European Journal of Pharmaceutical Sciences 93 (2016) 410–418

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Pharmacokinetic modeling of a gel-delivered dapivirine microbicide in humans

Michael E. Halwes [a], Jill M. Steinbach-Rankins [a,b,c,d,1], Hermann B. Frieboes [a,b,e,*,1]

[a] Department of Bioengineering, University of Louisville, Louisville, KY, USA
[b] Department of Pharmacology and Toxicology, University of Louisville, Louisville, KY, USA
[c] Department of Microbiology and Immunology, University of Louisville, Louisville, KY, USA
[d] Center for Predictive Medicine, University of Louisville, Louisville, KY, USA
[e] James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA

ARTICLE INFO

Article history:
Received 2 July 2016
Received in revised form 17 August 2016
Accepted 19 August 2016
Available online 21 August 2016

Keywords:
Dapivirine
Computational modeling
Pharmacokinetics
Retroviral drug
Human immunodeficiency virus
Microbicide gel

ABSTRACT

Although a number of drugs have been developed for the treatment and prevention of human immunodeficiency virus (HIV) infection, it has proven difficult to optimize the drug and dosage parameters. The vaginal tissue, comprised of epithelial, stromal and blood compartments presents a complex system which challenges evaluation of drug kinetics solely through empirical effort. To provide insight into the underlying processes, mathematical modeling and computational simulation have been applied to the study of retroviral microbicide pharmacokinetics. Building upon previous pioneering work that modeled the delivery of Tenofovir (TFV) *via* topical delivery to the vaginal environment, here we computationally evaluate the performance of the retroviral inhibitor dapivirine released from a microbicide gel. We adapt the TFV model to simulate the multicompartmental diffusion and uptake of dapivirine into the blood plasma and vaginal compartments. The results show that dapivirine is expected to accumulate at the interface between the gel and epithelium compartments due to its hydrophobic characteristics. Hydrophobicity also results in decreased diffusivity, which may impact distribution by up to 2 orders of magnitude compared to TFV. Maximum concentrations of dapivirine in the epithelium, stroma, and blood were 9.9e7, 2.45e6, and 119 pg/mL, respectively. This suggests that greater initial doses or longer time frames are required to obtain higher drug concentrations in the epithelium. These observations may have important ramifications if a specific time frame is required for efficacy, or if a minimum/maximum concentration is needed in the mucus, epithelium, or stroma based on combined efficacy and safety data.

1. Introduction

The field of pharmacokinetics has benefited greatly in the past decade from the development of increasingly sophisticated mathematical modeling and computer simulation techniques. *In silico* models allow researchers to test and optimize theoretical drug delivery systems complementary to *in vitro* and *in vivo* experimentation, thus reducing costs and laboratory resources. Likewise, experimental validation of simulation predictions allows for increased precision and greater understanding of kinetic parameters and chemical principles governing pharmacokinetics. Computational simulation has also been applied in research areas such as computational oncology (Argyri et al., 2016; Curtis et al., 2016), drug-drug interactions (Thelingwani et al., 2009), and pediatric antibiotics (Bloomfield et al., 2016).

One area in which pharmacokinetic (PK) models are being used is in the treatment and prevention of human immunodeficiency virus (HIV), particularly with the antiretroviral microbicide tenofovir (TFV). Previous clinical trials have shown efficacy of this drug in preventing HIV infection in women (the CAPRISA 004 trial) (Abdool Karim et al., 2010; Vermund and Walker, 2016), and researchers have analyzed the PK parameters of TFV for use in various drug-delivery systems. One such pioneering study was led by Gao and Katz to analyze the delivery of TFV *via* a gel to vaginal tissue (Gao and Katz, 2013). A multicompartmental PK model using a mass transport based approach was presented to create a discretized system of difference equations to govern the diffusion of TFV through the vaginal mucosa. The concentration of TFV in the blood compartment was analyzed over time, as well as the effects on certain pharmacological parameters of the system due to different compartmental length changes. The goal of the study was to provide insight into the determinants of microbicide pharmacokinetics by presenting a mechanistic compartmental analysis framework enabling spatiotemporal prediction of concentrations of gel-delivered drugs to the vaginal environment (Gao and Katz, 2013).

* Corresponding author at: Department of Bioengineering, Lutz Hall 419, University of Louisville, KY 40208, USA.
E-mail address: hbfrie01@louisville.edu (H.B. Frieboes).
[1] Joint senior authorship.

http://dx.doi.org/10.1016/j.ejps.2016.08.037
0928-0987/

Similar to TFV, dapivirine (TMC120) is an antiretroviral inhibitor that has previously been integrated into polymer gels (often hydroxyethyl cellulose, HEC), intravaginal rings (IVR), and polymeric nanoparticles (NP) for HIV prophylaxis (das Neves and Sarmento, 2015; das Neves et al., 2014; Devlin et al., 2013; Nel et al., 2010a; Romano et al., 2009). However, unlike TFV, dapivirine is significantly less soluble in water due to an increased number of benzene rings. Furthermore, dapivirine's slightly larger molecular mass (392.40 g/mol (National Center for Biotechnology Information, 2016a) compared to 287.21 g/mol for Tenofovir (National Center for Biotechnology Information, 2016b)) indicates a slightly lower rate of penetration in diffusion-based applications. While this is advantageous to reduce accumulation in blood circulation, it is disadvantageous relative to TFV in clinical application for rapid drug diffusion into vaginal tissues. Furthermore, current microbicide gels in development use micronized dapivirine due to the inherent instability of the drug in aqueous media (das Neves et al., 2015). Although multiple computational investigations into the diffusive properties of dapivirine from an IVR have been published (Geonnotti and Katz, 2010; Van Niekerk et al., 2014), computational models for dapivirine released from microbicide gels are limited. Yet models which validate empirical data for known agents and delivery vectors would aid researchers to investigate theoretical drug formulations and therapies while limiting costly and time-consuming experimental effort for applications which could ultimately prove ineffective.

