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Mathematical Model of Microbicidal Flow Dynamics and Optimization of Rheological Properties for Intra-vaginal Drug Delivery: Role of Tissue Mechanics and Fluid Rheology

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Abstract

Topically applied microbicide gels can provide a self-administered and effective strategy to prevent sexually transmitted infections (STIs). We have investigated the interplay between vaginal tissue elasticity and the yield-stress of non-Newtonian fluids during microbicide deployment. We have developed a mathematical model of tissue deformation driven spreading of microbicidal gels based on thin film lubrication approximation and demonstrated the effect of tissue elasticity and fluid yield-stress on the spreading dynamics. Our results show that both elasticity of tissue and yield-stress rheology of gel are strong determinants of the coating behavior. An optimization framework has been demonstrated which leverages the flow dynamics of yield-stress fluid during deployment to maximize retention while reaching target coating length for a given tissue elasticity.

Keywords

Microbicide gel, Non-Newtonian fluid, Yield stress, Thin film flow, Numerical optimization, Tissue biomechanics

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1. Introduction

Recent clinical trials of the vaginal gel formulation of the anti-retroviral drug Tenofovir have shown the efficacy of topically applied microbicides against HIV transmission to women (Karim, 2011). Microbicides could provide us with a self-administered and low cost strategy to fight HIV and other sexually transmitted infections (STIs). A microbicide gel is deployed as a delivery vehicle of anti-HIV and other anti-STI agents, and it is also used to act as a physical barrier between the pathogens and the biological tissue. The efficacy of a microbicide gel depends on the extent of coating and retention on the epithelial surface of the lower female reproductive tract (LFRT) (Kieweg *et al.*, 2004).

The coating mechanism of a microbicide gel is complex in nature and driven by the combined effect of physical mechanisms in the LFRT and the rheological properties of the gel. Gravity and the squeezing force arising from the elasticity of vaginal tissue are physical mechanisms that play important roles in the coating mechanism. Variation of the elasticity of vaginal tissue can change the extent of coating of these gels due to different magnitudes of the resulting squeezing force. These polymer gels usually exhibit shear-thinning behavior and may also have a yield stress (Kieweg and Katz, 2006; Kieweg and Katz, 2007; Owen *et al.*, 2007). Certain important anatomical and physiological features of the vaginal environment, such as pH, volume and composition of vaginal fluid, should be kept in mind while designing an effective microbicide gel. The long term goal of our research is to develop a framework for rational design of microbicide gels with active ingredients. As a step towards achieving that goal, we have used squeezing flow mechanics and polymer rheology to develop a framework for optimizing the gel rheological properties to achieve optimal spreading and retention which could be further extended later by incorporating target properties such as biocompatibility and activity against STIs.

Studies on thin film flows for biological applications are growing in number (Jin and Dowson, 2005). Most common biological applications include lining of pleural surfaces of the lung (Gouldstone *et al.*, 2003), flow of synovial fluid between joints (Jin and Dowson, 2005), and tear film between the eye and eyelid (Jones *et al.*, 2008; Jossic *et al.*, 2009). Thin film theory has been applied in the study of vaginal drug delivery systems by several researchers in recent past. Kieweg and Katz *et al.* performed experimental and numerical studies on microbicidal gel deployment under constant squeezing force and concluded that squeezing force, gel consistency, shear-thinning behavior and yield stress are strong determinants of the coating performance of gels (Kieweg *et al.*, 2004; Kieweg and Katz, 2006; Kieweg and Katz, 2007). Szeri *et al.* developed a mathematical model involving wall elasticity to demonstrate the effect of compliant vaginal wall on the deployment dynamics of microbicidal gels and indicated the important role that vaginal biomechanics plays in gel deployment (Szeri *et al.*, 2008). Tasoglu *et al.* showed that yield stress can improve the long time retention performance of a Carreau-like fluid (Tasoglu *et al.*, 2011). The goal of this study is (1) to develop a mathematical model for understanding the effect of elasticity of the tissue and yield-stress rheology of the fluid on the spreading of microbicidal gels, and (2) to demonstrate an optimization framework to estimate gel rheological properties for a given tissue elasticity in order to achieve both optimal tissue coverage and maximum retention.

