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Cyclodextrin microparticles for drug delivery to the posterior segment of the eye: aqueous dexamethasone eye drops

Thorsteinn Loftsson, Dagný Hreinsdóttir and Einar Stefánsson

Abstract

Delivery of steroids to the retina is currently undertaken with invasive injections into the vitreous cavity. This paper describes a non-invasive method to deliver steroids in therapeutic levels to the retina in rabbits. Dexamethasone was formulated as somewhat water-soluble dexamethasone/γ-cyclodextrin (γCD) microparticles in a low-viscosity aqueous eye drop suspension. The mean (± standard deviation) diameter of the particles was 20.4 ± 10.3 μm, with no particles larger than 60 μm. The aqueous suspension formulation was tested in rabbits and compared with an aqueous dexamethasone eye drop solution containing randomly methylated β-cyclodextrin (RMβCD). The dexamethasone concentration was identical in both formulations (15 mg mL^{-1}). The drug was administered to the left eye but determined in both eyes. The amount reaching different eye tissues via the topical route was determined by subtracting the amount found in the right eye from the amount found in the left eye. Two hours after single application of the dexamethasone/γCD eye drops to rabbits the mean (± s.d.) concentration in vitreous was 29 ± 16 ng g^{-1}, 86% of which reached vitreous via the topical route and in retina the concentration was 57 ± 22 ng g^{-1} (49% via topical route). For the RMβCD the values were 22.6 ± 9 and 66 ± 49 ng g^{-1} (73 and 14% via topical route), respectively. These steroid levels are comparable with the dexamethasone concentration achieved 1 month after intravitreal injection. The aqueous dexamethasone/γCD eye drop formulation was chemically stable during 7 months storage and well tolerated with no visible short-term side effects.

Faculty of Pharmacy, University of Iceland, Hofsvallagata 53, IS-107 Reykjavik, Iceland

Thorsteinn Loftsson, Dagný Hreinsdóttir

Department of Ophthalmology, National University Hospital, University of Iceland, Landspitalinn, IS-101 Reykjavik, Iceland

Einar Stefánsson

Correspondence: Thorsteinn Loftsson, Faculty of Pharmacy, University of Iceland, Hofsvallagata 53, IS-107 Reykjavik, Iceland.
E-mail: thorstlo@hi.is

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Introduction

Intravitreal injections of triamcinolone are commonly used to treat macular oedema in diabetic retinopathy, branch retinal vein occlusion and uveitis (Degenring & Jonas 2005; Jonas et al 2006). Invasive ocular inserts with dexamethasone are under study for the same purpose (Beeley et al 2005; Jaffe et al 2006). Sub-tenon injections of anecortave acetate is also under investigation for the treatment of age-related macular degeneration (Slakter et al 2006). All of these approaches are based on the premise that non-invasive topical methods to effectively deliver drugs, such as corticosteroids, to the posterior segment of the eye are not available, and invasive methods are the only alternative (Raghava et al 2004; Beeley et al 2005; Myles et al 2005; Yasukawa et al 2005). There is a pressing need for a non-invasive method to deliver steroids by topical application to the posterior segment of the eye, but this has to date been an elusive goal (Jonas 2005).

The cornea is composed of three main layers – the lipophilic epithelium, the hydrophilic stroma and the endothelium. The conjunctiva is a thin transparent mucous epithelial barrier that lines the inside of the eyelids and covers the anterior one-third of the eyeball. Sclera is composed of collagen fibrils embedded in a glycosaminoglycans matrix (Washington et al 2001; Hosoya et al 2005). The eye surface is covered by continuous tear flow. The tear film consists of three layers (i.e. the adsorbed mucin layer, the middle aqueous layer and the superficial oily layer), with a total thickness of about 7–8 μm (Sasaki et al 1996). Drug molecules must first permeate through the aqueous tear film before they can partition into the membrane barrier. The tear film, especially the very viscous mucin layer immediate to the membrane surface, can make a significant contribution to the overall barrier to drug delivery into the eye (Loftsson et al 2006a; Loftsson & Stefánsson 2007). Passive drug permeation

