (26, 27). A significant amount of polar lipids, viz., free fatty acids and triglycerides, are present in such instances.

In addition to the above-mentioned pathological conditions of the eye, the instillation of many low molecular weight surface active agents (artificial tear preservatives and anesthetic agents) also reduces BUT (28, 29). Even the past history of blinking and the quality of blink immediately preceding the BUT measurement also results in some variability in the measurement of BUT (28), as do the extreme environmental conditions. Thus it is not an isolated measurement of BUT, but the robust mean of a statistical sample that appears to be more relevant for the diagnosis of a pathological eye (6).

We now turn towards a suitable model of the tear film and the analysis of its stability characteristics.

THEORY AND ANALYSIS

I. A Tear Film Model

A normal tear film consists of a mucus-coated microvillus structure of the epithelium, an overlying aqueous film, and a superficial lipid layer making the tear–air interface. The characteristic dimensions of epithelial protru-
sions, the so called microvilli and microplicae, are about 0.5 μm over the corneal epithelium. If the thickness of the mucus layer is an order of magnitude smaller than these characteristic dimensions (as is believed to be the case, except for one study (7b)), the support of the mucus layer may essentially be viewed as flat. This model of the precorneal tear film is depicted in Fig. 1. If on the other hand, the maximum thickness of the mucus layer is of the same order as the dimension of microvilli (7b) the thickness of the mucus layer, as measured from the surface supporting it, is not uniform. It is minimum over the tip of a microvilli and is maximum over the valleys existing between two adjacent microvilli. Thus, although the incorporation of the morphology of the epithelium in this event is desirable, the essential physics is retained in a manageable description of a flat epithelium. Indeed, the mucus layer thickness may now be interpreted as a local quantity, which is minimum over the microvilli and thus the rupture first occurs at these spots.

The only significant aqueous tear flow occurring during the interblink period is confined to the tear meniscus that extends along the entire margin of the upper and lower eyelids, the so called “lacrimal river” (7a, 28). This flow, however, does not affect the stability of the mucus layer as showed earlier (10) and is thus neglected. The normal lipid layer located at the tear-air interface acts as a lipid reservoir and thus maintains a constant concentration of lipids at the lipid–aqueous interface. This interfacial concentration equals the solubility of normal lipids in the aqueous tears. As discussed earlier, the shear created during blinking restores the structural integrity of the mucus layer on the corneal epithelium and as the eyelids open, the mucous–aqueous interface is relatively homogeneous in appearance. This sheetlike mucus smeared over the epithelial surface (immediately after a blink) does not have a completely planar mucous–aqueous interface, because of the uneven shear and surface characteristics and also because the mucus layer is expected to be thicker at the mouths of the goblet cells. The initial nonhomogeneities begin to amplify because of the van der Waals forces acting on the molecules of the mucus layer. At the same time, the resulting flow (or velocities) redistributes the dissolved solutes such as lipids, ions, etc., which results in the generation of concentration gradients along the interface and consequently in an interfacial tension gradient along the mucus–aqueous interface. The interfacial tension gradient so generated induces a flow from the lower interfacial tension regions to regions with higher interfacial tension. This is the so called Marangoni flow which retards the thinning of the film when it opposes the flow produced by the perturbations. Finally an interplay of the factors delineated above determines the overall stability or instability of the mucous–aqueous interface and the possible rupture of the mucus layer. Thus we investigate the stability of the mucous–aqueous interface with the following initial state:

\[ C = C_0 \text{ and various velocities} = 0, \]

where \( C_0 \) is the solubility of lipids in the aqueous tears.

II. The Hydrodynamics of the Tear Film

The attractive, intermolecular London–van der Waals forces between a molecule of the film and the other molecules of the film and the molecules of the surrounding phases are important when the range of these forces, which is usually a few thousand Ångstroms,
is larger than the thickness of the film. The London–van der Waals forces decay rather rapidly as the thickness of the film increases. Their effect is thus quite pronounced for thin films, such as the mucus coating of the conjunctival and corneal epithelium (10).

The relevant equations describing the hydrodynamics are the Navier–Stokes equations, which incorporate the van der Waals forces acting on the unit volume of materials as body forces. This body force approach is rigorous and has been used extensively in investigating the stability of thin films (31–35). The dispersion forces are assumed to be nonretarded for the mucus layer because of its small thickness (<400 Å) and retarded for the aqueous layer. However, the Keesom interactions arising due to the interactions between permanent dipoles also appear important here, as is the case for water molecules. The retardation effect is accounted for while investigating the stability of a mucus layer thicker than 0.1 μm (Appendix B). The mucus layer is thin and thus the most effective or selectively amplified interfacial perturbations are those that have wavelength far exceeding the thickness of the film. It is because of this that one needs to consider Navier–Stokes equation in the “thin film” or the “lubrication-approximation” only. This approach has been used for a single film by Ruckenstein and Jain (33) and more formally by Williams and Davis (34).

Denoting by $h_0$ and $h'_0$ as the initial locations of mucous-aqueous and aqueous-lipid interfaces and selecting $h_0$ and $(v/h_0)$ as the basic units of lengths and velocities, the time and pressures may be scaled by $(h_0^2/v)$ and $(v^2/h_0^2)$, respectively. $v$ and $\rho$ are the kinematic viscosity and density, respectively. In view of the above scalings and denoting the mucus and aqueous properties by unprimed and primed variables, one may write the following simplified nondimensional Navier-Stokes equations in the lubrication-approximation:

\begin{align}
   u_{zz} - p_x - \phi_x &= 0, \quad [1] \\
   -p_z - \phi_z &= 0, \quad [2]
\end{align}

for $0 \leq z \leq h$; $-\infty < x < \infty$

and

\begin{align}
   \left(\frac{\nu'}{\nu}\right)u'_{zz} - \left(\frac{\rho'}{\rho}\right)p'_z - \phi'_x &= 0, \quad [3] \\
   -\left(\frac{\rho'}{\rho}\right)p'_z - \phi'_z &= 0, \quad [4]
\end{align}

for $h \leq z \leq h'$, $-\infty < x < \infty$.

Here the subscripts refer to partial differentiation, $u$ and $w$ are the dimensionless mucus layer velocities in the $x$ and $z$ directions and $u'$ and $w'$ are the corresponding dimensionless velocities in the aqueous layer; $\rho'$ and $\nu'$ are the aqueous layer density and kinematic viscosity, respectively; $\phi$ and $\phi'$ are the dimensionless van der Waals interaction potentials in the mucous and aqueous layers and are specified later. The derivatives of the potentials thus represent the component of the forces per unit volume acting on the corresponding layers.

The following two continuity equations hold for the mucous and aqueous layers, respectively:

\begin{align}
   u_x + w_z &= 0 \quad [5] \\
   u'_x + w'_z &= 0. \quad [6]
\end{align}

In addition, the following linearized boundary conditions are specified at various interfaces.

The no slip boundary condition at the epithelium-mucous interface:

\begin{align}
   \text{at } z = 0, \quad u = w = 0. \quad [7a]
\end{align}

The balance of tangential forces at the mucous–aqueous interface:

\begin{align}
   \text{At } z = h(x, t), \quad \mu u_z = \mu' u'_z + (h_0/v)\sigma_x, \quad [7b]
\end{align}

where $h(x, t)$ is the dimensionless location of the mucus–aqueous interface and $\mu$ and $\mu'$ are the dynamic viscosities of the mucous and aqueous layers, respectively.

The last term in the right hand side of the above equation represents the stress generated due to the mucous–aqueous interfacial tension gradient.

The relation of the pressure jump to the interfacial tension:

\begin{align}
   \text{At } z = h(x, t), \quad p' - p = 3Sh_{xx}, \quad [7c]
\end{align}
where \( S = (h_0 \sigma / 3 \rho v^2) \) is a dimensionless number and \( \sigma \) is the mucous–aqueous interfacial tension.

The continuity of velocities across the mucous–aqueous interface:

At \( z = h(x, t) \), \( u = u' \) and \( w = w' \). \[7d\]

Similarly, the following boundary conditions hold at the tear–air interface:

At \( z = h'(x, t) \), \( u' = 0 \) \[7e\]

and

\[-p' = 3S'h''_x, \]

where \( h' \) is the dimensionless location of tear–air interface, \( S' = (h_0 \sigma' / 3 \rho v^2) \), and \( \sigma' \) is the air–tear surface tension.


\[ p + \phi = p(x, t) + \phi(x, t) = p(h) + \phi(h) \] \[8\]

and

\[ p' + \alpha \phi' = p'(h') + \alpha \phi'(h') = p'(h) + \alpha \phi(h). \] \[9\]

Using boundary conditions [7f] and [7c] in conjunction with Eqs. [8] and [9] shows that

\[ p' + \alpha \phi' = -3S'h''_x + \alpha \phi'(h') \] \[10\]

and

\[ p + \phi = \phi(h) - \alpha \phi(h) + \alpha \phi'(h') - 3S'h''_x - 3S h''_x, \] \[11\]

where \( \alpha = (\rho' / \rho) \) and various potentials are evaluated at the interfaces indicated within the parenthesis. Equations [1] and [3] are now easily solved with the help of expressions [10] and [11] and the remaining boundary conditions, giving

\[ u' = \psi_1 z^2 / 2 + a_1 z + a_2, \quad h \leq z \leq h' \] \[12\]

and

\[ u = \psi_2 z^2 / 2 + a_3 z, \quad 0 \leq z \leq h, \] \[13\]

where

\[ r\psi_1 = (-3S'h'''_x + \alpha \phi''_x), \quad r = (\mu' / \mu), \] \[14\]

\[ \psi_2 = [\phi_x(h) - \alpha \phi'_x(h) + \alpha \phi'_x(h') - 3S h'''_x - 3S'h''_x]. \] \[15\]

\[ a_1 = -\psi_1 h', \] \[16\]

\[ a_2 = -\psi_2 h^2 / 2 + \psi_1 h[r(h - h')] - (h/2) + h' + h_0(\mu / \mu) \sigma_x \] \[17\]

and

\[ a_3 = r(h - h')\psi_1 - \psi_2 h + (h_0 / \mu \nu) \sigma_x. \] \[18\]

