Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye

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ABSTRACT.

Cyclodextrins are cylindrical oligosaccharides with a lipophilic central cavity and hydrophilic outer surface. They can form water-soluble complexes with lipophilic drugs, which 'hide' in the cavity. Cyclodextrins can be used to form aqueous eye drop solutions with lipophilic drugs, such as steroids and some carbonic anhydrase inhibitors. 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 drugs, including steroids of any kind, carbonic anhydrase inhibitors, pilocarpine, cyclosporins, etc. Their use in ophthalmology has already begun and is likely to expand the selection of drugs available as eye drops.

In this paper we review the properties of cyclodextrins and their application in eye drop formulations, of which their use in the formulation of dexamethasone eye drops is an example. Cyclodextrins have been used to formulate eye drops containing corticosteroids, such as dexamethasone, with levels of concentration and ocular absorption which, according to human and animal studies, are many times those seen with presently available formulations. Cyclodextrin-based dexamethasone eye drops are well tolerated in the eye and seem to provide a higher degree of bioavailability and clinical efficiency than the steroid eye drop formulations presently available. Such formulations offer the possibility of once per day application of corticosteroid eye drops after eye surgery, and more intensive topical steroid treatment in severe inflammation.

While cyclodextrins have been known for more than a century, their use in ophthalmology is just starting. Cyclodextrins are useful excipients in eye drop formulations for a variety of lipophilic drugs. They will facilitate eye drop formulations for drugs that otherwise might not be available for topical use, while improving absorption and stability and decreasing local irritation.

Keywords: drug delivery – eye drops – cyclodextrin – steroids – solubility.

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A new group of pharmaceutical excipients called cyclodextrins has recently been introduced into ophthalmology (Table 1). This group of excipients is able to solubilize many lipophilic water-insoluble drugs which previously were impossible to formulate in aqueous eye drop solutions. Aqueous cyclodextrin containing eye drop solutions have already been registered in Europe. A chloramphenicol eye drop solution (Clorocil®) was recently registered in Portugal; 2001 saw the registration of a diclofenac eye drop solution (Voltaren Ophthalmic®) in France. Previous reviews on this subject include those by van Dorne (1993); Rajewski & Stella (1996); Loftsson & Stefánsson (1997); and Loftsson & Järvinen (1999). 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. The formulation and *in vivo* testing of dexamethasone eye drops as performed within our own research group are used as examples.

Corticosteroids in ophthalmology

The most common use of corticosteroids in eye drops is for inflammation following eye surgery, such as cataract surgery and corneal operations. In mild cases it is usually adequate to apply the eye drops one to four times per day and in some cases topically applied nonsteroidal 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. Rather than using commercially available eye drops, it would then be

more advantageous to use corticosteroid containing eye drops of greater bioavailability. Furthermore, topically applied corticosteroids are generally not effective in the posterior segment of the eye and, therefore, systemic corticosteroids are needed to fight inflammatory disease in this area.

Corticosteroids are generally lipophilic and dissolve very poorly in water. The commercially available eye drop formulations solve this dilemma by forming prodrugs, usually acetate or phosphate esters such as prednisolone acetate (Pred forte ®, Pred mild ®) and dexamethazone phosphate or suspensions, such as dexamethazone alcohol suspension (Maxidex®).

Various researchers have studied the penetration of topically applied ocular steroids into the anterior chamber of the human eye (Watson et al. 1988; McGhee et al. 1990). They found that of the commercially available formulations, those containing 1% prednisolone acetate *(Pred forte®)* gave the highest concentration in the aqueous humour per average 96 ng/mL. Eye drops containing 0.1% dexamethasone alcohol suspension *(Maxidex®)* gave a considerably lower concentration. However, if we take into account the fact that dexamethasone is seven times more potent than prednisolone, then the dexamethasone concentration obtained in the aqueous humour corresponded to about 60 ng/mL of prednisolone. The most effective corticosteroid eye drops available today give aqueous humour concentration of less than 100 ng/mL (prednisolone equivalents). This bioavailability can be improved through the use of cyclodextrin formulation, where a single drop topical application gives aqueous humour concentration of about 140 ng/mL (prednisolone equivalents) and also extends its duration in the eye, as will be discussed later.