2. Mathematical model

In this section, we develop the nonlinear partial differential equation that describes the evolution of the fluid/solid interface as a function of time and space ($h(x, t)$). Figure 1 shows the schematic of the flow conditions of the two dimensional (2-D) model i.e. one dimensional (1-D) spreading, where the fluid is spreading due to gravity and an elastic response from the vaginal tissue. This model considers a homogenous tissue compartment which represents the entire vaginal tissue (including epithelium, smooth muscular layers, and the underlying lamina

propria), as well as further surrounding/underlying structures which may contribute to the closing pressures exerted on the gel in the vagina (e.g. nearby bladder wall). The flow domain is symmetric about the center axis since we are considering only vertical flow (along x -direction) in this study. In this approximation, the portion of the vaginal axis shown in Figure 1 is aligned with the x -axis, and gravity is downhill along the x -axis. In a human, the orientation of the vaginal axis with respect to gravity depends on both the location along the s-shaped vaginal axis and the orientation of the woman. The axis orientation in this model allows consideration of the full range of the impact of gravity on a gel.

Since the thickness of the gel bolus is much smaller than the extent of the spreading, the thin film lubrication approximation (Acheson, 1990) allows us to neglect the convective terms in the equations of conservation of linear momentum. The Herschel-Bulkley constitutive law which is used to represent the rheology of a yield stress fluid is as follows:

$$\tau_{zx} = \tau_0 + m \left| \frac{\partial u}{\partial z} \right|^{n-1} \frac{\partial u}{\partial z} \quad (1)$$

where τ_{zx} is the shear stress, τ_0 is the yield stress, u is the velocity in the x -direction, m is the consistency and n is the power-law index.

The elasticity of the vaginal wall is incorporated in the pressure term of the model. A linear elastic tissue behavior is considered which assumes that the vaginal wall is homogeneous and isotropic, and the pressure p acting on the fluid boundary due to tissue elasticity is directly proportional to strain in the distensible tissue. The pressure for a deformation $h(x, t)$ is given by $p = E \cdot \epsilon = E \cdot h(x, t)/T$ (Szeri *et al.*, 2008). Here, E is the elastic modulus of the tissue, T is the thickness of the tissue layer and $\epsilon = h(x, t)/T$ is the strain in the tissue. We apply a no-slip condition at the fluid-solid interface and zero shear stress at the symmetry line.

By using the above pressure formulation, thin film approximation, and Herschel-bulkley constitutive relation, we arrive at the following nonlinear partial differential equation describing the evolution of the fluid-solid interface. Refer to (Balmforth *et al.*, 2006) for more details about deriving a similar evolution equation for gravity-driven thin film flow of a Herschel-bulkley fluid.

$$\frac{\partial h}{\partial t} + \left(\frac{1}{m}\right)^n \left(\frac{n}{1+n}\right) \left(\frac{n}{1+2n}\right) \frac{\partial}{\partial x} \left[\left(\frac{E}{T} \frac{\partial h}{\partial x} - \rho g \right) \left| \frac{E}{T} \frac{\partial h}{\partial x} - \rho g \right|^{\frac{1}{n}-1} Y^{\frac{1+n}{n}} \left(Y - \left(\frac{1+2n}{n} \right) h \right) \right] = 0 \quad (2)$$

Here, $Y = \max \left(h - \frac{\tau_0}{\left| \frac{E}{T} \frac{\partial h}{\partial x} - \rho g \right|}, 0 \right)$ defines the yield surface. The surface $z = Y(x, t)$, separates a shearing flow region (between the yield surface and the vaginal wall) and the adjacent plug region. This central plug region is not a true plug, but rather a weakly yielding zone (Balmforth and Craster, 1999). For a constant volume spreading such as in our case, a no-flux boundary condition ($\partial h / \partial x = 0$) was applied at the two ends of the spatial domain which was taken large enough to ensure that the fluid would not reach the ends.