Now the solutions of the continuity Eqs. [5] and [6] are straightforward with the help of boundary conditions [7a] and [7d] and the expressions [12] and [13]. This gives

\[ w = -\psi_2 z^2 / 2 - a_3 z^2 / 2 \] \[19\]

and

\[ w' = -\psi_1 x (z^2 / 2 - h' z^2 / 2) + \psi_1 h' x z^2 / 2 - a_2 x z + a_4, \] \[20\]

where

\[ a_4 = (\psi_1 x - \psi_2 x) h^3 / 6 \]

\[ - h^2 (a_3 x + \psi_2 h' x + h' \psi_1 x) / 2 + h a_2 x. \] \[21\]

The evolution equations for the mucous–aqueous interface and the aqueous surface are now derived by using the following kinematic conditions:

\[ h_t + h_x u - w = 0 \quad \text{at } z = h \] \[22\]

and

\[ h'_t + h'_x u' - w' = 0 \quad \text{at } z = h'. \] \[23\]

Substitution of various velocities, viz. expressions [12], [13], [19], and [20], in the above equations give the lowest order, rigorous equations of evolution for the interfaces. These are, however, highly nonlinear and henceforth we focus our attention to the analysis of the linear equations only, awaiting quantitative information regarding various physicochemical and especially morphological parameters characterizing the mucus layer and the epithelium. Linearizing Eqs. [19], [20], and [22], and [23] around the planar locations of the interfaces, viz. \( h = 1 \) and \( h' = (h_0 / h_0) = \beta \), and combining them, gives the following linear equations in the dimensionless variables:

\[ a_1 = -\psi_1 h', \] \[16\]

\[ a_2 = -\psi_2 h^2 / 2 + \psi_1 h[r(h - h')] - (h/2) + h' + h_0(\mu / \mu) \sigma_x \] \[17\]

and

\[ a_3 = r(h - h')\psi_1 - \psi_2 h + (h_0 / \mu \nu) \sigma_x. \] \[18\]
LIPID ABNORMALITIES

\[ h_t + (1 - \beta)\psi_{1x}/2 - \psi_{2x}/3 \]
\[ + h_0\sigma_{xx}(h)/2\mu \nu = 0 \]  \[24\]

and

\[ h'_t + \psi_{1x}\theta/6 + (1 - 3\beta)\psi_{2x}/6 \]
\[ + h_0\sigma'_{xx}(h'/(\beta - \frac{1}{2}))/\mu \nu = 0, \]  \[25\]

where

\[ \theta = (\beta - 1)[1 - 2\beta(\beta + 1) \]
\[ + 6(\beta - \frac{1}{2})(1 - r)]. \]  \[26\]

It may be noted that for the tear film, \( \psi'(h') = 0 \), because the aqueous–lipid surface has a constant concentration of lipids and thus an interfacial tension gradient does not exist at this interface.

The coefficients, \( \psi_{1x} \) and \( \psi_{2x} \), may be now written explicitly by making use of expressions [14] and [15] and by prescribing the Hamaker type approximations for the dispersion potentials arising at the mucous–aqueous and the aqueous–lipid interfaces. The retarded dispersion potentials are prescribed for the aqueous layer, since it is quite thick (~10 \( \mu \)m) (9). The derivation of the dispersion potential arising at the two interfaces is straightforward and proceeds on the same lines as those pursued in Ref. (33) for a single film. In view of the scalings used to nondimensionalize the Navier–Stokes equations, the second derivatives of the linearized dimensionless potentials may be written as

\[ \phi_{xx}(h) = -3e_2(A_{22} - A_{23})h_{xx} \]
\[ + 4B_{21}e_1(h'_{xx} - h_{xx}), \]  \[27a\]

\[ \phi'_{xx}(h') = 4e_1(B_{12} - B_{11})(h'_{xx} - h_{xx}) \]
\[ + 4(B_{13} - B_{12})h'_{xx}e_3 \]  \[27b\]

and

\[ \phi'_{xx}(h) = -3e_2(A_{12} - A_{13})h_{xx}/\alpha \]
\[ + 4B_{11}(h'_{xx} - h_{xx})e_1, \]  \[27c\]

where

\[ e_1 = (\beta - 1)^{-2}(\rho h_0^2\nu^2)^{-1}, \]
\[ e_2 = (6\pi \rho h_0^2\nu^2)^{-1} \]
\[ e_3 = (\rho h_0^2\nu^2)^{-1}. \]

\( A_{ij} \) and \( B_{ij} \) are the nonretarded and the retarded Hamaker constants for the interactions between the molecules of type \( i \) and \( j \). The subscripts 1, 2, and 3 refer to the aqueous layer, mucus layer, and the epithelium molecules, respectively.

The evaluation of the mucous–aqueous interfacial tension gradient, \( \sigma_{xx}(h) \), requires the solution of a mass transfer problem in conjunction with the hydrodynamic equations [24] and [25].

III. Interfacial Tension Gradients

The mucous–aqueous interfacial tension is expected to be very low, in view of the extreme hydrophilicity of mucus molecules and the highly hydrated state of the mucus layer. It is reasonable to assume it to be of the same order of magnitude as that encountered for cell membranes with a glycoprotein coat. This has been reported to be in the range of \( 10^{-3} \) to 1 dyn/cm (36a). The presence of dissolved lipids tends to augment this interfacial tension (28, 36b). In view of the fact that the presence of lipids in the vicinity of mucus–aqueous interface is thermodynamically unfavorable, their concentration in the aqueous layer increases away from the mucous–aqueous interface. This results in a negative surface excess concentration, as opposed to the positive surface excess concentration in the case of energetically favorable adsorption of surfactants (15). The lipids (and some other constituents of the aqueous phase, a possible exception being the dissolved mucin) may thus be characterized as antisurfactants (sometimes referred to as inverse surfactants), with reference to the mucous–aqueous interface, in recognition of their interfacial tension augmenting capacity. Some aspects of the role of surfactant adsorption on the van der Waals force mediated rupture of thin films have been investigated (33), but no such study has been undertaken for the anti-surfactants to the best of our knowledge.

The nonuniform solute concentration distribution normal to the interface may be as-
cribed to the presence of an interaction potential, which acts within a short distance, $\delta$, from the interface and it is because of this that the concentration distribution in the boundary layer, $h \leq z \leq h + \delta$, is expected to differ from the concentration in the bulk, $h + \delta < z < h'$. The excess concentration of a component is defined here as the difference between the actual moles contained in the boundary layer and the moles contained assuming that the concentration is that governed by the convective diffusion equation without the presence of the interaction potential

$$\Gamma = \int_h^{h+\delta} (C^* - C)dz,$$  \[28\]

where $\Gamma$ is the surface excess concentration, $C^*$ is the solute concentration in the boundary layer, $h \leq z \leq h + \delta$, and $C$ is the concentration distribution in the absence of the interaction potential. $\delta$ is the characteristic thickness of the boundary layer in the vicinity of the interface over which $C^*$ differs from $C$ due to the interaction potential, $\psi(z)$. This potential is operative within a few tens of Ångstroms from the interface and is attractive for surfactants and repelling for antisurfactants. For surfactants, the concentration in the vicinity of the interface is usually very large compared to their concentration in the bulk, viz. $C^* \gg C$. Therefore, this thin boundary layer, $h \leq z \leq h + \delta$, is often envisaged as a two-dimensional surface and the excess concentration is viewed as the actual interfacial concentration of surfactants. In the case of antisurfactants, however, this picture is inaccurate insomuch as $C^* < C$ here and thus $\Gamma < 0$, viz. their concentration in the bulk is the highest.

The determination of the surface excess concentration is important because the change in the interfacial tension does not depend on the solute concentration present in the vicinity of the interface per se, but on the excess surface concentration, $\Gamma$ (15). In what follows, we first formulate an ideal hydrodynamic description of the interface, applicable both to surfactants and antisurfactants.

Consider an interface whose location is given by $h(x, t)$ and a thin boundary layer of thickness $\delta(x, t)$ adjacent to it over which the interaction potential, $\psi(z)$, is operative. The following convective diffusion equation may be written for the solute concentration within the boundary layer, $C^*$:

$$C^*_t + u'C^*_x + w'C^*_z = (D/v)\nabla^2 C^* + (D/k_b T)\psi(C^*_z),$$  \[29\]

where $k_b$ is Boltzmann's constant and $T$ is the temperature.

The contribution of the potential $\psi(z)$ is negligible outside the boundary layer and thus the convective diffusion equation for the bulk is

$$C_t + u'C_x + w'C_z = (D/v)\nabla^2 C.$$  \[30\]

Subtracting Eq. [30] from Eq. [29], integrating the resulting equation over the thickness of the boundary layer, viz. the domain, $h \leq z \leq h + \delta$, and simplifying, gives the following equation relating the variations in the surface excess concentration to the solute flux from the bulk phase (the derivation is outlined in Appendix A):

$$\theta C_z = \Gamma + (uT)_x \quad \text{at} \quad z = h(x, t),$$  \[31\]

where $\theta = (Dh_0/v)$.

