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Transient spreading and swelling behavior of a gel deploying an anti-HIV topical microbicide

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ABSTRACT

Drug delivery of topical microbicidal molecules against HIV offers promise as a modality to prevent sexual transmission of the virus. Success of any microbicide product depends, in an interactive way, upon its drug (the microbicide active pharmaceutical ingredient, API) and its delivery system (e.g. a gel, film or intravaginal ring). There is a widespread agreement that more effective drug delivery vehicles, as well as better APIs, must be developed to improve the efficacy of microbicide products. Non-Newtonian gels are primary microbicide vehicles, but those to date have been created with limited understanding of how their properties govern their spreading and retention in the vagina, which, in turn, govern successful drug delivery. Here, we apply fundamental fluid mechanical and physicochemical transport theory to help better understand how successful microbicide API delivery depends upon properties of a gel and the vaginal environment. We address several critical components of this complex process, including: elastohydrodynamic flow of the bolus of a non-Newtonian fluid; and mass transfer due to inhomogeneous dilution of the gel by vaginal fluid contacting it along a moving boundary (the locally deforming vaginal epithelial surface). Local dilution of gel alters local rheological properties. We evaluated this experimentally, delineating the way that constitutive parameters of a shear-thinning gel are modified by dilution. We supplement the Reynolds lubrication equation with a mass conservation equation to model diluting fluid movement across the moving vaginal epithelial surface and into the gel bolus. This is a physicochemically complex phenomenon that is not well understood. We implement a boundary flux model based upon the elevated hydrodynamic pressures in the cells. Results show that this model produces fluxes that lie within the range of mean values that have been reported. Further experimental characterization of the vaginal wall is required for a more precise set of parameters and a more sophisticated theoretical treatment of epithelium.

1. Introduction

The prevention of transmission of HIV and other sexually transmitted pathogens remains a major global health priority. Although there is a substantial amount of research on creating vaccines against HIV infection, an alternative approach is being developed that delivers molecules that act topically against invading HIV virions within the vaginal environment. These molecules are termed "microbicides" and are being studied in several types of drug delivery systems including gels and intravaginal rings [1,2]. Gels are the delivery system about which the most is currently known, and have been evaluated in a number of clinical trials. Most of those trials failed, but one did succeed in demonstrating a significant reduction in HIV transmission [3]. The reasons for this success and the numerous failures are not well understood. Poor adherence by participants in the trials to proper gel use may have been a factor [4]. This is believed to have derived from the messiness of using some of the gels, which tended to leak out from the vagina. Such leakage, and gel deployment throughout the vagina in general, are biomechanical processes, the details of which depend upon gel properties, applied volume, the geometry of the vaginal canal and the forces acting against the gel (which include elastic squeezing by the compliant vaginal walls, and gravity). Gel deployment along the vaginal canal creates an expanding surface across which microbicidal molecules can be delivered to target fluids (e.g. semen) and tissues (e.g. the vaginal epithelium and underlying stroma). Clearly, there is a need to understand the mechanisms of gel deployment within the vaginal canal, in order to better understand gel design and to interpret biological tests of gel performance in clinical trials.

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There have been a series of analyses of the fluid mechanics of gel flow along the vaginal canal [5–8]. The polymeric backbones of gels give rise to non-Newtonian rheological behavior [9–13]. This behavior is central to understanding gel flow. It generally involves shear thinning and, in some cases, the existence of a yield stress [7]. Early analyses of gel flow approximated the effects of vaginal wall elasticity as a constant squeezing stress along the length of the gel, with no spatial variation in wall deformation along the gel [10–12]. Effects of gravity were considered separately [9–13]. More recently, we began to create a second generation of models that implemented elastic squeezing by distended vaginal walls; effects of gravity could be included simultaneously [5]. In our most recent analysis, we began to address the effect of the ambient fluid within the vagina on gel flow [6]. A relatively small amount of such fluid is sometimes present, but at other times, the ratio of fluid volume to gel volume can approach about 50%. The microbicide gels being developed are highly hydrated, and typically contain small amounts (if any) of cross linking. As a result, their contact with fluid at their boundaries gives rise to a process that is essentially dilution rather than swelling (in which pore fluid pressure may not equal total mechanical stress in the gel). We previously introduced an initial approximate analysis of the gel dilution process, and its effect on gel flow [6]. We supplemented the central elastohydrodynamic problem with a convection–diffusion equation to characterize water transport into the gel. However, we constrained gel volume to be constant, i.e. we implemented a small dilution approximation. As a result, the effect on gel flow was primarily due to time- and space-dependent changes in local gel rheological properties due to inhomogeneous dilution. We measured such properties via serial dilutions of a test gel, and input these to the model. However, because gel volume was constrained to be constant, this model could not characterize the changes in elastic squeezing forces from the vaginal walls due to increasing gel volume. The present analysis addresses that problem directly.

