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Coupled gel spreading and diffusive transport models describing microbicidal drug delivery

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HIGHLIGHTS

- A biophysically advanced squeezing flow and mass transport model is created.
- Three gels of differing rheological properties and dilution responses are analyzed.
- Gel dilution by fluid emission from the mucosal surfaces alters mass transport of drug.
- Tradeoffs in gel volume and drug loading show smaller gel volumes are effective.

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ABSTRACT

Gels are a drug delivery platform that is being evaluated for application of active pharmaceutical ingredients, termed microbicides, that act topically against vaginal and rectal mucosal infection by sexually transmitted HIV. Despite success in one Phase IIb trial of a vaginal gel delivering tenofovir, problems of user adherence to designed gel application scheduling have compromised results in two other trials. The microbicides field is responding to this dilemma by expanding behavioral analysis of the determinants of adherence while simultaneously improving the pharmacological, biochemical, and biophysical analyses of the determinants of microbicide drug delivery. The intent is to combine results of these two complementary perspectives on microbicide performance and epidemiological success to create an improved product design paradigm. Central to both user sensory perceptions and preferences, key factors that underlie adherence, and to vaginal gel mucosal drug delivery, that underlies anti-HIV efficacy, are gel properties (e.g. rheology) and volume. The specific engineering problem to be solved here is to develop a model for how gel rheology and volume, interacting with loaded drug concentration, govern the transport of the microbicide drug tenofovir into the vaginal mucosa to its stromal layer. These are factors that can be controlled in microbicide gel design. The analysis here builds upon our current understanding of vaginal gel deployment and drug delivery, incorporating key features of the gel's environment, the vaginal canal, fluid production and subsequent gel dilution, and vaginal wall elasticity. These have not previously been included in the modeling of drug delivery. We consider the microbicide drug tenofovir, which is the drug most completely studied for gels: *in vitro*, in animal studies *in vivo*, and in human clinical trials with both vaginal or rectal gel application. Our goal is to contribute to improved biophysical and pharmacological understanding of gel functionality, providing a computational tool that can be used in future vaginal microbicide gel design.

1. Introduction

Topically acting microbicidal molecules against sexually transmitted HIV infection are emerging as an alternative to vaccines in the urgent effort to create methods of prevention, not just treatment, of HIV/AIDS (Stone, 2002). These molecules act to prevent infection by sexually transmitted HIV by a range of mechanisms. Most of them act on cells infectible by sexually transmitted HIV virions. In the vagina, those cells reside primarily in the stromal layer of the mucosa. Multiple dosage forms, i.e. drug

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delivery vehicles, are being evaluated for vaginally acting microbicides. These include gels, intravaginal rings, films, suppositories, fast dissolving inserts and fiber meshes (Nuttall et al., 2007; Karim et al., 2010; das Neves et al., in press). Different dosage forms may be best suited to different drugs. For example, relatively soluble drugs such as tenofovir are suitable for hydrous dosage forms such as gels and films. In contrast, hydrophobic, less water soluble drugs such as dapivirine may be better suited to solid polymeric dosage forms such as rings. Gels and rings are the most advanced microbicide vehicles, and both have demonstrated efficacy in clinical trials (Phases IIb and III) (das Neves et al., in press; Karim et al., 2010). However, successful implementation of both is challenged by disappointing user adherence to designed scheduling of vehicle application (e.g. in relation to sexual activity), which compromises biological and epidemiological efficacy (Microbicide Trial Network, 2011; FACTS, 2015). As the microbicides field moves forward, it is addressing the substandard adherence challenge simultaneously with embracing a broader scientific and technical approach to microbicide drug and vehicle choice, design and performance evaluation. This includes more complete and mechanistic analyses of how properties of the drugs and vehicles govern drug delivery to target locations (e.g. in the stromal layer of the mucosa), i.e. how they achieve desired pharmacokinetics (PK). Such knowledge can feed back to choices of vehicle composition and applied volume in product design. This feedback approach was initiated several years ago, using a preliminary model of drug release by a gel as the key outcome variable (Mahalingam et al., 2010).