through the membranes is influenced by several factors, such as lipophilicity of the drug molecule, its molecular weight and ionization. For cornea the epithelium is generally the rate-limiting barrier for transcorneal drug permeation (Prausnitz & Noonan 1998). The barrier favorably depends on the lipophilicity of the drug molecules. The small pores in the cornea allow paracellular permeation of small molecules (molecular weight < 500 Dalton) (Hämäläinen et al 1997). Drug permeation through sclera does not appear to be affected by the lipophilicity of the permeating molecules but is strongly affected by their diameter (Prausnitz & Noonan 1998). Sclera is approximately 10 times more permeable than cornea and conjunctiva is about two times more permeable than sclera (Hämäläinen et al 1997). There is some evidence that transscleral delivery of drugs can be achieved (Geroski & Edelhauser 2001). Our previous studies in rabbits indicated that topical drug delivery to retina, optic nerve and vitreous proceeded via the transscleral route as well as systemic delivery via nasal absorption after drainage of the drug containing tear fluid to the nasal cavity (Sigurðsson et al 2005; Sigurdsson et al 2007).

The rate of passive drug permeation from the surface into the eye is, according to Fick's first law, proportional to the concentration of dissolved drug in the aqueous tear fluid. However, in man the average tear secretion is 1.2 μL min^{-1} and, thus, about 15% of the tear volume is replaced every minute (Sasaki et al 1996). Conventional eye-drop volume is 35–50 μL and the normal tear volume (i.e. 7–9 μL) is restored 2–3 min after installation of excess fluid, with the largest fluid reduction occurring the first 15–30 s after the installation (Shell 1982; Van Ooteghem 1993). γ-Cyclodextrin (γCD) and drug/γCD complexes have only limited aqueous solubility (Loftsson et al 2005b) and, thus, the dexamethasone/γCD complex investigated has limited aqueous solubility resulting in formation of an aqueous dexamethasone/γCD eye drop suspension. After topical administration, the dexamethasone/γCD particles are retained on the eye surface where they are somewhat slowly dissolved resulting in sustained drug saturation of the tear fluid. The goal was to enhance topical dexamethasone delivery through sclera into the posterior segment of the eye.

Cyclodextrins are hydrophilic oligosaccharides that are able to form water-soluble complexes with many lipophilic drugs, thus making it possible to formulate lipophilic drugs as aqueous eye drop solutions (Loftsson & Stefánsson 1997). Due to their size and hydrophilicity, cyclodextrins do not readily permeate biological membranes (Loftsson et al 2005b). Cyclodextrins enhance permeation of lipophilic drugs through the aqueous tear film to the membrane surface increasing drug availability immediate to the surface (Loftsson et al 2006a; Loftsson & Stefánsson 2007). Previously we have investigated ophthalmic drug delivery after topical administration of cyclodextrin-containing eye drop solutions (Loftsson & Stefánsson 1997, 2002).

Materials and Methods

Materials

[1,2,4,6,7–^{3}H]-Dexamethasone in ethanol solution with specific activity of 88 Ci mmol^{-1} was purchased from Amersham Biosciences (UK). Dexamethasone was purchased from Bufa (Netherlands). Randomly methylated β-cyclodextrin with degree of substitution 1.8 (RMβCD) and γ-cyclodextrin (γCD) were purchased from Wacker-Chemie GmbH (Germany). Analytical-grade disodium edetate dihydrate (EDTA) and sodium chloride were purchased from Norsk Medisinaldeport (Norway). Hydroxypropyl methylcellulose (HPMC) and benzalkonium chloride were purchased from Sigma (USA). Soluene-350 solubilizer and liquid scintillation fluids, Hionic Fluor and Ultima Gold, were purchased from Perkin Elmer (UK). All other chemicals used in this study were commercially available compounds of special reagent or analytical grade.