The corticosteroid concentrations achieved in the aqueous humour from application of Maxidex ® or Pred Forte ® is usually sufficient for mild to moderate ocular inflammation. More potent formulations may allow topical treatment of more severe intraocular inflammation and also less frequent applications for mild to moderate inflammation.

Table 1. Cyclodextrins in topical formulations for ocular drug delivery.

Drug	Cyclodextrin	References
Acetazolamide	HPβCD	(Loftsson et al. 1994; Loftsson et al. 1996)
Anandamides	HPβCD	(Jarho et al. 1996;Pate et al. 1996)
Cannabinoids (various)	HPβCD	(Pate et al. 1998)
Cyclosporin	αCD	(Kanai et al. 1989; Sasamoto et al. 1991; Cheeks et al. 1992
Dehydroepiandrosterone	HPβCD	(Kearse et al. 2001)
Dexamethasone	HPβCD	(Usayapant et al. 1991; Loftsson et al. 1994; Kristinsson et al. 1996; Gavrilin et al. 1999)
Diclofenac	HPβCD, RMβCD	(Reer et al. 1994)
Dipivefrine	SBEβCD	(Jarho et al. 1997)
Fluorometholone	HPγCD	(Morita et al. 1996)
Hydrocortisone	HPβCD	(Davies et al. 1997; Bary et al. 2000
Loteprednol etabonate	HPβCD, DMβCD	(Reddy et al. 1996)
Pilocarpine	αCD, βCD, HEβCD, HPβCD	(Freedman et al. 1993; Järvinen et al. 1994;
	SBEβCD	Keipert et al. 1996; Siefert & Keipert 1997)
Prostaglandins	HPβCD	(Wheeler 1991)
Talidomide	HPβCD	(Siefert et al. 1999)
Tropicamide	HPβCD	(Cappello et al. 2001)
Δ9-Tetrahydrocannobinol	αCD, βCD, HPβCD, γCD	(Green & Kearse 2000; Kearse & Green 2000)

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

Physiological considerations

In ophthalmology, local drug administration in the form of topically applied low viscosity aqueous eye drop solutions is generally preferred. Topically applied drugs must be, at least to some degree, soluble in the aqueous tear fluid. However, they must also be somewhat lipid-soluble in order to penetrate the lipophilic corneal epithelium, through the corneal stroma and the lipophilic endothelium into the aqueous humour (Ahmed et al. 1987; Wang et al. 1991). In other words, for successful formulation in an aqueous eye drop solution. a drug must be both water-soluble (i.e. hydrophilic) and lipid-soluble (i.e. hydrophobic) (Loftsson & Stefánsson 1997). 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 (Chrai et al. 1973). Consequently, less than 5% of a topically applied drug is absorbed through the cornea into the eye (Gangrade et al. 1996; Loftsson & Järvinen 1999; Washington et al. 2001). 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, 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 (Tammara & Crider 1996).

Common adjuvants to aqueous eye drop formulations can enhance ocular bioavailability of steroids by reducing the barrier function of, for example, the cornea (e.g. benzalkonium chloride and other surfactants (Lang & Stiemke 1996) or by increasing the contact time of the drug with the eye surface (e.g. viscosity enhancers such as water-soluble poly-