In order to approach this problem, a source term is included within the central Reynolds lubrication equation, to model the mass transfer that takes place across the moving vaginal wall and into the gel bolus. We supplement the lubrication equation with a mass conservation equation for the gel component in the presence of entering water. This treatment derives from multicomponent mass transfer theory. It provides the dilution distribution within the non-Newtonian gel–water solution, and is not restricted to modest dilutions as was necessary in our earlier work [6]. The theory models non-Newtonian fluid flow driven by a longitudinal force (e.g., gravity) and a transversal force (e.g., wall compliance). The gel flow influences transport of fluid from the boundary, which, in turn, causes the volume of the gel to increase. In this analysis we make, and validate, the reasonable approximation that the concentration of water imbibed by the gel is uniform across the height of the thin layer, over timescales relevant to the overall coating flow. We begin by considering a boundary condition in which the fluid velocity at the boundary is constant in time and space. Values of this velocity derive from experimental data on production of human vaginal fluid. This was the boundary condition applied in our previous work [6]. We compare the new results here with our initial ones: these did include a 2-D concentration field solution [6], albeit in the absence of increases in gel volume. Finally, we employ a mechanism for the boundary flux based upon the elevated hydrodynamic pressures in the epithelial cells. The governing Reynolds lubrication equation and convective–diffusive transport equation are solved simultaneously using an implicit multi-step numerical scheme, for each of these cases.

The theory developed here will help shed light on the problem of fluid uptake by microbicide gels and the consequent impact on the time course of gel flow along the vaginal canal. This, in turn, will help improve our understanding of delivery of anti-HIV microbicides, and other molecules, by vaginal gels. More generally, we have created a framework in which to analyze transient dilution of non-Newtonian fluids due boundary fluxes of diluting fluid. This may have broader applicability in fluid mechanics, and in other biological flows that involve such dilution, e.g. fluid flow in the cornea [14].

2. Problem formulation

In this section, we derive a Reynolds lubrication equation appropriate to a multi-component mass transfer problem. This equation must be supplemented by a separate mass conservation equation for gel. The equations are developed in the symmetric domain $-h(x,\ t) \leqslant y \leqslant h(x,\ t)$ and a body force is included in the x-direction. The physical problem and computational domain are sketched in Fig. 1. The model is formulated in a two-dimensional Cartesian domain. The simplification of two-dimensional flow is quite relevant anatomically; the cross section of the undistended human vaginal canal is "H" shaped, with the transverse dimension large compared to the vertical openings on its two sides [15].

For the constitutive model we take the form:

$$\dot{\gamma}_{xy} = \tau_{xy} F(\tau_{xy}) \tag{1}$$

Here, $\dot{\gamma}_{xy}$ is the shear rate and τ_{xy} is the shear stress. One can choose $F(\tau_{xy}) = 1/m_0$ for a Newtonian fluid or, as we do below and have done in our earlier work [5–7]:

$$F(\tau) = \frac{1}{m_0} + \frac{1}{m}\left(\frac{|\tau|}{m}\right)^{(1-n)/n} \tag{2}$$

This is a Carreau-like fluid which exhibits shear thinning and a finite viscosity at zero-shear rate, m_0. Here, m is a viscosity parameter of the Carreau-like fluid and n is the power index. The original Carreau model can be written as $\eta/\eta_0 = (1 + (\lambda\dot{\gamma})^2)^{(n-1)/2}$. Here, η is the viscosity of the Carreau model, η_0 is the zero shear viscosity, and λ is the relaxation time of the fluid. The parameters of the Carreau model can be converted into those of Carreau-like model asymptotically [5] in the relationship $m_0 = \eta_0$ and $m = \eta_0/\lambda^{1-n}$. The two models may be matched at small and large strain rates although they are not exactly equivalent.

The primary assumption in the lubrication approximation is that the thickness of the gel bolus is small relative to its longitudinal extent, i.e. $\epsilon = H/L \ll 1$, where H and L are length scales for the transverse (thickness) and longitudinal directions, respectively. The x coordinate is in the longitudinal direction and the y direction is transverse. In the usual way, we take the limits $\epsilon Re \to 0$ and $\epsilon \to 0$ to obtain the lubrication approximation. The Reynolds number is $Re = HU/\nu$, where ν is a representative kinematic viscosity and U is

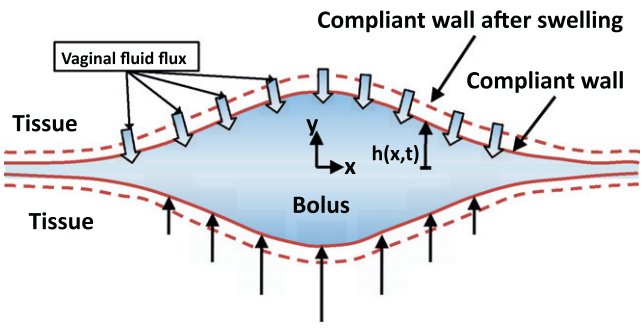

Fig. 1. Definition sketch of the vaginal canal, emphasizing the longitudinal direction. The introitus is to the right. Lower arrows represent the squeezing forces applied by the vaginal epithelium. The transverse direction has an "H" shaped cross section; see text.

