available at www.sciencedirect.com

ScienceDirect

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

Modeling the drug transport in the anterior segment of the eye

*Ram Avtar, Deepti Tandon**

Department of Mathematics, Harcourt Butler Technological Institute, Kanpur 2008002, India

ARTICLE INFO

Article history:
Received 12 May 2008
Accepted 7 June 2008
Published on line 21 June 2008

Keywords:
Metabolism
Anterior chamber
Pharmacokinetic
Topical

ABSTRACT

Purpose: The aim of the present work is the development of a simple mathematical model for the time course concentration profile of topically administered drugs in the anterior chamber aqueous humor and investigation of the effects of various model parameters on the aqueous humor concentration of lipophilic and hydrophilic drugs.

Method: A simple pharmacokinetic model for the transient drug transport in the anterior segment has been developed by using the conservation of mass in the precorneal tear film, Fick's law of diffusion and Michaelis–Menten kinetics of drug metabolism in cornea, and the conservation of mass in the anterior chamber. An analytical solution describing the drug concentration in the anterior chamber has been obtained.

Result: The model predicts that an increase in the drug metabolic (consumption) rate in the corneal epithelium reduces the drug concentration in the anterior chamber for both lipophilic and hydrophilic molecules. A decrease in the clearance rate and distribution volume of the drug in the anterior chamber raises the aqueous humor concentration significantly. It is also observed that decay rate of drug concentration in the anterior chamber is higher for lipophilic molecules than that for hydrophilic molecules.

Conclusion: The bioavailability of drugs applied topically to the eye may be improved by a rise in the precorneal tear volume, diffusion coefficient in corneal epithelium and distribution coefficient across the endothelium anterior chamber interface, and by reducing the drug metabolism, drug clearance rate and distribution volume in anterior chamber.

1. Introduction

Topical drug administration is a preferred method for the therapeutic treatment of most of the ocular problems and is the most common treatment for the diseases of the anterior segment of the eye, such as glaucoma and cataract (Kakuji, 1988). The bioavailability of topically administered drug in the anterior chamber aqueous humor is extremely low due to the protective barrier function of the cornea, its rapid clearance by the tear–fluid drainage, its absorption into the conjunctiva and its washout by aqueous humor from the anterior chamber. Topically applied drugs can reach the intraocular tissues by either the corneal and/or the non-corneal (conjunctiva-scleral) pathways. It is common to see that about 1% or less of an applied dose absorbed across the cornea and conjunctiva reaches the anterior segment of the eye (Isowaki et al., 2003).

Under normal conditions, the eye can accommodate only a very small volume of administered drugs without overflowing. Commercial eye drops have a volume of ~30 μL, which is about the volume of the conjunctival sac in humans, however, after a single blink, only an estimated 10 μL remains (Border and Buchwald, 2005; Schoenwald, 1990; Mitra and Mikkclson,

* *Corresponding author.*
E-mail address: deepti_hbti@yahoo.co.in (D. Tandon).
0928-0987/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2008.06.004

1988; Davies, 2000). Consequently, there is a window of only ~ 5–7 min for any topically introduced drug to be absorbed and in many cases, no more than 2% of the medication introduced to the eye will actually be absorbed. The rest will washed away and absorbed through the nasolacrimal duct and the mucosal membranes of the nasal, oropharyngeal and gastrointestinal tract.

After topical instillation, drug is absorbed and diffuses in the cornea and conjunctiva/sclera. Thus, the drug penetrates to the intraocular tissues through the corneal route and non-corneal (conjunctiva/sclera) route. Drug absorption across the conjunctiva and sclera is generally regarded as nonproductive, based on the assumption that drug entering these membranes is picked up by the general circulation and does not contribute to intraocular drug levels (Patton and Ahmed, 1985). However, conjunctiva and scleral absorption may be important for drug entry into the eye in some cores. Hence, most of the efforts at improving ocular drug delivery are aimed at enhancing transcorneal drug transport. When such studies are conducted in vivo, the anterior chamber generally serves as the sampling compartment for measuring intraocular drug bioavailability.

