Advanced Drug Delivery Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Vaginal drug distribution modeling

David F. Katz [a,b,*], Andrew Yuan [a], Yajing Gao [a]

[a] Department of Biomedical Engineering, Duke University, Durham, NC, USA
[b] Department of Obstetrics and Gynecology, Duke University, Durham, NC USA

ARTICLE INFO

Available online xxxx

Keywords:
Vagina
Microbicides
HIV
Modeling
Gel
Ring
Diffusion
Convection
Mucosa

ABSTRACT

This review presents and applies fundamental mass transport theory describing the diffusion and convection driven mass transport of drugs to the vaginal environment. It considers sources of variability in the predictions of the models. It illustrates use of model predictions of microbicide drug concentration distribution (pharmacokinetics) to gain insights about drug effectiveness in preventing HIV infection (pharmacodynamics). The modeling compares vaginal drug distributions after different gel dosage regimens, and it evaluates consequences of changes in gel viscosity due to aging. It compares vaginal mucosal concentration distributions of drugs delivered by gels vs. intravaginal rings. Finally, the modeling approach is used to compare vaginal drug distributions across species with differing vaginal dimensions. Deterministic models of drug mass transport into and throughout the vaginal environment can provide critical insights about the mechanisms and determinants of such transport. This knowledge, and the methodology that obtains it, can be applied and translated to multiple applications, involving the scientific underpinnings of vaginal drug distribution and the performance evaluation and design of products, and their dosage regimens, that achieve it.

1. Introduction

The human vagina is a fibromuscular tract that connects the vulva to the cervix and uterus and thence the organs of the upper reproductive tract [1]. It is about 10–15 cm long, and its lumen is largely collapsed, resulting in a relatively flat cross section (width about 2–3 cm), except at the innermost region, the fornix. Its net surface area is about 80–110 cm^2. Its mucosa consists of two layers: a stratified squamous epithelium, that varies in thickness during the menstrual cycle from about 200–400 μm; and a lamina propria (connective tissue, also termed the stroma) that is about 2.5–3 mm thick. The stroma is about 10% vasculature by volume (there is no vasculature in the epithelium), and it contains host cells that HIV virions can infect (e.g. $CD4^+$ T cells and macrophages). Below the stroma are muscular and outer connective tissue layers. The vagina does not secrete fluid per se. Mucus from the cervix leaks down through the external cervical os into the floor of the fornix, primarily at midcycle. It may then be distributed in a thin layer over the epithelial surfaces of the vaginal canal, although details of this are not well understood. Sexual stimulation increases the pressure in the vasculature in the stroma, resulting in transudation of fluid through the epithelium to its surface ("lubrication") [2]. We have only approximate knowledge of the quantitative amount and distribution of ambient fluid in the vagina [3]. It is maximal under conditions of maximum estrogen presence in the vaginal environment (e.g. at the midportion of the menstrual cycle) and minimal in conditions of low estrogen and high progesterone (viz. in the luteal phase of the cycle, and post menopause; here the epithelium in thinnest). The maximum volume of ambient vaginal fluid is believed to about around 1–2 ml (Fig. 1).

Delivery of drugs via the vagina has been implemented for many years, for many purposes [4]. Commercial and in-development vaginal products now introduce a variety of drugs intended for systemic delivery (e.g. contraceptive hormones and prostaglandins [5]) and topical delivery (e.g. spermicides, agents against urinary tract infections and candida infections, anti-bacterial vaginosis medications, labor inducing agents, etc. [6–10]). At present there is much activity directed at development of products that deliver drugs—termed *microbicides*—which act topically in the vaginal environment to inhibit infection by sexually transmitted HIV and/or other pathogens, e.g. human papilloma virus (HPV) and herpes simplex virus (HSV) [11–13]. Complementary approaches have focused on delivering antimicrobial antibodies. This application of drug delivery was pioneered by Saltzman and colleagues in the mid 1990s [14,15]. Drug delivery via the vagina is currently implemented or being developed via administration of a range of dosage forms to the vaginal canal: monolithic solid materials (e.g. intravaginal rings, IVRs) and soft, semi-solid materials (e.g. gels, creams, suppositories, films, non-woven porous textile materials, dissolving tablets, and fiber-woven meshes) [16–18]. A number of review articles have already

* Corresponding author at: Department of Biomedical Engineering, Box 90281, Durham, NC 27708 USA.
E-mail address: dkatz@duke.edu (D.F. Katz).

