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Effect of Cyclodextrins on Topical Drug Delivery to the Eye

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ABSTRACT

Cyclodextrins are oligosaccharides which form a new group of pharmaceutical excipients. Cyclodextrins have been added to aqueous eye drop preparations to solubilize lipophilic water-insoluble drug, to increase the chemical stability of drugs, or to reduce local drug irritation in the eye. Hydrophilic cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin, have been shown to be nontoxic to the eye and are generally well tolerated in aqueous eye drop formulations. However, improper formulation of aqueous cyclodextrin containing eye drop solutions can reduce the topical availability of the drug molecule. This paper reviews the effects of cyclodextrins and aqueous cyclodextrin eye drop formulations on the ocular bioavailability of drugs.

INTRODUCTION

Drugs used in ophthalmology are either administered systematically (e.g., by oral route) or locally to the eye. Usually local drug administration is preferred, and then in the form of topically applied, low-viscosity aqueous eye drop solutions. Other topically applied drug formulations, such as suspensions, oily drops, gels, ointments, and solid inserts, have also been used but most of these formulations give rise to unwanted side effects (e.g., eye irritation and blurred vision). The ocular bioavailability of topically applied drugs is generally very low. The main barriers to drug absorption into the eye are the cornea, conjunctiva, and sclera (1,2). The cornea consists of five layers. The outermost layer is the epithelium, which consists of five or six cell layers. The tight junctions around the epithelial cells make it difficult for hydrophilic drug molecules to penetrate into the eye. Penetration enhancers, like benzalkonium chloride, make the cornea more permeable by disrupting these tight junctions. The conjunctival epithelium also constitutes a relatively tight barrier to drug penetration. Although it is not as tight as the corneal epithelium, the vasculature of the conjunctiva will absorb a substantial part of the

drug (2). The drug fraction which is able to reach the sclera appears to have relatively good access into the eye.

The surface of the eye is constantly being cleaned and moisturized by the aqueous tear fluid (lacrimal fluid). To prevent side effects such as blurred vision, the eye drop solution must be mixable with the aqueous tear fluid. Also, it will be difficult for drug molecules to reach the eye surface unless they are soluble in the tear film covering the surface. Thus the drug must be, at least to some degree, water soluble. The drug molecules must also be somewhat lipid soluble to be able to penetrate through the lipophilic corneal epithelium, through the corneal stroma and the lipophilic endothelium into the aqueous humor. In other words, for successful formulation in aqueous eye drop solution, the drug must both be water soluble (i.e., hydrophilic) and at the same time lipid soluble (i.e., hydrophobic). It is not surprising that relatively few molecules fulfill these criteria. Acetazolamide clearly displays this dilemma. The sodium salt of acetazolamide (pK_{a1} = 7.2) is water soluble and as such can be applied to the eye. However, absorption is low, probably since the ionized drug cannot pass the cornea. The nonionized form of acetazolamide is lipophilic and poorly water soluble (solubility 0.7 mg/ml) and cannot be dissolved in adequate concentration in an aqueous eye drop solution unless excipients, such as cyclodextrins, are added to the aqueous eye drop formulation to formulation to facilitate its solubilization (3). There are other methods which have been used to get around this problem. Steroids used to treat ocular inflammation are lipophilic water-insoluble compounds that have been introduced into aqueous eye drop formulations as suspensions or as water-soluble prodrugs. In both cases the ocular bioavailability can be seriously hampered by the low aqueous solubility or the hydrophilic properties, respectively, of the penetrating molecules.