velocity scale in the longitudinal dimension. The magnitude of the Reynolds number is small. Given the small magnitude of the Reynolds number and the thin layer assumption, a pressure scale is constructed from the shear stress as $P = (m_0 U)/H$. After making the lubrication approximation, the balance of linear momentum in the x-direction is integrated with respect to y to obtain:

$$\left[-\frac{\partial p}{\partial x}+\sum_{i=1}^{r}\rho_i g\right]y+\frac{1}{F(\tau_{xy})}\frac{\partial u}{\partial y}+c_1=0 \tag{3}$$

where r is the total number of components in the solution (here $r = 2$)), ρ_i is the density of the ith component, and u is the mass-average velocity. Although unusual, it is convenient if we regard one component as the gel (polymer plus water as prepared) and the other component as the added water in the vaginal fluid. This makes it straightforward to relate dilution of the original gel, due to uptake of vaginal fluid, to composition. By symmetry, $\partial u/\partial y = 0$ on $y = 0$; hence the constant of integration c_1=0. Next we solve this equation for $\partial u/\partial y$, integrate with respect to y, and use the boundary condition $u(x, y = -h(x, t)) = 0$. This yields:

$$u=\int_{-h}^{y}F(\tau_{xy})\left[\frac{\partial p}{\partial x}-\sum_{i=1}^{r}\rho_i g\right]y\,dy \tag{4}$$

The global mass conservation equation and gel mass conservation equation can be written as [16]:

$$\begin{aligned}&\frac{\partial \rho}{\partial t}+\vec{\nabla}\cdot(\rho\vec{u})=0\\&\frac{\partial \rho_g}{\partial t}+\vec{\nabla}\cdot(\rho_g\vec{u})=\vec{\nabla}\cdot\rho D_{gw}\vec{\nabla}w_g\end{aligned} \tag{5}$$

where ρ and ρ_g are the densities of the solution and the gel as prepared (including polymer and water), respectively, and $D_{gw}(=D_{wg})$ is the mutual diffusion coefficient. Here, w_g is the density ratio of the gel as prepared to the further diluted solution (ρ_g/ρ) and, $\vec{u}$ is the velocity vector ($= u\hat{\imath} + v\hat{\jmath}$). We assume that the incoming flux is directed only in the y-direction, i.e. $u|_{y=\pm h} = \pm q(x, t)$. In the following, we consider a prototype gel that is prepared as 97% water and 3% hydroxyethylcellulose. The densities of both gel as prepared and added water are close to 1 g/cm^3. Therefore, for simplicity, we assume that the density of the solution remains constant during dilution and swelling. Then, global mass conservation and gel mass conservation read

$$\begin{aligned}&\vec{\nabla}\cdot\vec{u}=0\\&\frac{\partial \phi}{\partial t}+\vec{\nabla}\cdot(\phi\vec{u})=\vec{\nabla}\cdot D_{gw}\vec{\nabla}\phi\end{aligned} \tag{6}$$

Here, $q(x, t)$ is the local vaginal wall flux, which is negative for swelling, and $\phi(x, t)$ is the local volume fraction of the gel as prepared. After substituting Eq. (4) into Eq. (6) and integrating Eq. (6) in the y-direction from $-h$ to h, global mass conservation and gel mass conservation read

$$\begin{aligned}&\frac{\partial h}{\partial t}+\frac{1}{2}\frac{\partial}{\partial x}\left[\left(M\frac{\partial h}{\partial x}-\rho g\right)m_2\right]=-q\\&\frac{\partial(\phi h)}{\partial t}+\frac{1}{2}\frac{\partial}{\partial x}\left[\phi\left(M\frac{\partial h}{\partial x}-\rho g\right)m_2\right]=\frac{\partial}{\partial x}\left(hD_{gw}\frac{\partial \phi}{\partial x}\right)\\&m_2=\int_{-h}^{h}\left[\int_{-h}^{y}F(\tau)y\,dy\right]dy\end{aligned} \tag{7}$$

where M is the compliance of the elastic wall. As in our earlier work, we employ the one-dimensional constrained continuum model [17] approximation to model vaginal wall elasticity. In this approximation, the fluid pressure near a compliant wall is proportional to the local deformation of that wall. In general, for a deformation h, the fluid pressure is given by $p = (E/T)h \equiv Mh$. Here, E is the elastic (Young's) modulus of the compliant layer, and T is its thickness. We take for M the value 20 kPa/cm, as in our earlier work [5,6]. Here, we make the reasonable approximation that the concentration of the gel and water are uniform across the gel thickness, over the timescales of relevance. We also neglect effects of gravity; these are small compared to the squeezing of the elastic wall [5], and such neglect does not detract from the focus of the analysis here.

