Experimental and Numerical Models of Three-Dimensional Gravity-Driven Flow of Shear-Thinning Polymer Solutions Used in Vaginal Delivery of Microbicides

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HIV/AIDS is a growing global pandemic. A microbicide is a formulation of a pharmaceutical agent suspended in a delivery vehicle, and can be used by women to protect themselves against HIV infection during intercourse. We have developed a three-dimensional (3D) computational model of a shear-thinning power-law fluid spreading under the influence of gravity to represent the distribution of a microbicide gel over the vaginal epithelium. This model, accompanied by a new experimental methodology, is a step in developing a tool for optimizing a delivery vehicle's structure/function relationship for clinical application. We compare our model with experiments in order to identify critical considerations for simulating 3D free-surface flows of shear-thinning fluids. Here we found that neglecting lateral spreading, when modeling gravity-induced flow, resulted in up to 47% overestimation of the experimental axial spreading after 90 s. In contrast, the inclusion of lateral spreading in 3D computational models resulted in rms errors in axial spreading under 7%. In addition, the choice of the initial condition for shape in the numerical simulation influences the model's ability to describe early time spreading behavior. Finally, we present a parametric study and sensitivity analysis of the power-law parameters' influence on axial spreading, and to examine the impact of changing rheological properties as a result of dilution or formulation conditions. Both the shear-thinning index (n) and consistency (m) impacted the spreading length and deceleration of the moving front. The sensitivity analysis showed that gels with midrange m and n values (for the ranges in this study) would be most sensitive (over 8% changes in spreading length) to 10% changes (e.g., from dilution) in both rheological properties. This work is applicable to many industrial and geophysical thin-film flow applications of non-Newtonian fluids; in addition to biological applications in microbicide drug delivery. [DOI: 10.1115/1.4024140]

Keywords: non-Newtonian, microbicides, topical drug delivery, cellulose, power-law fluid, parametric study, sensitivity analysis, thin film, gravity-driven flow

1 Introduction

HIV/AIDS is a pandemic affecting approximately 33.3 million people worldwide [1]. A microbicide is a vaginally or rectally delivered formulation, consisting of a pharmaceutical agent suspended in a delivery vehicle, intended for preventing HIV transmission during intercourse [2]. The vehicle must have the capability to coat the vaginal epithelium for a specific amount of time, and sustain its structural integrity under the influence of gravity [3], surface tension [4], shearing, squeezing [5–7], and dilution [8,9]. A microbicide delivery vehicle can come in many forms (e.g., gel, cream, vaginal ring, film). Polymer solutions of hydroxyethylcellulose (HEC) (referred to as “gels” by the pharmaceutical research community) have served as a drug delivery platform for potential microbicidal drugs, and have been implemented as the universal placebo for microbicide clinical trials [10].

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The long-term objective of our research group is to use structure-property-function relationships to design an effective topical epithelial drug delivery vehicle. A mathematical model, along with an experimental counterpart for validation, can be used to rationally adjust vehicle structure and properties for a large variety of anatomical, biophysical, and environmental factors. A complete computational model will allow us to investigate the relationship between rheological properties and epithelial coverage, which will impact clinical efficacy.

This study focused on free-surface, thin-film flow of non-Newtonian polymer solutions to represent the gravity-driven flow of a HEC gel (as the delivery vehicle for potential microbicidal drugs) over the vaginal epithelial surface. The shear-thinning rheological behavior of HEC gels can be characterized by the power-law constitutive equation, which has been previously used in fluid flow models utilizing the lubrication approximation [11]. The power-law model has advantages in its tractability for derivations, and in that power-law data can be easily obtained from typical rheometers available to pharmaceutical companies or manufacturers. Non-Newtonian fluid flow is often examined in geophysics, but due to the nature of their applications, most studies use a Hershel-Bulkley constitutive equation, which accounts

for a yield stress as well as shear-thinning behavior [12,13]. Most studies were focused on how yield stress impacted flow behavior with less attention to shear-thinning effects [14–16]. Although not the focus of their paper, using the Herschel-Bulkley model, Huang and Garcia [17] used an analytical solution to identify general trends between power-law parameters and spreading, in the absence of yield stress. Balmforth et al. [18] used a numerical Herschel-Bulkley model to discuss the impact of power-law parameters on the slumping of a yield stress fluid in a symmetric extrusion model.

Most gravity-driven flow models of a power-law fluid have been examined with analytical solutions, which are restricted to inclination angle extremes [19–21]. Perazzo and Gratton have introduced a series of traveling wave solutions [22,23], and have analytically modeled the deformation of the trailing edge of a power-law fluid spreading on a nearly vertical incline [22]. Their work showed that the shear-thinning index had an impact on spreading, but the analysis did not separate the effects of consistency and shear thinning. Haeri and Hashemabadi [24] compared 3D experimental and numerical spreading simulations for a power-law fluid using a volume of fluid (VOF) framework. Kieweg [25] developed a 2D numerical simulation of a power-law fluid, which solved for the evolution of the free surface. Hu and Kieweg [4] isolated the effects of surface tension and shear-thinning parameters on the film thickness in a 2D model. These previous studies motivate the focus of this work of a 3D power-law model which includes lateral flow, and to evaluate if the 3D model predicts experimental measures of axial spreading better than a 2D model.

We have developed an experimental apparatus and accompanying image processing software for conducting gravity-induced, free surface, flow experiments and obtaining surface topography at any instant of time. Previous experiments have been designed for other applications (e.g., geophysical flow [18] and industrial flow [26]), and use several possible strategies to obtain a local fluid thickness (i.e., surface topography) as a function of time, such as an anamorphic Schlieren system [27,28], a laser focus displacement instrument [29], or a fluorescence imaging technique [30,31]. However, the previous methods do not meet all of the criteria we require: a tabletop apparatus and software, a temperature/humidity-controlled environment, a release mechanism to produce a contact-free initial condition for shape, and an algorithm for obtaining spreading measurements and approximating surface topography.

Thus, the objectives of this study were to: (1) develop a 3D computational model of a power-law fluid spreading on an incline and (2) develop a new experiment for obtaining time-dependent free-surface flow characteristics, which was used as model validation. In addition, we investigated two important computational model considerations by evaluating the impact of accounting for lateral spreading and investigating the use of the real experimental initial condition for shape. Finally, an additional objective was to use the numerical model for a parametric study to determine critical parameters, their impact on axial spreading, and their sensitivity to change.

2 Methods

2.1 Problem Formulation. In this study we derive the thin film equation for a power-law fluid spreading in two directions (x and y). The thin film equation is a second-order nonlinear partial differential equation describing the evolution of the free surface as a function of time and space in the x and y direction, $h(x,y,t)$. Figure 1 shows the coordinate system diagram of the three-dimensional (x , y , and z) flow. We start with the conservation of linear momentum (Eq. (1)) where $\mathbf{u}$ and $\mathbf{g}$ are the velocity and gravity vectors, respectively, $\boldsymbol{\tau}$ is the shear stress tensor, p is the pressure, and ρ is the density.

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla) \mathbf{u} = -\frac{1}{\rho} \nabla p + \frac{1}{\rho} \nabla \cdot \boldsymbol{\tau} + \mathbf{g} \quad (1)$$

Fig. 1 Coordinate system and definitions of spreading characteristics in the x (axial) direction and the y (lateral) direction. All experiments and numerical simulations in this study used an $\alpha = 30$ deg inclination angle, except for the steep inclination angle $\alpha = 60$ deg required for the similarity solution in Fig. 3.

The thin-film lubrication approximation [32] reduced the momentum equation (Eq. (1)) to the following three governing equations of motion:

$$x\text{-direction} : 0 = -\frac{\partial p}{\partial x} + \frac{\partial \tau_{zx}}{\partial z} + \rho g \sin \alpha \quad (2)$$

$$y\text{-direction} : 0 = -\frac{\partial p}{\partial y} + \frac{\partial \tau_{zy}}{\partial z} \quad (3)$$

$$z\text{-direction} : 0 = -\frac{\partial p}{\partial z} - \rho g \cos \alpha \quad (4)$$

where α is the angle of the ramp with respect to the horizontal plane (Fig. 1). The power-law constitutive equation [33]:

$$\tau_{ij} = m |\Pi_{2D}|^{\frac{n-1}{2}} (2D_{ij}) \quad (5)$$

relates the shear stress tensor to the strain rate tensor $2\mathbf{D} = (\nabla \mathbf{u})^T + \nabla \mathbf{u}$, where m is the consistency (P s^{n-1}), n indicates the level of shear-thinning behavior ($n < 1$; $n = 1$ corresponds to a Newtonian fluid), and $\Pi_{2D} = (1/2)[(\text{tr } 2\mathbf{D})^2 - \text{tr}(\mathbf{D} \mathbf{D})]$ is the second invariant of the strain rate tensor.