Tear fluid is continuously secreted by the lacrimal gland and under normal conditions the turnover rate is about 16% of the total tear volume per minute (4). This short turnover rate limits the contact time of topically applied drugs with the eye surface, which again reduces their ocular bioavailability, especially after drug application in low-viscosity aqueous eye drop solution. Typically less than 5% of topically applied drug is absorbed through cornea into the eye (5). Most of the drug lost from the eye surface will be absorbed into the systemic circulation, and this can cause systemic side effects varying from mild to life-threatening incidents (6). The risk of systemic side effects might be decreased by increasing the ocular/systemic ratio of drug absorption, that is, by increasing the ocular bioavailability of the drug (5). This can be achieved by increasing the contact time of topically applied drugs through, for example, formation of hydrogels, bioadhesive dosage forms, in situ gelling systems, and colloidal systems including liposomes and nanoparticles (7). However, the viscous drug delivery systems, such as the in situ gelling systems, can cause blurred vision after topical application to the eye, which will limit their usage.

The following is a short review of the usage of cyclodextrins in aqueous eye drop formulations with emphasis on the more recent developments. Some of generated reports on this subject have been reviewed previously (8–10).

PHYSICOCHEMICAL PROPERTIES OF CYCLODEXTRINS

Cyclodextrins form a group of structurally related oligosaccharides which are formed by enzymatic cyclization of starch by a group of amylases called *glycosyltransferases*. The important structural characteristics of the cyclodextrin molecules are their cylindrical shape, somewhat hydrophobic central cavity, and hydrophilic outer surface. The polarity of the cyclodextrin cavity has been estimated to be similar to that of 40% mixture of ethanol in water (9). Due to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are to some extent cone shaped. All the primary hydroxyl groups are located on the narrow side while all the secondary hydroxyl groups are located on the wider side. The most common natural cyclodextrins are α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin consisting of 6, 7, and 8 α-1,4-linked glucopyranose units, respectively. To improve their physicochemical and biological properties the molecular structures of the parent cyclodextrins (i.e., α-, β-, and γ-cyclodextrin) have been modified. Branched cyclodextrins can be obtained by reacting cyclodextrin with glucose or maltose in the presence of pullulance enzyme. Other common cyclodextrin derivatives are formed by alkylation (e.g., methyl- and ethyl-β-cyclodextrin) or hydroxyalkylation (e.g., hydroxypropyl and hydroxyethyl derivatives of α-, β-, and γ-cyclodextrin) of the hydroxyl groups (Fig. 1). These manipulations frequently transform the crystalline cyclodextrins into amorphous mixtures of isomeric cyclodextrin derivatives and, thus, the aqueous

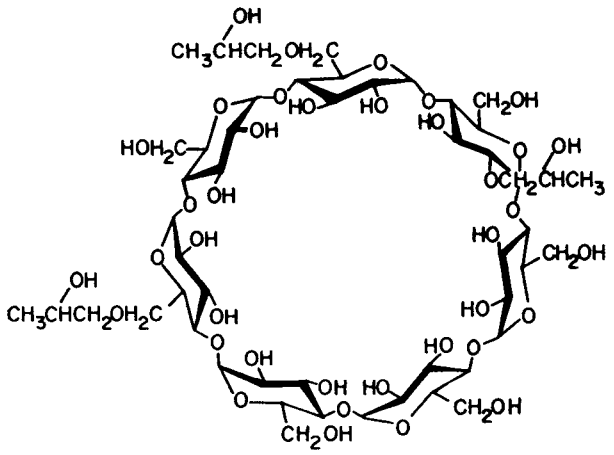

Figure 1. Representative structure of 2-hydroxypropyl-β-cyclodextrin.

solubility of the derivatives is usually much larger than that of the parent cyclodextrin (11).

Cyclodextrins are capable of forming inclusion complexes with many molecules by taking up a whole molecule, or some part of it, into the cavity (9,12,13). No covalent bonds are formed or broken during the complex formation, and in aqueous solutions the complexes are readily dissociated and free guest molecules are in equilibrium with the molecules bound within the cyclodextrin cavity. The main driving force for the complex formation is thought to be release of enthalpy-rich water from the cyclodextrin cavity. The water molecules located inside the cavity cannot satisfy their hydrogen-bonding potentials and therefore they are of higher enthalpy (14). The energy of the system is lowered when these enthalpy-rich water molecules are replaced by suitable guest molecules which are less polar than water. The release of ring strain, van der Waals interactions, hydrogen bonding, hydrophobic interactions, and changes in solvent–surface tensions may also participate in the complex formation.