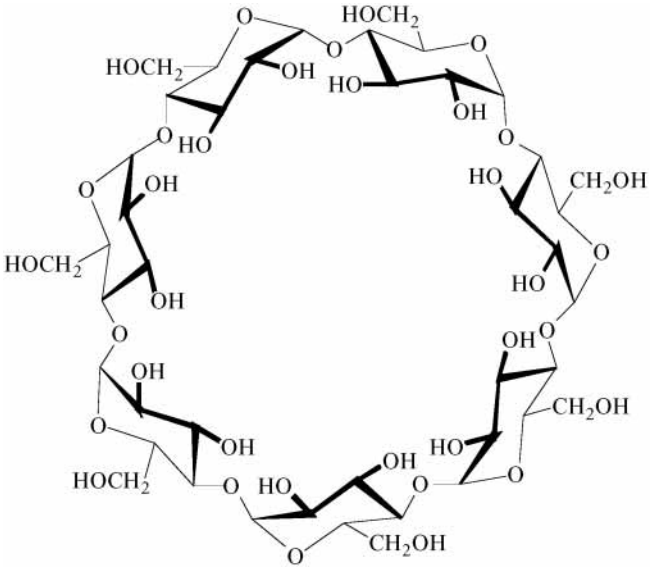

Fig. 1. β-Cyclodextrin.

mers). Specialized ocular delivery systems such as hydrogels, microemulsions, solid inserts and liposomes have also been designed in order to enhance bioavailability of topically applied ophthalmic drugs (Reddy 1996). However, these have never gained much popularity, due to both their side-effects (such as blurred vision and local irritation) and their instability (i.e. limited shelf-life).

Cyclodextrins are novel, chemically stable adjuvants that enhance ocular bioavailability of ophthalmic drugs without affecting the barrier function of the eye or increasing the viscosity of the aqueous eye drop formulation (Loftsson & Masson 2001).

Cyclodextrins

Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose. These cyclic oligosaccharides consist of (α-1,4)-linked α-D-glucopyranose units with a hydrophilic outer surface and a lipophilic central cavity. The natural α-, β- and γ-cyclodextrins consist of six, seven and eight glucopyranose units (Fig. 1), respectively. The aqueous solubility of these natural cyclodextrins is somewhat limited and thus several different water-soluble derivatives have been synthesized. 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 (Table 1).

In an aqueous environment, cyclodextrins form inclusion complexes with many lipophilic molecules through a process in which water molecules located inside the central cavity are replaced by either a whole molecule, or, more frequently, by some lipophilic structure of the molecule. Cyclodextrin complexation of a drug molecule changes the physicochemical properties of the drug, such as its aqueous solubility and chemical stability (Loftsson & Brewster 1996). Since the cyclodextrin molecule is hydrophilic on the outside, the complex formation usually increases the water-solubility of lipophilic water-insoluble drugs. Thus, it has been possible through cyclodextrin complexation to formulate lipophilic water-insoluble steroids as aqueous eye drop solutions (Usayapant et al. 1991; Loftsson et al. 1994; Kristinsson et al. 1996; Morita et al. 1996; Reddy et al. 1996; Davies et al. 1997; Gavrilin et al. 1999; Bary et al. 2000; Kearse et al. 2001). Furthermore, the chemical stability of the drug molecule is enhanced by the inclusion complexation (Loftsson & Brewster 1996). This increases the shelf-life of the aqueous eye drop formulation.

Once included in the cyclodextrin cavity, the drug molecules may be dissociated from the cyclodextrin molecules through complex dilution in the aqueous tear fluid. The included drug may also be replaced by some other suitable molecule (such as lipids), or, if the complex is located in close approximation to a lipophilic biological membrane (such as the eye cornea), the guest may be transferred to the matrix for which it has the highest affinity. Importantly, since no covalent bonds are formed or broken during the guest-host complex formation, the complexes are in dynamic equilibrium with free drug and cyclodextrin molecules.

