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Cyclodextrins in Eye Drop Formulations

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Abstract

Ideally, eye drop formulations are aqueous solutions. Many drugs that are useful in topical application to the eye are not sufficiently water soluble to be dissolved in simple aqueous solutions. This problem is approached through hydrophilic prodrugs, suspensions, lipid based solutions and excipients such as cyclodextrins. Cyclodextrins can be used to form aqueous eye drop solutions with lipophilic drugs, such as steroids. The cyclodextrins increase the water solubility of the drug, enhance drug absorption into the eye, improve aqueous stability and reduce local irritation. Cyclodextrins are useful excipients in eye drop formulations of various ophthalmic drugs, including steroids of any kind, carbonic anhydrase inhibitors, pilocarpine and cyclosporins. Their use in ophthalmology has already begun and it is likely to expand the selection of drugs available as eye drops. In this paper we review the use of cyclodextrins in eye drop formulations. The use of cyclodextrins to formulate dexamethasone eye drops is an example of their usefulness. Cyclodextrins have been used to formulate eye drops containing corticosteroids, such as dexamethasone, with concentration and ocular absorption, which in human and animal studies is many fold that seen with presently available formulations. Such formulations offer the possibility of once a day application of corticosteroid eye drops after eye surgery, and more intensive topical steroid treatment in severe inflammation.

Introduction

Cyclodextrins are especially well suited for eye drop formulations and they are already used in ophthalmology. Cyclodextrins are able to solubilize many lipophilic water-insoluble drugs, drugs which previously were impossible to formulate in aqueous eye drop solutions. Aqueous cyclodextrin containing eye drop solutions have already been registered in Europe. Recently, a Chloramphenicol eye drop solution (Clorocil®) was registered in Portugal and in 2001 diclofenac eye drop solution (Voltaren Ophthalmic®) was registered in France. The object of this short review is to describe how cyclodextrins enhance aqueous solubility and bioavailability of lipophilic water-insoluble drugs in aqueous eye drop formulations. Formulation and *in vivo* testing of dexamethasone eye drops, a work performed within our own research group, is used as an example.

Corticosteroids in ophthalmology

The most common use of corticosteroids in eye drops is for inflammation following eye surgery, such as after cataract surgery and corneal operations. In mild cases it is usually adequate to apply the eye drops one to four times a day and in some cases topically applied non-steroidal anti-inflammatory drugs may be sufficient. However in cases of severe inflammation, such as after complicated eye surgery, corneal transplant rejection or severe uveitis, applications as frequently as once every hour may not be adequate. In these severe cases the eye drops have to be supplemented with systemic steroids, such as prednisolone, or with subconjunctival or subtenon injection of steroids. In these cases it would be advantageous to have corticosteroid containing eye drops of greater bioavailability than the commercially available eye drops. Furthermore, topically applied corticosteroids are generally not effective in the posterior segment of the eye and, thus, systemic corticosteroids are needed to fight inflammatory disease in this area. Corticosteroids are generally lipophilic and dissolve very poorly in water.

Watson *et al.* studied the penetration of topically applied ocular steroids into the anterior chamber of the human eye [1, 2]. They found that of the commercially available formulations containing 1% prednisolone acetate (Pred forte®) gave the highest concentration in the aqueous humor or on the average 96 ng/ml. Eye drops containing 0.1% dexamethasone alcohol suspension (Maxidex®) gave a considerably lower concentration. However, if it is taken into the account that dexamethasone is seven times more potent than prednisolone then the dexamethasone concentration obtained in the aqueous humor corresponded to about 60 ng/ml of prednisolone. The most effective corticosteroid eye drops give aqueous humor concentration of less than 100 ng/ml (prednisolone equivalents). This bioavailability can be im-

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proved through the use of cyclodextrin formulation, as will be discussed in later sections.

Physiological considerations

In ophthalmology local drug administration is preferred and in the form of topically applied low viscosity aqueous eye drop solutions. Fick's First Law can be used to describe drug delivery from aqueous eye drop solution into the eye:

