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Cyclodextrins and topical drug delivery to the anterior and posterior segments of the eye

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ABSTRACT

It is generally believed that it is virtually impossible to obtain therapeutic drug concentrations in the posterior segment of the eye after topical application of aqueous, low viscosity eye drops. Thus, intravitreal drug injections and drug implants are currently used to treat diseases in the posterior segment such as macular edema. Here it is described how, through proper analysis of the drug permeation barriers and application of well-known pharmaceutical excipients, aqueous eye drops are designed that can deliver lipophilic drugs to the posterior segment as well as how such eye drops can maintain high drug concentrations in the anterior segment. Through stepwise optimization, eye drops containing solid drug/cyclodextrin complex microparticles with a mean diameter of 2–4 μm, dissolved drug/cyclodextrin complex nanoparticles and dissolved drug molecules in an aqueous eye drop media of low viscosity were designed. After administration of the eye drops the microparticles slowly dissolved and maintained close to saturated drug concentrations in the aqueous tear fluid for several hours. Studies in rabbits and clinical evaluations in humans, using dorzolamide and dexamethasone as sample drugs, show that the eye drops deliver significant amounts of drugs to both the posterior segment and anterior segment of the eye. Clinical studies indicate that the eye drops can replace intravitreal injections and implants that are currently used to treat ophthalmic diseases and decrease frequency of drug administration, both of which can improve patient compliance.

1. Introduction

Drug permeation from the eye surface into the eye encounters multiple barriers resulting in topical bioavailability that is generally well below 5% with most of the drug dose entering the general blood circulation. In spite of this very low topical bioavailability aqueous eye drops are the patient preferred dosage form, especially in treatment of diseases of the anterior eye tissues, accounting for over 90% of the market (Vadlapudi et al., 2015). For treatment of diseases of the posterior eye intravitreal injections and ocular implants are frequently preferred since it is generally believed that topically applied ophthalmic drugs are unable to give therapeutic drug concentrations in the posterior eye tissues. However, there are some reports on effective drug delivery from the eye surface to its posterior segment applying a matrix film in rabbits (Adelli et al., 2015), liposomes in rats (Davis et al., 2014), eye drops in rabbits (Lin et al., 2015), eye drops in rats (Ozaki et al., 2015) and nano-micelles in rabbits (Vaishya et al., 2014). Several general reviews on ophthalmic drug delivery have recently been published describing the eye's physiology, the drug permeation barriers, and novel drug delivery techniques and devices under development (Achouri et al., 2013; Fangueiro et al., 2016; Vadlapudi et al., 2015). Here cyclodextrin-based formulations for topical drug delivery to the eye are reviewed.

2. Drug delivery to the eye

2.1. The eye anatomy and physiology

The eye is an isolated organ with surface that is easily accessible for topical drug administration. It consists of an anterior segment that includes the cornea, aqueous humor, iris and lens, and a posterior segment that comprises the vitreous humor, retina, sclera and optic nerve (Fig. 1). The main routes of drug penetration into the eye are the corneal route (i.e., cornea → aqueous humor → intraocular tissues) and the scleral route (i.e., conjunctiva → sclera → choroid/retinal pigment epithelium) (Chastain et al., 2016; Novack and Robin, 2016; Raghava et al., 2004; Vadlapudi

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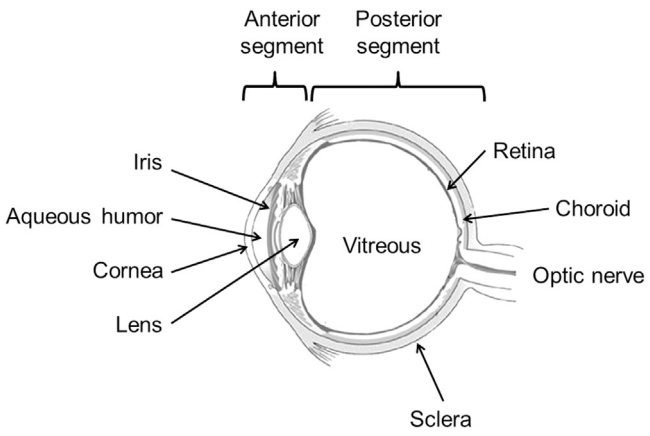
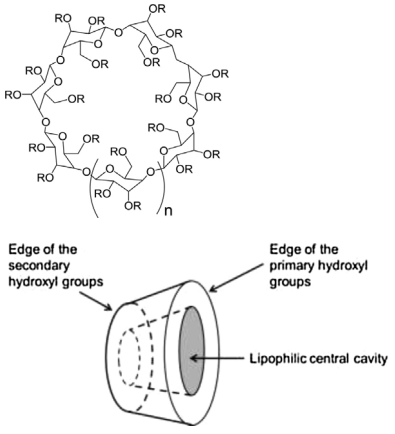