Cyclodextrin encapsulation of a hydrophobic guest molecule will affect many of its physicochemical properties. In the solid state the cyclodextrin complexes frequently increase the rate of dissolution of the guest molecule, increase its chemical stability, and reduce its volatility and sublimation. In aqueous solutions cyclodextrin complexes can both increase the solubility and stability of the guest molecule and reduce its volatility and absorption into or adsorption on surfaces and membranes. For these reasons various pharmaceutical applications of cyclodextrins and their derivatives are now being tested.

CYCLODEXTRINS IN AQUEOUS EYE DROP SOLUTIONS

Solubilization

Some of the more recent examples of cyclodextrin-containing aqueous eye drop solutions are listed in Table 1. Other examples have previously been reviewed (8–10). The cyclodextrins are mainly added to the aqueous eye drop solutions as drug solubilizers but there are a few examples where they are added to reduced drug irritation (24,28). The solubilizing abilities of cyclodextrins depends largely on their abilities to form water-soluble drug · cyclodextrin complexes. The efficacy of the complexation is frequently very low, in which case large amount of a water-soluble cyclodextrin is needed to solubilize relatively small amounts of a lipophilic drug. To add to this difficulty, vehicle additives commonly used in aqueous eye drop formulations—such as sodium chloride, buffer salts, and preservatives—very often reduce the efficiency. Isotonic solutions can contain up to 25% (w/v) cyclodextrin, but at such high cyclodextrin concentration evaporation of water has been shown to leave hypertonic cyclodextrin solutions on the eye surface that are irritating. Further evaporation of water results in formation of cyclodextrin crusts.

Thus, optimum cyclodextrin concentration in aqueous eye drop solutions is considered to be below about 15%. It is possible to enhance the complexation. For example, it has been shown that polymers, such as water-soluble cellulose derivatives and other rheological agents, can form complexes with cyclodextrins, and that such complexes possess physicochemical properties different from those of individual cyclodextrin molecules (30,31). In aqueous solutions, water-soluble polymers increase the solubilizing effect of cyclodextrins on various hydrophobic drugs by increasing the apparent stability constants of the drug–cyclodextrin complexes. For example, the solubilizing effect of 10% (w/v) 2-hydroxypropyl-β-cyclodextrin solution on a series of drugs and other compounds was increased from 12% to 129% when 0.25% (w/v) polyvinylpyrrolidone was added to the aqueous cyclodextrin solution (30). Addition of 0.1% (w/v) polyvinylpyrrolidone to the aqueous complexation medium resulted in about 45% increase in the apparent stability constant of the hydrocortisone · 2-hydroxypropyl-β-cyclodextrin complex. However, to obtain this solubilization enhancement, the solutions have to be heated to 120°C for 20 to 40 min. Comparable effect has been obtained through formation of drug · hydroxyl acid · cyclodextrin ternary complexes with basic drugs (32).

Table 1

Some of the More Recent Publications on the Usage of Cyclodextrins in Aqueous Eye Drop Solutions

Drug	Cyclodextrin[a]	Ref.
Acetazolamide	HPβCD	3, 15, 16
	αCD, HPβCD	17
Arachidonylethanolamide	HPβCD	18
Cyclosporine	αCD	19, 20
Dexamethasone	HPβCD	21–23
Dexamethasone acetate	HPβCD	23
Diclofenac	HPβCD, MβCD	24
Ethoxyzolamide	HPβCD	15
Pilocarpine	HPβCD	25
	αCD, βCD, HPβCD	26
	SBEβCD	27
Pilocarpine prodrugs	HPβCD	28, 29

[a]αCD: α-cyclodextrin; βCD: β-cyclodextrin; HPβCD: 2-hydroxypropyl-β-cyclodextrin; MβCD: methylated β-cyclodextrin; SBEβCD: sulfobutyl ether β-cyclodextrin.