Integrating the z -momentum equation (Eq. (4)) and using a pressure condition on the free-surface $p|_{(z=h)} = p_0$ yields expressions for $\partial p / \partial x$ and $\partial p / \partial y$. Surface tension was not included in the pressure expression because surface tension effects with a power-law fluid were examined in our previous study [4]; the effects of surface tension are discussed in Secs. 3 and 4. We integrate the x and y momentum equations (Eqs. (2) and (3)) to obtain expressions for τ_{zx} and τ_{zy} using the free-surface boundary conditions $\tau_{zx}|_{(z=h)} = \tau_{zy}|_{(z=h)} = 0$. By using the power-law constitutive equation (Eq. (5)), and applying the no-slip boundary conditions $u|_{z=0} = v|_{z=0} = 0$, we solve for the velocities in the axial direction $u(x,y,z,t)$ and lateral direction $v(x,y,z,t)$:

$$u = \left(\frac{\rho g}{m}\right)^{1/n} \left(\frac{n}{n+1}\right) \left(\frac{\partial h}{\partial x} \cos \alpha - \sin \alpha\right) \left[\left(\frac{\partial h}{\partial x} \cos \alpha - \sin \alpha\right)^2 + \left(\frac{\partial h}{\partial y} \cos \alpha\right)^2 \right]^{\frac{1-n}{2n}} \left[(h-z)^{\frac{1}{n}} + 1 - h^{\frac{1}{n}} + 1 \right] \quad (6a)$$

$$v = \left(\frac{\rho g}{m}\right)^{1/n} \left(\frac{n}{n+1}\right) \left(\frac{\partial h}{\partial y} \cos \alpha\right) \left[\left(\frac{\partial h}{\partial x} \cos \alpha - \sin \alpha\right)^2 + \left(\frac{\partial h}{\partial y} \cos \alpha\right)^2 \right]^{\frac{1-n}{2n}} \left[(h-z)^{\frac{1}{n}} + 1 - h^{\frac{1}{n}} + 1 \right] \quad (6b)$$

The flow rates per unit width (flux), in the axial and lateral directions, are found by inserting the velocity expressions into Eq. (7):

$$q_x = \int_0^{h(x,y,t)} u(x,y,z,t) dz, \quad q_y = \int_0^{h(x,y,t)} v(x,y,z,t) dz \quad (7)$$

The resulting expressions for flow rate per unit width are

$$q_x = \Lambda \left(\tan \alpha - \frac{\partial h}{\partial x} \right) \left[\left(\tan \alpha - \frac{\partial h}{\partial x} \right)^2 + \left(\frac{\partial h}{\partial y} \right)^2 \right]^{\frac{1-n}{2n}} h^{\frac{1}{n}} + 2 \quad (8)$$

$$q_y = -\Lambda \left(\frac{\partial h}{\partial y} \right) \left[\left(\tan \alpha - \frac{\partial h}{\partial x} \right)^2 + \left(\frac{\partial h}{\partial y} \right)^2 \right]^{\frac{1-n}{2n}} h^{\frac{1}{n}} + 2 \quad (9)$$

where

$$\Lambda = \left(\frac{n}{1+2n} \right) \left(\frac{\rho g \cos \alpha}{m} \right)^{1/n}$$

The final equation describing the evolution of the free-surface height is obtained by incorporating the flux terms into the conservation of mass:

$$\frac{\partial h(x,y,t)}{\partial t} + \frac{\partial q_x}{\partial x} + \frac{\partial q_y}{\partial y} = 0 \quad (10)$$

Equation (10) was previously written by Perazzo and Gratton [22] and reduces to the Newtonian evolution equation when $n=1$ and m equals the Newtonian viscosity.

The governing equation (Eq. (10), the evolution equation) was rendered dimensionless using the following scalings: $h' = h/H$, $x' = x/H$, $y' = y/H$, and $t' = t/T$, where H was the initial maximum height of the free surface, and T was determined by substituting the scalings into the evolution equation. Thus, the relevant dimensionless groups were n (the power-law parameter which was already dimensionless) and a dimensionless time $t' = t/T = t/(m/\rho g H)^{1/n}$, which represents the ratio of gravity effects to viscous effects. The dimensionless evolution equation becomes

$$q'_{x'} = \Lambda' \left(\tan \alpha - \frac{\partial h'}{\partial x'} \right) \left[\left(\tan \alpha - \frac{\partial h'}{\partial x'} \right)^2 + \left(\frac{\partial h'}{\partial y'} \right)^2 \right]^{\frac{1-n}{2n}} h'^{\frac{1}{n}} + 2 \quad (8')$$

$$q'_{y'} = -\Lambda' \left(\frac{\partial h'}{\partial y'} \right) \left[\left(\tan \alpha - \frac{\partial h'}{\partial x'} \right)^2 + \left(\frac{\partial h'}{\partial y'} \right)^2 \right]^{\frac{1-n}{2n}} h'^{\frac{1}{n}} + 2 \quad (9')$$

$$\frac{\partial h'(x',y',t')}{\partial t'} + \frac{\partial q'_{x'}}{\partial x'} + \frac{\partial q'_{y'}}{\partial y'} = 0 \quad (10')$$

where $\Lambda' = (n/1+2n)(\cos \alpha)^{1/n}$.

Most of the results in this study will be presented in dimensional form for three reasons: (a) the units of the parameters m (P s^{n-1}) and n (no units) in the power-law constitutive equation require that the dimensionless group involving m must also include n , (b) for constant volume applications (as opposed to a constant-flux source of fluid), the dimensional effects of the power-law parameters are important and most easily viewed through a dimensional study (see, e.g., [4]), and (c) the dimensional analysis is more relevant for future studies in the design and optimization of microbicidal gel delivery.

2.2 Numerical Solution. The free-surface evolution equation for a power-law fluid (Eq. (10)) is a nonlinear PDE and was solved numerically for $h(x,y,t)$ using an implicit finite difference scheme which was second order in both space and time, as described in this section. An initial fluid topography $h(x,y,0)$ was used as the initial condition (IC), and the technique to obtain that initial condition for shape is described in the Sec. 2.3. The numerical domain on the inclined spreading surface in the x - y plane (Fig. 1) was a rectangle divided into a finite number of grid points over the given length and width of the simulation dimensions (Fig. 2). The surface was defined by $0 \leq x \leq x_{\max}$ and $0 \leq y \leq y_{\max}$, which was uniformly divided into rectangular cells defined by $N \times M$ points in the x and y directions, respectively. The uniform user-defined cell dimensions were Δx and Δy in the x and y directions, respectively, and were not necessarily equal to each other.

Fig. 2 Domain (Ω) for the numerical method. The domain is divided into N points along the axial direction and M points along the lateral direction. Points along the axial and lateral direction are divided by Δx and Δy , respectively. To improve computational performance, the domain size (and thus N and M) expanded over time to accommodate the spreading fluid, such that the fluid never neared the boundaries, and calculations never used boundary values for h . The spatial index for points in the computational domain is k , and the $M_{1/2}$ indicial notation (used in Eqs. (11) and (13)) indicates the temporary designation of the flux at the node interfaces between the k , $k+M$, and $k-M$ grid nodes.

Figure 2 indicates the use of k as a spatial index in the computational stencil. To improve computational performance, the domain was designed to dynamically expand to accommodate the spreading fluid. Therefore, N and M were not fixed values, and along with the total number of grid points ($TOT = N * M$), were constantly growing throughout the computation.

The spatial derivatives of the fluxes in the evolution equation (Eq. (10)) were discretized using central difference approximations as follows (using the computational stencil in Fig. 2):

$$\left(\frac{\partial q_x}{\partial x}\right)_k = \frac{(q_x)_{k+M_{1/2}} - (q_x)_{k-M_{1/2}}}{\Delta x} \quad (11)$$

$$\left(\frac{\partial q_y}{\partial y}\right)_k = \frac{(q_y)_{k+1/2} - (q_y)_{k-1/2}}{\Delta y} \quad (12)$$

where the $M_{1/2}$ indicial notation indicates the temporary designation of the flux at the node interfaces between the k , $k+M$, and $k-M$ grid nodes. The spatial derivatives of h within the above flux expressions (see Eqs. (8) and (9)) were further discretized using central differences centered about the node interfaces as follows:

$$(q_x)_{k+M_{1/2}} = \Lambda \left(\tan \alpha - \frac{h_{k+M} - h_k}{\Delta x} \right) \left[\left(\tan \alpha - \frac{h_{k+M} - h_k}{\Delta x} \right)^2 + \left(\frac{\partial h}{\partial y} \right)^2 \right]^{\frac{1-n}{2n}} \left(\frac{1}{2} h_k^n + 2 + \frac{1}{2} h_{k+M}^n \right) \quad (13a)$$