Solubility studies

Phase-solubility study was performed to determine the exact amount of RMβCD and γCD needed to solubilize dexamethasone. An excess amount of dexamethasone was added to a solution containing 0–25% (w/v) RMβCD and solution or suspension containing 0–10% (w/v) γCD in pure water or aqueous solution containing benzalkonium chloride (0.02% w/v), EDTA (0.1% w/v), sodium chloride (0.00–0.72% w/v) and HPMC (0.1%). The dexamethasone suspensions formed were heated in an autoclave (Midmark M7 SpeedClave) in sealed containers at 121°C for 20 min. The suspensions were allowed to cool to room temperature (22–23°C). Then a small amount of dexamethasone was added to the suspension and it was allowed to equilibrate for 7 days under constant agitation (Loftsson et al 2005a). After equilibrium was attained, the suspension was filtered through a 0.45-μm membrane filter, and the filtrate was diluted and analysed by HPLC. The phase-solubility in aqueous RMβCD solutions was determined to be of A_L type (i.e. linear increase in dexamethasone solubility was observed with increasing RMβCD concentration). The phase-solubility diagram in pure aqueous γCD solution or suspension was determined to be of B_S-type (i.e. at low γCD concentrations the dexamethasone solubility increased with increasing γCD concentration but the solubility levels off at higher γCD concentrations due to the limited solubility of the dexamethasone/γCD complex) (Higuchi & Connors 1965).

Chromatographic determinations

The quantitative determination of dexamethasone was performed on HPLC equipment consisting of a Merck-Hitachi AS-2000A autosampler, Merck-Hitachi L-6200A pump and a Merck-Hitachi L-4250 lamp fixed wavelength UV detector operated at 241 nm. The column used was a C18, reversed-phase column (Phenomex, USA), 150 mm, 4.6 mm i.d., 5 μm bead. The flow rate was 1.5 mL min^{-1}. The mobile phase consisted of acetonitrile–tetrahydrofuran–water (33:1:66) and the retention time was 4.4 min.

Formulation of the eye drops

Cold solution containing RMβCD

From the phase-solubility studies in the aqueous eye drop solution it was determined that about 16% (w/v) RMβCD was

needed to solubilize 1.5% (w/v) dexamethasone. To prevent drug precipitation during storage, 10% excess RMβCD was included in the aqueous eye drop formulation. Thus, the final formulation contained 18% (w/v) RMβCD. Previous studies have shown that addition of small excess (approx. 10%) of cyclodextrin to aqueous complexation media does not affect drug availability from aqueous cyclodextrin solutions (Loftsson & Stefánsson 1997; Loftsson & Järvinen 1999). Aqueous 1.5% (w/v) dexamethasone eye drop solution was prepared by dissolving 750 mg of dexamethasone in 45 mL of aqueous solution containing benzalkonium chloride (10 mg), EDTA (50 mg), HPMC (50 mg) and RMβCD (9.0 g) and then filled up to 50 mL. The solution was heated in an autoclave in a sealed container at 121 °C for 20 min. The solution was allowed to cool to room temperature (22–23°C) and equilibrate for 7 days. The osmolality of the solutions was measured by the freezing-point depression method using a Knauer Osmometer Automatic (Netherlands). The viscosity was determined by a Brookfield digital viscometer model DV-1+ (USA) operated at room temperature. The osmolarity of the eye drops was determined to be 262 mOsm kg^{-1}. The viscosity was about 2.7 cps and the pH of the unbuffered aqueous eye drop solution was 4–5.

Cold suspension containing γCD

Aqueous 1.5% (w/v) dexamethasone eye drop suspension was prepared by suspending 750 mg of dexamethasone in 50 mL of aqueous solution containing benzalkonium chloride (10 mg), EDTA (50 mg), HPMC (50 mg), sodium chloride (100 mg) and γCD (9.0 g). The suspension was heated as previously described. The osmolarity of the eye drop suspension was determined to be 140 mOsm kg^{-1}. The viscosity was about 2.4 cps and the pH of the unbuffered eye drops was 4–5. The amount of dissolved dexamethasone in the aqueous eye drop suspension was determined to be 0.7–0.9 mg mL^{-1}, or only about 5% of the total amount of dexamethasone in the eye drop formulation. The solubility of dexamethasone in pure water is 0.16 mg mL^{-1} (Loftsson & Hreinsdóttir 2006).