The effects of cyclodextrins on drug solubility, permeability, chemical stability and delivery through biological membranes have been investigated by a number of research groups (Rajewski & Stella 1996; Uekama et al. 1998; Loftsson & Järvinen 1999; Masson et al. 1999; Stella et al. 1999; Uekama 1999; Loftsson & Masson 2001). 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

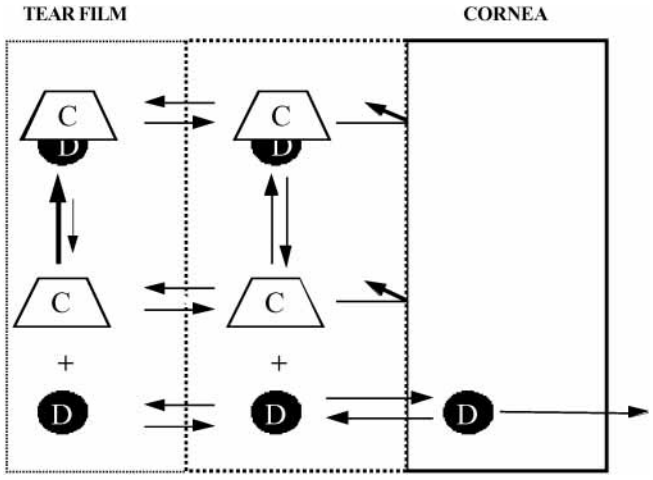

Fig. 2. The mechanism of drug (D) penetration into the eye from an aqueous cyclodextrin (CD) containing eye drop solution in the tear film. Modified from Loftsson & Järvinen (1999) with permission from Advanced Drug Delivery Reviews.

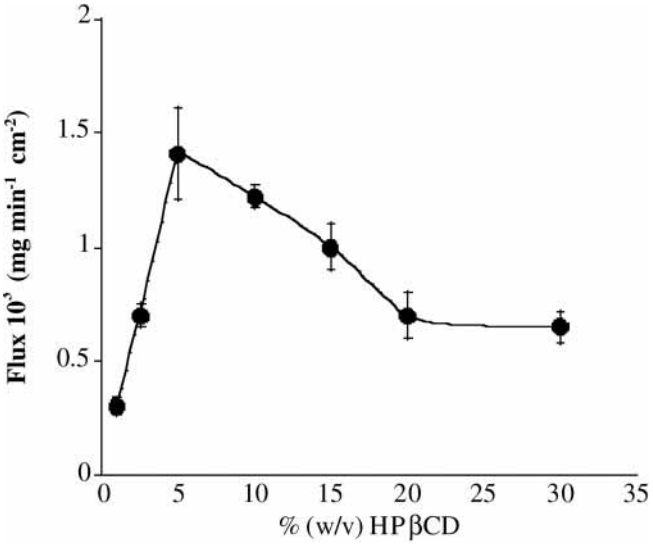

Fig. 3. The effect of 2-hydroxypropyl-β-cyclodextrin (HPβCD) concentration on the flux of dexamethasone from an aqueous HPβCD solution containing 0.5% (w/v) dexamethasone through a semipermeable cellophane membrane (mean ± SEM, $n = 4$). The dexamethasone was in suspension at HPβCD concentration below 5% but in solution at higher HPβCD concentrations. Modified from Loftsson et al. (1994) with permission from the International Journal of Pharmaceutics.

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 (Fig. 2) (Loftsson & Masson 2001).

Formulation with cyclodextrin

Since neither cyclodextrins nor their complexes are absorbed into lipophilic barriers, cyclodextrins can both increase and decrease drug availability at the eye surface. For example, the effect of cyclodextrin concentration on the permeability of the lipophilic water-insoluble drug dexamethasone through semipermeable membrane is shown in Fig. 3. 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. Figure 3 shows that it is very important to optimize the dexamethasone release from an aqueous eye drop formulation by adjusting the cyclodextrin concentration in the aqueous eye drop formulation. Too much or too little cyclodextrin will result in less than optimum drug availability. Some of the ingredients of the eye drop formulation will compete with dexamethasone for a space in the cyclodextrin cavity, thereby reducing the solubilizing effect of the cyclodextrin. At the same time, some other ingredients may have a solubilizing effect on the drug, thereby 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 which must contain all necessary excipients (e.g. preservatives, polymers and buffer salts).