$$(q_x)_{k-M_{1/2}} = \Lambda \left(\tan \alpha - \frac{h_k - h_{k-M}}{\Delta x} \right) \left[\left(\tan \alpha - \frac{h_k - h_{k-M}}{\Delta x} \right)^2 + \left(\frac{\partial h}{\partial y} \right)^2 \right]^{\frac{1-n}{2n}} \left(\frac{1}{2} h_k^n + 2 + \frac{1}{2} h_{k-M}^n \right) \quad (13b)$$

$$(q_y)_{k+1/2} = -\Lambda \left(\frac{h_{k+1} - h_k}{\Delta y} \right) \left[\left(\tan \alpha - \frac{\partial h}{\partial x} \right)^2 + \left(\frac{h_{k+1} - h_k}{\Delta y} \right)^2 \right]^{\frac{1-n}{2n}} \left(\frac{1}{2} h_k^n + 2 + \frac{1}{2} h_{k+1}^n \right) \quad (14a)$$

$$(q_y)_{k-1/2} = -\Lambda \left(\frac{h_k - h_{k-1}}{\Delta y} \right) \left[\left(\tan \alpha - \frac{\partial h}{\partial x} \right)^2 + \left(\frac{h_k - h_{k-1}}{\Delta y} \right)^2 \right]^{\frac{1-n}{2n}} \left(\frac{1}{2} h_k^n + 2 + \frac{1}{2} h_{k-1}^n \right) \quad (14b)$$

The discretization for the h^{1+2} expressions in the gravity terms at the end of the flux equations shown above is the power-law version of the discretization used by Kondic and Diez for the h^3 expression in the gravity terms for a Newtonian fluid [34,35].

Next we describe how each of the two $\partial h / \partial y$ terms in the axial flux equations (Eqs. (13a) and (13b)) and each of the $\partial h / \partial x$ terms in the lateral flux equations (Eqs. (14a) and (14b)) were discretized. As mentioned above, the domain Ω was allowed to dynamically grow to accommodate the spreading fluid, such that no fluid reached the boundary of the domain, and no calculation used the h values at the boundaries (i.e., the height remained zero at and near the domain boundaries). With no flux across the domain boundaries, the total volume V of the fluid must stay constant throughout the simulation, as represented in Eq. (15):

$$\frac{\partial V}{\partial t} = \frac{\partial}{\partial t} \iint_{\Omega} h(x, y, t) dx dy = 0 \quad (15)$$

The flux terms must be discretized in such a way to ensure volume is conserved. Therefore, in order to properly discretize these terms, the sum of each discretization over the entire domain must be equal to zero, leading to the following expression (axial flux only shown for brevity):

$$\frac{\Delta t}{\Delta x} \sum_{k=0}^{TOT} \left[(q_x)_{k+M_{1/2}} - (q_x)_{k-M_{1/2}} \right] = 0 \quad (16)$$

According to Eq. (16), if one considers an arbitrary point on the computational grid $k=b$, the following condition must be true to satisfy the conservation of mass:

$$(q_x)_{k+M_{1/2}} \Big|_{k=b} - (q_x)_{k-M_{1/2}} \Big|_{k=b+M} = 0 \quad (17)$$

This results in a technique for discretizing each of the two $\partial h / \partial y$ terms in the axial flux equations (see Eqs. (13a) and (13b)) and each of the two $\partial h / \partial x$ terms in the lateral flux equations (see Eqs. (14a) and (14b)):

$$\text{In Eq. (13a) for } (q_x)_{k+M_{1/2}}: \frac{\partial h}{\partial y} \cong \frac{h_{k+M+1} - h_{k+M-1}}{2\Delta y} \quad (18)$$

$$\text{In Eq. (13b) for } (q_x)_{k-M_{1/2}}: \frac{\partial h}{\partial y} \cong \frac{h_{k+1} - h_{k-1}}{2\Delta y} \quad (19)$$

$$\text{In Eq. (14a) for } (q_y)_{k+1/2}: \frac{\partial h}{\partial x} \cong \frac{h_{k+M+1} - h_{k-M+1}}{2\Delta x} \quad (20)$$

$$\text{In Eq. (14b) for } (q_y)_{k-1/2}: \frac{\partial h}{\partial x} \cong \frac{h_{k+M} - h_{k-M}}{2\Delta x} \quad (21)$$

The need for the above discretizations (Eqs. (18)–(21)) arises from the use of the power-law shear-thinning constitutive equation. The discretizations extend the five-point computational stencil of a Newtonian computation [36] to an eight-point computational stencil (see Fig. 2), and are required to satisfy the conservation of mass. This demonstrates a new attribute of the power-law computational model presented in this paper. The larger computational stencil increases the computational complexity, and calls for careful time discretization and iterative techniques, described next.

The evolution equation (Eq. (10)) was discretized in time using a Θ scheme [34]:

$$\frac{h_k^{p+1} - h_k^p}{\Delta t} + \Theta f_k^{p+1} + (1 - \Theta) f_k^p = 0 \quad (22)$$

where $f^p = f(h^p)$ is defined from the evolution equation as

$$f_k^p = \left(\frac{\partial q_x}{\partial x} \right)_k^p + \left(\frac{\partial q_y}{\partial y} \right)_k^p \quad (23)$$

where $h^p = h(x, t^p)$, p is the time index, and $\Theta = 1/2$, which provided a second-order accurate, implicit, Crank-Nicholson scheme. Applying the discretization to every point in the domain resulted in $TOT = N * M$ nonlinear equations F_k ,

$$F_k(h_k^{p+1}, h_{k+M+1}^{p+1}, h_{k-M+1}^{p+1}, h_{k+1}^{p+1}, h_{k-1}^{p+1}, h_{k+M}^{p+1}, h_{k-M}^{p+1}, h_{k+M-1}^{p+1}) = 0 \quad (24)$$

for $(0 \leq k \leq TOT - 1)$

with $TOT = N * M$ unknown, where the superscript p represents the time index and the subscript k is the computational node in space. The nonlinear system was solved using Newton's method, which was set to converge as the first norm of the height changes fell below 10^{-9} . At each iteration of Newton's method, the linear system was solved using a preconditioned biconjugate gradient method (considered converged as first norm fell below 10^{-6}), where the preconditioner was found using incomplete LU

factorization of the Jacobian matrix. A simple positivity preserving scheme was implemented by setting $h = 0$ wherever a negative numerical solution occurred at a mesh point—a numerical phenomenon common to these type of numerical methods for the thin film equation [37]. As reported below, volume was monitored and conserved with this scheme.

In the event that either Newton's method or the bioconjugate gradient method did not converge within a user-defined number of iterations, the time step dt was decreased and Newton's method was repeated for that time step. Alternatively, if Newton's method converged within an acceptable number of iterations, the time step dt was gradually increased at each time point. This time adaptation technique was confirmed to yield acceptable spreading results compared to a simulation continuously ran at $dt = 10^{-5}$ s. The benefits of employing this downward and upward time adaptation strategy were immediately evident as the computation time for 90 s of spreading resulted in approximately 5 days of computation, as opposed to an approximated 29 days if the code was to continuously compute at $dt = 2.5 \times 10^{-4}$ s. We note that the computational expense of these methods were anticipated, as 3D finite difference numerical solutions of the Newtonian thin film equation are known to be computationally expensive [35,38], as we also found in our previous work with 2D numerical simulations of a power-law fluid with surface tension [4].

The numerical model was validated with convergence, volume conservation, and similarity solution studies. A mesh convergence study showed spatial mesh convergence for refinement in both x and y directions. After performing the mesh convergence study, all simulations in this study used $dx = dy = 0.01$ cm, which provided a reasonable computation time. For all computations, the volume was conserved within 0.0001%. In addition, a similarity solution [4] to the 2D version of the power-law evolution equation was found using the method of characteristics (as outlined by Huppert [39] for a Newtonian fluid), and used to verify the numerical solution for a relatively steep case required for the self-similar solution.

2.3 Experimental Methods. We experimentally investigated the free-surface spreading of a hydroxyethylcellulose (HEC) polymer, with varying HEC concentrations. The experiments served two purposes: (a) measure the initial shape of the fluid to be used as the initial fluid thickness $h(x,y,0)$ input into the computational model, and (b) to measure the shape of the fluid as it spreads over time, and compare with numerical solutions. Gravity-induced spreading experiments of a 2.4%, 2.7%, and 3.0% HEC gel (manufacturer: Hercules, lot C1763, type: Natrosol 250 HX PHARM) were conducted in a temperature/humidity-controlled chamber (see the Appendix for more details on the custom experimental apparatus), with each concentration tested in triplicate. The HEC formulation and concentrations for this study were based upon, and centered about, the 2.7% formulation used as the universal placebo in microbicide trials [10], and resulted in a consistency range (Table 1) which spanned values used in commercial vaginal gels [3,6]. The legend of Table 1 states the methods used for collecting rheological data at 37 °C. The densities of HEC solutions are close to 1 g/cm³ and stay constant under dilution (see, e.g., [9]); thus, a density of 1 g/cm³ was used for all HEC concentrations throughout this study. Blue food coloring dye (0.3 ml) added to the gel accentuated the gel edges from the background and improved image analysis. The gel was allowed to spread on a Plexiglas surface tilted at a 30 deg incline with respect to the horizontal plane. The gel was released using a mechanism designed to produce a “contact free” initial condition for shape to ensure that the gel would be remotely released from a syringe onto the spreading surface at a rate which is consistent between experiments (see the Appendix for more details on the release mechanism).