$$J = P \cdot C_{\mathrm{Aq}},$$

where J (mass/area/time) is the drug flux through the lipophilic ocular barrier (e.g. cornea), P is the drug permeability coefficient through the ocular barrier and C_{Aq} is the drug concentration in the aqueous tear fluid. Thus, topically applied drugs must be, at least to some degree, soluble in the aqueous tear fluid but at the same time they must be somewhat lipid-soluble to be able to partition into and penetrate through the lipophilic corneal epithelium, through the corneal stroma and the lipophilic endothelium into the aqueous humor [3, 4]. 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) [5–7]. Only one drop or about 0.05 ml of the eye drop solution can be applied to the eye which means that in aqueous eye drop solution the drug dose must be soluble in 0.05 ml of the formulation. In other words, the dose : solubility ratio (D : S) is 0.05 which is extremely low compared to other drug formulations such as tablets (D : S 250) and nasal sprays (D : S 0.3) [8]. The continuous secretion of tear fluid adds to this difficulty by limiting the contact time of topically applied drugs with the eye surface which again reduces their ocular bioavailability, especially after application in low viscosity aqueous eye drop solutions [9]. Consequently less than 5% of a topically applied drug is absorbed through cornea into the eye [6, 10, 11]. Steroids used to treat ocular inflammation are lipophilic water-insoluble compounds that have to be introduced into aqueous eye drop formulations as suspensions or as water-soluble prodrugs. In both cases the ocular bioavailability is seriously hampered by the low aqueous solubility or the hydrophilic properties of the penetrating molecules, respectively. In addition, insufficient chemical stability of the steroid prodrugs in aqueous solution, as well as poor *in vivo* conversion to parent steroid, has limited their use in ophthalmology. Specialized ocular delivery systems such as hydrogels, micro-emulsions, solid inserts and liposomes have also been designed in order to enhance bioavailability of topically applied ophthalmic drugs [12]. However, these have never gained much popularity, either due to their side effects (such as blurred vision and local irritation) or due to their instability (i.e. limited shelf-life).

Cyclodextrins in opthalmology

The effects of cyclodextrins on drug solubility, permeability, chemical stability and delivery through biological membranes have been investigated by a number of research groups [6, 13–17]. Their studies show that hydrophilic cyclodextrins act as true carriers by keeping the lipophilic water-insoluble drug molecules in solution and delivering them to the membrane surface where they partition from the cyclodextrin cavity into the lipophilic membrane. The relatively lipophilic membrane has low affinity for the large hydrophilic cyclodextrin molecules or the hydrophilic drug/cyclodextrin complexes, which thus remain in the aqueous skin exterior, e.g. the aqueous tear fluid. Conventional penetration enhancers, such as benzalkonium chloride, disrupt the ophthalmic barrier, whereas hydrophilic cyclodextrins enhance drug penetration into the eye by carrying the lipophilic water-insoluble drug molecules through the aqueous mucin layer and thereby increasing drug availability at the lipophilic eye surface (Figure 1) [6]. Cyclodextrin derivatives which have been applied in ophthalmology include the hydroxypropyl derivatives of β- and γ-cyclodextrin, the randomly methylated β-cyclodextrin and sulfobutylether β-cyclodextrin. Thus, through cyclodextrin complexation it has been possible to formulate lipophilic water-insoluble steroids as aqueous eye drop solutions (Table I). Furthermore, the chemical stability of the drug molecule is enhanced by the inclusion complexation. This results in enhanced shelf-life of the aqueous eye drop formulations.

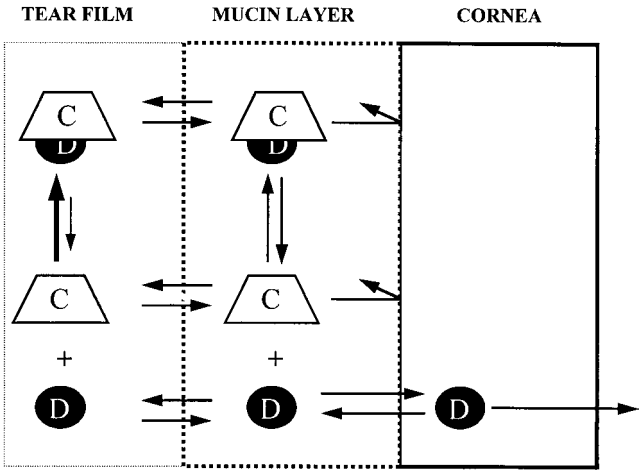

Figure 1. The mechanism of drug (D) penetration from aqueous cyclodextrin (CD) containing eye drop solutions into the eye.