It is possible to increase drug availability in aqueous cyclodextrin formulations by including small amounts of water-soluble polymer. Polymers enhance the cyclodextrin complexation of the drug, thereby reducing the amount of cyclodextrin needed in the formulation, while simultaneously enhancing the absorption of the drug/cyclodextrin complex to the eye surface through the formation of ternary complexes or co-complexes (Kristinsson et al. 1996). This increases the drug availability at the eye surface (Loftsson 1998; Loftsson & Järvinen 1999). The 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} (Loftsson & Stefánsson 1997). At the same time, the polymer increases the availability of dexamethasone in the aqueous eye drop formulation (Kristinsson et al. 1996). Using the described op-

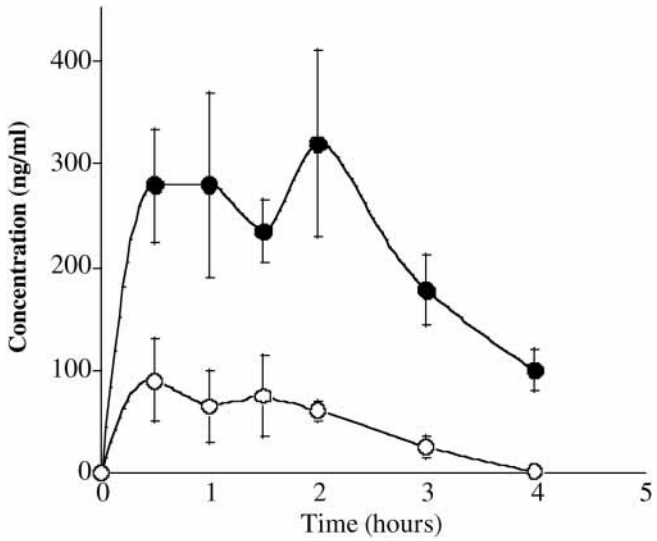

Fig. 4. Dexamethasone concentration in aqueous humour of rabbits after administration of 50 µL of 1.3% dexamethasone in an aqueous cyclodextrin solution or a 0.1% dexamethasone alcoholic suspension (Maxidex®) (O) (mean ± SEM, $n = 3$). Modified from Loftsson et al. (1994) with permission from the International Journal of Pharmaceutics.

timization 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) was tested in English brown rabbits in an aqueous eye drop solution containing 2-hydroxypropyl-β-cyclodextrin and Maxidex® (Loftsson et al. 1994). A single drop of the solution was applied in the rabbit's eye and aqueous humour 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 a significantly higher concentration of dexamethasone in the aqueous humour than did Maxidex, even though the difference in concentration in the aqueous humour was less than the 13-fold difference in the concentration of dexamethasone in the eye drop. Four hours after the application of Maxidex®, the concentration of dexamethasone in the aqueous humour was essentially zero, whereas the cyclodextrin-dexamethasone solution gave about 100 ng/mL (Fig. 4). The cyclodextrin-dexamethasone eye drop solution was well tolerated and no irritation was seen on clinical examination of the rabbits.

The ocular absorption of dexamethasone eye drops containing 2-hydroxypropyl-β-cyclodextrin was also tested in human patients and compared with Maxidex® (0.1% dexamethasone alcohol suspension). The patients received the eye drops at a certain time prior to cataract surgery and, at the time of cataract surgery, an aqueous humour sample was withdrawn and dexamethasone levels determined. Figure 5 shows the dexamethasone concentration in the aqueous humour after administration of 0.32% dexamethasone/2-hydroxypropyl-β-cyclodextrin and Maxidex® (Kristinsson et al. 1996). The concentration of dexamethasone in the aqueous humour was significantly higher ($P < 0.001$) and the area under the curve was 2.6 times higher with the 0.32% 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) (Fig. 6). However, as can be seen by concentration values obtained 9 hr after administration, the duration of activity was increased (Table 2). It is interesting to compare these results with the measurements of Watson and associates and McGhee and associates (see Table 2) (Watson et al. 1988; McGhee et al. 1990). The 0.32% (w/v) dexamethasone solution gives a considerably higher effective concentration in the aqueous humour than does prednisolone acetate, which is the most potent corticosteroid eye drop on the market.