After the release, gel spreading was recorded using a high definition camcorder (Aiptek HD-DV, 1280 × 720 HD, 30 fps) posi-

Table 1 Power-law parameters. Power-law parameters for gels of three different HEC concentrations, with each concentration tested in triplicate. m = consistency, n = shear-thinning index. Rheology testing was done at 37 °C, on an AR 2000 Rheometer (TA Instruments), with a 40 mm 2 deg aluminum cone geometry. The gel was tested using shear-rate sweep over 0.1 to 100/s, on a log scale sampling for 3 min at each shear rate. Plots of shear stress versus shear rate were similar to that in published literature for HEC solutions, e.g., the microbicide “universal placebo” [10], and are not shown for brevity. R^2 values represent the goodness of fit of the mean rheological data to the power-law equation.

HEC concentration % (w/w)	m (P s ^{$n-1$})	n	R^2
2.4	227.92	0.5951	0.9806
2.7	343.39	0.5543	0.9793
3.0	479.62	0.5207	0.9789

tioned directly outside the chamber, with an approximately 0.5 mm resolution for each pixel. In order to avoid the complexities of synchronizing two separate cameras, for the side and top view, a mirror was installed with the reflective plane 45 deg to both the spreading surface and the camera. Acquiring gel measurements and reconstructing the free-surface topography at an instant of time was done using custom image processing/reconstruction software, developed in LabVIEW (NI Vision). (See the Appendix for more details on image processing methods.) Fluid bolus dimensions were directly measured from the binary image, and defined the fluid shape as follows.

The free-surface topography was reconstructed on the $N \times M$ grid. N and M were the number of spatial nodes in the axial and lateral direction, respectively (see Fig. 2). The topography of the fluid was constructed by combining the views of the axial (side-view profile seen in camera view) and z planes (footprint seen in mirror), while assuming a cross section along the lateral plane, which was not captured in the camcorder view. (See the Appendix for more details on the cross-section assumption in the fluid topography measurement.) The resulting topography defined $h(x,y,t)$, and the shape's initial condition is called the “real IC” throughout this study. In addition, summary dimensions were measured and defined as: maximum length, width, and height at the *initial* time (L, W, H) as well as the maximum length, width, and height at each *subsequent* time point ($L_{\text{front}}, W_{\text{max}}, h_{\text{max}}$).

This analysis was applied to the entire 180 s sequence to arrive at a plot representing bolus dimensions with respect to time. In this study, the experimental data are presented for the first 90 s in order to compare with the 90 s numerical simulations. As mentioned above, the numerical computations were expensive, as expected, and thus restricted to this timeframe.

2.4 Experimental and Numerical Comparisons. To compare with a total of nine experiments (three HEC concentrations tested in triplicate), a numerical simulation was computed in accordance with each of the nine experimental runs. Each simulation used the initial topography of the experiment as the computational initial condition. Power-law parameters for the HEC gels (Table 1) were determined from rheological data (described in the Table 1 legend) and used as input to the computational model. These comparisons were used to study the effects of:

- 1. Lateral spreading:** We compare the 3D model and experiment to determine if accounting for lateral spreading is a critical consideration for computing axial spreading length, and if it is an improvement over a 2D model that does not include the lateral dimension.
- 2. Initial condition:** A study was conducted to determine the importance of the initial condition for the shape used in the 3D numerical simulation. Initial values for $h(x,y,t)$ describe the initial condition of the shape, and were input into the

computations. For each of the nine experimental runs, we performed a numerical simulation that used: (a) the real experimental initial condition (IC) of the shape reconstructed using the technique outlined in Sec. 2.3 (referred to as real IC), and (b) an approximation of the initial condition that used the initial maximum shape dimensions (L, W, H) from the experiment, but approximated the footprint and side profile instead of using the measured images. The approximate shape was described as

$$h(x, y) = -\left(\frac{x}{a_1}\right)^4 - \left(\frac{y}{a_2}\right)^4 + H \quad (25)$$

where the coefficients a_1 , a_2 , and H were chosen to create a profile to match the experiment's initial maximum length, width, and height (L, W, H) within 1 mm of the measured values (referred to as "approximate IC"). Thus, both the real IC and approximate IC used the initial maximum length, width, and height of the fluid, but only the real IC incorporated the side profile and footprint details to describe the fluid's topography.

2.5 Parametric Study and Sensitivity Analysis. The 3D numerical model was used for the parametric study and sensitivity analysis to analyze the impact of power-law parameters on flow, and how sensitive the solution was to changes in parameters. All simulations for the parameter and sensitivity analysis were conducted for 90 s of spreading on a 30 deg incline. For the parametric study and sensitivity analysis, Eq. (25) was used again, but without experimental input, to construct a generic initial condition for a shape with $W \times L \times H$ (defining the maximum dimensions of the fluid at initial time) set to $2 \text{ cm} \times 2 \text{ cm} \times 0.5 \text{ cm}$. The shear-thinning and consistency parameter ranges most applicable to vaginal gels [3,6] were considered: pseudoplastic index in the range of $n=0.3$ to 0.9 , and a consistency within the range of 200 to 600 P s^{n-1} .

3 Results

In addition to numerical model validation through mesh convergence and volume conservation studies described in Sec. 2, the numerical model was also verified using the power-law similarity solution [4]. The 3D numerical model showed agreement with the similarity solution, as seen in Fig. 3. The solution for $h(x, y, t)$ in the fastest-flowing simulation ($m=200 \text{ P s}^{n-1}$, $n=0.9$) and the

Fig. 3 Numerical model verified through comparison with similarity solution for power-law fluid. Comparison of side-view height profile, at 90 s of spreading, obtained from the 3D numerical model and the 2D similarity solution. There is agreement between the numerical and similarity solution, verifying the numerical method. Input parameters for both solutions: $\alpha = 60$ deg, $m = 1000 \text{ P s}^{n-1}$, $n = 0.75$. Note: The profile of the 3D numerical model is cut at the centerline along the lateral axis.

axial velocity equation (Eq. (6a)) was used to estimate the largest axial velocity (U) for an estimate of the largest Reynolds number, Re . A modified Reynolds number for a power-law fluid (e.g., see [22]) is $Re_{PL} = (\rho U^{2-n} H^n / m)$; with $H = 0.5 \text{ cm}$, the maximum Reynolds number was approximately 0.001.

Figure 4 shows example images (Fig. 4(a)) and the resulting surface topography (Fig. 4(b)) obtained with the new experimental method, and includes an example of topography at both initial and later time points. The results show agreement between the photographed images and resulting digitized surface meshes. As expected, we did not observe a fingering pattern (an emerging, lateral corrugation of a moving contact line observed in many thin films flowing down an incline, see, e.g., [35]) at the spreading front for this small fixed volume and shape of liquid. The presence of a capillary ridge, which heralds the fingering instability, and the wavelength of a fingering pattern depends on many factors, including viscosity, surface tension, and inclination angle [4,36]. In these experiments, either the critical angle for an observed fingering instability in this viscous material was not reached, and/or the fingering wavelength exceeded the small width of these samples.

Figure 5 shows one example of experimental results for maximum length, width, and height over time, while Fig. 6 shows maximum length versus time for all nine experiments (numerical comparisons discussed in Sec. 3.1). The nine experiments are shown on separate plots so that they can be directly compared with their matched numerical simulations since each simulation is paired with the corresponding experimental initial condition. Table 2 provides a statistical summary of the experimental data sets at several time points. These data show that the experimental method can discern differences between the spreading lengths of these three gel concentrations, and that the experimental setup dispenses repeatable experiments. These three gel concentrations had similar spreading widths, as can be seen in the overlap of the mean $\pm$ SEM ranges for lateral spreading widths shown in Table 2. A wider range of gel concentrations may be required to discern differences between lateral spreading and height.