Preservatives in Cyclodextrin-Containing Eye Drop Solutions

Aqueous eye drop solutions are usually packaged in multiple-dose containers and, thus, should contain a suitable antimicrobial preservative. Through complexation cyclodextrins can reduce the antimicrobial activity of preservatives in much the same way as they reduce ocular bioavailability of drugs. Several investigators have screened chemically different preservatives with the aim of finding the most suitable compound for preserving aqueous cyclodextrin solutions (33–35). These studies show that the cyclodextrin inactivation of the preservatives depends on their ability to form cyclodextrin complexes. Highly water-soluble preservatives (e.g., thimerosal and bronopol), which have little tendency to form cyclodextrin complexes, showed little or no inactivation; but lipophilic preservatives (e.g., the parahydroxybenzoic acid esters), which have much greater tendency to form cyclodextrin complexes, showed strong inactivation when used in combination with cyclodextrin. To obtain a sufficient preservation it is necessary to increase the preservative concentration when cyclodextrin is present. In many cases effective preservation of cyclodextrin-containing aqueous eye drop solutions can be obtained with a mixture of benzalkonium chloride (e.g., 0.02% w/v) and sodium edetate (e.g., 0.05% w/v). However, in all cases an appropriate antimicrobial efficacy test should be performed on all new cyclodextrin-containing ophthalmic preparations.

Toxicity

The pharmacology and toxicology of cyclodextrins have recently been reviewed (9). In general, the hydrophilic cyclodextrins are nontoxic upon topical application. Studies in various animal species and humans have shown that the natural cyclodextrins (i.e., α-, β-, and γ-cyclodextrin) are essentially nontoxic when given orally but toxic effects have been observed after parenteral administration of α- or β-cyclodextrin. Extended studies in animals have shown that γ-cyclodextrin has no embryotoxic or teratogenic effects. Of the three parent cyclodextrins, probably only γ-cyclodextrin can be used in parenteral drug formulations. Hydrophilic cyclodextrin derivatives, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutyl ether β-cyclodextrin, can be used in parenteral drug formulations. However, methylated cyclodextrins, such as dimethyl-β-cyclodextrin—which has amphiphilic properties and causes hemolysis at low concentrations (about 150 mg/kg in mice)—cannot be used in parenteral formulations. The hydrophilic cyclodextrins are probably not transported through the

eye cornea. They consist of relatively large hydrophilic molecules which only permeate lipophilic biological membranes with great difficulty. If two drops of a pure isotonic cyclodextrin eye drop solution (contains 20–25% w/v cyclodextrin) were administered to each eye three times a day the total cyclodextrin dose would be between 100 and 150 mg/day, or about 1.7 mg/kg/day for an adult. Under more normal usage the daily cyclodextrin doses would be less than 1/10th of this (10). Thus, no systemic side effects would be expected after topical administration of hydrophliic cyclodextrins in eye drop solutions.

Jansen et al. (36) studied the effects of single and multiple applications of 12.5% 2-hydroxypropyl-β-cyclodextrin and 5% and 12.5% dimethyl-β-cyclodextrin eye drop solutions on the corneal epithelium of rabbits. They concluded that dimethyl-β-cyclodextrin is toxic to the corneal epithelium and, thus, should not be used in ophthalmic formulations. 2-Hydroxypropyl-β-cycodextrin was well tolerated and nontoxic when evaluated by a slit lamp biomicroscopy and scanning electron microscopy. Also, Reer et al. (24) studied the effect of 2-hydroxypropyl-β-cyclodextrin and methylated β-cyclodextrins in the eye and showed that 2-hydroxypropyl-β-cyclodextrin possessed the most favorable toxicological properties. Javitt et al. (37) have studied aqueous 45% (w/v) 2-hydroxypropyl-β-cyclodextrin solutions containing acetazolamide or methazolamide in rabbits. In general, the solutions were well tolerated.