Figure 6 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

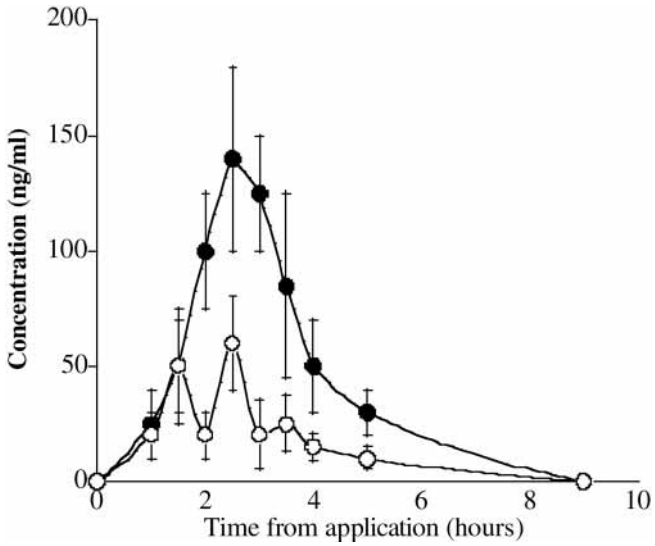

Fig. 5. Dexamethasone concentration in aqueous humour after administration of 1 drop (50 µL) of 0.32% dexamethasone in an aqueous cyclodextrin solution (?)or a 0.1% dexamethasone alcoholic suspension (Maxidex®) (O). The concentration (mean ± SEM, $n = 3$) is shown at appropriate time points after administration of the eye drops to human volunteers. Reprinted from Kristinsson et al. (1996) with permission from Investigative Ophthalmology and Visual Science.

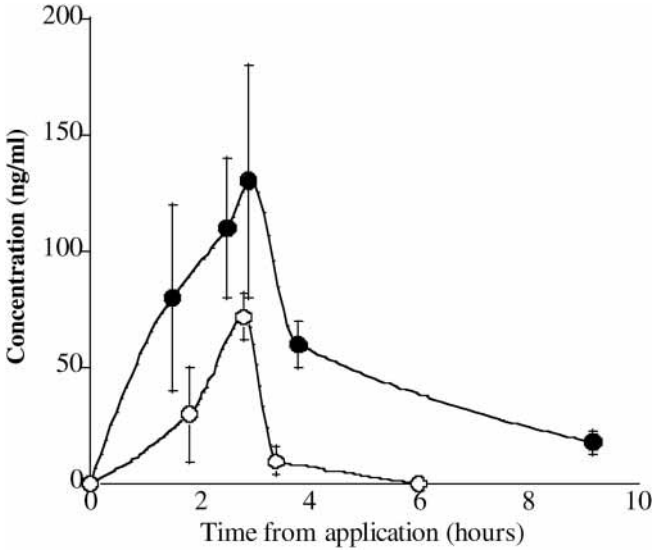

Fig. 6. Dexamethasone concentration in aqueous humour after administration of 1 drop (50 µL) of 0.67% dexamethasone in an aqueous cyclodextrin solution; the dexamethasone/cyclodextrin/polymer co-complex (?), the simple dexamethasone/cyclodextrin complex (O). The concentration (mean ± SEM, $n = 3$) is shown at appropriate time points after administration of the eye drops to human volunteers. Reprinted from Kristinsson et al. (1996) with permission from Investigative Ophthalmology and Visual Science.

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