3.1 Effect of Inclusion of Lateral Spreading in Model. Two numerical simulations were compared for each of the nine experimental runs: (a) 3D numerical simulation, which used the real experimental topography as the numerical initial condition (real IC), and (b) 2D numerical simulation, which used a cross section, cut along the midline in the lateral plane, of the real experimental topography for the numerical initial condition. Figure 5 shows one example of experimental results in comparison with corresponding numerical solutions. Figure 6 shows the comparison of all nine experiments for maximum length with the corresponding 3D and 2D numerical simulations. Table 3 shows the error between the experiment and each type of simulation, for length, width, and height at $t = 90 \text{ s}$. In each comparison, regardless of HEC concentration, the 3D model showed an improvement over the 2D model for axial spreading: at $t = 90 \text{ s}$, the rms errors of the 3D models were 7% or less than the mean experimental value, and the rms errors of the 2D models were almost 50% of the mean experimental value. However, the 3D models overestimated lateral diffusion (see also Fig. 5(b)): rms error was 31.0%–52.1% of the mean experimental value at $t = 90 \text{ s}$. The possible reasons for the overestimation in lateral spreading, such as surface tension and wettability, are described in Sec. 4. Both the 2D and 3D simulations underestimated the maximum height [see also Fig. 5(b)]: rms error was 26.1%–52.6% of mean experimental values at $t = 90 \text{ s}$. This was expected based on our previous study [4] which focused on the effects of surface tension on spreading and height of a power-law fluid in a 2D model. That study showed that the inclusion of surface tension simulated the increased height of the experimentally observed capillary ridge near the spreading front, and slightly restrained the spreading length. It also showed that the capillary ridge effect is less

Fig. 4 Example of experimental images and reconstruction of surface topography. (a) Comparison of photo image (immediately after the gel was dispensed on the spreading surface) with resulting digital surface topography of three repeated experiments (runs 1–3) of the 2.7% HEC gel. Left: Top and side view of the photograph image of experiment initial condition. Right: Top contour and side profile of the resulting digital surface topography. (b) Isometric views of the evolution of the digital surface topographies of a spreading experiment at $t = 0, 60$ and 120 s (RUN1 of 2.7% HEC gel). (c) Diagram showing how the experimental top and side view were used to define the footprint, height, and cross-sectional shape of the surface topography at any time point (see Appendix). The values for d_b , d_t , and h_{peak} (in mm) were measured from the footprint (top view) and side-profile images along each value of x , and used to define the approximate lateral shape not seen by the camera [see Eq. (A1) in the Appendix]. The resulting measurements of $h(x,y)$ at $t = 0 \text{ s}$ defined the initial condition for the experimental shape (real IC) and were used as input in the numerical model. The maximum length, width, and height obtained from $t = 0 \text{ s}$ footprint and side-profile images were also used to describe the approximate IC.

pronounced for more shear-thinning fluids. The effect of surface tension on height for a power-law fluid was isolated in that previous study, and thus surface tension was not included in this 3D model as it greatly increases computational expense. Therefore, the sensitivity and parametric studies focus on spreading length, and not height.

Figure 5(a) also shows how the 3D numerical velocity, calculated by differentiating the L_{front} versus time data, approaches the experiment velocity much earlier and plateaus much closer to the experiment than the 2D numerical model. However, even the 3D numerical velocity behaves differently than experimental velocity at early times, and this was reflected in the differences in spreading lengths at early times. Thus, these new experimental results indicate that the numerical simulations of constant volume flow do not capture the early time experiment velocity behavior for these fluids. The sharp early time drop in velocity in this numerical model is similar to other numerical results in the literature for Newtonian fluids, e.g., [40]. Possible explanations for these differences in front velocity between numerical simulations and experiments are summarized in Sec. 4.

We also explored whether incorporating an initial shape from a later experimental time point as the numerical initial condition

would improve the 3D numerical model. For each experiment, we compared an additional 3D numerical simulation (not shown in figure for clarity) to the original simulation. The additional numerical simulation used the experimental topography starting at $t = 60 \text{ s}$ (rather than $t = 0 \text{ s}$) for the initial condition, when H/L ratio is substantially smaller. Like the original simulation, starting the computation at $t = 60 \text{ s}$ showed an overestimation at early times, and then matched the original simulation within 30–40 s.

3.2 Effect of Real Versus Approximate IC in Model. Table 3 also provides rms errors for the simulations using the real and approximate initial condition (IC) defining the 3D surface topography $h(x,y,0)$. At $t = 90 \text{ s}$ the IC which provided the smaller rms error varied over gel concentration and the measurement (length, width, or height). Figure 7 shows an example of numerical and experimental spreading data over the full time range for a 2.7% HEC gel. In this experiment, for the spreading length measurement at $t = 90 \text{ s}$, the approximate IC model was closer to experiment than the real IC (see also Table 3 for the smaller rms error for the approximate IC compared to the real IC for the three 2.7% gel experiments). At the earliest times, Fig. 7 shows that the

Fig. 5 Example experimental result with corresponding numerical simulations. Sample spreading characteristics (L_{front} , W_{max} , h_{max} : maximum length, width, and height at each time point) and the axial velocity of the moving front for a sample run of 2.4% HEC (run 1) with real IC used in the numerical simulations. This figure is an example showing that both the 2D and 3D numerical models overestimate axial spreading when compared with experiment, but the 3D model is an improvement over the 2D model (see Table 3 for quantified errors). (a) Black (left axis): Maximum axial length (L_{front}) over time for 2D and 3D models, and experiment. (a) Red (right axis): Velocity of the moving front over time for 2D and 3D models, and experiment. (b) Black (left axis): Maximum lateral width (W_{max}) over time for 3D model and experiment. (b) Red (right axis): Maximum height (h_{max}) over time for 2D and 3D models, and experiment.

approximate IC simulation took approximately 0.5 s for the center of mass to move closer to the leading edge and advance the contact line (defined as a “waiting time solution” [41]). As seen in the Fig. 7 example, the real IC simulations did not show waiting time behaviors. The waiting time behavior was observed for all approximate IC simulations.

3.3 Parametric Study. The contour lines in Fig. 8(a) show the final position of the moving front L_{front} after 90 s of spreading, over a range of power-law parameters. In general, it shows that a fluid with smaller values of m and smaller shear-thinning effects (i.e., larger n) will spread further in the axial direction, at a given inclination angle. The angle of each contour line represents the

relative impact of the two parameters n and m . For example, a vertical contour would indicate that axial spreading was independent of the consistency. A horizontal contour would indicate that axial spreading is independent of the shear-thinning index. A contour slanted at a 45 deg angle represents that both parameters have an impact on spreading in this parameter range, which is evident in this analysis. Figure 8(b) is a dimensionless plot of the parametric study of axial spreading showing the same trends. Dimensionless analysis reveals that the effect of consistency m are only found in dimensionless time, and the axial spreading is a function of the ratio of gravity to viscous effects.

Figure 9 examines how the change in velocity of the traveling front depends upon the power-law rheological parameters. We define a change-of-rate indicator ζ ,

$$\zeta = \frac{(A_{L_f} - A_s)}{A_s} \quad (26)$$

where A_{L_f} is the area under the L_{front} versus t plot, and A_s is the area under the same plot assuming that it was a straight line between the first and last time points (i.e., constant velocity). Thus, the change-of-rate indicator ζ represents the relative deviation of a L_{front} versus t plot from a straight line (i.e., constant velocity), to a plot of L_{front} showing decelerating spreading (as it does in Figs. 5 and 6). For example, if the velocity of the spreading front was more constant, then the change-of-rate indicator would approach zero. Figure 9 indicates that both the consistency and the shear-thinning index influence the acceleration and deceleration of the spreading front. Figure 9 also shows that minimizing the shear-thinning index would result in a smaller value for ζ , and thus a more constant velocity, especially for a larger consistency m . In addition, increasing the consistency would result in a more constant spreading velocity.

3.4 Sensitivity Analysis. We define percent sensitivity of axial spreading to percent changes in a power-law parameter, as $(L_{\text{front, change}} - L_{\text{front, original}})/L_{\text{front, original}} \cdot 100\%$, where $L_{\text{front, original}}$ is the value of L_{front} at 90 s of spreading for a given power-law parameters (i.e., n and m), and $L_{\text{front, change}}$ is the value of L_{front} at 90 s of spreading after making a 10% change to the power-law parameter. The original values for L_{front} were presented in the axial spreading data in Fig. 8(a) for the nine numerical simulations in the parametric study, and 27 additional simulations were used to calculate percent sensitivity.

Figure 10(a) shows percent sensitivity of axial spreading to 10% increase in the shear-thinning index. For these simulations, a gel with a large value of m and $n=0.6$ was most sensitive to changes in n . Figure 10(b) shows percent sensitivity of axial spreading to 10% decrease in the consistency. Making 10% changes to m will result in the most changes to axial spreading at the lowest values of n and m of these simulations. Comparison of Figs. 10(a) and 10(b) indicates percent sensitivity to individual changes in m or n in the range of 3%–5%. Figure 10(c) shows percent sensitivity of over 8% in axial spreading after making 10% changes to n (increase) and m (decrease) combined. For these simulations, the largest increase in axial spreading occurred when changing m and n at mid ranges.