Previous literature reported that the extent of gel coating increases with the increase of E and n , and decreases with the increase of m and τ_0 (Kieweg and Katz, 2007; Szeri *et al.*, 2008). In order to understand the interplay between the tissue's elastic properties and the fluid's yield stress on the deployment dynamics, we use appropriate scaling to create a non-dimensional evolution equation for the fluid/solid interface ($\bar{x} = x/L$, $\bar{h} = h/H$, $\bar{t} = tU/L$, $\bar{P} = P/\rho g T$ and $\bar{\tau}_{xz} = \tau_{xz}/\rho g H$, where $U = H^{\frac{1}{n}+1}(\rho g/m)^{\frac{1}{n}}$ is the characteristic flow velocity).

$$\frac{\partial \bar{h}}{\partial \bar{t}} + \left(\frac{n}{1+n}\right) \left(\frac{n}{1+2n}\right) \frac{\partial}{\partial \bar{x}} \left[\left(E G \frac{\partial \bar{h}}{\partial \bar{x}} - 1 \right) \left| E G \frac{\partial \bar{h}}{\partial \bar{x}} - 1 \right|^{\frac{1}{n}-1} \bar{Y}^{\frac{1+n}{n}} \left(\bar{Y} - \left(\frac{1+2n}{n} \right) \bar{h} \right) \right] = 0 \quad (3)$$

$$\text{where } \bar{Y} = \max \left(\bar{h} - \frac{Bi}{\left| E G \frac{\partial \bar{h}}{\partial \bar{x}} - 1 \right|}, 0 \right)$$

This non-dimensional form provides us with two important dimensionless variables: the yield stress to gravity ratio $Bi = \tau_0 / \rho g H$, and the tissue elasticity to gravity ratio $EG = E \epsilon / \rho g L$. Here, H and L are the characteristic lengths along the height and flow direction. A dimensional interpretation, along with approximate dimensional values for tissue elasticity and gel properties, will be discussed in the Results and Discussion section.

In the following discussion, we first explore the effects of varying tissue elasticity and yield stress by solving the non-dimensional form of the evolution equation for different ranges of these parameters. The nonlinear evolution equation was solved by an implicit finite difference scheme which is similar to the technique used in our previously published research (Hu and Kieweg, 2012; Kheifets and Kieweg, 2013a, b). We used first order backward difference in time and second order central difference in spatial derivatives. Newton's method was used to solve the system of algebraic equations resulting from the discretization. A spatial mesh interval $dx = 0.01$ and an adaptive time-stepping scheme was used to match our tolerance requirement of $1e-6$ (default time-step size was set to $dt = 0.001$). We also monitored the volume of fluid since insufficient spatial or temporal resolution results in a violation of mass conservation. Next, we demonstrate a framework for optimizing the gel rheological properties by leveraging the yield stress of the gel for a given tissue elasticity. Optimization methods are described below in the analysis contained in the Results and Discussion section.

3. Results and Discussion

Rheological properties of gels and elasticity of tissue are required as input parameters of the mathematical model. Based on measured properties of some commercial gels, a reasonable range of rheological properties could be considered as following: $m = 10-80 \text{ Pa}\cdot\text{s}^n$, $n = 0.25-1.0$ and $\tau_0 = 0-100 \text{ Pa}$ (Kieweg *et al.*, 2004; Kieweg and Katz, 2006). Exact elasticity of vaginal tissue is still unknown and wide ranges of elasticity such as 3-10 kPa (Egorov and Sarvazyan,

2011) and 12-36 kPa (Katz *et al.*, 2011) are reported. The length of the vaginal canal can range from 7-10 cm, with a wall thickness between 0.5-2.0 cm (Rohan and Sassi, 2009; Szeri *et al.*, 2008). For our numerical simulation, a constant tissue thickness of $T = 1.5$ cm was considered and represents the entire vaginal wall and the effect of surrounding tissues. The initial bolus shape was parabolic (see Fig. 1) with a length $L = 4$ cm and maximum height $H = 0.3$ cm. This configuration yields a bolus volume of 1.6 ml/width dimension of the vagina.