The labelled formulations

The required volume of radioactive dexamethasone ethanolic solution was pipetted in a vial and as much as possible of the ethanol allowed to evaporate to almost dryness without precipitation of dexamethasone. Then, a required amount of dexamethasone eye drop suspension was added and that solution was sonicated for 30 min and shaken at room temperature for at least 24 h.

The method described in the European Pharmacopoeia, Edition 5.3, Section 2.9.37, Optical Microscopy (01/2006: 20937) was used to determine the particle size distribution in the aqueous γCD eye drop formulation. Briefly, the samples were examined in an Olympus BH-2 microscope under 40-fold magnification. The aqueous eye drop formulations were shaken and then one small drop of each was placed on a glass microscope slide and the drop covered by a glass coverslip. Then 50 particles were measured at random by measuring the maximum diameter of particles positioned on straight lines across the sample. In other words, the size of the particles is reported as the longest dimension from edge to edge when the particle is orientated parallel to the ocular scale.

In-vivo studies

Un-anaesthetized female albino rabbits (Harlan Netherlands B.V., Horst, Netherlands), about 3 kg, were used. The rabbits were fed on a regular diet. The study adhered to the Association for Research in Vision and Ophthalmology (ARVO) declaration for the use of laboratory animals in research. Eye drops (50 μL) were instilled topically using a micropipette inside the centre of the lower cul-de sac (RMβCD eye drops, n = 6; γCD eye drops, n = 8). During instillation, the lower eyelid was pulled slightly away form the globe and was returned to its normal position immediately after instillation. Great care was taken not to irritate the eye or to touch the corneal surface. Blood samples were taken at 30-min intervals from the marginal ear vein of the rabbits. After 2 h, the rabbits were sacrificed by intravenous injection of sodium pentobarbital and both eyes were proptosed and enucleated immediately and rinsed with an isotonic saline solution. All solutions were well tolerated by the rabbits and no macroscopic signs of irritation, redness or other toxic effects were observed.

Sample preparation

The aqueous humour was removed from the eye after enucleation, using a 1-mL syringe attached to a 26-gauge needle, and placed in a polyethylene (scintillation) vial. One lateral incision was performed in the sclera (center of the eyeball) and the eye was totally opened (anterior part and posterior part). From the anterior part, the lens and the iris–ciliary body were removed and the cornea was separated from the remaining anterior sclera. From the posterior part, the vitreous humour was emptied into a vial. The retina was gently scraped away and the optic nerve cut off. While dissecting the eyes, all the samples were immediately put in dry scintillation vials and weighed. Great care was taken to prevent cross-contamination between individual tissue samples and eye fluids. The entire procedure took less than 15 min per eye so that any errors due to redistribution of drug were minimized.

Quantitative determination

For aqueous humour, 10 mL of Ultima gold was added to aqueous humour samples (about 0.2 g), the vials were sealed with a screw cap, shaken and kept in the dark for at least 12 h before counting in a liquid scintillation counter.

Blood samples were prepared by adding 1 mL mixture of Soluene-350:isopropanol to 0.1–0.2 mL of the blood and incubated at 50°C for 60 min. The vials were then allowed to cool down to room temperature and 0.5 mL of 30% hydrogen peroxide solution was then added drop-wise with swirling to each vial for decolorization. The solutions were allowed to stand at room temperature for 10 min. The vials were then incubated again at 50°C for 30 min to remove excess hydrogen peroxide. After cooling to room temperature, 10 mL of Hionic fluor was added to each vial, and the vials were sealed with a screw cap, shaken and kept in the dark for at least 12 h before counting in a liquid scintillation counter.

Other ocular tissue samples were handled in the same way as the blood samples except 0.5–2.0 mL of Soluene-350 was added to the samples, depending on the size of the tissue sample.

No isopropanol or hydrogen peroxide was used and the samples were incubated for 240 min at 50°C before adding the Hionic Fluor (5–20 mL, depending on sample size). Dexamethasone was detected in all blood samples and in all tissue samples from the eyes. Blank tissue samples were spiked with various amounts of labelled dexamethasone from the dosing solution and used as a standard.

Statistical analysis

The effect of CD type (γCD, RMβCD), eye location (left, right) and tissue type (all tissues except blood) in Table 1 were analysed using three-way analysis of variance (JMP6 from SAS Institute Inc., USA). The values in Figures 1 and 2 were analysed by two-way analysis of variance.