4 Discussion

4.1 Model Versus Experiment—Critical Considerations. In order to use computational data to optimize ideal spreading characteristics of potential delivery vehicles, the numerical model must capture the relationship between a gel’s physicochemical properties (e.g., constitutive equation) and spreading length. We show that the power-law constitutive equation can be used to simulate HEC polymer flow, and that the power-law parameters are critical values for predicting spreading behavior *in vivo*. The final model can be used to easily quantify the influence of other

Fig. 6 Experimental and numerical results for all nine experiments. Comparison of axial spreading of all nine experimental runs (three runs [R1, R2, R3] of 2.4%, 2.7%, and 3.0% HEC concentration), and the matched numerical simulations that used the corresponding real experimental initial condition (real IC). Experiment (dot), 3D numerical model (solid), 2D numerical model (dashed).

Table 2 Summary of all experimental results over several time points. Mean and SEM (standard error of the mean) are reported for three repeated experiments for each gel concentration (% HEC). (The length data for each of the nine experiments are plotted over all time points in Fig. 6.)

HEC	Time (s)	L_{front} (mm) (mean $\pm$ SEM)	W_{max} (mm) (mean $\pm$ SEM)	h_{max} (mm) (mean $\pm$ SEM)
2.4% HEC	0	40.7 $\pm$ 0.18	23.8 $\pm$ 0.51	7.5 $\pm$ 0.28
	30	59.4 $\pm$ 0.02	27.4 $\pm$ 0.60	5.5 $\pm$ 0.25
	60	70.8 $\pm$ 0.02	28.0 $\pm$ 0.38	5.1 $\pm$ 0.26
	90	80.0 $\pm$ 0.18	27.5 $\pm$ 0.88	4.6 $\pm$ 0.26
2.7% HEC	0	38.9 $\pm$ 0.75	23.1 $\pm$ 0.90	7.3 $\pm$ 0.07
	30	50.3 $\pm$ 0.75	25.8 $\pm$ 1.34	5.3 $\pm$ 0.25
	60	57.6 $\pm$ 1.36	26.5 $\pm$ 1.05	4.7 $\pm$ 0.24
	90	63.4 $\pm$ 1.04	27.2 $\pm$ 1.07	4.4 $\pm$ 0.26
3.0% HEC	0	37.4 $\pm$ 0.32	22.5 $\pm$ 0.59	8.6 $\pm$ 0.15
	30	46.6 $\pm$ 0.77	24.5 $\pm$ 0.85	7.1 $\pm$ 0.24
	60	52.4 $\pm$ 0.77	25.6 $\pm$ 0.91	6.4 $\pm$ 0.14
	90	56.6 $\pm$ 1.06	26.3 $\pm$ 0.76	6.2 $\pm$ 0.01

external factors, such as inclination angle and geometrical differences. Additionally, we demonstrated an imaging methodology for constant-volume experiments which can be used for future studies and comparisons to simulations.

Neglecting flow in the lateral direction, when modeling gravity-induced flow, resulted in up to 47% overestimation of the experimental axial spreading after 90 s. In contrast, the inclusion of lateral spreading in 3D computational models resulted in rms errors in axial spreading under 7% after 90 s. Even with the 3D model's decreased rms errors compared to the 2D model, the initial numerical velocity overestimated experiment, as was shown in velocity plots in Fig. 5(a). A study by Khayat [42] suggests that this overestimation at the onset of spreading could be because the constitutive equation does not account for the gel's elastic component,

and thus future studies will incorporate the elastic behavior in addition to shear-thinning. Additionally, consideration of surface tension or contact angle may also be needed, as discussed next.

For the 3D model, lateral spreading was due only to the gravity component perpendicular to the incline (i.e., slumping behavior) and not the downhill gravity component (i.e., parallel gravity terms). The experimental data showed that lateral spreading plateaus early (at approximately 30 s in the example in Fig. 5), and therefore, a balance was reached between the gel's internal (e.g., viscous and surface tension) and external driving factors (e.g., gravity). As expected, the early lateral spreading plateau was not observed in the numerical model. This was most likely because the model did not account for surface tension, which would act to slightly constrain both axial and lateral spreading. We observed this effect in our previous study for the power-law model with surface tension [4], which showed that the surface tension did slightly constrain axial spreading in a 2D model. However, we also showed that shear-thinning fluids are less sensitive to changes in surface tension as compared to Newtonian fluids. In addition, the inclusion of surface tension in the 3D simulation is expected to improve the simulation of height, as it would result in a capillary ridge near the front (as we showed in our previous study [4]).

While surface tension effects are very important near the moving contact line and for simulating the capillary ridge in the height near the front [4,36], those effects alone may not account for the differences observed in the numerical and experimental front velocities and spreading plateaus. As mentioned above, a recent numerical solution of a constant volume of Newtonian fluid, which also considered surface tension, also had a large initial front velocity that dropped sharply at early times [40]. Another possible consideration is the contact angle to represent the wettability since the wettability of a fluid/solid interaction influences spreading behavior [24,36,43]. However, incorporation of contact angle into thin film equations is an open problem in thin film research [44]. While the thin film equation has many computational benefits, it does not account for contact angle effects which would impact the balance between lateral and axial spreading. While volume of

Table 3 rms error between numerical simulations and the corresponding experiments. Percentages in parentheses indicate the percentage of the rms error with respect to the mean experimental value at $t = 90$ s. These data show that the 3D simulations for lateral spreading have smaller rms error than the 2D simulations compared with the experiment, but the 3D simulations overestimate the lateral spreading. Both 2D and 3D simulations underestimate the experimental height, most likely due to the surface tension effect on a capillary ridge formation in the experiment. IC = initial condition.

Gel	Numerical simulation type	L_{front} (mm) rms error at $t = 90$ s	W_{max} (mm) rms error at $t = 90$ s	h_{max} (mm) rms error at $t = 90$ s
2.4% HEC	3D real IC	0.14 (0.175%)	12.0 (43.5%)	2.42 (52.6%)
	3D approx. IC	1.47 (1.84%)	14.3 (52.1%)	2.37 (51.5%)
	2D	36.0 (45.0%)	NA	1.87 (40.7%)
2.7% HEC	3D real IC	3.95 (6.23%)	10.0 (36.9%)	1.72 (39.1%)
	3D approx. IC	3.02 (4.78%)	10.2 (37.5%)	1.71 (38.9%)
	2D	26.9 (42.5%)	NA	1.15 (26.1%)
3.0% HEC	3D real IC	3.97 (7.01%)	8.16 (31.0%)	3.01 (48.5%)
	3D approx. IC	3.49 (6.17%)	10.4 (39.4%)	2.76 (44.5%)
	2D	26.6 (46.9%)	NA	2.18 (35.2%)

fluid (VOF) models [24] can examine the influence of contact angle, those effects still cannot completely describe lateral spreading, partly due to simplifications of the variable contact angle [24], which is also a function of contact line velocity [43]. For a contact angle with Plexiglas, we may expect the fluid to hold more towards the centerline and have less lateral spreading, than if we had a complete wetting scenario [24]. A previous experiment of spreading of commercial cellulose gels [3] used the extremes of hydrophilic and hydrophobic inclines which bracket a wide possible range of wettability for epithelium (see [3]) and of the Plexiglas in this study. The gels with a surfactant spread faster on a steep, hydrophobic, silanized glass surface than on a hydrophilic glass surface. However, the spreading of the gel without surfactant (like those in this study) was not influenced by surface wettability, except that some of the cellulose gels exhibited retraction, or dewetting, at the trailing edge of the bolus. Thus, in addition to the viscoelastic nature of the fluid, future numerical and

experimental studies will incorporate contact angle (wettability) and surface tension effects on lateral fingering patterns in shear-thinning fluids.

With this study we cannot conclusively determine whether the real IC or the approximate IC is better for predicting overall spreading dimensions. However, at very early times we observed general differences between the simulations. Both used experimentally measured initial maximum length, width, and height, but the real IC used image analysis to quantify the actual shape along the entire side profile and footprint. At early times (<1 s), the approximate IC simulations exhibited waiting time behavior [41] (which describes the commonly observed experimental flow during a finite early time, when the profile changes shape in the downhill direction but the front contact line does not advance). However, the real IC simulations did not provide the waiting time behavior. This is likely because they captured the actual variations in the real surface topography, which likely had areas that were

Fig. 7 Comparison of real versus approximate IC in the 3D numerical model. An example of 3D numerical results using two different initial conditions (IC) and compared with experiment for a 2.7% HEC gel. Top left: Surface topography of real IC. Bottom left: Surface topography of approximate IC, obtained using Eq. (24) with bulk geometry dimensions of real IC. Top right: Axial spreading (L_{front}) versus time for computations using real and approximate initial conditions, compared with experiment (same as Figs. 4—2.7% HEC run 1). Bottom right: Axial spreading versus time for computations using approximate and real initial conditions at early stage of spreading. This figure also illustrates how using the real IC removes the waiting time solution.