3.1 Parametric study in dimension-less form

In this section, a series of numerical simulations were carried out in dimension-less form (eq. 3) to investigate how tissue elasticity and gel yield stress influence the coating mechanism. Numerical simulations were performed for $EG = 1, 5, 15$ and 25 to investigate the effect of tissue elasticity. Using our non-dimensional scaling, $EG = 1-25$ corresponds to tissue elasticity of approximately 2-50 kPa. Results show that increasing the magnitude of tissue elasticity increases the extent of coating and also causes noticeable upward flow (Fig. 2). At low values of EG , the flow is mostly downwards due to the influence of gravity. Effect of yield-stress on spreading was investigated by performing numerical simulations for $Bi = 0, 0.2, 0.5$ and 1 . This range of Bi number corresponds to a dimensional yield-stress of approximately 0-30 Pa. Results show that increasing the yield stress (or Bi ratio) decreases the extent of spreading (Fig. 3) by reducing the yielding region of the flow domain. Fig. 4 shows the shear stress contours at $\bar{t} = 10$ for two different Bi values: 0.2 and 0.5. The thick contour line shows the yield surface which separates the yielding region from the plug flow region. The fluid is yielding in regions where the dimensionless shear stress is higher than the Bi value. As shown in Fig. 4, the yielding region for $Bi = 0.5$ is much smaller than the yielding region for $Bi = 0.2$. We can easily calculate the percentage of the fluid domain that is yielding at any given time since we know the location of the yield surface and the fluid/solid interface. Fig. 5 shows the influence of yield stress on the

coating length and percentage yielding area over a period of time. The percentage yielding drops rapidly over time for the higher yield stress fluid and this behavior can be leveraged to improve the retention time of microbicidal gels.

3.2 Gel property estimation for optimal coating performance

Running a series of numerical simulations provides us useful insight about the transient coating behavior of gels for different tissue elasticity and rheological properties. However, we would also like to estimate the rheological properties required to achieve an optimal epithelial coverage and maximize retention. In particular, we would like to optimize delivery for a given tissue elasticity in a target deployment time. Mahalingam *et al.* used a response surface methodology, which is a visual technique, to design semi-solid microbicidal gels based on the squeezing flow model of gel spreading between rigid boundaries (Mahalingam *et al.*, 2010). Our approach is to estimate the gel rheological properties such that it minimizes the percentage yielding at the end of a target deployment time while achieving the target epithelial coating for a given tissue elasticity.

The approach involves three analysis steps: (1) we performed a set of numerical flow simulations in dimensional form, (2) we developed nonlinear regression models for coating length and percentage yielding by fitting the output data from the numerical flow simulations, and (3) we solved the inverse problem for several cases. First, we created 500 quasi-random test points within our parameter ranges by using the *sobolset* function in Matlab[®]. We used the rheological property ranges mentioned previously ($m = 10\text{-}80 \text{ Pa}\cdot\text{s}^n$, $n = 0.25\text{-}1.0$ and $\tau_0 = 0\text{-}100 \text{ Pa}$) and a range of tissue elasticity $E = 1\text{-}50 \text{ kPa}$ for creating the model building set. These 500 parameter sets were inputs to the numerical simulation in dimensional form (eq. 2). We considered a maximum deployment time of 180 seconds, relevant for the coitally-dependent drug delivery method where the user inserts the gel prior to intercourse.