The boundary fluid velocity, $q(x, t)$ is a quantity that is not well understood. There is remarkably little research on the presence and flow of human vaginal fluid [18–20]. This fluid is produced primarily by a transudation process through the vaginal epithelium [18]. In general it is believed that the rate of fluid percolation through the vaginal epithelium may be variable, depending upon the time of day, the phase of the menstrual cycle, and/or other factors. It is also increased during sexual stimulation [19]. In principle, one might expect that vaginal fluid flow out from the epithelial surface and into a gel coating may be affected by osmotic phenomena, and/or by the hydrodynamic pressure in the vaginal lumen. Here, absent more detailed physiological information, two cases will be studied. First, the boundary fluid velocity is taken as physiological relevant values. This provides a baseline for analysis, and is also the condition utilized in our earlier work [6]. Thereafter the fluid velocity across the epithelial surface boundary is taken as being produced by the elevated hydrodynamic pressure in epithelial cells. We explore other possibilities in another work [21].

The concentration of gel (and therefore of water) is assumed to be uniform over the gel thickness, over relevant timescales. Indeed, taking into account a 2-D concentration field in the analysis would render the model unnecessarily complex, especially with a deformable interface. We studied the 2-D concentration distribution problem in [6] in the limit of modest fluid uptake by the gel, i.e. without gel swelling behavior. The governing equations here are solved implicitly by the Crank–Nicolson method. The Thomas algorithm is used to solve the resulting tri-diagonal linear systems. Central differences are used for the first and second order spatial derivatives.

The initial condition for the shape of the bolus is taken as [5]:

$$h(x, t = 0) = h_\infty + b \cdot \exp[-(x/a)^2] \tag{8}$$

This shape is a mathematical convenience and the details have little effect on the evolution of the fluid flow and dilution profile [5]. The fluid volume of such a bolus (above the offset h_∞) is $V_b = 2abc\sqrt{\pi}$, where c is the vaginal width, i.e. 2 cm. We take the volume to be 3 mL, which is a value typical of microbicide gels. As a scale for the height H, we choose 0.5 cm; this is of the order of magnitude of the maximum height of the bolus at time zero. We choose $h_\infty = 0.05H$ and $b = 0.45H$, and obtain $a = V_b/2bc\sqrt{\pi}$. The boundary conditions at the outlets of the channel far from the gel bolus are given as:

$$\text{at}\quad x=\mp L:\frac{\partial h}{\partial x}=0;\quad \frac{\partial^2 h}{\partial x^2}=0;\quad \frac{\partial \phi}{\partial x}=0 \tag{9}$$

Here, L is the half of the vaginal length, and taken as 20 cm to vanish end effects. These boundary conditions make sense only until such time as the bolus reaches $x = L$, at which point leakage would become an issue. Because we have made no attempt at modeling the introitus or the cervical end of the vaginal lumen, treating the problem after leakage (or pooling at the cervical end) is beyond the scope of our work. It should be pointed out that leakage is a serious issue from the point of view of user acceptability.

3. Results

3.1. Constant boundary flux

The production of vaginal fluid is measured as 1–10 cm^3/day, depending on the phase of the menstrual cycle [20]. If we take

the vaginal surface area as about 100 cm^2, this corresponds to a fluid velocity at the boundary of $q \approx 10^{-9}$–10^{-8} m/s. Hence, for a typical gel vehicle volume of 3 mL the range of dilution by vaginal secretions is 10–30% [13]. It is possible that in this case, a theory that applies for modest dilutions and neglects swelling may be appropriate. However, there is also a volume of native vaginal fluid present in the vagina (approximately 0.5–0.75 mL [18]). Thus, the range of dilution can reach up to values larger than 30%. Here, we treat such a case in order to draw parallels between the present theory – which can take into account significant transient swelling – and our earlier theory, which cannot.

In order to conduct these analyses, the effect of dilution by vaginal secretions on an actual gel, that is biologically relevant, must be included. We obtained data for an aqueous gel containing 3% hydroxyethylcellulose; this gel is very similar to the placebo gel used in the successful microbicide trial [3]. Gel rheological properties at body temperature (37 °C) were obtained for serial dilutions of the gel with vaginal fluid simulant [18], using a constant stress protocol on a TA Instruments model AR 1500ex rheometer, with a 4° cone and 20 cm plate configuration. Shear rates ranged from 10^{-4} to 42 s^{-1} and data were fitted to the Carreau-like model. Measurements were performed for serial dilutions of the gel as prepared (with thorough mixing) with vaginal fluid simulant [18] in 5% increments from 0% to 75%. Parameters of the constitutive equation were obtained for each dilution. Then, these data were fit to a polynomial representation of effects of dilution [6], which took the form:

$$m_0/(\text{Pa s}) = 916.8 \times \exp(-[(1.123-\phi)/0.2915]^2)$$
$$n = -0.6905(1-\phi)^3 + 1.9704(1-\phi)^2 - 0.9217(1-\phi) + 0.6601$$

$$\lambda/(s) = 27936.6(1-\phi)^3 - 18848.0(1-\phi)^2 + 1847.4(1-\phi) + 382.1 \quad (10)$$

where $(1-\phi)$ is the local volume fraction of the added water, and ϕ is the local volume fraction of the pharmacological vehicle, which consists of HEC + water as prepared. We have taken the value $D = 10^{-6}$ cm^2/s for the diffusion coefficient of water through the gel [6].