The cornea which acts a biological barrier, is composed of three layers, the epithelium, the stroma and the endothelium permitting less than 10% of most drugs to penetrate into the front of the eye. The drug partitioned on the corneal surface diffuses very slowly through the epithelium to the epithelium–stroma boundary. The resistance to drug transport across the corneal endothelium is usually not appreciable for most drugs, comparing to that across the epithelium and stroma, because of the extremely thin layer of the endothelium.

In the past, the efforts have been focused on either enhancing transcellular drug penetration by increasing drug lipophilicity through the use of prodrugs or analogs, or improving paracellular penetration by using enhances to open tight junctions. Apparently, lipophilic drugs are absorbed better than the hydrophilic drugs via the transcellular route. Since hydrophilic drugs penetrate only via parcellular pathway, i.e. between the cells through the tight junctions (Border and Buchwald, 2005), the penetration area for any hydrophilic drugs is extremely small compared to the surface offered by transcellular routes for absorption of the hydrophilic drugs.

There is an urgent need to estimate the concentration of topically administered drugs in the aqueous humor and investigate the effects of the precorneal, corneal and anterior chamber model parameters on the aqueous humor concentration which are required to ensure the optimal concentration of topically applied drugs for the treatment of any disease of the anterior segment. Mathematical modeling of the drug transport across the cornea to the anterior chamber and the analysis of models may enhance the present understanding of drug bioavailability in the anterior segment of the eye.

Several compartmental (Schowenwald et al., 1997; Lee and Robinson, 1986) and pharmacokinetic models (Lee and Robinson, 1986; Himmelstein et al., 1978; Miller et al., 1981) have analyzed the drug transient diffusion across the cornea to the anterior chamber of the eye. Previous studies have assumed an experimental approach for determining the diffusivity and partition coefficient in the multilayer membrane. Kakuji (1988) developed a pharmacokinetic model for a transcorneal drug delivery after dose instillation by taking into account the corneal diffusion, metabolism, aqueous-humor elimination, and tear flow dynamics. They considered the empirical first-order absorption equation for the drug concentration in the precorneal tear film and anterior chamber. Zhang et al. (2004) developed a mathematical model for transient drug diffusion across the cornea to the anterior chamber of the eye for topical drug delivery. They concluded that drug bioavailability can be increased by lowering the conjunctival to corneal permeability ratio and reducing precorneal solute drainages. They neglected the drug metabolism consumption in the cornea.

The present work is concerned with the development of a simple mathematical model for transient drug diffusion across cornea to the anterior chamber after topical drug delivery. The model takes into consideration the tear flow dynamics in the precorneal area, diffusion and metabolism in the cornea, and drug distribution /clearance in the anterior chamber. An analytical expression for the drug concentration in the anterior chamber aqueous humor is obtained. Thus, the prime objective of the present study is to investigate the effects of the drug metabolic consumption rate in the corneal epithelium on the aqueous humor drug concentration for lipophilic and hydrophilic drugs.

2. Mathematical formulation

The various compartments of the ocular system involved in the transcorneal drug transport to the anterior segment have been shown in Fig. 1(a and b) The illustration of physical model relevant to the present study is shown in Fig. 2. The model developed in this study is comprised of four compartments: precorneal area, conjunctiva sac (palpebral and bulbar), corneal tissue (epithelium, stroma, endothelium) and the anterior chamber. As a drop of solution is instilled into eyelid sac, it is mixed instantly with tear fluid due to reflex blinks. The drug, delivered into the precorneal area is diluted by lacrimal secretion and cleared by four different mechanisms: the drainage with the tear fluid towards the nasal cavity, the absorption in bulbar and palpebral conjunctiva, and the absorption into the cornea. The drug penetration across the cornea is a combined process of the diffusion, partitioning, enzymatic reaction (metabolism), and the drug binding. The drug after penetration into the cornea reaches the aqueous humor, in which the drug is partially eliminated by enzymatic bioconversion, aqueous flow washout, and/or distribution to surrounding tissues such as lens and iris. The drug, absorbed by the tissues such as the conjunctiva and washed away from the aqueous flow, reaches the systematic circulation.

In order to obtain the basic differential equations governing the transport phenomena occurring in the precornea, corneal tissue, and anterior chamber, the following set of additional assumptions is introduced.

2.1. *Assumptions*

(1) Drug enters the anterior chamber through the corneal route exclusively.