Results and Discussion

The two aqueous formulations were low-viscosity eye drops. The RMβCD formulation was isotonic colorless solution but the γCD containing formulation was slightly hypotonic white suspension. The largest particle seen in the suspension was about 60 μm in diameter, but the most common diameter was approximately 15 μm. The mean (± s.d.) particle size was 20.4 ± 10.3 μm. No dexamethasone degradation was observed during storage at room temperature (22–23°C) for up to 7 months. No precipitation was observed in the RMβCD eye drop solution during storage. Although sedimentation was observed in the aqueous suspension during the 7 months storage, the particle size distribution remained essentially constant and the suspension was regenerated upon shaking.

The amount of dissolved dexamethasone in the aqueous γCD eye drop suspension was 0.7–0.9 mg mL^{-1}, or only about 5% of the total amount (i.e. 15 mg mL^{-1}) of dexamethasone in the eye drop formulation, but in the RMβCD eye drop solution all dexamethasone (i.e. 15 mg mL^{-1}) was in solution. Nonetheless, the amount of dexamethasone in the posterior segments (i.e. vitreous and retina) after topical administration of the γCD eye drops was comparable, or even slightly higher than after administration of the same amount in the RMβCD eye drop solution (Table 1). The dexamethasone blood levels were three times lower after administration of the γCD suspension than after administration of the RMβCD solution; the mean dexamethasone blood level (mean ± s.d.) 30–120 min after topical administration was 8.8 ± 2.4 ng g^{-1} for the γCD eye drops but 28 ± 10 ng g^{-1} for the RMβCD eye drops (Figure 1). Both eye drop formulations were well tolerated in the rabbits, with no signs of local irritation or adverse effects.

It is important to note that this experiment was conducted in albino rabbits and not in man. The contribution of systemic drug return to the ocular tissues would probably be lower in man since the apparent volume of drug distribution is much greater in a 70-kg man than in a 3-kg rabbit. The amount of dexamethasone was determined in both eyes after topical administration to only the left eye. The amount reaching a given eye tissue via the topical route was determined by subtracting the amount found in the right eye from the amount found in the left eye (Table 1). The average fraction reaching vitreous via the topical route did increase from 73% from the RMβCD eye drops to 86% from the γCD eye drops, and from 14% to 49% in retina (Figure 2). This increase resulted in about a 2- to 3-fold increase in the amount of drug reaching the posterior segment of the eye vial topical routes. Thus, the mean dexamethasone concentration in retina resulting from topical penetration of the drug after a single application of the γCD suspension was 28 ng g^{-1} compared with 9 ng g^{-1} after administration of the RMβCD eye drop solution (Table 1). Human sclera has been shown to be somewhat more permeable to dexamethasone than rabbit sclera (Rudnick et al 1999) and this indicates that dexamethasone concentrations in the posterior segment in man after topical administration of the dexamethasone eye drops will not be significantly different from those reaching the posterior segment via the topical route (Table 1).

Previously we have studied topical delivery of dexamethasone from aqueous CD-containing eye drops into aqueous humour and our previous results, together with the present ones, are shown in Table 2 (Loftsson et al 1994; Sigurdsson et al 2007). The dexamethasone concentrations in aqueous

Table 1 Dexamethasone concentration in blood and various ocular tissues 120 min after topical administration to rabbits

Tissue	1.5% Dexamethasone γCD suspension			1.5% Dexamethasone RMβCD solution		
	Left eye	Right eye	Topical[a]	Left eye	Right eye	Topical[a]
Cornea	1155 ± 324*	18 ± 12	1137	1668 ± 633	44 ± 44	1624
Sclera	404 ± 300	23 ± 12	381	231 ± 121	31 ± 20	200
Aqueous humour	236 ± 67**	4 ± 2***	232	576 ± 226	9 ± 4	567
Iris–ciliary body	290 ± 101**	27 ± 23	263	548 ± 290	43 ± 36	505
Lens	11 ± 6*	5 ± 5	6	19 ± 9	5 ± 3	14
Vitreous	29 ± 16	4 ± 4	25	22 ± 9	6 ± 3	16
Retina	57 ± 22	29 ± 15*	28	66 ± 49	57 ± 41	9
Blood	10 ± 7***			45 ± 24		