Evolution of the height profile of the bolus is plotted in Fig. 2. Here, as an upper bound, q is set to 1×10^{-7} m/s. This exceeds somewhat the physiologically estimated mean boundary flux ($q \approx 10^{-9}$–10^{-8} m/s); we have applied it so that swelling can be easily observed in the analysis. At 30 min, the net percent increase of volume of the gel–solvent mixture is 94%, owing to water uptake from the boundaries. Next, we check the accuracy of our assumption that the concentrations of the gel and water are uniform over the gel thickness. The assumption requires the following to be true:

$$t_D \ll t_{flow}; \quad \frac{H^2}{D} \ll \frac{L}{U}; \quad \epsilon^2 = \frac{H^2}{L^2} \ll \frac{1}{Pe} \quad (11)$$

where the Péclet number $Pe = UL/D$ and $U = (MH^3)/(2m_{0L})$. Here, we choose L as a physiological value for the size of the domain in x, i.e. 20 cm, while H is chosen as maximum height of the bolus, which is not fixed, i.e. $H = 0.25$ cm at $t = 0$, and $H = 0.1$ cm at 5 min. At $t = 0$, $\epsilon^2 \sim 10^{-4}$ and $1/Pe \sim 10^{-6}$. After 2 elapsed minutes, the parameters are: $\epsilon^2 \sim 10^{-5}$ and $1/Pe \sim 10^{-5}$. For the rest of the computation, H keeps decreasing. Note that, Eq. (11) can be written as, $H^5 \ll 2m_0DL^2/M$; thus the left-hand-side decreases by the power 5. Consequently, we conclude that over the timescales of interest, the assumption of uniform concentrations over the height of the cross section is well motivated. Moreover, this case is for the highest boundary velocity of fluid, and is a therefore a conservative test of the assumption. For the remainder of the analyses here, lower and more physiologically realistic fluid velocity values at the boundary will be used, which will further support the assumption regarding the concentration profile in y.

The evolution of the volume fraction as a function of longitudinal position in the gel is plotted in Fig. 3. As can be seen, the decrease in gel fractions at the spreading edges of the bolus is more rapid, due to the smaller thickness of the gel there.

Next, we analyze a physiological range of boundary fluid velocities that derives from the data on mean production rates of human vaginal fluid. The height profile of the bolus at 2 h and coating area as a function of time are plotted for several boundary velocity values: $q = 0$ m/s, 1×10^{-9} m/s, 5×10^{-9} m/s, and 1×10^{-8} m/s in Figs. 4 and 5, respectively. As can be seen from the figures, as boundary flux increases the coated area grows more rapidly with respect to time.

3.2. Effect of swelling

The effects of the swelling behavior of the gel on spreading are shown in Figs. 6 and 7. The height profile of the bolus is plotted for several boundary fluid velocity values (zero velocity, 1×10^{-9} m/s,

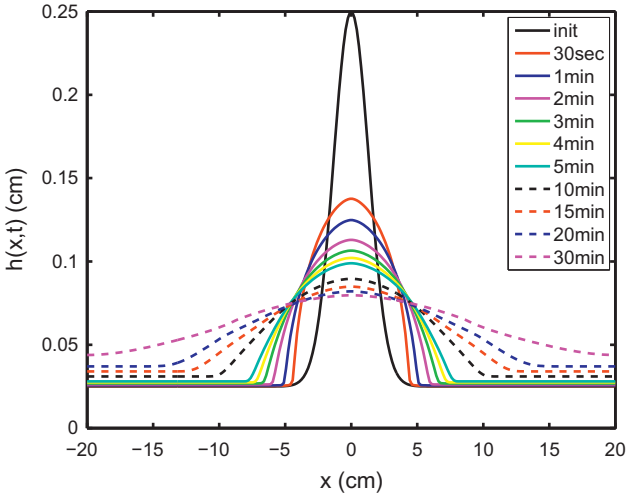

Fig. 2. Height profile of bolus at $t = 0$, 30 s, 1–30 min ($q = 1 \times 10^{-7}$ m/s and $D = 10^{-6}$ cm^2/s).