Since that time, analysis and understanding of the determinants of vaginal gel deployment and drug delivery have progressed substantially. The fluid mechanics of gel spreading along the lumen of the vaginal canal is now much better understood (Tasoglu et al., 2011–2013); and initial modeling of drug mass transport from a gel into the vaginal mucosal has begun (Gao and Katz, 2013). Predictions from models of gel spreading have shown agreement with imaging studies of vaginal gel distributions (Katz, 2014; Katz et al., 2015). The initial model of tenofovir transport into vaginal tissue *in vivo* also showed good agreement with human pharmacokinetic data (Gao and Katz, 2013). These improvements in the analysis of microbicide pharmacokinetics progressively account more completely for properties of the vehicles, drugs and their environment that govern the mass transport mechanisms. For example, the kinetics of gel dilution and the elasticity of the walls of the vaginal canal have been included in the modeling of gel spreading, albeit not drug delivery. The present work fits directly into this evolving model. We consider effects of an important physiological and pharmacological characteristic of the vaginal environment, the presence of ambient vaginal fluid and consequent gel swelling and dilution by it. These alter gel rheology and effective volume. Gel spreading is therefore altered (analyzed by Tasoglu et al., 2012) and consequently so is drug mass transport from the gel into the vaginal mucosal tissue (a key endpoint of the new analysis here). The elasticity of the vaginal walls is included as an explicit factor in the mechanics of gel swelling. The analysis here is organized to vary gel volume and loaded concentration of drug, as well as gel rheological properties and their responses to dilution. These are salient gel-based factors that can be controlled in product design.

We consider the microbicide drug tenofovir, which is the drug most completely studied for gels, *in vitro*, in animal studies *in vivo*, and in human clinical trials with both vaginal or rectal gel application (Karim et al., 2010; Cranage et al., 2008). Other vehicles (e.g. rings, solid dosage forms) or other active pharmaceutical ingredients (e.g. dapivirine) would also benefit from the approach we take here for gels loaded with tenofovir, with differences in the details. The next generation of clinical trials of microbicide pharmacokinetics can benefit from modeling: in product design per se; and in the design of sampling of fluids and tissues in the trials for drug concentration measurements, e.g. with respect to the sampling times after product application and in the control of the phase of menstrual cycle, which influences vaginal water content (see below). Our goal is to contribute to improved biophysical and pharmacological understanding of gel functionality, providing a computational tool that can be used in future vaginal microbicide gel design.

2. Methods

2.1. Mathematical formulation

The drug delivery process begins after placement of a gel bolus, loaded here with the microbicide tenofovir, into the vaginal canal (typically using a piston type applicator). The gel spreads into a thin layer, primarily due to squeezing of the vaginal walls, and flows along the vaginal canal over the course of hours. During this time, drug diffuses out from the gel coating layer and into the vaginal mucosal tissue that contains two layers, the epithelium and the stroma. The stroma, but not the epithelium, contains vasculature (about 10% by volume) and tenofovir molecules enter the blood vessels there and are cleared in the circulation. Tenofovir (TFV) enters cells and is converted to tenofovir diphosphate (TFV-DP). This is the bioactive form of TFV which inhibits enzymatic conversion of viral RNA to DNA, a critical early step in the infectious processes (Gao and Katz, 2013). This occurs primarily in the stroma. A relatively small amount of total TFV is lost to TFV-DP conversion, and we can neglect that loss in developing transport equations for tenofovir alone within the two mucosal layers. Human pharmacokinetic studies have shown that TFV and TFV-DP concentrations measured in vaginal mucosal biopsies are proportional (Schwartz et al., 2011).Thus, it is pharmacologically meaningful to focus on TFV alone in the fundamental analysis here. Transport of TFV to the stromal tissue derives from two coupled processes: gel spreading driven by squeezing and drug diffusion driven by concentration gradients. The former is independent of the latter, and is used as an input to a numerical solution of the diffusion process. Salient outputs of the overall transport process are the distance spread by gel along the canal vs. time and measures of drug concentration vs. time in the gel, epithelial, stromal, and blood compartments.

The gel spreading model embodies a Reynolds lubrication approximation applied to conservation statements for total fluid mass (gel plus diluting fluid) and applied gel mass in order to derive the equations of motion governing gel dilution and spreading (Tasoglu et al., 2013). A scaling argument has been made here because the vaginal canal, which has an H-shaped cross section, is long and shallow with $\epsilon = \frac{H}{L} \ll 1$, where H and L represent the transverse (y) and longitudinal (x) direction length scales respectively. For reference, see Fig. 1. This shallowness (thinness in depth) assumption also leads to a simplifying assumption of relatively rapid mixing of gel with water in the y direction, allowing the gel fraction (ϕ) to be a function of x only. The gel fraction is defined as the volume fraction of gel as prepared in the mixture of applied gel with diluting fluid. In addition, an argument can be made that curvature of the wall is negligible, and therefore phenomena such as traction forces occurring at the vaginal wall act purely in the y direction.

A one dimensional constrained continuum model is used for the pressure field in the fluid resulting from the force of the vaginal wall. Thus, the local deformation of the compliant wall (h) is approximated as proportional to local pressure (p) of the fluid