CYCLODEXTRINS AS PERMEABILITY ENHANCERS

Simple Cyclodextrin Complexes

The cyclodextrin molecules are relatively large (molecular weight ranging from about 1000 to over 2000), with a hydrated outer surface; and under normal conditions, cyclodextrin molecules will only permeate biological membranes with some difficulty (38–40). For example, numerous in vitro and in vivo experiments have demonstrated that only insignificant amounts of orally administered cyclodextrins are absorbed unmetabolized from the intestinal tract, and that, under normal conditions, hydrophilic cyclodextrins are not absorbed transdermally. Also, it has been shown that percutaneous absorption of 2-hydroxypropyl-β-cyclodextrin is extremely low (40). It is generally recognized that cyclodextrins act as true carriers by keeping the hydrophobic drug molecules in solution and deliver them to the surface of the biological membrane, for example, the eye cornea, where they partition into the membrane (39). The relatively lipophilic membrane has much lower affinity for the hydrophilic cyclodextrin molecules and therefore they remain in the aqueous vehicle system or aqueous tear fluid.

The ocular availability of drugs in aqueous cyclodextrin-containing eye drop solutions depends on several factors such as the release of the drug from the cyclodextrin complex and partition of the drug molecules into and then through the cornea or the conjunctival epithelium. However, relatively little is known about the effect of cyclodextrins on ocular bioavailability of drugs. The effect of cyclodextrin complexation on the permeability of drugs through biological membranes has mainly been evaluated using semipermeable cellophane membranes and hairless mouse skin (39–41). The relatively large hydrophilic cyclodextrin molecules are able to permeate the cellophane membrane, although they do this somewhat more slowly than the smaller drug molecules. Thus, the total drug flux (I_t) from an aqueous cyclodextrin solution through the cellophane membrane is:

$$I_t = I_D f_D + I_{D\cdot CD}(1 - f_D)$$

where I_D is the flux of the free drug, f_D is the fraction of free drug, $I_{D\cdot CD}$ is the flux of the drug · cyclodextrin complex and $(1 - f_D)$ is the fraction of drug in the complex. The value of f_D can be calculated from the stability constant of the drug–cyclodextrin complex and I_D and $I_{D\cdot CD}$ from series of permeability measurements. For example, it has been shown by studying the permeability of hydrocortisone through a semipermeable cellophane membrane (cutoff molecular weight 12,000) from aqueous 2-hydroxypropyl-β-cyclodextrin solutions, that the free-drug molecules permeate the membrane about 13 times faster than the drug · cyclodextrin complex (39,42). This supports the previously mentioned notion that under normal conditions only the free-drug molecules, and not the hydrated drug · cyclodextrin complexes or the hydrated cyclodextrins themselves, permeate the tight lipophilic biological membranes such as skin or the eye cornea (Fig. 2). In the case of biological membranes, the value of $I_{D\cdot CD}$ will be basically zero, and the flux of the drug molecules through the membranes will be described by:

$$I_t = I_D f_D$$

That is, addition of cyclodextrins to a vehicle will not automatically lead to greater drug permeability through biological barriers. In a number of skin permeability studies, with lipophilic water-insoluble drugs in aqueous