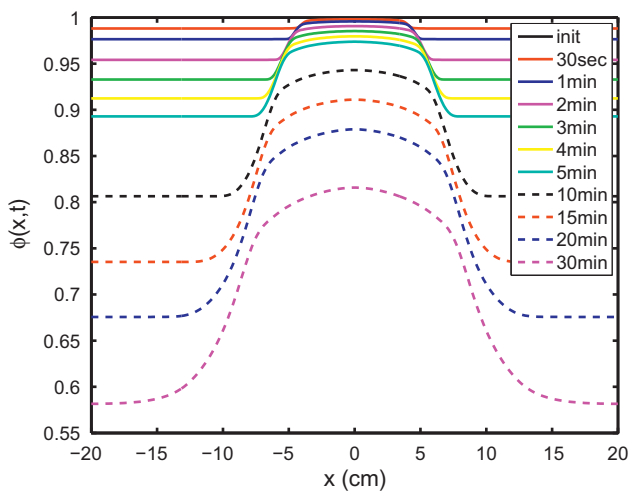

Fig. 3. Volume fraction of pharmacological vehicle vs. x (cm) at $t = 0$, 30 s, 1–30 min ($q = 1 \times 10^{-7}$ m/s and $D = 10^{-6}$ cm^2/s).

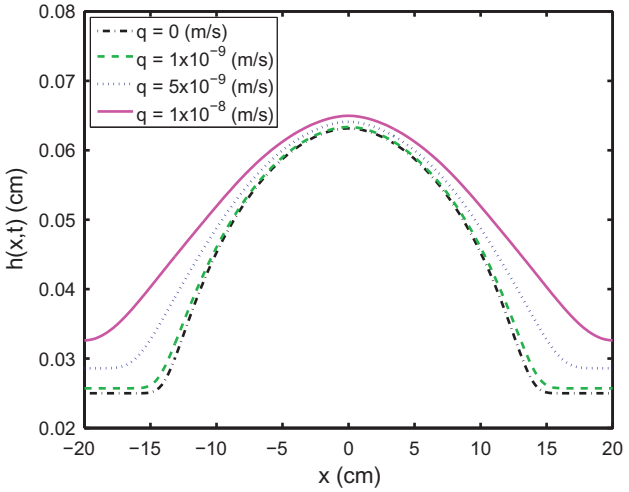

Fig. 4. $D = 10^{-6}$ cm^2/s. Height profile of bolus at 120 min for $q = 0$ m/s (dash-dot), 1×10^{-9} m/s, 5×10^{-9} m/s, and 1×10^{-8} m/s.

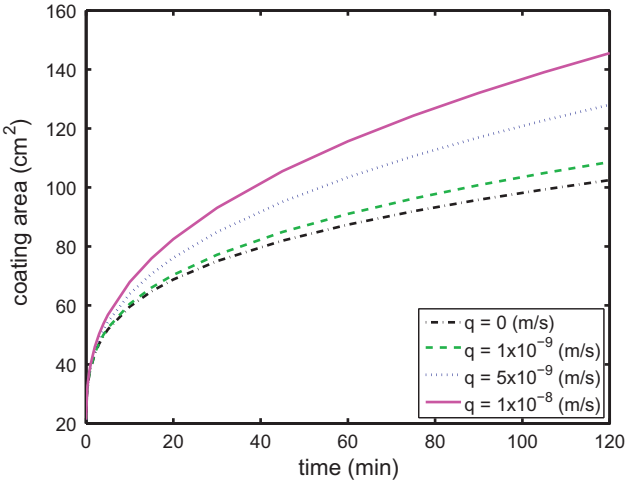

Fig. 5. $D = 10^{-6}$ cm^2/s. Coating area of the gel on the surface for $q = 0$ m/s (dash-dot), 1×10^{-9} m/s, 5×10^{-9} m/s, and 1×10^{-8} m/s.

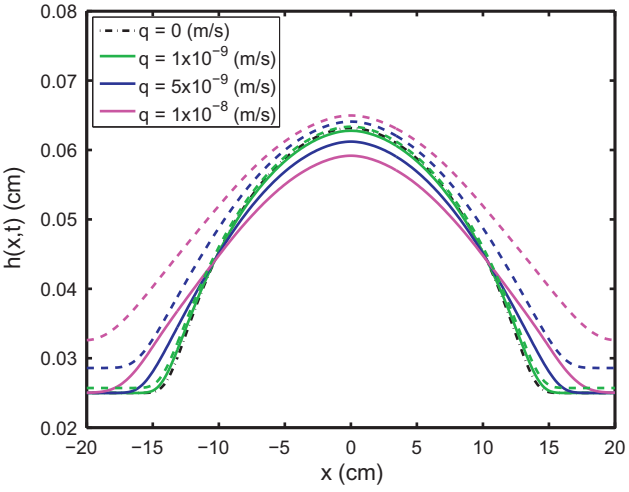

Fig. 6. $D = 10^{-5}$ cm^2/s. Height profile of bolus at 120 min for $q = 0$ m/s (dash-dot), 1×10^{-9} m/s, 5×10^{-9} m/s, and 1×10^{-8} m/s. Solid lines are for the cases without swelling [6]. Dashed lines are for the cases with swelling.