Since neither cyclodextrins nor their complexes are absorbed into lipophilic barriers, cyclodextrins can both increase and decrease the drug availability at the eye surface. For example, the effect of cyclodextrin concentration on the permeability of the lipophilic water-insoluble drug dexamethasone through semi-permeable cellophane membrane is shown in Figure 2. At low cyclodextrin concentrations, when the drug is in suspension, the flux of the drug increases with increasing cyclodextrin concentration. At higher cyclodextrin concentrations, when the entire drug is in solution, the flux decreases with increasing cyclodextrin concentration. Maximum permeability is observed when just enough cyclodextrin is added to the vehicle to solubilize the entire drug [29]. Too much or too little cyclodextrin will result in less

Table 1. Cyclodextrins in topical formulations for ocular drug delivery

Drug	Cyclodextrin[a]	Reference
Acetazolamide	HPβCD	[18, 19]
Anandamides	HPβCD	[20, 21]
Cannabinoids (various)	HPβCD	[22]
Cyclosporin	αCD	[23–25]
Dehydroepiandrosterone	HPβCD	[26]
Dexamethasone	HPβCD	[27–31]
Diclofenac	HPβCD, RMβCD	[32]
Dipivefrine	SBEβCD	[33]
Fluorometholone	HPγCD	[34]
Hydrocortisone	HPβCD	[35, 36]
Loteprednol etabonate	HPβCD, DMβCD	[37]
Pilocarpine	αCD, βCD, HEβCD, HPβCD, SBEβCD	[38–41]
Prostaglandins	HPβCD	[42]
Thalidomide	HPβCD	[43]
Tropicamide	HPβCD	[44]
Δ9-Tetrahydrocannobinol	αCD, βCD, HPβCD, γCD	[45, 46]

[a] HPβCD = 2-hydroxypropyl-β-cyclodextrin; αCD = α-cyclodextrin; RMβCD = randomly methylated β-cyclodextrin; SBEβCD = sulfobutylether β-cyclodextrin; HPγCD = 2-hydroxypropyl-γ-cyclodextrin; DMβCD = heptakis(2,6-di-*O*-methyl)-β-cyclodextrin; HEβCD = hydroxyethyl-β-cyclodextrin; βCD = β-cyclodextrin; γCD = γ-cyclodextrin.

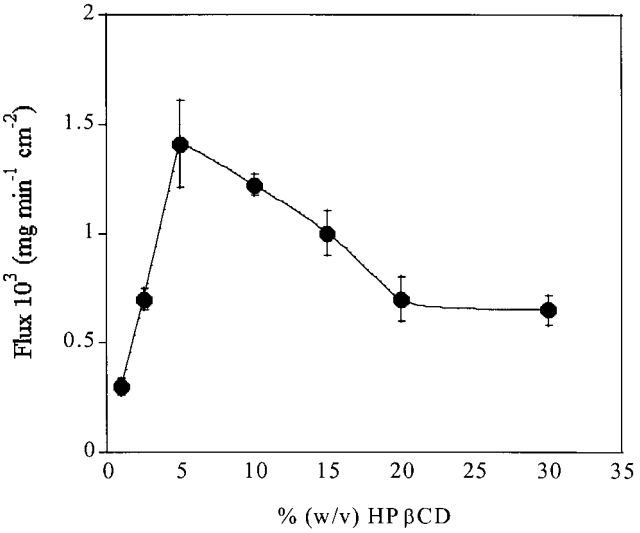

Figure 2. Effect of 2-hydroxypropyl-β-cyclodextnn (HPβCD) concentration on the flux of dexamethasone from an aqueous HPβCD solutions containing 0.5% (w/v) dexamethasone through a semi-permeable cellophane membrane (mean $\pm$SEM, n = 4). Dexamethasone was in a suspension at HPβCD concentration below 5% but in solution at higher HPβCD concentrations.

than optimum drug availability. Some of the ingredients of the eye drop formulation will compete with dexamethasone for a space in the cyclodextrin cavity reducing the solubilizing effect of the cyclodextrin. At the same time, some other ingredients can have solubilizing effect on the drug reducing the amount of cyclodextrin needed to solubilize the drug. Consequently, the amount of cyclodextrin included in the aqueous eye drop formulation has to be based on availability studies performed on the actual eye drop formulation, that is eye drop formulation containing all the excipients needed (e.g. preservatives, polymers and buffer salts) in the formulation.

It is possible to increase drug availability in aqueous cyclodextrin formulations by including small amount of water-soluble polymer. The polymers enhance the cyclodextrin complexation of the drug, and thereby reducing the amount of cyclodextrin needed in the formulation, and at the same time they enhance the absorption of the drug/cyclodextrin complex to the eye surface through formation of ternary complexes or co-complexes [30]. This increases the drug availability at the eye surface. Addition of 0.10% hydroxypropyl methylcellulose increases the apparent stability constant of dexamethasone/2-hydroxypropyl-β-cyclodextrin complex from 1200 M^{-1} to 1600 M^{-1} [5]. At the same time the polymer increases the availability of dexamethasone in the aqueous eye drop formulation. Using the described optimization technologies aqueous eye drops containing 0.32, 0.67 and 1.3% (w/v) dexamethasone were prepared and tested both in animals and humans.