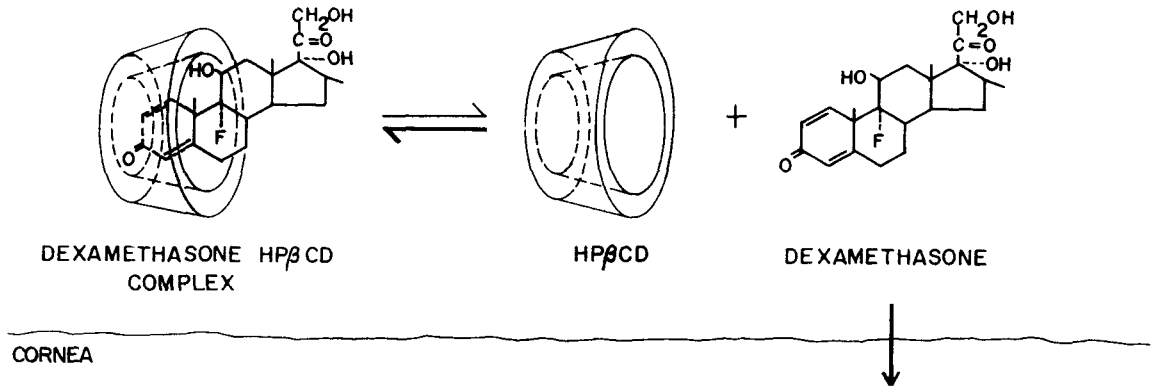

Figure 2. The effect of 2-hydroxypropyl-β-cyclodextrin on the delivery of dexamethasone from aqueous eye drop solution through the eye cornea.

cyclodextrin vehicle systems, it has been shown that optimum penetration enhancement is obtained when just enough cyclodextrin is used to solubilize all drug in the vehicle (21,39,41-43).

Conflicting results have been reported on the effect of cyclodextrin complexation on bioavailability after ocular administration (8,10). In some studies addition of cyclodextrin to the aqueous cyclodextrin formulations resulted in enhanced drug bioavailability; in other studies addition of cyclodextrin resulted in decreased bioavailability (25,26,28,44). These conflicting results could be due to improper usage of cyclodextrins since optimum bioavailability would be expected when just enough cyclodextrin is added to the aqueous eye drop solution to solubilize the lipophilic water-insoluble drug. Addition of too much cyclodextrin will decrease the bioavailability by retaining the drug molecules in the aqueous tear fluid. Similarly, cyclodextrins can decrease ocular bioavailability of water-soluble drugs. The effect of 2-hydroxypropyl-β-cyclodextrin on the pharmacological effect of the water-soluble drug timolol maleate is shown in Fig. 3. Timolol is a β-adrenergic antagonist which has been used to lower intraocular pressure (IOP) for the treatment of glaucoma. Addition of cyclodextrin to the aqueous eye drop solution reduces the availability of free timolol due to timolol · cyclodextrin complex formation and, since the complex is unable to permeate into the eye, this leads to decreased ocular bioavailability of timolol. Consequently, administration of the cyclodextrin-containing timolol eye drop solution gives less intraocular pressure decrease than comparable formulation containing no cyclodextrin.

The Effects of Water-Soluble Polymers

As mentioned before, it is possible to enhance complexation and, thus the solubilizing effect of cyclodextrins by addition of polymers to the aqueous eye drop solutions. Also, addition of the polymers (and heating to 120°C for 20 to 40 min) enhances drug permeability from the aqueous cyclodextrin solution through biological membranes. For example, addition of 0.25% (w/v) polyvinylpyrrolidone resulted in about

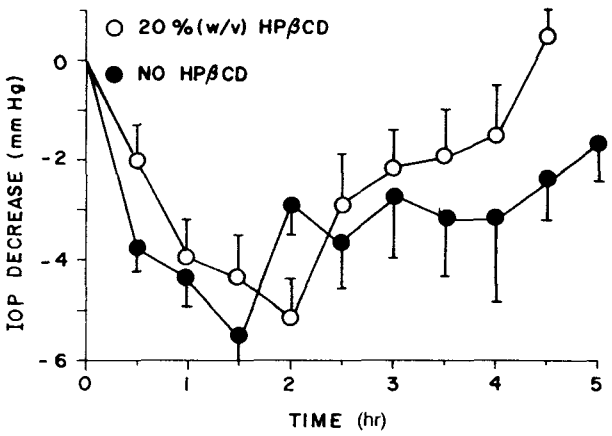

Figure 3. Change in intraocular pressure (IOP) after administration of one drop (50 μl) of isotonic aqueous timolol maleate eye drop solution [containing equivalent to 0.5% (w/v) timolol] with or without 20% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) to English brown rabbits. The experimental conditions are described in Ref. 15.