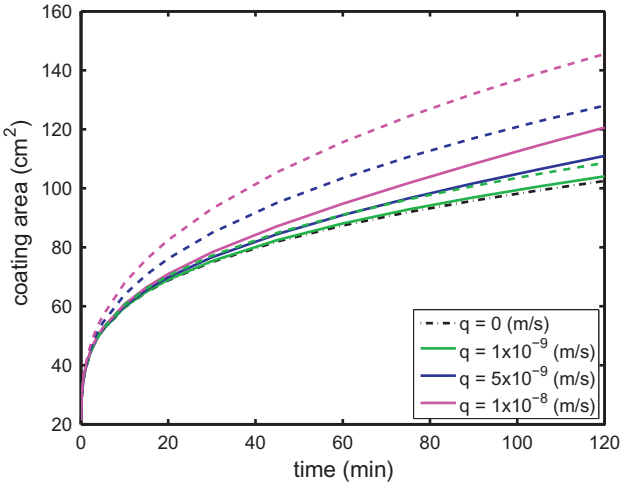

Fig. 7. $D = 10^{-5}$ cm^2/s. Coating area of the gel on the surface for $q = 0$ m/s (dash-dot), 1×10^{-9} m/s, 5×10^{-9} m/s, and 1×10^{-8} m/s. Solid lines are for the cases without swelling [6]. Dashed lines are for the cases with swelling.

5×10^{-9} m/s, and 1×10^{-8} m/s); these are contrasted with our earlier results for these same cases, that did not include swelling, but did allow for a 2-D concentration distribution field [6]. Here, we choose the higher diffusion coefficient cases ($D = 10^{-5}$ cm^2/s), Figs. 10 and 11 in [6]. For $D = 10^{-5}$ cm^2/s, the concentration is almost uniform across the thickness of the gel (see Fig. 13 in [6]) from the very first moment due to fast diffusion in y-direction. Therefore, we can easily compare the results of the same vaginal fluid fluxes and see the effects of swelling behavior. As can be seen from Figs. 6 and 7, the model here (that includes swelling behavior of the gel) indicates more rapid coating. This can be explained by the larger volume of the diluted bolus due to mass transfer and thus, enhanced squeezing forces.

3.3. Boundary flux dependent on the hydrodynamic pressure

In ultrafiltration models, pure solvent flux is governed by $\Delta P/R_m$ [22]. As one potential mechanism – and associated boundary condition – we consider the possibility that the elevated hydrodynamic pressures in epithelial cells drives the flux. In this approach, we assume that the boundary flux is governed by:

$$q(x,t) = \frac{P_{cell}}{R_m} \tag{12}$$

Here, P_{cell} is the pressure elevated in the cell surroundings, and R_m is the membrane resistance. The vaginal epithelium is a stratified squamous epithelium resting on a lamina propria [23]. To our best knowledge, there is no experimental value of the intracellular pressure of epithelial cells. Here, as a biologically based estimate, we use the intracellular pressure of red blood cells, which is approximated as ~20–30 Pa [24,25]. A typical membrane resistance is given as 5×10^{10} Pa s/m in [22].

For this model, height profiles of the gel bolus at 2 h, and coating area as a function of time, are plotted for several membrane resistance values: 5×10^{9} Pa s/m, $R_m = 5 \times 10^{10}$ Pa s/m, and 5×10^{11} Pa s/m in Figs. 8 and 9, respectively. As can be seen from figures, coating area decreases as epithelial membrane resistance increases.

This model, for a boundary fluid velocity that is based on membrane resistance and epithelial intracellular pressure, produces fluxes that lie within the range of mean values that have been measured in experimental work [20].

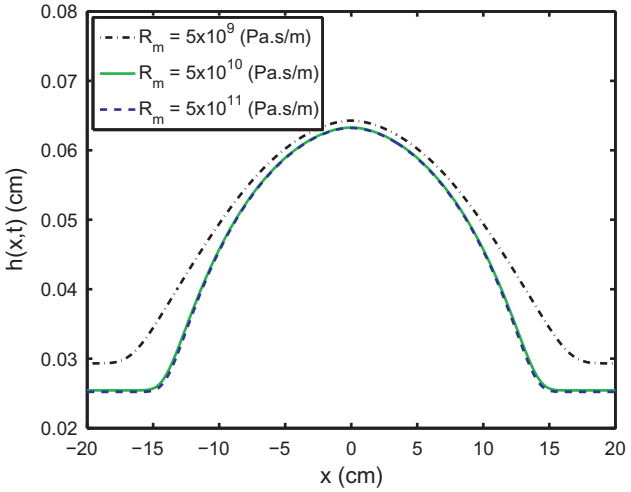

Fig. 8. $D = 10^{-6}$ cm^2/s. Height profile of bolus at 120 min for 5×10^9 Pa s/m, $R_m = 5 \times 10^{10}$ Pa s/m, and 5×10^{11} Pa s/m.