The equilibrium may be assumed to prevail in the boundary layer because it is extremely thin and thus the equilibrium isotherm is derived by noting that the concentration in the boundary layer (Eq. [29]) satisfies

$$k_b T C^*_z + (C^*_\psi)_z = 0,$$  \[32\]

which, when integrated twice and combined with the zero flux condition and the boundary condition, $C^* = C$ at $z = h + \delta$, gives

$$C^* = C \exp\{-\psi(z)/k_b T\}.$$  \[33\]

It is instructive to note that the same result may also be obtained by thermodynamic considerations, viz. by making use of the equality of the chemical potentials at different locations.
The definition of \( \Gamma \), (Eq. [28]), in conjunction with expression [33] yields the desired isotherm, viz.

\[
\Gamma = C \int_0^5 (e^{-\psi/k_BT} - 1)dz = \theta_0 C,
\]

where

\[
\theta_0 = \int_0^5 (e^{-\psi/k_BT} - 1)dz.
\]

For surfactants, \( \psi < 0 \) and consequently, \( \theta_0 > 0 \), whereas for antisurfactants, \( \psi > 0 \) and thus \( \theta_0 < 0 \). The linear isotherm, Eq. [34], may be recognized to be the isotherm for a "gaseous monolayer" type adsorption. This behavior is somewhat restrictive for surfactants, as it cannot predict the surface (or boundary layer) saturation obtained at higher bulk concentrations. This may be remedied by assuming a more realistic isotherm, such as the Langmuir isotherm, that accounts for the "surface exclusion" and thus predicts the saturation of the interface at higher bulk concentration of the surfactants. This, however, is of less concern for antisurfactants for which the concentration in the boundary layer is lower than in the bulk and thus the saturation is more likely to occur first in the bulk (when the bulk concentration of antisurfactants attains its solubility limit).

The linearized mass transport equation for the diffusion of lipids in the bulk is now written as

\[
C_t = (D/\nu)\nabla^2 C,
\]

which is to be solved together with the boundary conditions

\[
C = C_0 \quad \text{at} \quad z = \beta
\]

and

\[
\theta_1 C_z = \Gamma_z + \Gamma_0 \mu_s' \quad \text{at} \quad z = 1,
\]

where \( \Gamma_0 = \Gamma(C_0) \).

The dynamic interfacial tension, which accounts for the surface viscosity, \( \mu_s \), is defined as

\[
\sigma(\Gamma) = \sigma_0(\Gamma) + (\mu_s/\rho_0)u_x \quad \text{at} \quad z = 1.
\]

Substitution of \( (du/dx)_{z=1} \) from Eq. [13] in Eq. [37] yields the following differential equation for the interfacial tension \( \sigma \):

\[
\sigma_{xx} - (h_0\mu/\mu_s)(\sigma - \sigma_0)

+ (\nu/\rho_0)[\psi_1(1 - \beta) - \psi_2]/2 = 0.
\]

Having completed the description of the hydrodynamic and the mass transport problems and the determination of interfacial tension gradient, we now turn towards the linear stability analysis of these equations.

IV. Linear Stability

In reality, the location of the mucous-aqueous interface is not absolutely flat, but is nonhomogeneous because of the uneven shear created during the lid motion, the thermal perturbations, nonhomogeneous epithelium, and the presence of the goblet cells. In what follows, we seek to determine the growth of local inhomogeneities due to dispersion interactions and the surfactant or antisurfactant concentration driven Marangoni motion. Any arbitrary disturbance originating at the interfaces may be represented by a sum of Fourier components of the form

\[
h \approx 1 + \epsilon_1 e^{ikx+\omega t}
\]

and

\[
h' \approx \beta + \epsilon_2 e^{ikx+\omega t},
\]

where \( \epsilon_1 \) and \( \epsilon_2 \) are the nondimensional initial amplitudes of the perturbations, \( k \) is a dimensionless wavenumber, and \( \omega \) is a dimensionless growth coefficient which shows the rate of amplification (for \( \omega \) positive) or decay (if \( \omega \) is negative) of the initial interfacial perturbations. The perturbations in the location of the interface induce convective velocities and, consequently, a deviation in the concentration from its equilibrium value. This may be represented as

\[
C = C_0 + \eta(z)e^{ikx+\omega t}
\]

and consequently from Eq. [34a],

\[
\Gamma - \Gamma_0 = \theta_0\eta(z)e^{ikx+\omega t}.
\]
Perturbation in interfacial tension is now obtained as
\[ \sigma_\theta - \sigma_\theta(\Gamma_0) = (\partial \sigma_\theta / \partial \Gamma)_r = \Gamma - \Gamma_0 \] [39d]
\[ = M \eta(z) \theta_0 e^{i \kappa x + i \omega t}, \] [39e]
where \( M = (\partial \sigma_\theta / \partial \Gamma)_r = \Gamma - \Gamma_0 \) is a parameter that shows the variation of the interfacial tension with the surface excess concentration. An estimate for this may be arrived at by using the Gibbs adsorption equation
\[ d\sigma_\theta = -\Gamma d\mu, \] [40a]
where the concentration dependent part of the chemical potential, \( \mu \), is given by \( RT \ln C \), and consequently,
\[ d\sigma_\theta = -RT \Gamma d(\ln C). \] [40b]
Making use of the isotherm [34a], one obtains
\[ M = (d\sigma_\theta / d\Gamma) = -RT. \] [40c]
Thus \( M \) is about \(-2.4 \times 10^{-10} \text{ erg/mole}\) which is consistent with the values reported for a gaseous monolayer adsorption.

Substituting expressions [39] in Eq. [38] and solving gives
\[ \alpha_4(h_0/\mu)(\phi x') = e^{i \kappa x + i \omega t}[-M \eta(z) \theta_0 - \epsilon_1 \mu_s \]
\[ \times (3S'k^4/2 + b_1k^2/2 + (1 - \beta)\alpha a_3k^2) \]
\[ - \epsilon_2 \mu_s \{3S'k^4/2 + b_2k^2/2 + (\beta - 1) \]
\[ \times (3S'k^4 + \alpha a_2k^2)\}, \] [41]
where the various coefficients are defined by
\[ b_1 = 4\alpha B_{11} \epsilon_1 + 3\alpha \epsilon_2(A_{12} - A_{13}) \]
\[ - 4(B_{12} - B_{11}) \epsilon_1 \]
\[ - 3 \epsilon_2(A_{22} - A_{23}) - 4B_{21} \epsilon_1, \] [42a]
\[ b_2 = 4B_{21} \epsilon_1 - 4\alpha B_{11} \epsilon_1 + 4\alpha(B_{12} - B_{11}) \epsilon_1 \]
\[ + 4\alpha(B_{13} - B_{12})/\beta^2 \rho \mu h_0 \nu^2, \] [42b]
\[ a_{31} = 4(B_{12} - B_{11}) \epsilon_1, \] [42c]
\[ a_{32} = 4(B_{12} - B_{11}) \epsilon_1 + 4(B_{13} - B_{12})/\beta^2 \rho \mu h_0 \nu^2 \] [42d]
and
\[ \alpha_4 = (\mu_s + h_0 \mu/k^2). \] [42e]
With the help of Eqs. [13], [39b], and [39c], the diffusion Eq. [35] and boundary conditions [36a] and [36b] become
\[ \eta_x = a^2 \eta, \] where \( a = (k^2 + \omega \nu / D)^{1/2} \), [43a]
\[ \text{at } z = \beta, \quad \eta = 0, \] [43b]
\[ \text{at } z = 1, \quad \theta_1 \eta_x = \alpha_1 \eta + \epsilon_1 \alpha_2 + \epsilon_2 \alpha_3, \] [43c]
where
\[ \alpha_1 = \theta_0 \omega - (\Gamma_0 \theta_0 h_0/\alpha_4), \] [44a]
\[ 2\alpha_2 = \Gamma_0 \{3Sk^4 + b_1k^2 \]
\[ + 2(1 - \beta)\alpha a_3k^2\}(1 - \mu_s/\alpha_4) \] [44b]
and
\[ 2\alpha_3 = \Gamma_0 \{3S'k^4 + b_2k^2 + 2(\beta - 1) \]
\[ \times (3S'k^4 + \alpha a_2k^2)\}(1 - \mu_s/\alpha_4). \] [44c]

The solution of Eqs. [42a]-[42c] is given by
\[ \eta = 2(\epsilon_1 \alpha_1 + \epsilon_2 \alpha_3)e^{\alpha \theta} \sinh\{a(1 - \beta)\}, \] [45]
where
\[ \alpha_2 = \alpha_2 e^{-\alpha \theta}[a \theta \cosh\{a(1 - \beta)\} \]
\[ + \alpha \sinh\{a(1 - \beta)\}]^{-1} \] [45a]
and
\[ \alpha_3 = \alpha_3 \alpha_2 / \alpha_2. \] [45b]