Fig. 1. Schematic drawing of the eye.

et al., 2015). The cornea is a transparent five layer biomembrane. The outermost layer is the epithelium, followed by the Bowman's membrane, stroma (which represents about 90% of the membrane thickness), Descement's membrane and the inner most endothelium layer. The main barrier layer towards drug penetration through the cornea is the lipophilic epithelium, which contributes about 90% of the barrier towards hydrophilic drugs and about 10% of the barrier towards lipophilic drugs. The epithelium consists of three to six layers of tightly adherent epithelial cells. The epithelial surface is covered with microvilli. Drugs penetrate the epithelium either transcellularly (i.e. through the cells) or paracellularly (i.e. through pores between the cells). The transcellular route predominates for lipophilic drug molecules whereas the paracellular route predominates for hydrophilic molecules and small ions. The highly hydrophilic stroma forms a permeation barrier for some lipophilic drugs (Rabinovich-Guilatt et al., 2004). The conjunctiva is a thin mucus membrane that covers the inner surface of the eyelid and sclera. It is a moist and highly vascular epithelial tissue that secrets mucus. The sclera is composed primarily of collagen fibers embedded in a mucopolysaccharides matrix. The primary route for drug permeation through the sclera is passive diffusion through an aqueous pathway. The permeability of sclera does not display any apparent dependence on the drug lipophilicity but displays a strong dependence on the molecular weight of the drug, i.e. the hydrodynamic radius of the permeating drug molecule, the permeability coefficient decreasing with increasing molecular weight (Prausnitz and Noonan, 1998). The conjunctiva is approximately 15 to 25 times more permeable than cornea and sclera is approximately 10 times more permeable (Hämäläinen et al., 1997). Although drug transporters have been located in the eye epithelium it is believed that most drugs permeate from the eye surface into the eye via passive diffusion.

The surface of the eye is covered with mucus, a gel-like fluid (mucus) containing mainly water (90–98%) and mucins (2–5%). Mucins are large, flexible glycoproteins having molecular weights ranging from 0.5 to 20 MDa (one megadalton [MDa] is one million Da). Mucins form hydrogen bonds with surrounding water molecules, leading to a significant increase in the thickness and

Table 1
Physiochemical properties of the most common natural cyclodextrins and some of their derivatives that are of pharmaceutical interest.



Cyclodextrin	n	R = H or	Abbreviation	Synonyms	PC[a]	MS[b]	MW (Da)	Solubility[c] (mg/ml)	$LogK_{o/w}$[d]
α-Cyclodextrin	0		αCD	alfadex	EUR, USP, JPC	–	972.8	130	−13
β-Cyclodextrin	1		βCD	betadex	EUR, USP, JPC	–	1135	18.4	−14
2-Hydroxypropyl-β-cyclodextrin	1	$-CH_2CHOHCH_3$	HPβCD	hydroxypropyl betadex	EUR, USP	0.65	1400	>600	−11
Randomly methylated β-cyclodextrin	1	$-OCH_3$	RMβCD			1.8	1312	>600	−6
Sulfobutylether β-cyclodextrin sodium	1	$-(CH_2)_4SO_3^-Na^+$	SBEβCD	betadex sulfobutyl ether sodium	USP	0.9	2163	>500	<−10
γ-Cyclodextrin	2		γCD		USP, JPC	–	1297	249	−17
2-Hydroxypropyl-γ-cyclodextrin	2	$-CH_2CHOHCH_3$	HPγCD		–	0.6	1576	>500	−16

[a] Pharmacopoeia monographs: EUR (European Pharmacopoeia), USP (United States Pharmacopoeia – National Formulary), JPC (Japanese Pharmaceutical Codex).
[b] Molar substitution (MS) is defined as the average number of substituents per glucopyranose repeat unit.
[c] From references (Kurkov et al., 2011; Sabadini et al., 2006).
[d] Calculated logarithm of the octanol/water partition coefficient at neutral pH. From SciFinder (scifinder.cas.org). These are approximate values. The exact values for the cyclodextrin derivatives depend on their MS well as the location of the substituents.