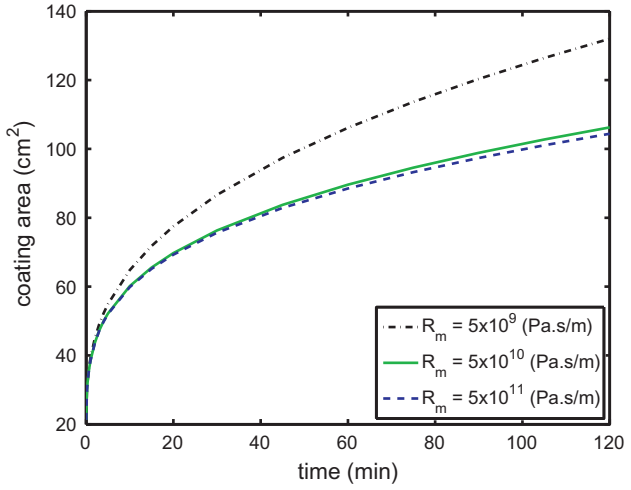

Fig. 9. $D = 10^{-6}$ cm^2/s. Coating area of the gel on the surface for 5×10^9 Pa s/m, $R_m = 5 \times 10^{10}$ Pa s/m, and 5×10^{11} Pa s/m.

4. Discussion

In this analysis, we considered the biophysically realistic context of finite volume changes in a non-Newtonian fluid, due to a different fluid (with properties like water) that is imbibed from its boundary, during the course of an elastohydrodynamic squeezing flow. This improved upon an initial, approximate approach to the problem in which swelling was ignored during dilution [6]. The flow simulates vaginal deployment of a non-Newtonian gel, intended for delivery of topically acting drugs such as anti-HIV microbicides. To model the mass transfer that takes place across the moving boundary surface (which is the vaginal epithelium) and into the gel bolus, we added a source term in the Reynolds lubrication equation. We supplemented the lubrication equation with a mass conservation equation of the gel component, in a treatment that derives from multi-component mass transfer theory. This provided the dilution distribution within the non-Newtonian gel–water solution, and overcomes the restriction of modest dilutions that was inherent in our earlier theory [6]. The resulting theory models fluid flow driven by a longitudinal force (e.g., gravity) and a transversal force (e.g., wall compliance), although in the examples here we considered only the transverse squeezing force (which is a more complex problem than flow due to gravity alone). This flow influences transport of the fluid from the boundary, which is responsible for the swelling of the gel. In order to conduct analysis of the consequences of inhomogeneous boundary dilution, the parameters of the constitutive equation and the volume fraction of vaginal fluid were linked to data from the rheological measurements of a test vaginal gel used in human microbicide research.

We first checked the accuracy of our assumption that the concentrations of the gel and water are uniform across the height of the thin layer. We adapted a conservative approach, actually applying a boundary flux that exceeds somewhat the physiologically estimated mean boundary flux. We concluded that over the timescales of interest, the assumption of uniform concentrations is well motivated.

Scientific inquiry into the mechanism behind the flux from the vaginal wall has scarcely begun. This flux is thought to vary, depending for example on the time of day, or the phase of the menstrual cycle. We first employed a fluid flux at the boundary that is constant in time and space; values of this flux were derived from data on the mean production rate of human vaginal fluid. As boundary flux increased, the coated area was logically found to grow more rapidly with time. This phenomenon of boundary dilution is therefore important to understand from the point of view of the application we have in mind. The model including swelling shows more rapid coating – i.e. larger coating areas – than when swelling is neglected. This can be explained by an increase in the volume of the bolus due to transient swelling and, consequently, increased squeezing forces that drive the spreading process.

We then considered a model where flux is a function of elevated hydrodynamic pressures in epithelial cells. This model leads to estimates the vaginal flux in the experimentally measured range. However, it is not known whether the fluid supply from the first cell layers at the apical side into the lumen can be sustained. These cells would otherwise be depleted as reservoirs of fluid unless upper layers transfer fluid into them over the timescales of relevance.

The fluid transport across the vaginal epithelial surface might be dependent on electro-osmotic forces and/or osmotic gradients, as well. These boundary flux models have been proposed for a range of epithelia [26], including simpler surfaces such as corneal epithelium [27,28]. In other work, we have studied osmotic and electro-osmotic models in the context of an alternative anti-HIV microbicide delivery vehicle, i.e. films [21].

The theory developed here for a vaginal flow of a swelling, non-Newtonian microbicide gel will be useful to the microbicide community. Models such as this can be used to interpret gel performance, including their implementation in analyses of microbicide drug delivery per se [29]. The creation of microbicide gels has only recently begun to implement objective analysis of microbicide deployment within the vagina [30–32]. The improved flow theory can be incorporated into approaches such as these. In addition to the specific application here, this theory may find application in other elastohydrodynamic problems that involve swelling, e.g. fluid flows in the cornea.

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