40% increase in the flux of hydrocortisone through hairless mouse skin from aqueous 2-hydroxypropyl-β-cyclodextrin solutions and about 270% increase from aqueous carboxymethyl-β-cyclodextrin solutions (41,43). Addition of 0.10% (w/v) hydroxypropyl methylcellulose and heating increases the apparent stability constant of the dexamethasone · 2-hydroxypropyl-β-cyclodextrin complex from 1230 M^{-1} to 1550 M^{-1}. At the same time the heating also enhances the dexamethasone delivery into the eye (22). Figure 4 shows the concentration of dexamethasone in aqueous humor after application of two identical solutions; one was heated in an autoclave and the other was filtered through a membrane filter. Both solutions contained 0.67% (w/v) dexamethasone as determined after heating or filtration. The area under the curve from 0 to 9 hr was over 4-fold larger for the heated solution and the drug levels were always higher after application of the heated solution, especially at extended time points. Thus, the heating results not only in enhanced drug delivery into the eye but also extended drug delivery. Similar observations were obtained with acetazolamide and other carbonic anhydrase inhibitors, where it has been shown that it is possible to lower IOP in rabbits by formulating the drugs in aqueous eye drop solutions containing both 2-hydroxypropyl-β-cyclodextrin and hydroxypropyl methylcellulose (Table 2). Addition of 0.10% (w/v) hydroxypropyl methylcellulose increased the apparent stability constant of the acetazolamide · 2-hydroxypropyl-β-cyclodextrin complex increased from 76 M^{-1} to 150 M^{-1}, but at the same time the acetazolamide delivery into the eye was enhanced (3). The mean peak IOP lowering activity of 1% (w/v) acetazolamide eye drops in ocular hypertensive human subjects was 15.6%, at 2 hr after installation of the eye drops and 3, 7, 14, and 28 days after beginning of treatment (Fig. 5). This is less than after topical application of 0.5% timolol but not much less to what has been observed after application of 2% dorzolamide eye drops (about 18%) (45). The results show that addition of hydroxypropyl methylcellulose to aqueous 2-hydroxypropyl-β-cyclodextrin eye drop solutions and heating the solutions in an autoclave enhances both the cyclodextrin complexation of drugs, resulting in enhanced drug solubilization, and the drug permeability into the eye.

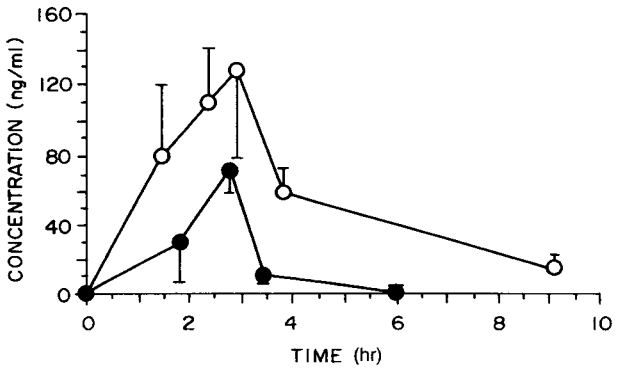

Figure 4. Dexamethasone concentration in aqueous humor after administration of one drop (50 μl) of aqueous 2-hydroxypropyl-β-cyclodextrin eye drop solution containing 0.67% (w/v) dexamethasone in a heated complex (○) or an unheated complex (●). From Ref. 22.