Second, we used nonlinear regression to fit the numerical results (for coating and % yielding) to the parameters m, n, τ_0, E and t . A regression model is needed for the subsequent step in mathematical optimization. We chose a regression model-based approach because, we are not optimizing the primary variable of the PDE ($h(x, t)$) and the nonlinear problem has many local optima. The resulting regression model for coating length and percentage yielding is given in Appendix-A. Several models containing various combination of the parameters were generated in the R[®] software. Model selection was based on Mallow's C_p statistic which indicates potential over-fitting of model with increasing number of parameters. The model with good coefficient of determination (*adjusted R^2*) and lowest Mallow's C_p was selected. A k -fold cross-validation (for $k = 10$) was performed to calculate the predictive squared correlation coefficient (Q^2). The calculated Q^2 of the proposed models were very close to R^2 , which indicates that the models are adequate for predicting the spreading and percentage yielding of the injected gel bolus over time. The resulting statistical indicators are reported in Table 1.

Third, the above regression models were used to solve the inverse problem using a nonlinear optimization method in order to estimate the gel rheological properties (τ_0, m and n) that result in minimum percentage yielding and achieve the target coating length for a given tissue elasticity and deployment time. The optimization problem was formulated as follows:

$$\begin{aligned}
 &\text{minimize} \quad \%Yielding \\
 &\text{s.t.} \\
 &\quad Coating\ length \geq Target\ length \\
 &\quad m_{min} \leq m \leq m_{max} \\
 &\quad n_{min} \leq n \leq n_{max} \\
 &\quad \tau_{0min} \leq \tau_0 \leq \tau_{0max} \\
 &\quad E = \text{Given tissue elasticity}
 \end{aligned}$$

$$t = \text{Deployment time}$$

The optimization problem was solved to local optimality by using the optimization software GAMS and applying the CONOPT nonlinear solver (GAMS Development Corporation, 2013). Table 1 provides an example list of estimated rheological properties for different tissue elasticity and deployment times. Two sets of feasible solutions are reported in the table to emphasize the possibility of multiple feasible solutions for nonlinear optimization problems. Solution of the problem that is obtained may vary depending on the initial guess. Moreover, the solver can be forced to find solutions within a specific range of a particular rheological parameter by enforcing a constraint on the maximum or minimum allowable limit. These estimations can provide microbicide designers with a specific set of target rheological properties which can be used to rationally design gels. Results in Table 2 show that the estimated m is reaching towards the lower limit of our model ($10 \text{ Pa}\cdot\text{s}^n$) when longer coating lengths at a relatively lower tissue elasticity are required. This indicates an important conclusion: a larger initial bolus volume is necessary if longer coating length (with maximized retention) is required for tissues with lower elasticity.

4. Conclusion

The study has presented a model framework which can be used to design gel formulations and delivery location (along the vaginal axis) for specific groups of women, whose vaginal tissue properties may vary with parameters such as age or parity. Importantly, it demonstrates a framework for optimizing more than one target behavior simultaneously – a method we can extend in the future to a larger set of target gel functions (e.g. biocompatibility or anti-STI activity). While using this type of regression model based optimization, it is always important to ensure that an appropriate range of rheological properties, tissue elasticity, deployment time and initial bolus volume is chosen for the model building set. Our model neglected the effect of boundary dilution. In the future, we would like to investigate whether

boundary dilution has any significant effect within such a short time scale of deployment (2-5 minutes). The results of the presented numerical study will also enable us to investigate the effect of viscoelastic properties of vaginal and surrounding tissue on the microbicidal flow dynamics. This model also assumes the tissue of the vaginal and surrounding structures to be homogeneous and isotropic which is not the case in reality. Future studies may incorporate layers of different tissues (e.g. vaginal epithelium, smooth musculature, and underlying tissues such as bladder structures) in the surrounding “tissue” compartment of the model. Therefore, it is crucial that efforts are made towards developing new instruments so that vaginal mechanical properties could be measured *in vivo*, and the impact of the surrounding underlying tissues on the closing pressures of the vaginal tissue could be quantified and modeled. These measured properties can then be used in numerical models to study the deployment dynamics more accurately.