The determination of \( \eta \) completes the mass transfer problem since the interfacial tension gradient, \( \sigma_x \), is now immediately determined from Eq. [41]. The dispersion relation is obtained by combining Eqs. [24], [25], [39a], [41], and [45], giving
\[ \epsilon_1[\omega + \alpha a_1(1 - \beta)k^2/2 \]
\[ + Sk^4 + b_1k^2/3 + N_1] \]
\[ + \epsilon_2[(1 - \beta)(-3S'k^4 - \alpha a_2k^2)/2 \]
\[ + S'k^4 + b_2k^2/3 + N_2] \]
\[ = a_{11} \epsilon_1 + a_{12} \epsilon_2 = 0 \] [47a]
and
\[ \epsilon_1[\omega - \theta (3S'k^4 + \alpha a_3k^2)/6r \]
\[ + \epsilon_2[\omega - \theta (3S'k^4 + \alpha a_3k^2)/6r] \]
\[ + (1 - 3\beta)(-3S'k^4 - b_2k^2)/6 \]
\[ = a_{21}\epsilon_1 + a_{22}\epsilon_2 = 0 \quad [47b] \]

where

\[ 2\alpha_4N_1 \]
\[ = \mu_s\{(\beta - 1)\alpha a_{31}k^2 - 3S'k^4/2 - b_1k^2/2\} \]
\[ - 2M\theta_0\alpha_2\epsilon_{a}^a\epsilon_{a}^d\sinh\{a(1 - \beta)\}, \quad [48a] \]

and

\[ 2\alpha_4N_2 = \{(1 - \beta)(3S'k^4 + \alpha a_{32}k^2) \]
\[ - 3S'k^4/2 - b_2k^2/2\}\mu_s \]
\[ - 2M\theta_0\alpha'_2\epsilon_{a}^a\epsilon_{a}^d\sinh\{a(1 - \beta)\}. \quad [48b] \]

The coefficients \( N_1 \) and \( N_2 \) contain the effects of the interfacial tension gradient driven convective motion on the stability of the mucus layer.

The set of homogeneous, algebraic equations \([47a]\) and \([47b]\) have a nontrivial solution if the following solvability condition is satisfied:

\[ \begin{vmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{vmatrix} = 0. \quad [49] \]

This equation, when written out in full, is highly nonlinear and somewhat unwieldy. However, a simplification may be noted when the thickness of the aqueous layer is large compared to the thickness of the underlying mucus layer, which is almost always the case for a tear film. Due to a rapid decay of the dispersion forces with an increased thickness of the aqueous layer and a high surface tension of the aqueous layer, we found that the thickness dependence of the dispersion interactions at the tear–air interface may be neglected for the aqueous layer thicknesses in excess of 5000 Å. In this case, \( a_{21}/a_{22} \to 0 \) and the dispersion relation, Eq. \([49]\), reduces to

\[ a_{11} = 0. \quad [50] \]

This is tantamount to neglecting the thinning of the aqueous film due to dispersion forces during the time in which the mucus layer ruptures.

Noting this simplification and reverting back to the original dimensional variables, the dispersion relation \([50]\) becomes

\[ \lambda = \left\{ (A/2\pi h_0^2 - \sigma_0(\Gamma_0)K^2)h_0K^2/3\mu \right\} \]
\[ \times \left\{ 1 - 3(N + \mu_4/2)/2\alpha'_4 \right\}, \quad [51] \]

where \( \lambda \) is the dimensional growth coefficient, \( K \) is the dimensional wavenumber, and \( A \) is an effective Hamaker constant defined as

\[ A = A_{22} + A_{13} - A_{23} - A_{12}. \quad [52] \]

Further, parameters \( N, \alpha'_4, \) and \( \alpha' \) are defined as

\[ 2N = -M\theta_0(1 - \mu_4/\alpha_4)dD \coth\{d(h_0 - h_0)\} \times \theta_0 + \lambda - \Gamma_0M/\alpha_4, \quad [53] \]

\[ \alpha'_4 = \mu_4 + \mu/K^2h_0 \quad [54] \]

and

\[ \alpha' = (K^2 + \lambda/D)^{1/2}. \quad [55] \]

The static part of the interfacial tension in the presence of a surfactant or antisurfactant may be expressed by a MacLaurin series approximation, viz.

\[ \sigma_0(\Gamma_0) \approx \sigma_0(0) + M(\Gamma_0 - \Gamma_0(0)) \quad [56] \]

Assuming that \( \sigma_0(0) \) represents the mucus–aqueous interfacial tension when the aqueous phase is pure, viz., \( \Gamma_0(0) = 0 \), the dispersion relation \([50]\) is rewritten as

\[ \lambda = \left\{ \lambda_0 - M\Gamma_0h_0^3K^4/3\mu \right\} \]
\[ \times \left\{ 1 - 3(N + \mu_4/2)/2\alpha'_4 \right\}, \quad [57] \]

where \( \lambda_0 \) is the growth coefficient of a clean mucus interface when the aqueous phase is devoid of any surfactants or antisurfactants, viz.

\[ \lambda_0 = \frac{h_0^3K^2}{3\mu} \left( \frac{A}{2\pi h_0^2} - \sigma_0(0)K^2 \right). \quad [58a] \]

If the London dispersion interactions are assumed to be retarded for the mucus layer thicknesses in excess of 0.1 μm, viz. one uses the potential of the form \( B/h^4 \) instead of \( A/6\pi h^3 \), the growth coefficient is given by
\[
\lambda = \frac{h_0^3 K^2}{3 \mu} \left[ \frac{4B}{h_0^2} - \sigma_0 K^2 \right] \times \left[ 1 - 3(N + \mu_\alpha/2)/2 \alpha_4 \right]. \quad [58b]
\]

At this point, it is instructive to recall that for antisurfactants, \( \theta_0 < 0 \) and \( \Gamma_0 \) is a negative quantity, whereas for surfactants, \( \theta_0 > 0 \) and \( \Gamma_0 \) is positive. Thus, the parameter \( N \) may in general be written as

\[
2N = \left| \Gamma_0 M \right| \alpha_4 \left[ \frac{\alpha_0}{\alpha_4} \right]^{1/2} \left[ \frac{\alpha_0}{\alpha_4} \right]^{-1} \coth \left\{ \alpha_4 (h_0 - h_0) \right\} \pm \lambda + \left| M \Gamma_0 \right| \alpha_4^{-1}. \quad [59]
\]

The sign in \( \pm \lambda \) is determined by whether the material is a surfactant (positive sign) or an antisurfactant (negative sign).

An estimate for the time of rupture of the mucus layer is given by

\[
\tau \approx \lambda_m^{-1}, \quad [60]
\]

where \( \lambda_m \) is the maximum growth rate for a given set of parameters that is maximized with respect to the wave number, \( K_\alpha(0, \infty) \). The Fourier component of the initial disturbance with the wavenumber corresponding to the solution of \( (dX/dK) = 0 \) is selectively amplified until the layer ruptures.

The analytical determination of the wavenumber for which \( \lambda \) is a maximum is not possible due to the transcendental nature of the dispersion equation \([57]\) and is thus done numerically. Before undertaking this however, it is instructive to synopsize certain asymptotic cases and the physics of the phenomena involved, lest they are obscured by the mathematical derivations.

**ASYMPTOTIC CASES AND PHYSICAL EXPLANATIONS**

**Marangoni Flow**

For large values of the parameter \( \left| \Gamma_0 M \right| \), the coefficient \( N \), given by Eq. \([59]\), reduces to

\[
N = (\alpha_4 - \mu_\alpha)/2 \quad [61a]
\]

which, when substituted into Eq. \([57]\), yields

\[
\lambda = \left[ \lambda_0 - M \Gamma_0 h_0^3 K^4/3 \mu \right]^{1/4} \quad [61b]
\]

Thus, the maximum stabilizing effect of surfactant or antisurfactant concentration gradient induced Marangoni flow is to increase the time of rupture by a factor of 4, compared to the case of a thin film with an apparent interfacial tension of \( \{ \sigma_0(0) + M \Gamma_0 \} = \sigma_{\text{app}} \). By maximizing \( \lambda \) as given by Eq. \([61b]\) with respect to \( K \), the time of rupture from Eq. \([60]\) is given as

\[
\tau = 192 \pi^2 \mu h_0^5 \left( \sigma_0(0) + M \Gamma_0 \right) A^{-2}, \quad [62]
\]

in contrast to a film with \( |M \Gamma_0| \to 0 \) and consequently, \( N \to 0 \), where it is given by

\[
\tau = 48 \pi^2 \mu h_0 \sigma_0(0) A^{-2}. \quad [63]
\]

Thus the presence of dissolved material in the aqueous phase stabilizes the film due to Marangoni convection and at the same time, alters the interfacial tension, \( \sigma_0(0) \), to \( \sigma_{\text{app}} \). This later effect, as shown by Eq. \([62]\), is stabilizing for antisurfactants as \( M \Gamma_0 \) is positive (the interfacial tension is augmented) and destabilizing for surfactants.

It is important to note that \( |M \Gamma_0| \) cannot be increased indefinitely, because of the saturation of the interface for surfactants and the saturation of the bulk for antisurfactants. In conclusion, the overall effect of antisurfactants is always stabilizing and that of surfactants may be stabilizing or destabilizing, depending on whether the stabilizing effect of Marangoni flow is strong enough to compensate for the destabilizing effect of reduced interfacial tension.

It is important to note that the stabilizing effects of the Marangoni flow as delineated above, hold only for a strictly linear isotherm, Eq. \([34]\), where the isotherm constant, \( \theta_0 \), may be assumed to be independent of the bulk concentration. In the event of the saturation of the interface with solute molecules, the surface excess concentration becomes constant (independent of the bulk concentration) and thus cannot be perturbed, viz. \( \theta \to 0 \) in Eq.
[37c]. As is apparent from Eq. [59], $N$ tends to zero in such an event and the stabilizing effect of the Marangoni flow is wiped out. Thus, in reality, there exists an intermediate solute concentration for which the stabilizing influence of the Marangoni flow is the maximum.