The goal of this paper is to adapt the model presented in Gao and Katz (2013) to create a preliminary model for the multicompartmental release of dapivirine from a gel into the vaginal and blood plasma compartments. Previous investigations into the PK parameters are used as a reference in determining model parameters, particularly one study by Nel et al. which evaluated the vaginal fluid, vaginal tissue, and blood plasma concentrations of dapivirine when delivered in a 0.05% (w/w) dapivirine HEC-based gel (Nel et al., 2010b). We describe the steps taken to build upon the previously published model and the adaptations that were made to create a model for dapivirine.

2. Methods

2.1. Model Geometry

The original model for TFV described a rectilinear geometric approximation of the human vaginal canal with a net surface area of 100 cm^2 (Gao and Katz, 2013). Symmetric about the centerline, if only half the geometry was considered, this corresponded to a rectangular prism with frontal area of 50 cm^2, with a depth initially set at 0.34 cm. The side length of the front-facing rectangle (*i.e.* square) was therefore 7.0711 cm. This side length was later used to calculate the volume of the stromal compartment. The length was originally discretized into 500 spatial points, with a Δx of 0.00068 cm. Since the depth in the new model could be adjusted, the number of spatial points was determined by calculating however many points would be required to maintain a Δx of 0.00068 cm. Studies into the geometry of the vaginal canal have shown that the average vaginal surface area is approximately 87.46 cm^2 (Pendergrass et al., 2003). Following the methods as above, the corresponding side length is 6.613 cm. A simulated gel volume of 2.65 mL was applied to the vaginal wall, which, if spread evenly across the surface area, gives a gel thickness, h_G, of 0.03 cm (Nel et al., 2009). The placement of the gel-epithelium and epithelium-stroma boundaries were adjusted automatically based on the relative depths of the different compartments (Fig. 1). For easier comparison between the results of this model and those with the TFV study presented in Gao and Katz (2013) and Gao et al. (2015), the thicknesses of the epithelium and stroma, h_E and h_S were maintained from those papers at 0.02 and .28 cm, respectively.

2.2. Main Equations

The equations presented by Gao and Katz (2013) were transformed from differential equations into difference equations in order to effectively cancel consideration of the x-dimension in the program implementation, allowing the standard ordinary differential equation solver (ode15s in MATLAB) to be used (MATLAB). The stiff solver was

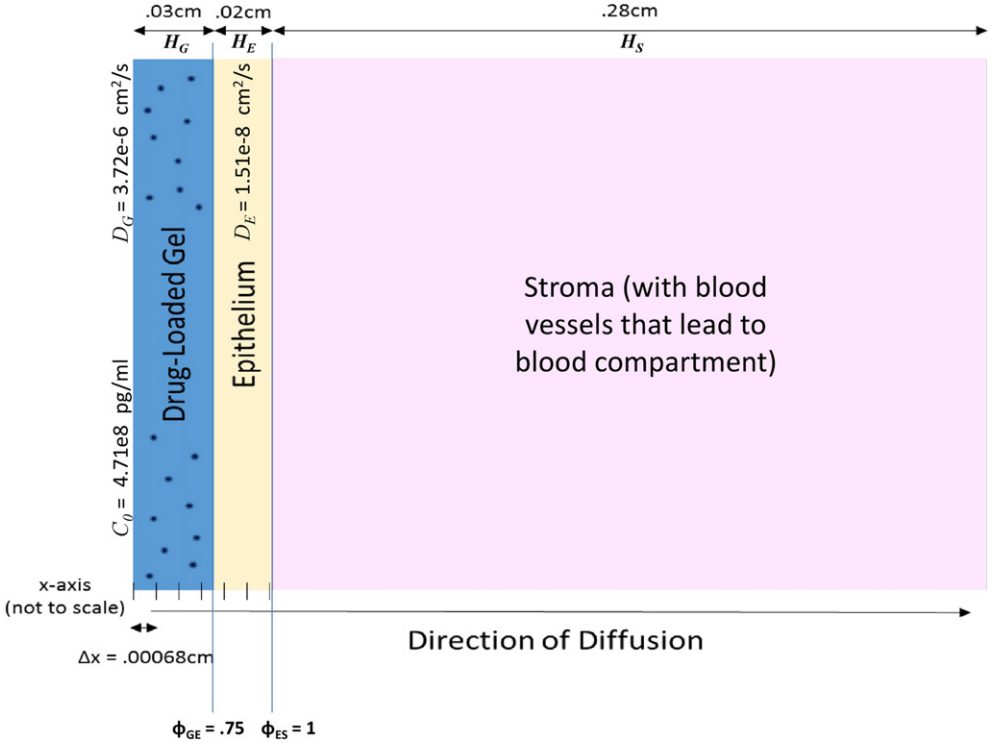

Fig. 1. Visualization of model geometry (not to scale).