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259 **Appendix A. Regression models**

260 A1. Model for coating length

Coating length

$$\begin{aligned} &= 6.875 - 0.05986 \cdot m - 0.06847 \cdot \tau_0 + 0.1816 \cdot E + 0.01462 \cdot t + 0.01349 \cdot m \cdot n \\ &+ 0.00044 \cdot m \cdot \tau_0 - 0.0002888 \cdot m \cdot E + 0.00002795 \cdot m \cdot t - 0.009097 \cdot n \cdot \tau_0 \\ &+ 0.006034 \cdot n \cdot E + 0.006619 \cdot n \cdot t - 0.0003147 \cdot \tau_0 \cdot E - 0.0001388 \cdot \tau_0 \cdot t \\ &+ 0.0001238 \cdot E \cdot t + 0.0001746 \cdot m^2 - 0.2784 \cdot n^2 + 0.0003893 \cdot \tau_0^2 - 0.001456 \\ &\cdot E^2 - 0.00005235 \cdot t^2 \end{aligned}$$

261

262 $adjusted R^2 = 0.9745, \quad Q^2 = 0.9744, \quad p - value < 2.2e - 16$

263

264 A2. Model for percentage yielding

$$\begin{aligned} \%Yielding &= 76.45 + 0.704 \cdot m - 47.10 \cdot n - 1.801 \cdot \tau_0 + 0.4776 \cdot E - 0.1765 \cdot t - 0.2081 \cdot m \cdot n \\ &- 0.002518 \cdot m \cdot \tau_0 + 0.003108 \cdot m \cdot E - 0.0006389 \cdot m \cdot t + 0.1954 \cdot n \cdot \tau_0 \\ &+ 0.06795 \cdot n \cdot E - 0.06903 \cdot n \cdot t + 0.0006749 \cdot \tau_0 \cdot t - 0.00104 \cdot E \cdot t - 0.002236 \\ &\cdot m^2 + 24.3 \cdot n^2 + 0.01159 \cdot \tau_0^2 - 0.006644 \cdot E^2 + 0.0007944 \cdot t^2 \end{aligned}$$

265

266 $adjusted R^2 = 0.9278, \quad Q^2 = 0.9275, \quad p - value < 2.2e - 16$

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324

325 **Table Legends**

326 **Table 1.** Statistical indicators for regression models

327 **Table 2.** Estimation of required rheological properties for achieving target coating and
328 maximizing retention for specific tissue elasticity at a given time. Possibility of multiple feasible
329 solutions are demonstrated here.

330

Tables

Table 1. Statistical indicators for regression models

Model name	Adjusted R^2	Q^2	p-value
Coating length	0.9745	0.9744	< 2.2e-16
% Yielding	0.9278	0.9275	< 2.2e-16

Table 2. Estimation of required rheological properties for achieving target coating and maximizing retention for specific tissue elasticity at a given time. Possibility of multiple feasible solutions are demonstrated here.

Target length (cm)	Tissue elasticity (kPa)	Deployment time (sec)	Estimated (m, n, τ_0) ($Pa \cdot s^n$, no unit, Pa)	Estimated Spreading (cm)	Estimated % Yielding at the end of deployment time
7	15	150	(20.0, 0.9, 45.218)	7.00	1.038
			(27.0, 1.0, 43.671)	7.00	2.911
8	25	120	(25.0, 1.0, 46.554)	8.00	4.229
			(50.0, 0.95, 37.019)	8.00	16.505
9	20	150	(10.0, 1.0, 30.34)	9.00	8.489
			(20.0, 0.9, 25.539)	9.00	16.941
10	20	180	(10.0, 1.0, 19.468)	10.0	18.92
			(16.0, 0.95, 16.667)	10.0	24.574
	10		(10.0, 1.0, 2.514)	10.0	38.287

Figure Legends

Fig. 1. A schematic representation of the fluid bolus in vaginal canal (drawing is not to scale).