Concentration is expressed as ng g^{-1} (mean ± s.d., n = 6 (RMβCD), n = 8 (γCD)). One eye drop was applied to the left eye and the right eye was untreated. The term topical denotes how much (ng g^{-1}) the topical absorption contributed to the dexamethasone level. *$P \le 0.10$, **$P < 0.05$, ***$P < 0.01$, γCD vs RMβCD. The differences between the left and the right eye were significant ($P < 0.05$) for cornea, slera, aqueous humour, iris–ciliary body, lens and vitreous, as well as for blood. [a]Topical = mean concentration in the left eye − mean concentration in the right eye.

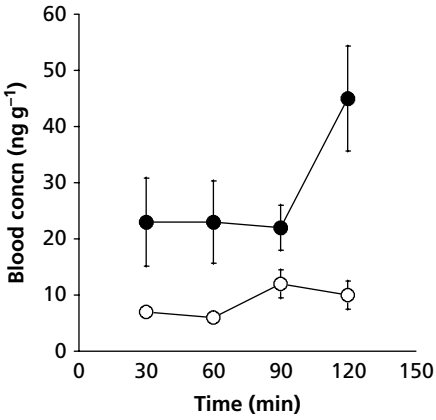

Figure 1 Blood dexamethasone concentrations (ng g^{-1}, mean ± s.e.m., n = 6 (RMβCD), n = 8 (γCD)) after topical administration of 1.5% dexamethasone/RMβCD eye drop solution (closed circles) and 1.5% dexamethasone/γCD eye drop suspension (open circles) to rabbits ($P < 0.05$ at 30, 60 and 120 min; $P = 0.064$ at 90 min).

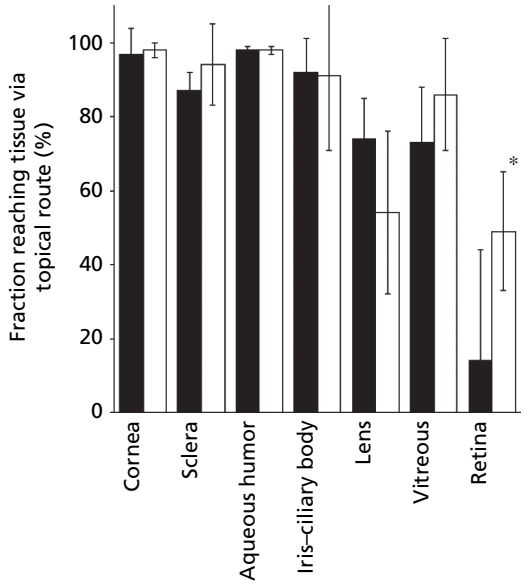

Figure 2 Relative contribution (mean ± s.d., n = 6 (RMβCD), n = 8 (γCD)) of topical delivery in the various eye tissues of rabbits after topical administration of 1.5% dexamethasone eye drops containing the drug in aqueous RMβCD solution (shaded columns) and aqueous γCD suspension (open columns). The amount of dexamethasone was determined in both eyes after topical administration to the left eye. The amount reaching given eye tissue via topical route was determined by subtracting the concentration in the right eye ($C_{right\ eye}$) from the concentration in the left eye ($C_{left\ eye}$): Topical route (%) = $[(C_{left\ eye} - C_{right\ eye})/C_{left\ eye}] \times 100$. *$P = 0.02$, RM$\beta$CD vs γCD.

humour were somewhat higher after topical administration of the drug in a RMβCD containing vehicle compared to vehicles containing either γCD or 2-hydroxypropyl βCD and significantly higher than after administration of the commercial eye drops, Maxidex, that contain 0.1% (w/v) dexamethasone

Table 2 Concentration of dexamethasone in aqueous humour 2 h after administration of aqueous dexamethasone eye drop solutions or suspensions containing either randomly methylated β-cyclodextrin (RMβCD), 2-hydroxypropyl-β-cyclodextrin (HPβCD) or γ-cyclodextrin (γCD) in rabbits