The physical origin of concentration differential driven Marangoni motion is explained in Figs. 2a and b. Figure 2a shows that any interfacial perturbation of the mucus layer induces a flow from the depressed regions to the elevated regions. Due to this convective transfer, the concentration, and consequently, the excess concentration of surfactant or antisor surfactant becomes larger at the elevated locations compared to the depressed ones. In view of the Gibbs equation, Eq. [40a], the interfacial tension at the elevated regions is thus lower than that prevailing at the depressed regions. The interfacial tension gradient so generated induces a convective Marangoni flow from the low interfacial tension regions to the regions with higher interfacial tension (Fig. 2b). As shown in Fig. 2b, this flow tends to counter the flow generated due to the film thinning and thus exerts a stabilizing effect.

**Surface Viscosity**

The effect of surface viscosity is also delineated within the above framework by noting that the dynamic part of the surface tension, $\sigma_d$, is related to the velocity differential by

$$\sigma_d = \mu_s u_x \text{ at } z = 1, \quad [64a]$$

where

$$\sigma = \sigma_0 + \sigma_d. \quad [64b]$$

The dynamic part of the interfacial tension, $\sigma_d$, vanishes when either the surface viscosity, $\mu_s$, is zero or the surface is unperturbed, viz. $u_x = 0$. For a finite $\mu_s$ and a perturbed interface, however, the variation of the lateral velocity in $x$ direction, viz. $u_x$, is negative at the elevated points as opposed to a positive $u_x$ at the depressed points. This process is depicted in Fig. 3. Again as is clear from Eq. [64b], the interfacial tension at elevated regions is lower compared to depressed regions and a stabilizing flow ensues. It is easy to verify that when $\mu_s \to \infty$, there is a fourfold increase in the time of rupture as compared to the case of a film with an apparent interfacial tension, $\sigma_{app}$, viz. Eq. [62] applies to this case as well.

**Thickness of Aqueous Layer**

The effect of the thickness of the aqueous layer is contained in the parameter, $L = \coth\{a'(h' - h_0)\}$, which appears in the definition of $N$, Eq. [59]. As the thickness, $(h' - h_0)$, decreases, $L$ increases and consequently, $N$ decreases. In the limiting case of $h' \to h_0$, $L \to \infty$ and thus $N \to 0$. The stabilizing effect of the Marangoni convection is completely wiped out in this case. In general, a decreased aqueous layer thickness makes the stabilizing effect of Marangoni flow less pronounced. This is expected physically because since the concentration of lipid is constant at the aqueous–lipid interface, a decreased aqueous layer thickness facilitates a faster redistribution of lipids in the layer because of

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Fig. 2. The physical origin of antisurfactant or surfactant concentration differential driven Marangoni flow.

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the diffusion. This results in a tendency to even out the concentration gradients generated due to the convective flow and consequently, the interfacial tension gradients are also reduced. The stabilizing Marangoni flow resulting from the interfacial tension gradients is thus minimized.

Having expounded on the qualitative aspects of the rupture of the thin mucus layer, we now see how it enhances our understanding of the issues (which have been discussed earlier) related to the breakup of tear film.

RESULTS AND DISCUSSION

An exact a priori prediction of BUT is not possible, not only because of the complexity of the eye and the present limited knowledge concerning the value of the various physico-chemical and morphological parameters, but also because the breakup of the mucus layer is a nonlinear phenomenon and is affected, among other factors, by the extent and the nature of the initial interfacial perturbations or inhomogeneities. In view of this, and some other factors that are explained later, it is not surprising that the repeated clinical measurements of BUT tend to show a deviation (6, 37) even for the same patient. Fortunately, what is of paramount importance here is a rational understanding of the causes affecting the tear-film breakup (and BUT), which albeit semiquantitative, paves a way to a causal approach to the explanation of the numerous clinical and experimental observations, selective experimentation, and the diagnosis and treatment of dry eyes. The discussion that follows should be viewed in this spirit.

The interfacial tension of a clean mucous-aqueous interface is low and is assumed to be in the range of $10^{-3}$ dyn/cm to 1 dyn/cm, viz. $\sigma_0(0) = 10^{-3}$ to 1 dyn/cm, which is the same range as that obtained for the interfacial tension of the cell membranes with a glycoprotein coat (36a). The normal lipids are probably the most antisurface active material present in the eye, i.e., they augment the interfacial tension the most. Based on these estimates, and the physical parameter values reported earlier (10) (also provided in the figure captions), Eq. [57] may be maximized numerically with respect to the wavenumber $K$, and an estimate for the time of rupture may be computed from Eq. [60]. The region of compatibility for the mucus layers of thickness 400 Å and a rather high interfacial tension of 1 dyn/cm is depicted as the shaded region in Fig. 4. The values of the effective Hamaker constant, $A$, and the parameter $MT_0$ corresponding to the shaded regions are the ones that are compatible with the observed kinetics of tear film rupture (BUT) for a normal eye. The magnitudes of the effective Hamaker constant belonging to the shaded regions are entirely within a realistic range (31, 33, 38–40). It is thus concluded that even relatively weak van der Waals interactions break a mucus layer of thickness

![Fig. 4](image-url)
400 Å and a relatively high effective interfacial tension (about 5 dyn/cm) within a short period of about 20–100 s. The compatibility of the proposed mechanism with the observed range of BUT for thicknesses higher than 400 Å is demonstrated in Appendix B for the feasible values of the Hamaker constant and the mucous–aqueous interfacial tension.

Henceforth, we will illustrate various ramifications of the proposed mechanism with the help of a particular set of parameters (those corresponding to Fig. 4). However, it is to be understood that these conclusions remain the same if instead a different feasible set of parameters are chosen.

A more precise prediction of BUT, however, awaits the experimental availability of physicochemical parameters such as the effective Hamaker constant for the epithelium–mucous–aqueous layer system, viscosity and rheology of epithelial mucus layer, the mucous–aqueous interfacial tension, $M\Gamma_0$, and the thickness of the corneal mucus layer that prevails under the normal dynamic conditions of the tear film.

With this general background, we now go on to relate the specific deficiencies of the eye, the role of the tear substitutes and the contact lens tolerance to the proposed model of tear film breakup.

**Mucus Deficiency**

A decreased population of goblet cell density or a deficiency of mucus production in eye would decrease the thickness of the mucus coating of the corneal epithelium. A thinner mucus layer ruptures faster. This has been discussed in some detail in our previous papers (10, 11). This deficiency of the eye appears to be the most difficult to treat as there does not exist any direct method of replenishing the required mucus on the epithelium on a regular basis. The polymeric ingredients of the ophthalmic solutions may increase it by adsorption and absorption and may thus prolong the time of rupture. However, in the case of a moderate mucus deficiency, it appears possible to offset its effect on BUT by manipulating certain other factors which are discussed next.

**The Stabilizing Role of Normal Lipids**

The normal lipids, in conjunction with other dissolved materials of the tear film, augment the low mucous–aqueous interfacial tension and thus make the mucus layer more resistant to the interfacial deformations caused by the dispersion forces. In addition, they contribute toward the stability by enhancing the interfacial tension driven Marangoni motion. To see this dual stabilizing role of normal lipids in the most transparent way, their effect is displayed for a typical set of parameter values, $A = 10^{-13}$ erg and $1.5 \times 10^{-13}$ erg, $h_0 = 400 \, \text{Å}$, $\sigma_0(0) = 1 \, \text{dyn/cm}$, $\mu = 0.1 \, \text{g/cm} \cdot \text{s}$ and $\mu_s = 10^{-3} \, \text{g/s}$. The time of rupture of the mucus layer is shown as a function of antisufractant parameter, $M\Gamma_0$, in Fig. 5. The time of rupture increases with an increase in the parameter, $M\Gamma_0$. For illustrative purposes, we assume that $M\Gamma_0 = 3$ for a healthy tear film complete with superficial lipid layer and that in the absence of lipids, $M\Gamma_0 = 1$. This reduces BUT by about a factor of 2 (Fig. 5) and thus...
the presence of normal lipids seems imperative for maintaining a healthy tear film breakup time. Also in view of this, a complete destruction of meibomian glands or the absence of normal lipids may result in an unstable tear film.

**Lipid Abnormality (Increased Surface Activity of Normal Lipids)**

As discussed earlier, pathological conditions such as chronic blepharitis, facial skin infections, and increased activity of the lipase-secreting bacteria because of any number of reasons, alter the normal interfacial activity of lipids, making them much more surface active. The presence of these surface active lipids (free fatty acids, etc.) in the vicinity of the mucus-aqueous interface is energetically favored compared to the normal, less surface active lipids of the tear film. This is so because the polar lipids like fatty acids, triglycerides, and phospholipids have a nonpolar hydrocarbon tail and a polar carboxyl head. Their minimum free energy configuration at the mucus-aqueous interface thus corresponds to the polar, hydrophilic group being immersed in the aqueous tears and the hydrocarbon tail being imbedded in the mucus layer. The possible effect it has on the stability of the tear film is best understood by noting that:

(a) Such a change in the chemical composition of the normal lipids decreases the mucus-aqueous interfacial tension from the value that prevails in the presence of normal lipids. In other words, the interfacial tension decreases to a value of \( \sigma_{\text{app}} - |M\Gamma_0| \) from its normal value of \( \sigma_{\text{app}} = \sigma_0(0) + M\Gamma_0 \), where \( |M\Gamma_0| \) is the decrease in the magnitude of interfacial tension because of the more surface active lipid components (free fatty acids, etc.).