Only half plane is shown due to symmetry. The vaginal introitus at the canal opening is towards the bottom. This simplified two dimensional model assumes that the vaginal canal is perfectly aligned with the x-axis. Placing a constant volume bolus distends the tissue surfaces. This serves as the initial state of our model. Flow starts immediately due to the combined effect of gravity and boundary squeezing pressure from the elastic tissue.

Fig. 2. Effect of wall elasticity on the spreading of bolus. EG ratios used for simulation are 1, 5, 15 and 25. Plots are shown at $\bar{t} = 0, 1, 10$ and 100. The value of $Bi = 0$ and $n = 1$ used for all simulations. At low EG , the flow is mostly downward due to the dominance of gravity. Higher EG increases the coating length and also causes noticeable upward flow.

Fig. 3. Effect of yield stress on the spreading of bolus. Bi ratios used for simulation are 0, 0.2, 0.5 and 1. Plots are shown at $\bar{t} = 0, 1, 10$ and 100. The value of $EG = 10$ and $n = 1$ used for all simulations. Increase in the yield stress (increase in Bi) reduces the coating length.

Fig. 4. Dimensionless shear stress contours at $\bar{t} = 10$ for 2 different Bi ratio = 0.2 and 0.5. The value of $EG = 10$ and $n = 1$ used for both simulations. The thick contour line indicates the yield surface below which we have the non-yielding plug layer.

Fig. 5. Effect of yield stress on coating length and the percentage yielding area of fluid over dimensionless time. The value of $EG = 10$ and $n = 1$ used for all simulations. The yielding area was calculated by subtracting the plug area from the total fluid area and expressed as a percentage of the total area.

361 **Figures**

363 **Fig. 1.** A schematic representation of the fluid bolus in vaginal canal (drawing is not to scale).
 364 Only half plane is shown due to symmetry. The vaginal introitus at the canal opening is towards
 365 the bottom. This simplified two dimensional model assumes that the vaginal canal is perfectly
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 367 serves as the initial state of our model. Flow starts immediately due to the combined effect of
 368 gravity and boundary squeezing pressure from the elastic tissue.

Fig. 2. Effect of wall elasticity on the spreading of bolus. EG ratios used for simulation are 1, 5, 15 and 25. Plots are shown at $\bar{t} = 0, 1, 10$ and 100. The value of $Bi = 0$ and $n = 1$ used for all simulations. At low EG , the flow is mostly downward due to the dominance of gravity. Higher EG increases the coating length and also causes noticeable upward flow.

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377 **Fig. 3.** Effect of yield stress on the spreading of bolus. *Bi* ratios used for simulation are 0, 0.2,
 378 0.5 and 1. Plots are shown at $\bar{t} = 0, 1, 10$ and 100. The value of $EG = 10$ and $n = 1$ used for all
 379 simulations. Increase in the yield stress (increase in *Bi*) reduces the coating length.

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383 **Fig. 4.** Dimensionless shear stress contours at $\bar{t} = 10$ for 2 different Bi ratio = 0.2 and 0.5. The
 384 value of $EG = 10$ and $n = 1$ used for both simulations. The thick contour line indicates the yield
 385 surface below which we have the non-yielding plug layer.

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389 **Fig. 5.** Effect of yield stress on coating length and the percentage yielding area of fluid over
 390 dimensionless time. The value of $EG = 10$ and $n = 1$ used for all simulations. The yielding area
 391 was calculated by subtracting the plug area from the total fluid area and expressed as a
 392 percentage of the total area.

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