Fig. 8 Parametric study of axial spreading. (a) Contour lines of axial spreading ($L_{\text{front}} [=]$ cm) as a function of power-law rheological parameters. Contour lines were drawn using axial spreading values at $t = 90$ s from nine 3D numerical simulations (combinations of $n = 0.3, 0.6$, and 0.9 and $m = 200, 400$, and 600) with a MATLAB interpolation algorithm. **(b)** Dimensionless plot of parametric study of axial spreading. The dimensionless L_{front}/H is plotted against the dimensionless time $t' = t/T = t/(m/\rho g H)^{1/n}$ for three values of the dimensionless power-law parameter n . The lines represent all time points for each of the simulations in the parametric study. The nine dots indicate the $t = 90$ s end time points used in the dimensional results shown in (a) and Fig. 9, and the base of the sensitivity analysis in Fig. 10. Each dot on each of the lines represent the $t = 90$ s data point for $m = 600, 400$, and 200 P s^{n-1} , moving left to right across the constant n line. This figure shows that within the ranges of m and n considered, both parameters have an impact on axial spreading. Also, maximum spreading in the axial direction occurred at higher values of n (near Newtonian) and lower values of m (i.e., larger values of t').

already past a center of mass, and ready to start spreading downhill, unlike in the approximate IC. A waiting time behavior may have occurred in the nine experiments (see Fig. 7 bottom right for an example of a possible waiting time behavior still occurring at the first experimental time point at $t = 1$ s). Future studies may need images at time resolution < 1 s to better capture this phenomenon and determine if it occurred in any or all experiments. While the use of the approximate IC requires less image processing, we expect the real IC will be needed in future 3D studies incorporating surface tension because it captures the actual local curvature. For future experiments with larger volumes to observe lateral fingering instabilities, we expect the small fluctuations in the shape (see Fig. 7, top left) to provide initial noise perturbations that may lead to the fingering patterns.

4.2 Parametric Study and Sensitivity Analysis. We presented a parametric study showing that both the consistency and the shear-thinning index influence spreading length for the ranges considered. For a microbicide design application, one would need to consider that as the shear-thinning index decreases, the axial distance the fluid would spread in a given time will decrease.

Fig. 9 The effect of the shear-thinning index n and the consistency m (P s^{n-1}) on the change-of-rate indicator ζ . A larger ζ represents a deviation from a constant spreading velocity. This figure shows that increasing m and decreasing n resulted in a more constant axial spreading velocity (i.e., $\zeta \rightarrow 0$). The figure data points were calculated using axial spreading values at $t = 90$ s for nine 3D numerical simulations (combinations of $n = 0.3, 0.6$, and 0.9 and $m = 200, 400$, and 600), and lines connecting points were drawn to aid viewing data at the same n values.

Also, as the consistency decreases, the axial distance the fluid would spread will increase. Therefore, both parameters had an influence on spreading.

We also found that the deceleration of the spreading front was dependent on both power-law parameters (Fig. 9). We conclude that the velocity of the moving front becomes more constant as the consistency increases and the shear-thinning index decreases. For a microbicide application, it might be desirable to use gels with constant velocity spreading characteristics so that the final coating distribution can be targeted. In addition, the deceleration for different shear-thinning values provides insight into the effects of contact angle, elasticity, and surface tension for future 3D simulations.

The sensitivity analysis showed that the spreading of a gel with midrange m and n values would be most sensitive (over 8% in spreading length) to changes of 10% in both rheological parameter, within the ranges and simulations considered in this study. For a microbicide application, a critical design consideration is to limit a gel's sensitivity to small changes in the rheological properties, resulting from external factors such as dilution or formulation conditions. Thus, a gel could be designed with target rheological properties outside of a sensitive range, or a gel formulation could be selected that is less sensitive than another formulation. For example, Fig. 10(c) indicates that a gel with midrange m and n values ("gel 1") is expected to have greater sensitivity to dilution than either a nearly Newtonian gel ("gel 2") with a low consistency, or a very shear-thinning gel ("gel 3") with a relatively high consistency. So, while an undiluted gel 1 may spread more than gel 3, and less than gel 2 (see results in Fig. 8), once diluted their spreading behaviors may compare differently due to differing sensitivity. It is also instructive to know that for these free-surface coating flows, a 10% change in both rheological parameters can yield over 8% change in coating length. Contrast these results with those for a model with combined elastic squeezing and gravitational sliding [5], where under some conditions (higher Newtonian viscosity) there was negligible difference in spreading even for a twofold change in viscosity—much greater changes in viscosity were needed to substantially change the coating in some cases.

4.3 Assumptions and Limitations: Physiological Complexity of Microbicidal Drug Delivery. The successful delivery of a microbicidal drug in a polymer solution ("gel") to the vagina will be determined both by the gel properties and its interactions with the complex physical and chemical environment. Several

Fig. 10 Percent (%) sensitivity of axial spreading (L_{front} ($t = 90 \text{ s}$)) to changes in m and n . (a) Percent (%) sensitivity to 10% increase in n . This figure shows highest sensitivity for these simulations at $m = 600 \text{ P s}^{-1}$ and $n = 0.6$. (b) Percent (%) sensitivity to 10% decrease in m . This figure shows highest sensitivity for these simulations at $m = 200 \text{ P s}^{-1}$ and $n = 0.3$. (c) Percent (%) sensitivity to 10% decrease in m and increase in n . This figure shows highest sensitivity for these simulations at $m = 400 \text{ P s}^{-1}$ and $n = 0.6$. Sensitivity calculations used 27 additional simulations and were based on percent changes from the original nine 3D numerical simulations in the parametric study (combinations of $n = 0.3, 0.6$, and 0.9 and $m = 200, 400$, and 600). Lines connecting points were drawn to aid viewing data at the same n values.

mechanical processes will act to distribute the gel, such as gravity, capillarity, and squeezing between the apposing epithelial walls. At some locations and times, one mechanism may dominate, while at other instances, multiple physical mechanisms may conflict or synergize, and most will depend upon the woman's physical position and tissue properties. For example, the gel may be located near the wider vaginal fornix (near the cervix) and flow with a free surface with air in a downhill direction, which will depend upon the orientation of the axis of the vaginal canal. Later, the gel may be sandwiched between the relaxed apposing walls of the vagina, and spread due to both squeezing and gravity [5], or perhaps dominated by squeezing alone [6]. Similarly, the chemical environment is complex and the polymer solution will interact with ambient fluids, such as vaginal transudate, cervical mucus, and semen—swelling and dilution will be involved (e.g., [9]). The drug mechanism of action, drug stability, release kinetics, and

safety, all need to be characterized and optimized with respect to its formulation in a gel [45]. The time scale of gel flow, dilution, and swelling, along with the drug delivery, will range from rapid initial distribution under gravity and squeezing within minutes, up to dilution, retention, and possible leakage from the vagina over minutes to hours (e.g., [9]). Mathematical models can inform the appropriate timing of the gel application by the woman prior to coitus.

For this complex application, mathematical models can be very valuable for understanding the critical variables that determine an outcome, and can be used as mathematical tools for optimizing those variables for a desired outcome. However, to broach the complexity, we must start with tractable mathematical models, and use the analysis to inform which components should be added to future simulations and experiments. This study was focused on the free-surface flow of the non-Newtonian gel flowing down the vaginal epithelium due to gravity. Assumptions included a thin-film lubrication approximation, no-slip at the vaginal walls, simplified geometry and gravity-driven direction, and the presence of a free surface. In a previous study [4], we isolated the effect of surface tension with a 2D model, and do not include surface tension in this more computationally expensive 3D model. The shear-thinning behavior of the gel was included, but not the low-shear-rate viscosity or viscoelastic behavior. The wettability of the experimental surface, or the physiological epithelial surface, was not included in the model (e.g., with a contact angle). This study contains some possible experimental limitations which may affect comparisons with numerical results, such as camera resolution, range of gel properties (and thus spreading) in this study, and approximation of the lateral spreading shape without the third camera view. Some of these limitations were most applicable to measurements in the lateral direction (which did not spread as much) and height (which was thinner), and thus, the parametric and sensitivity studies were focused on axial spreading.