In vivo observations

Dexamethasone (1.3% w/v) in aqueous eye drop solution containing 2-hydroxypropyl-β-cyclodextrin and Maxidex were tested in English brown rabbits [18]. A single drop of the solution was applied in the rabbit's eye and aqueous humor samples withdrawn at specified times following the administration. Dexamethasone (0.1% w/v) alcohol suspension (Maxidex®, Alcon Inc., Texas, USA) was used for control. The 1.3% dexamethasone/2-hydroxypropyl-β-cyclodextrin eye drops gave significantly higher dexamethasone concentration in the aqueous humor than Maxidex, even though the difference in concentration in the aqueous humor was less than the 13-fold difference in dexamethasone concentration in the eye drop. Four hours following the application of Maxidex® the dexamethasone concen-

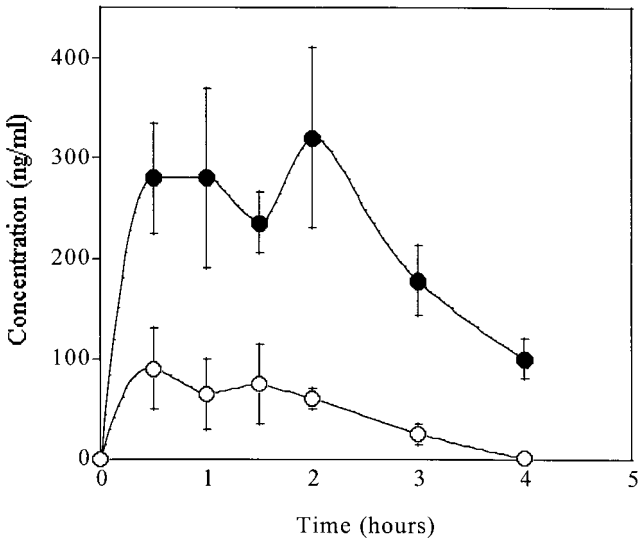

Figure 3. Dexamethasone concentration in aqueous humor of rabbits after administration of 50 μ1 of 1.3% dexamethasone in an aqueous cyclodextrin solution (●) or a 0.1% dexamethasone alcoholic suspension (Maxidex®) (○) (mean ±SEM, n = 3).

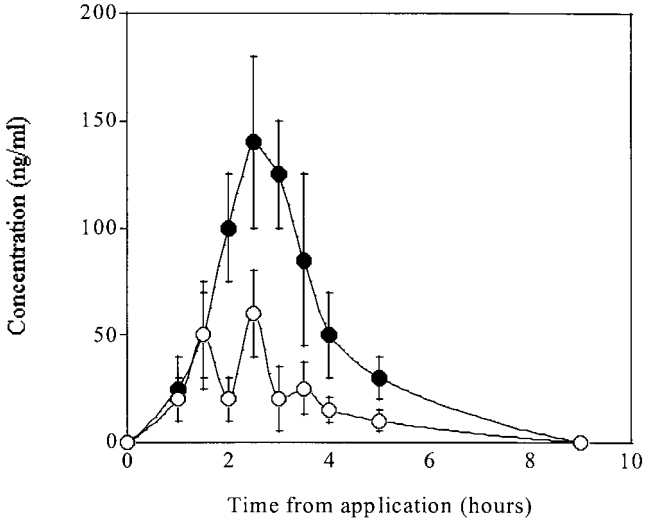

Figure 4. Dexamethasone concentration in aqueous humor after administration of one drop (50 μl) of 0.32% dexamethasone in an aqueous cyclodextrin solution (●) or a 0.1% dexamethasone alcoholic suspension (Maxidex®) (○). The concentration (mean ±SEM, n = 3) is shown at appropriate time points after administration of the eye drops to human volunteers.

tration in the aqueous humor was essentially zero, whereas the cyclodextrin-dexamethasone solution gave about 100 ng/ml (Figure 3). The cyclodextrin-dexamethasone eye drop solution was well tolerated by the rabbits, no irritation was seen on clinical examination.