(b) It contributes to the stabilizing effect of interfacial tension driven Marangoni motion as the Marangoni motion is enhanced both by the surface active and antisurfactant solutes alike. Thus assuming no synergistic or interactive effects between the normal and surface active lipids, the Marangoni parameter, \( N \), in Eq. [59] is modified by replacing \( |M\Gamma_0| \) with \( |M\Gamma_0| + |M\Gamma_0| \).

The overall effect of the surface active lipids on the time of rupture is depicted in Fig. 6 for a typical set of parameter values and for varying parameter, \( |M\Gamma_0| \). Curves 1 and 2 show the decrease in the time of rupture as the concentration of surface active lipids is increased. As is apparent from this figure, the marginal increase in the stabilizing effect of the Marangoni motion is completely dominated by the destabilizing effect of the reduction in the interfacial tension. This is expected because as is shown by Eqs. [62] and [63], the Marangoni motion can stabilize the mucus layer only to a certain extent and increasing the parameter, \( N \), by further adding \( |M\Gamma_0| \) to the already existing value of \( |M\Gamma_0| \), does not affect the Marangoni motion significantly. This point is also clear by comparing curves 1 and 3 of Fig. 6 for \( |M\Gamma_0| \) = 0. Curve 3 is drawn for parameter values which are the same as that of curve 1 but by ignoring the stabilizing effect of the Marangoni convection. It is ap-

![Fig. 6. The effect of added surfactant characterized by parameter, \( |M\Gamma_0| \), on the time of rupture of the mucus layer for \( \sigma_{\text{app}} = 5 \) dyn/cm, where \( \sigma_{\text{app}} \) is the mucus-aqueous interfacial tension in the absence of surfactants. The other parameter values are those indicated in Fig. 4.](image)
LIPID ABNORMALITIES

parent that even in the absence of any surface active lipids, the stabilizing effect of the Marangoni convection has reached its asymptotic value due to the presence of normal lipids and other solutes of tear film. The further presence of chemically altered or contaminating lipids thus does not enhance it any further.

It appears that the surface activity of the normal tear components is greatly augmented in a variety of other conditions of immunologic origins as well. Holly et al. (41) detected a pathological increase in the surface activity of the tear components in tears from Stevens-Johnson syndrome patients. The surface activity of these components, which was probably due to highly surface active inflammation products, surpassed even the surface activity of a pure mucin solution (mucin is known to be the most surface active component of the normal tears). A pathologically short BUT of less than 5 s was observed for these patients (41). It appears likely that the rupture of the mucus layer was rather instantaneous in these subjects because of a synergism between all three major deficiencies of a dry eye. The observed breakup times in these patients thus reflect essentially the detwetting times for the tear film supported on a hydrophobic epithelium.

In conclusion, the increased surface activity of normal eye lipids as in chronic blepharitis or the contamination of eye with surface active lipids of other origins (such as the lipids secreted from the sebaceous glands of skin and lipids of cosmetic aids) affect the stability of the tear film and BUT adversely by decreasing the mucous-aqueous interfacial tension that exists in the presence of nonpolar lipids. The same holds true for other conditions in which highly surface active products are formed due to inflammation or immune reaction.

The Role of Tear Substitutes and Surfactants

Closely related to the above discussion are the effects of highly surface active polymers, polymeric surfactants, and cationic surface active preservative such as benzalkonium chloride (BAC), instillation of which in the eye has been shown to affect BUT adversely at concentration levels as low as 0.01% (29, 42, 43). The polymeric substances dissolved in tear formulations presently available are usually substituted cellulose ether group, polyoxymethylene, and polysaccharides, all of which are hydrophilic and exhibit only a slight surface activity (44). The most surface active component of a group of tear substitutes with trade names Ultratears, Tears naturale, Lyteers, Isopototears, and Tearisol, is BAC which is used as preservative at 0.01% or lower concentration levels (44). As shown in Fig. 6, the incorporation of a highly surface active material such as BAC, in the eye, would actually tend to decrease the BUT, thus rendering the tear substitute less effective. In addition, small molecule solutes like BAC may also bring about an increased solubility of the mucus glycoproteins into the aqueous tears by the mechanism of polymer binding (45). This in turn will accelerate the rupture of the mucus layer. The principal role of tear substitutes, in addition to replacing the aqueous tears, appears to be in augmenting the thickness of the mucus layer by absorption and adsorption, increasing the mucous–aqueous interfacial tension, and aiding in Marangoni motion. The latter are important when there is a deficiency of naturally occurring antisurfactants in the tear film.

Based on these criteria, the tear substitutes with trade names Liquifilm and adsorbotears appear to be superior formulations, inasmuch as they are preserved with chlorobutanol (a bacteriocidal agent) and thimerosal, respectively (44), both of which display very little surface activity.

In addition to the effects of the added tear film solutes on the mucous–aqueous interfacial tension, the Marangoni-motion and the thickness of the mucus layer, their effects on the structure and the volume occupied by the mucus molecules may also be significant. It is well known that the hydrated mucus is a rheo-
logically and structurally complex, "fluid" or "sloppy" gel (46) and that the mucoprotein molecules are susceptible to conformational changes in the presence of various solutes (47). For instance, increasing the concentration of KCl and CsCl salts has been shown to decrease the volume occupied by the mucoprotein molecules and the apparent viscosity of the mucoprotein solutions (47). It appears likely that an anomalous decrease in BUT, that is witnessed after the instillation of cationic preservatives like BAC and fluorescein dyes, has its genesis not only in their detergentlike effect on the interfacial tension, but also because they may make the mucus layer collapse to smaller thicknesses. This will result in the reduction of the tear film breakup time.

Specific recommendations that arise from this discussion are that the most surface active ingredient of a tear substitute should not be such so as to have a deleterious effect on the normal mucous-aqueous interfacial tension that is being maintained in the presence of normal lipids and other antisurfactants of tear film and that the tear substitute ingredients should not either solubilize or reduce the mucus layer thickness. Also, in view of the interfacial tension augmenting capacity of the normal lipids, it is desirable to incorporate solubilized normal lipids in tear substitutes when one or more of the lipid abnormalities are detected. Such a formulation has indeed become available recently under the trade name Tear Gard, which, in addition to having a dissolved polymer hydroxyethyl cellulose, has a lipid-containing component called Ultrabase (48). The formulation is preserved with thimerosal, and thus appears to be well suited according to the criteria discussed earlier.

In the future, by refining the existing techniques (and inventing new ones) to detect the various physiological causes of dry eye (mucus and aqueous layer thicknesses and deficiencies and lipid abnormalities) independently, it may be possible to exploit the "specificity" of a tear substitute, i.e., use of only those ingredients that are required to remedy a specific detected cause of the dry eye. In view of this, it seems imperative to invent clinical methods to detect the thickness of the mucus and aqueous layers in vivo.

**Implications for the Clinical Measurement of BUT**

In view of the destabilizing effects of surface active materials (Fig. 7), the instillation of eye drops, fluorescein preparations or the application of topical anesthetics with surface active agents, while conducting a clinical measurement of BUT, may result in a misleading conclusion of a pathological eye when it is not. This, in fact has been pointed out (28) to be a plausible reason for some unsuccessful attempts to correlate clinical symptoms with abnormal BUTs. In addition, various stains such as fluorescein, rose bengal, methylene blue, and alcian blue are frequently used for the clinical evaluation of the various abnor-
malities of the tear film (1). Thus it is to be suggested that the clinical tests of BUT be conducted before the instillation of these stains. These and other precautions should thus lead to a more meaningful estimate of BUT, which was indeed found to be the case (49).

Aqueous Tear Deficiency

As discussed earlier, the effect of aqueous tear deficiency per se is to make the stabilizing effect of Marangoni motion less pronounced. The standard method of evaluating tear secretory volume is the Shirmer test (SCH) in which a filter paper measuring 5 mm in width and about 35 mm in length is placed under the lower eyelid and after 5 min the distance that the tears have extended down the strip is measured (1). A typical value averaged over the age groups is about 30 mm of wetting in 5 min (50). The Schirmer test results for the normals show about 60 mm/5 min wetting for people age 20 or below which declines to about 15 mm/5 min by age 70 (50). The volume of the entire tear film also undergoes about three- to fivefold reduction for the people over age 70 as compared to that existing for the people below age 19 (1). Also, a typical average thickness of tear film between two consecutive blinks is about 4–6 μm (51) and is maximum immediately after blinking (~10 μm). It has been an interesting and somewhat puzzling observation as to how despite such a large variation in the tear volume with age, the most individuals have little discomfort or irritation that accompanies dry eyes (1, 52).

Figure 7 depicts the variation in mucus layer rupture time as a function of aqueous layer thickness for two different values of the parameter, $M_\Gamma_0$. One distinctive feature to be noted is that the time of rupture is rather insensitive to the aqueous layer thicknesses in excess to 4 μm. This feature is in remarkable agreement with the observations cited above. A further reduction in the average thickness of the aqueous layer to about 1 μm, reduces the time of rupture to about 70% of its value in the presence of sufficient aqueous tears (thickness in excess of 4 μm). A Schirmer result of 5 mm/5 min or lower is usually considered abnormal clinically. This low wetting value probably corresponds to an aqueous film of thickness 1 μm or less. Thus, a marginally healthy eye may fall prey to the aqueous tear deficiency of this magnitude. Also a gradual onset of dry eyes in some individuals, which usually occurs in their fifth or sixth decade (7a), may be caused by a constant decline in their tear volume. That this does not happen in majority of cases, possibly indicates a marginal but not pathological eye in youth, which eventually succumbs to the aqueous tear deficiency with age. In the event of a more severe aqueous deficiency the effects become more pronounced (Fig. 7). In addition, for the sub-micrometer-sized tear films, the dispersion force induced thinning of the aqueous film may also become important.