5 Conclusions

The results presented here: (1) act as a guide to design and/or select shear-thinning fluids with specific spreading objectives and (2) forecast how a microbicidal gel might behave once it is introduced into the vaginal environment where it might be diluted by surrounding fluids. Thus, this study serves as a step towards our overall goal to computationally optimize non-Newtonian gel properties for ideal spreading behavior of microbicidal gels delivered to the vaginal epithelium. Here we found that neglecting lateral spreading, when modeling gravity-induced flow, resulted in up to 47% overestimation of the experimental axial spreading after 90 s. In contrast, the inclusion of lateral spreading in 3D computational models resulted in rms errors in axial spreading under 7%. Both the shear-thinning index (n) and consistency (m) impacted the spreading length and deceleration of the moving front. A 10% change in both m and n (e.g., from dilution) resulted in spreading changes of over 8%; a parameter range was identified for gels with the most sensitivity to a change such as dilution. This study provided a validation of new experimental and numerical models, which now form a base to add further physiological complexity in future studies. The most important next steps for the numerical component were identified in Sec. 4, and addressed with the most important limitations/assumptions in mind. In particular, the viscoelastic gel properties, the surface wettability, and surface tension effects on lateral fingering instabilities in 3D spreading were identified as the critical next steps in the numerical model. Experimentally, this study serves as a platform to examine microbicidal gel flow over different substrates, such as epithelial tissue explants.

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Nomenclature

x	= axial direction
y	= lateral direction
z	= direction of fluid height
$h(x, y, t)$	= fluid thickness (cm)
t	= time (s)
$\mathbf{u}$	= velocity vector (cm/s)
$u(x, y, z, t)$	= velocity in the axial direction (cm/s)
$v(x, y, z, t)$	= velocity in the lateral direction (cm/s)
$\mathbf{g}$	= gravity vector (cm/s ²)
$\boldsymbol{\tau}$	= shear stress tensor
p	= pressure
ρ	= density (g/cm ³)
α	= angle of the ramp with respect to the horizontal plane (deg)
$2\mathbf{D} = (\nabla \mathbf{u})^T + \nabla \mathbf{u}$	= strain rate tensor
$\mathbf{II}_{2D}$	= second invariant of the strain rate tensor $2\mathbf{D}$
m	= power-law consistency (P s ^{$n-1$})
n	= indicates level of shear-thinning behavior ($n < 1$) (dimensionless)
q_x	= flow rate per unit width in the axial direction; axial flux (cm ² /s)
q_y	= flow rate per unit width in the lateral direction; lateral flux (cm ² /s)
H and T	= characteristic height (initial maximum height) H (cm) and time T (s) used to nondimensionalize governing equations
Ω	= computational domain over x - y space
$x_{\max}$	= length (axial direction x) of the numerical domain (cm)
$y_{\max}$	= width (lateral direction y) of the numerical domain (cm)
N	= domain divided into N points along the axial direction
M	= domain divided into M points along the lateral direction
Δx	= uniform user-defined computational cell dimension in the x direction
Δy	= uniform user-defined computational cell dimension in the y direction
$TOT = N \times M$	= total number of grid points in computational domain
k	= spatial index for points in computational domain (see Fig. 2)
b	= arbitrary point $k = b$ on the computational grid (Eq. (17))
$M_{1/2}$	= indicial notation indicating the temporary designation of the flux at the node interfaces between the k , $k + M$, and $k - M$ grid nodes (see Fig. 2)
V	= volume of fluid
p	= indicial superscript notation for time step
dt	= computational time step
L	= initial length of fluid (maximum initial length in the axial direction) (cm)
W	= initial width of fluid (maximum initial width in the lateral direction) (cm)
H	= initial height of fluid (maximum initial height in the z direction) (cm)
$L_{\text{front}}(t)$	= maximum length at a given time of the moving front of the fluid (mm)

$W_{\max}(t)$	= maximum width at a given time of the spreading fluid (mm)
$h_{\max}(t)$	= maximum height of the fluid at a given time (mm)
a_1, a_2	= defines the approximate IC (initial shape) of the fluid (Eq. (25))
U	= estimate of maximum axial velocity
ζ	= change-of-rate indicator (dimensionless)
% Sensitivity	= defined as $\frac{L_{\text{front, change}} - L_{\text{front, original}}}{L_{\text{front, original}}} \cdot 100\%$ (dimensionless)
$L_{\text{front, original}}$	= value of L_{front} at 90 s of spreading for given power-law parameters (i.e., n and m) (mm)
$L_{\text{front, change}}$	= value of L_{front} at 90 s of spreading after making a 10% change to one or both power-law parameters (mm)
d_t, d_b , and h_{peak}	= measured from the footprint (top view) and side-profile images (Fig. 4(c)) (mm)

Appendix: Additional Details on Materials and Methods

Details of Temperature/Humidity-Controlled Chamber. The ambient temperature was set to 37 ± 1 °C, with humidity maintained at values greater than 60% to prevent any drying on the gel's surface. Temperature was acquired using two thermocouples (NI Type E) strategically placed to ensure that the whole environment in which the experiment was taking place was uniform. Temperature control (within 1 °C) was accomplished with a custom NI LabView 8.6.1 feedback control system program using a data acquisition card (NI PCI 6221 DAQ). Temperature was validated using two high accuracy Fisherbrand thermometers (Red-Spirit, partial immersion). Humidity was provided using an ultrasonic cool-mist air humidifier (Sunbeam Ultrasonic Humidifier 700), pumped at a constant rate, and measured with a humidity indicator (Fisher Scientific).

Details of Release Mechanism. A servo motor (JRSERVO DS8711) was controlled (using NI PCI 6221 DAQ data acquisition) to automatically dispense the gel out of the syringe and onto the spreading surface, and to retract the syringe for a contact-free initial bolus of gel. Once the servo was activated, the servo-rotating arm converted rotation to linear motion, thereby compressing the plunger. The first 90 deg of the rotation was responsible for compressing the plunger, while the second 90 deg retracted it from the gel. This mechanism allowed us to achieve a contact-free initial condition with a manageable shape, repeatable over multiple experiments.

Details of Image Analysis. Quick Time Player was used to export the movie into frames of 1-s intervals to analyze a successive 180 frames of spreading. We designed an image calibration procedure to account for camera perspective angle over the entire field of view. A separate image calibration for each experiment allowed for small changes in camera focus, zoom, or position between experiments without compromising measurement accuracy. Prior to starting each spreading experiment, a calibration was performed by placing a grid in the experimental spreading domain. Using a LabVIEW image calibration algorithm (NI Vision Assistant 8.6), the grid on the 80mm spreading domain was mapped and calibrated to account for the camera perspective angle. After calibration, all measurements were accurate within 0.5%, or within 1 mm over the entire 80mm domain. This image acquisition setup was appropriate for our application, but we note that higher precision could be obtained by improving the resolution of the camera or decreasing the camera distance.

Each image underwent a "color plane extraction" to convert all the pixels to a green plane, which made an image containing one color with different intensities. When the boundary between fluid edge and background was unclear due to a shadow, the image

underwent a logarithmic image sequence (LIS) and highlighted the details using a built-in LabVIEW 8.6 algorithm. Finally, each image was turned into a binary based on a threshold chosen using the first image of the 180 s video sequence.

Details of Fluid Topography Measurement and Reconstruction. At each time point, the camera captured images (see Fig. 4(a)) of the axial plane (side-view profile) and z plane (top-down footprint view), but not the lateral plane, i.e., $h(y)$. Section 2.3 described how the footprint and side-profile images were obtained and used. This section describes the assumptions for the cross-sectional shape in the lateral direction, which was not seen in the camera view. At each point along the x axis, the cross section at the lateral plane was described using measured dimensions and an assumed shape defined by a fourth-order polynomial:

$$h(y) = -F \cdot h_{\text{peak}} \left(\frac{y - d_b + \frac{d}{2}}{\frac{d}{2}} \right)^4 + h_{\text{peak}} \quad (\text{A1})$$

where $d = d_t + d_b$, and d_t , d_b , and h_{peak} define the shape as seen in Fig. 4(c). The values for d_t , d_b , and h_{peak} (in mm) were measured from the footprint (top view) and side-profile images, and defined as follows. The values d_t and d_b were distances from the centerline (CL) to the gel edge in the y direction, measured using the footprint image, and specified along the x axis. The h_{peak} value was the peak film thickness over $h(y)$ at a given x , and was obtained from the side-profile image. The curves of d_t , d_b , and h along the axial plane were smoothed using least squares method to find an approximate polynomial fit. The assumed shape in the lateral direction was selected with a shape factor (F), which iteratively adjusted the volume of the digitized shape to match the exact volume used in the experiments. The algorithm prompted the user to define the number of nodes ($N \times M$), and a mesh size (dx and dy , in mm). If the desired mesh size was finer than the one available by the resolution of the camera, linear interpolation was used to obtain three parameters (d_t , d_b , and h_{peak}) from the footprint and side-profile images. The result was a description of $h(x,y)$ at $t=0$ used as input for the initial fluid thickness in the numerical code. This could also be used at any time point to reconstruct the surface topography (see Fig. 4(b) for examples).

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