http://dx.doi.org/10.1016/j.addr.2015.04.017
0169-409X/

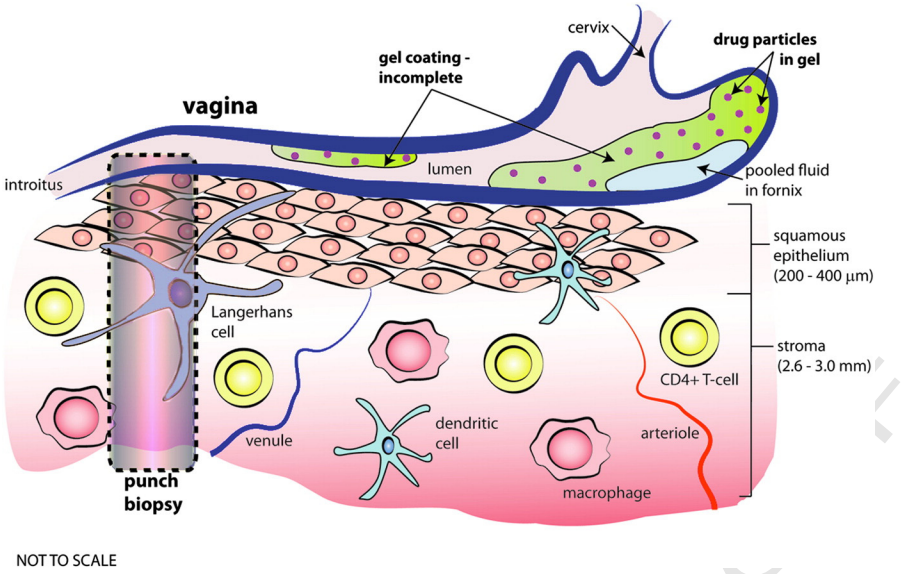

Fig. 1. Drawing of human vaginal canal and mucosal tissue (not to scale). The canal contains gel that partially coats the mucosal surface (anti-pathogenic microbicide molecules are depicted as red dots), and there is semen in the lumenal space not occupied by gel. On the left is a column that represents the tissue collected by a punch biopsy, typically used to collect tissue for measuring drug concentration in pharmacokinetic studies.

been written about vaginal drug delivery [6–10]. For the most part, these have focused upon the compositions and properties of the various delivery systems, with reference to the delivered drugs and vaginal physiology and anatomy. There has been relatively little attention to the use and potential impact of modeling of the drug delivery performance per se of the various products. To be sure, the benefits of modeling vary, depending upon the site and mechanism of action of the delivered drug. For example, therapeutic delivery of antifungal compounds by creams, gels or suppositories against candida infections essentially involves coating, if not filling, the vagina canal with drug that will subsequently mix with ambient vaginal fluids and complete the transvaginal distribution process over time. Maximizing retention of drug on the mucosal surfaces, e.g. via mucoadhesive agents, is important here. However, the time constraint on minimizing the interval before onset of therapeutic action is not acute. In contrast, prophylactic delivery of topically acting anti-HIV microbicide drugs (to vaginal fluids and/or mucosal tissues) is acutely time and space dependent. In a sense, it is a race against the arrival of infectious virions from semen to sites, distributed throughout the length of the mucosa, that are vulnerable to infection. The goal of drug delivery for prophylaxis is to rapidly achieve prophylactic concentrations of drugs at target sites, and to achieve and maintain a high level of prophylactic action as long as possible. Here, the value of modeling can be substantial, viz. it can predict the time interval after product application at which prophylactic concentrations of drug(s) are achieved and sustained, at the level of such prophylaxis, at target sites. More fundamentally, it can help guide the rational design and evaluation of candidate products. This was appreciated by Saltzman and colleagues in their studies of delivery of anti-HSV IgG antibodies by EVA disks [15]. They created a pharmacokinetic compartmental model of antibody concentration (volume averaged) in the vagina by diffusion out from a circular disk, and they applied the model to experimental data in the mouse. In follow up, Saltzman presented two additional model analyses: bolus delivery in the presence of vaginal fluid flow; and diffusion controlled drug release from an intravaginal ring (see section below on IVR modeling) [19,20].

Since those pioneering analyses (over a decade ago), there has been relatively little modeling of microbicide drug delivery to the vaginal (and rectal) environments. This has fundamentally limited our ability to understand the determinants of that performance and to incorporate such knowledge into objective product design and dosing schemas. The review article here is intended to help fill this gap. Our focus is upon drug delivery systems that introduce active pharmaceutical ingredients (APIs) that act topically within the vaginal environment (fluids and tissues), with particular emphasis upon microbicides. Quantitative illustrations of applications of modeling are presented for a leading microbicide drug tenofovir, although the general methodological approach extends more broadly to the spectrum of microbicide drugs being evaluated. Recently, some aspects of such modeling were reviewed [18].

In this article, we present a summary of the nature of deterministic modeling of vaginal drug delivery and distribution, achieved by multiple dosage forms. We then describe several specific applications of modeling that can have value to pharmacological and biological understanding of vaginal product functionality: (1) translating modeling of drug distribution per se (pharmacokinetics) to information about drug functionality (pharmacodynamics); (2) comparing effects of different gel dosage regimens; (3) interpreting consequences of gel aging during storage; (4) comparing modeling results for different dosage forms, viz. gels vs. intravaginal rings; and (5) planning and interpreting studies across multiple species, comparing humans to smaller animals.

The approach reviewed here is complementary to, but different in many ways from traditional empirical PBPK modeling, which has been applied in the context of vaginal drug delivery [21–24]. Both approaches implement conservation of drug mass principles, but deterministic modeling embodies additional biophysical principles that govern *how* drugs migrate within and between compartments. Our descriptions of how the modeling works necessarily involve technical language and use of equations to characterize cause and effect in the examples presented. We hope the information and illustrations of modeling here will be helpful to the broader field of vaginal drug delivery, and be useful in connecting scientific understanding and research to product development and dosing specification, e.g. in the current microbicide pipeline.

2. Building deterministic models

Distribution of a drug throughout the vaginal environment is a mass transport process in which several types of active forces (e.g. squeezing by the walls of the canal, pressure gradients imposed on

Please cite this article as: D.F. Katz, et al., Vaginal drug distribution modeling, Adv. Drug Deliv. Rev. (2015), http://dx.doi.org/10.1016/j.addr.2015.04.017