In reality, however, a large aqueous tear deficiency cannot typically be viewed in isolation with the mucus deficiency and lipid abnormality, because of the following two synergisms:

(a) In one of the most widespread causes of the aqueous tear deficiency, keratoconjunctivitis sicca, as well as in some other conditions, the goblet cell population and consequently, the mucus production also decreases in many instances (53).

(b) A reduced aqueous tear secretion rate or tear volume also correlates well with a decreased concentration of tear lysozyme content (54). The tear lysozyme minimizes the activity of gram positive, lipid-hydrolyzing, bacteria present in the gland ducts of the meibomian glands and the tear film. Thus, the aqueous tear deficiency would inadvertently catalyze the transformation of normal lipids into more surface active free fatty acids.

Although, the extent of the above two synergisms may vary from patient to patient, it is obvious that the reduction in the time of rupture as shown in Fig. 7 is an underestimate,
Fig. 8. The effect of the surface viscosity on the time of rupture of the mucus layer; the other parameter values are given in Fig. 4.

especially for the extreme conditions of aqueous deficiency.

Epitheliopathy and Impaired Lid Functions

The mechanism of tear film rupture suggests that if any of several factors such as the uneven or insufficient shear distribution during blinking, incomplete blinking, and the gross epithelial irregularities, result in thinner than normal and uneven mucus coating at some localized sites, the support of tear film will become nonwettable at these spots faster than the normal BUT. In addition, due to a decreased thickness of the aqueous layer over gross epithelial protrusions, the stabilizing effect of the Marangoni motion and consequently, BUT, would decrease. That the rupture of the tear film in these cases is essentially due to the formation of locally dewetting regions devoid of mucus coating is thus rightly identified in a study (16).

The concepts delineated above also help understand as to why the quality and frequency of blinks prior to the clinical test of BUT may also affect the tear film breakup times, as these are some of the factors that determine the thickness and the morphology of the thin mucus film coating the epithelium.

Finally, the stabilizing role of mucus layer surface viscosity is shown in Fig. 8. The effect is most pronounced at low values of $MT_0$. However, it appears that it is probably difficult to manipulate surface viscosity by any direct means when the normal antisurfactants are present in the tear film. In the absence or deficiency of dissolved components, however, the tear substitutes would also contribute towards a higher surface viscosity. This is another therapeutic value of tear substitutes in prolonging the time of tear film rupture.

The Contact Lens Tolerance

An important application of the understanding of tear film rupture is in the normal wearing and functionality of contact lenses. A well-fitted contact lens floats on a continuous tear film sandwiched between the corneal epithelium and the lens (postlens tear film) and is coated with a tear film on the outside (prelens tear film), which is complete with a superficial lipid layer (4, 28). It has been suggested that a premature rupture of the postlens tear film would result in the adhesion of the contact lens to cornea, and epithelial damage is sometimes seen to occur under such circumstances (3). It thus seems reasonable that the tolerance of a contact lens would depend on the postlens and prelens tear film BUTs, but, and it is important, this BUT is not necessarily the same as the tear film breakup time in the absence of a contact lens. The following are the known physiological changes that occur in the tear film due to the insertion of a contact lens:

(a) The adverse effect of contact lens on the lid–globe congruity makes the formation and rejuvenation of an evenly distributed mucus layer on the epithelium more difficult (4).

(b) The contact lens wearers sometimes become lazy blinkers and incomplete blinks are observed. This again affects the even distribution of mucus layer on the epithelium (4).

(c) The wetting characteristics of a lens surface are usually not the same as those of the clean corneal epithelium. Thus in the case...
of a relatively wettable lens surface, the post-
lens tear film may not break even if the corneal
epithelium becomes nonwettable. For a hy-
drophobic lens surface, however, the post-
lens film would break when the cornea be-
comes nonwettable (4).

In the case of a nonwettable lens surface
(silicone lens, etc.), the factors (a) and (b)
would result in a faster than normal rupture
of the mucus layer and thus of the postlens
film. In view of this, a marginally mucus de-
cicient eye, as characterized by a short BUT,
stands greater chances for the adherence of the
lens to the cornea.

In addition to the changes outlined above,
the following changes in the physiology of the
tear film seem imminent after the insertion of
a contact lens which is tightly or steeply fitted
with no congruity between the lens and the
cornea. In this case, the transport of normal
lipids and other antisurfactants of the tear film
(some of which are metabolites) to the mu-
cous–postlens tear film interface is hindered
and thus their capacity to impart stability to
the mucous–aqueous interface is also under-
mined. An increased pumping (the extent of
mixing of prelens and postlens tear films dur-
during blinking), thus seems necessary to replen-
ish the postlens tear film with antisurfactants.
It is indeed a clinical experience that steeply
fitted silicone lenses settle tightly sooner (3).
This is one of the factors that makes the proper
fitting of the contact lens imperative. It has
been shown that the pumping rate for PMMA
hard lenses is 10–15 times higher than that for
the hydrogel lenses (55). It is, however, not
always possible to strike a balance between
various conflicting demands by using presently
available lens materials. For instance, although
the PMMA hard lenses have a higher pumping
rate, they are less wettable than the hydrogels
and due to their initially higher interfacial
tension against aqueous tears (4), they would
be less biocompatible (56, 57).

A second important lens mediated change
that occurs in the physiology of the tear film
is that the contact lens divides the tear film
into two parts. It is likely that the stability of
the mucus layer is now determined by the
thickness of the postlens tear film and not by
the thickness of the entire tear film. As is
shown in the discussion related to the desta-
bilizing effects of the aqueous deficiency (Fig.
7), a division of the tear film would reduce
the postlens film BUT compared to the BUT in
the absence of the contact lens. The closer the
lens to the cornea, the greater would be this
effect and it is likely that in the event of
aqueous tear deficiency and the lack of reflex
tearing, the minimum thickness of the postlens
film formed is only about 1 μm or less. The
resulting 30% decrease in the time of rupture
(Fig. 7) may be devastating for an already
marginally deficient eye. Indeed, it is interest-
ing to note that in a rather novel clinical study
(3), it was found that the tolerance and adhe-
sion of the contact lens could be correlated
well with a composite linear function that in-
cludes both the BUT in the absence of contact
lens and the Schirmer value. Adhesion of the
contact lens to cornea occurred in 50% of the
cases when both the BUT and the Schirmer
value were low, which might have together
compounded the problem. In other groups,
either the BUT was somewhat low but
Schirmer value was high and thus this BUT
would not change significantly due to the in-
sertion of contact lens in the eye, or the BUT
was well above the pathological value and thus
would not alter to a great extent because of
the aqueous tear deficiency. Only 1 lens out
of a total of 11 lenses showed the adhesion of
lens to cornea in this group. Lens wearers with
both high BUT and high Schirmer value
showed excellent lens tolerance.

The qualitative discussion presented above
is a plausible explanation that results from the
proposed model and conclusions drawn
therein. It would, however, be of great interest
to formulate a more rigorous hydrodynamic
model of tear film in the presence of a contact
lens and thus to delineate the tear film–contact
lens interactions more fully.
Morphology of Ruptured Mucus Layer

Adams (58) investigated the morphology of the conjunctival mucus by "filter surface biopsy" and found essentially three types of structures displayed by the conjunctival mucus: (a) the sheet structure, (b) the clusters, and (c) the strands. It appears that these are generated due to the breakup of a relatively homogeneous mucus film caused by the van der Waals forces. The collapse of a relatively homogeneous mucus layer would cause a network-like structure, the retracting mucus being accumulated in the places where the mucus layer was initially thicker. The mucus layer is expected to be locally thicker at the mouths of the mucus secreting goblet cells and in the space between two adjacent goblet cells. The mucus islands and strands were indeed seen to appear on and in the immediate vicinity of the goblet cells, as well as filling the spaces between them and thus forming a network structure (58). A systematic *in vivo* examination of the alterations in the mucus layer, starting with a blink, would be very helpful in further clarifying these and the related issues. Care must, however, be taken so as not to alter the normal rate of thinning and breakup of mucus layer by instillation of surface active stains or fixation techniques. Any *in vitro* study of the rupture of the thin mucus layer should reproduce the physicochemical eye environment faithfully. The duplication of the effective Hamaker constant and the chemical composition of the aqueous tears appears to be necessary while studying the rupture of thin mucus layer *in vitro*.

CONCLUSIONS

Based on our proposed "two-step, double film" mechanism of tear film rupture, a self-consistent hydrodynamic formalism is developed that, aside from the role of mucus layer in the stability of tear film, also accounts for the effects of antisurfactants (or surfactants) and aqueous tear deficiency on the time of tear film rupture.

A reduced mucus production by goblet cells is identified to be one of the principal reasons for the rapid rupture of tear film.

It is shown that the central role of antisurfactants (with respect to the mucous–aqueous interface) of tear film, such as normal lipids, is to augment the interfacial tension of mucous–aqueous interface and to generate an interfacial tension driven Marangoni flow, both of which tend to oppose the thinning of mucus layer caused by the van der Waals forces.