The ocular absorption of dexamethasone eye drops containing 2-hydroxypropyl-β-cyclodextrin was also tested in human patients and compared with Maxidex® (i.e. the 0.1% dexamethasone alcohol suspension). The patients received the eye drops at certain time period before cataract surgery and at the time of cataract surgery an aqueous humor sample was withdrawn and dexamethasone levels determined. Figure 4 shows the dexamethasone concentration in the aqueous humor after administration of 0.32% dexamethasone/2-hydroxypropyl-β-cyclodextrin and Maxidex [30]. The dexamethasone concentration in the aqueous humor was significantly higher ($P < 0.001$) and the area under the curve was 2.6 times higher with the cyclodextrin-dexamethasone eye drop solution than with Maxidex®. The peak concentration of dexamethasone did not increase when the dexamethasone concentration in the aqueous cyclodextrin containing eye drops was increased from 0.32 to 0.67% (w/v). However, the duration of activity was increased as can be seen by the concentration values obtained at 9 hours after administration (Table II). This is of interest to compare these results with the measurements of Watson and McGhee [1, 2]. The 0.32% (w/v) dexamethasone solution gives a considerably higher effective concentration in the aqueous humor even compared to prednisolone acetate, which is the most potent steroid eye drops on the market.

Figure 5 shows the effect of the co-complexation involving the water-soluble polymer, hydroxypropyl methylcellulose, on the dexamethasone bioavailability *in vivo*. The two eye drop solutions were identical except the co-complex formation between the drug/cyclodextrin complex and hydroxypropyl methylcellulose. This co-complexation was induced through heating the study formulation but the control formulation contained simple drug/cyclodextrin complex. It can be seen that formation of the co-complex resulted in significant enhancement in the bioavailability of the drug.

Table 2. Adjusted mean peak concentration (±SEM) of dexamethasone and prednisolone acetate, and the concentration at 9 h, in aqueous humor of human volunteers after topical administration. Concentrations are adjustment for potency of prednisolone, which is a 7-fold weaker steroid than dexamethasone[2, 30, 47]

Eye drop solution	Mean peak conc. (ng/ml)	Conc. at 9 h (ng/ml)
Dexamethasone 0.32%	141 ± 36	0
Dexamethasone 0.67%	130 ± 50	18 ± 5
Maxidex[a]	60 ± 21	0
Prednisolone acetate 1%	96 ± 19	–

[a] Maxidex® contains 0.1% dexamethasone alcoholic suspension.

Clinical studies

Saari et al. [48] studied the use of dexamethasone-cyclodextrin eye drops following cataract surgery. The 0.67% dexamethasone-cyclodextrin eye drops used once a day were compared with 0.1% dexamethasone alcohol suspension (Maxidex®) used three times a day. Cell flare measurements of the aqueous humor and clinical evaluation revealed that the two treatment regiments were equal in their clinical efficiency. Once a day application of the cyclodextrin dexamethaone formulation was quite effective in controlling post-operative inflammation following cataract surgery.

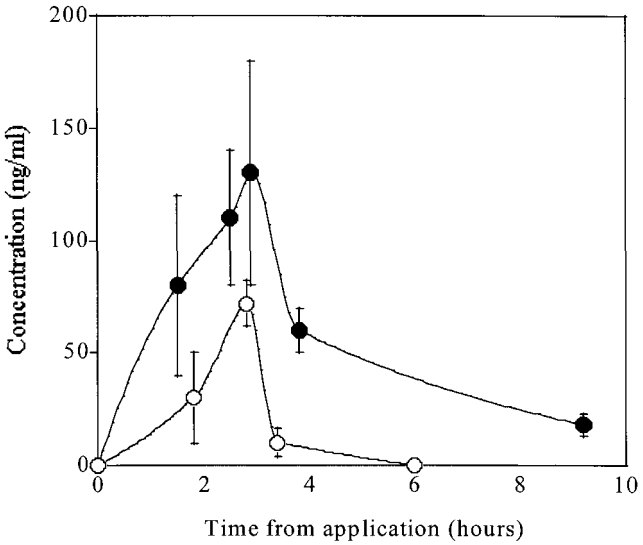

Figure 5. Dexamethasone concentration in aqueous humor after administration of one drop (50 μl) of 0.67% dexamethasone in an aqueous cyclodextrin solution; the dexamethasone/cyclodextrin/polymer co-complex (●), the simple dexamethasonelcyc]odextrin complex (○). The concentration (mean ±SEM, n = 3) is shown at appropriate time points after administration of the eye drops to human volunteers.

Conclusions

Cyclodextrins make it possible to formulate lipophilic drugs in aqueous eye drop solutions. This may be useful for the formulation of a variety of lipophilic drugs that hitherto have not been available as eye drops or in suboptimal formulations. Steroid drugs, including corticosteroids, are a good example of such drugs. They are lipophilic and have only been available in eye drops as prodrugs or suspensions with limited concentration and bioavailability. With cyclodextrins it is possible to increase the drug concentration and bioavailability and create formulations that offer more effective and less frequent treatment schedules for patients with ocular inflammation.

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