CONCLUSIONS

Through cyclodextrin complexation it is possible to enhance aqueous solubility of a water-insoluble drug without affecting the lipophilicity of the drug molecule. Cyclodextrins act as true drug carriers by keeping the drug molecules in solution and delivering them to the surface of the eye where they partition into the eye. However, the availability of the drug in the aqueous cyclodextrin-containing eye drop solution depends on the overall formulation. It is important to use just enough cyclodextrin to solubilize the drug. Addition of too much cyclodextrin will reduce the drug availability. Also, it is possible to enhance drug permeability into the

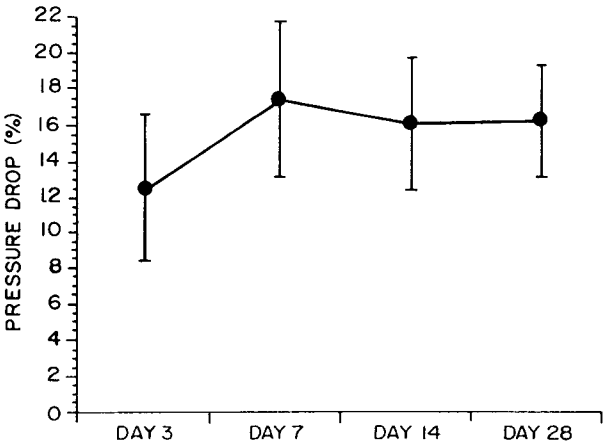

Figure 5. Mean pressure-lowering activity in ocular hypertensive eyes 2 hr after installation of 1% (w/v) acetazolamide 2-hydroxypropyl-β-cyclodextrin eye drop. From Ref. 3.

Table 2

IOP Lowering Effect of Three Different Carbonic Anhydrase Inhibitors in Rabbits (Mean ± Standard Error of the Mean)

Time (hr)	1% Acetazolamide Solution	2% Acetazolamide Suspension	0.3% Ethoxyzolamide Solution	0.7% Methazolamide Solution
0	0	0	0	0
0.5	−0.45 ± 0.49	−1.31 ± 0.43	−0.30 ± 0.99	
1	−2.11 ± 0.57	−2.52 ± 0.58	−2.23 ± 0.87	−0.94 ± 0.40
1.5	−1.97 ± 0.76	−3.00 ± 0.55	−2.63 ± 0.70	
2	−2.39 ± 0.76	−3.08 ± 0.77	−2.40 ± 0.54	−2.03 ± 0.38
2.5	−2.64 ± 0.95		−0.98 ± 0.57	
3	−1.69 ± 0.66	−2.78 ± 0.61	−0.51 ± 0.77	−1.71 ± 0.46
3.5	−1.70 ± 0.87		+0.00 ± 0.98	
4	+0.10 ± 0.44	−2.64 ± 0.48		−3.03 ± 0.63
5		−2.01 ± 0.56		−3.44 ± 0.77
6		−1.71 ± 0.74		−3.60 ± 0.51
7				−1.29 ± 0.78
8		−0.02 ± 1.35		
10				−0.47 ± 0.48

Note. Acetazolamide and ethoxyzolamide from Ref. 15. Methazolamide from authors' unpublished results. The carbonic anhydrase inhibitors were formulated in aqueous cyclodextrin/polymer eye drop solutions, where the co-complex consisted of the drug, 2-hydroxypropyl-β-cyclodextrin, and hydroxypropyl methylcellulose.

eye even further by adding small amount of a water-soluble polymer to the aqueous cyclodextrin-containing eye drop formulation and heating the formulation to, for example, 120°C for 20 to 40 min. Finally, cyclodextrin complexation of preservatives can reduce their activity and, thus, appropriate antimicrobial efficacy tests should always be performed on all new cyclodextrin-containing ophthalmic preparations.

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