An increased surface activity of eye lipids, that may be caused by various pathological conditions, is shown to have an adverse effect on BUT. Some highly surface active ingredients of artificial tear substitutes, various staining agents and dyes used for clinical testings, and topical anesthetics also undermine the stability of the tear film. This is so because the increased surface activity of dissolved material reduces the mucous–aqueous interfacial tension from that existing in the presence of normal lipids and other naturally occurring antisurfactants of a tear film. In addition, they also appear to encourage an increased dissolution of the mucus layer and make it thinner by inducing conformational changes in mucoprotein molecules (47). These, in turn, lead to a faster rupture of the mucus layer and consequently, a shorter BUT. An abnormally high surface activity of tear components (possibly due to inflammation products) such as that seen in Stevens–Johnson syndrome patients, thus also reduces the BUT.

The deficiency of aqueous tears, among other things, leads to a rapid diffusion or redistribution of normal lipids present in the tear film and thus tends to even out the concentration and interfacial tension gradients caused by the thinning mucous layer. This again undercuts the stabilizing effect of the Marangoni motion and leads to a shorter BUT. The general trend is that the BUT is nearly independent of the aqueous film thickness for all thicknesses in excess of 4 μm. About 30% reduction in BUT is predicted if the average thickness of the tear film within the interblink
period is about 1 μm. In addition to this direct effect of the aqueous tear deficiency, we have also accentuated certain synergisms that may cause a lipid abnormality and a reduced mucus production in the event of decreased aqueous tear secretion.

The various factors identified to cause the dry eye syndromes, and the semiquantitative predictions made are in line with numerous experimental and clinical findings.

Based on this mechanism of tear film rupture, it is suggested that the most active ingredient of a tear substitute should be such so as not to decrease the mucous–aqueous interfacial tension from its normal value prevailing in the presence of naturally occurring anti-surfactants of tear film.

Implications of this mechanism in the normal wearing and functionality of contact lenses are examined with an emphasis on the factors affecting the adhesion of contact lens to cornea.

Finally, it is to be noted that even a carefully conducted clinical test of BUT is only an overall manifestation of several factors discussed and their interactions thereof. Some variability in these measurements is expected to occur because, depending on the quality of the blink, the extent to which the mucus layer is restored or smeared over the epithelium may be different. A robust mean of a statistical sample should, however, be a good diagnostic indicator for a dry eye and its consequences. A widespread use, and refinement of existing techniques to isolate the factors causing the dry eye in a particular instance would lead to more rational and specific treatment policies.

**APPENDIX A**

Subtracting Eq. [30] from Eq. [29], neglecting the lateral diffusion and integrating over the depth of the boundary layer gives

\[
\int_{h}^{h+\delta} \frac{\partial}{\partial t} (C^* - C)dz + \int_{h}^{h+\delta} u' \frac{\partial}{\partial x} (C^* - C)dz
\]

\[
= \frac{D}{\nu} \int_{h}^{h+\delta} \frac{\partial^2}{\partial z^2} (C^* - C)dz + \frac{D}{k_B T} \int_{h}^{h+\delta} \frac{\partial}{\partial z} \left( \frac{\partial \psi}{\partial z} \right) dz. \quad [A1]
\]

Now making use of the definition of surface excess concentration, viz.

\[
\Gamma = \int_{h}^{h+\delta} (C^* - C)dz \quad [A2]
\]

and the Leibnitz's rule for the differentiation of an integral of an arbitrary function \( F(\alpha, x) \), viz.

\[
\frac{\partial}{\partial \alpha} \int_{\phi_1(x)}^{\phi_2(x)} F(\alpha, x)dx = \int_{\phi_1(x)}^{\phi_2(x)} \frac{\partial F}{\partial \alpha} dx + F(\phi_2, \alpha) \frac{\partial \phi_2}{\partial \alpha} - F(\phi_1, \alpha) \frac{\partial \phi_1}{\partial \alpha}, \quad [A3]
\]

one may transform Eq. [A1] to

\[
\frac{\partial \Gamma}{\partial t} - (C^* - C)_{z=h+\delta} \frac{\partial (h + \delta)}{\partial t}
\]

\[
+ (C^* - C)_{z=h} \frac{\partial h}{\partial t} + \int_{h}^{h+\delta} \left[ \frac{\partial}{\partial x} u'(C^* - C)
\]

\[
+ \frac{\partial}{\partial z} w'(C^* - C)dz
\]

\[
- \int_{h}^{h+\delta} (C^* - C) \left( \frac{\partial u'}{\partial x} + \frac{\partial w'}{\partial z} \right)dz
\]

\[
= \frac{D}{\nu}\left[ \left( \frac{\partial C^*}{\partial z} \right)_{z=h+\delta} - \left( \frac{\partial C^*}{\partial z} \right)_{z=h} \right] + \frac{D}{k_B T} \left[ \left( \frac{\partial \psi}{\partial z} \right)_{z=h+\delta} - \left( \frac{\partial \psi}{\partial z} \right)_{z=h} \right]. \quad [A4]
\]

Further, the following simplifications may be noted.
\[ \frac{\partial u'}{\partial x} + \frac{\partial w'}{\partial z} = 0, \quad [A5] \]

\[ \left( \frac{\partial \psi}{\partial z} \right)_{z=h+\delta} = 0, \quad [A6] \]

\[ \left( \frac{\partial C^*}{\partial z} \right)_{z=h} + (1/k_bT) \left( C^* \frac{\partial \psi}{\partial z} \right)_{z=h} = 0. \quad [A7] \]

The matching of concentrations and the fluxes at the end of the boundary layer provides

\[ (C^*)_{z=h+\delta} = (C)_{z=h+\delta}, \quad [A8] \]

\[ \left( \frac{\partial C^*}{\partial z} \right)_{z=h+\delta} = \left( \frac{\partial C}{\partial z} \right)_{z=h+\delta}. \quad [A9] \]

These observations transcribe Eq. [A4] to the following simple form

\[ \frac{\partial \Gamma}{\partial t} + (C^* - C)_{z=h} \frac{\partial h}{\partial t} + \int_h^{h+\delta} \frac{\partial}{\partial x} \left( u'(C^* - C) \right)dz \]

\[ \times u'(C^* - C)dz + \int_h^{h+\delta} \frac{\partial}{\partial z} \left( w'(C^* - C) \right)dz \]

\[ = D \left( \frac{\partial C}{\partial z} \right)_{z=h}. \quad [A10] \]

Now assuming that the variation of \( u \) over the length scale \( \delta \) is negligible, the first integral becomes

\[ \int_h^{h+\delta} \frac{\partial}{\partial x} u'(C^* - C)dz \]

\[ = \frac{\partial}{\partial x} (u'T) + u'(C^* - C)_{z=h} \frac{\partial h}{\partial x} \quad [A11] \]

and

\[ \int_h^{h+\delta} \frac{\partial}{\partial z} w'(C^* - C)dz \]

\[ = -w'(C^* - C)_{z=h}. \quad [A12] \]

The kinematic condition at the mucus-aqueous interface is

\[ \frac{\partial h}{\partial t} = -w - u \frac{\partial h}{\partial x}. \quad [A13] \]

Combining Eqs. [A10]-[A13] finally yields the following equation for the surface excess concentration (valid both for surfactants and antisufractants):

\[ \frac{\partial \Gamma}{\partial t} + \frac{\partial}{\partial x} (u'T) = D \left( \frac{\partial C}{\partial z} \right)_{z=h} \quad [A14] \]

where \( u' = u'(x, t) = u(h) \).

**APPENDIX B**

As discussed earlier, some recent experiments indicate different estimates of both the thickness of the mucus layer (7b) and the tear film breakup times (2b). A study of excised guinea pig cornea employed chemical fixation and freeze substitution techniques in conjunction with electron microscopy to show that the maximum thickness of the mucus layer over the "valleys" of the corneal epithelium is about 0.4–0.8 \( \mu m \) (7b). The minimum thickness is seen to be in the range of 0.05–0.2 \( \mu m \) in the same study (the thickness over the microvilli as shown in Fig. 4 of Nicholis et al.). This minimum thickness is a few times larger than that determined by earlier experiments. According to the proposed mechanism, the van der Waals force mediated rupture would first occur where the mucus layer is locally thin, i.e., on and in the vicinity of the tips of the microvilli. The solid curves in Fig. 9 depict the values of the Hamaker constants and the mucus layer thicknesses that are compatible with the breakup of tear film in 300 s (an estimate for the time of rupture as provided in Ref. (2b)). Separate curves are drawn for different feasible magnitudes of the mucus–aqueous interfacial tension. The dashed curves in the same figure represent the compatible values of the retarded Hamaker constants that can rupture the mucus layer in 10² s (a lower estimate of BUT). The dashed curves are drawn by assuming that the interactions remain retarded for all thicknesses up to the rupture of the film. It is in view of this and a low value of BUT corresponding to the dashed curves that the mucus layer thick-
FIG. 9. The solid curves represent the nonretarded Hamaker constants and the mucus layer thicknesses that are compatible with a BUT of 300 s. The dashed curves are drawn for the retarded van der Waals interactions and a BUT of 100 s.

Note added in proof. While the analysis of the tear film breakup is based in the present paper on the linear stability theory, we have shown recently (59) that the inclusion of nonlinearities does not alter any of the qualitative conclusions. Nonlinearities do, however, accelerate the growth of perturbations and lead therefore to a shorter BUT. The discrepancy between the times of rupture as computed from the present analysis and the nonlinear analysis increases as the amplitude of the initial perturbations (i.e., the corrugation of the mucous–aqueous interface after a blink) increases. Since the extent of interfacial corrugations is expected to depend on the quality and frequency of blinking, this constitutes yet another reason for variability in the clinical measurement of BUT for the same patient.

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