Aqueous eye drop solution	Dexamethasone concn (ng g^{-1})	No. of rabbits
0.5% Dexamethasone/ RMβCD soln	170 ± 76	6
1.5% Dexamethasone/ RMβCD soln	576 ± 226	6
1.3% Dexamethasone/ HPβCD soln	320 ± 230	4
1.5% Dexamethasone/ γCD suspension	236 ± 67	8
Maxidex (0.1% dexamethasone suspension)	66 ± 20	4

Values are expressed as mean ± s.d. The value for the 0.5% dexamethasone/RMβCD eye drop solution was obtained from Sigurdsson et al (2007) and the values for 1.3% dexamethasone/HPβCD eye drop solution and M (mean ± standard deviation). The value for the 0.5% dexamethasone/RMβCD eye drop solution was obtained from Sigurdsson et al (2007) and the values for 1.3% dexamethasone/HPβCD eye drop solution and Maxidex were obtained from Loftsson et al (1994, 2007).

as an alcoholic suspension. This was expected since the somewhat lipophilic and surface-active RMβCD is known, under certain conditions, to act not only as a solubilizer enhancing drug delivery through the aqueous mucin layer on the eye surface but also as a conventional penetration enhancer increasing drug permeability through biological membranes by decreasing their barrier function (Merkus et al 1999; Yang et al 2004). However, unlike the cornea, drug permeation through the sclera does not appear to be affected by the lipophilicity of the permeating drug molecules and sclera is about 10 times more permeable than cornea (Prausnitz & Noonan 1998). These results (Table 2), together with the relatively high dexamethasone concentrations in the posterior segment of the eye (vitreous and retina) and low blood concentrations after topical administration of the dexamethasone/γCD eye drop suspension (Table 1, Figure 1), show that this delivery system is more site specific with regard to vitreous and retina than conventional eye drop solutions.

The most direct approach for introduction of dexamethasone into vitreous is by intravitreal injection but invasive methods are not risk free and they can only be applied by trained ophthalmologists. In man, the half-life of dexamethasone is only a few hours and, thus, frequent injections are needed to maintain therapeutic drug levels in vitreous. Alternatively, ocular implants have been developed that release dexamethasone for extended periods of time. Recently a biodegradable polymer matrix implant was developed that releases dexamethasone in vitreous for about one month. In rabbit studies of the implant, the dexamethasone concentrations in vitreous were 120 ng mL^{-1} on day one, decreasing slowly to 53 ng mL^{-1} on day 28, while the aqueous humour

concentrations were 5–6 ng mL^{-1} and plasma concentrations were 1.5–1.0 ng mL^{-1} during this time period (Shiah et al 2005). Similar implants delivering dexamethasone in vitreous for more than one year have been developed (Nivaggioli et al 2005). The main advantage of ocular implants is that they deliver constant therapeutic levels of drug directly to the site of action, avoiding systemic site effects. These are, however, invasive delivery forms that are associated with increased risk of bacterial infection and intravitreal haemorrhage.

Conclusions

γCD complexation of dexamethasone increased the drug saturation concentration from about 0.16 mg mL^{-1} to almost 1 mg mL^{-1}. After topical administration of the aqueous eye drop suspension, the dexamethasone/γCD particles were retained on the eye surface where they were somewhat slowly dissolved, resulting in sustained drug saturation (at about 1 mg mL^{-1}) of the tear fluid. These water-soluble particles increased significantly the residence time of the drug on the aqueous eye surface. After topical administration of the eye drop suspension, relatively high dexamethasone concentrations were obtained in the posterior segment of the eye (vitreous and retina) but low concentrations in the blood. This indicates that this delivery system is more site specific with regard to vitreous and retina than conventional eye drop solutions.

References

Beeley, N. R. F., Rossi, J. V., Mello-Filho, P. A. A., Mahmoud, M. I., Fujii, G. Y., de Juan, E., Varner, S. E. (2005) Fabrication, implantation, elution, and retrieval of a steroid-loaded polycaprolactone subretinal implant. *J. Biomed. Mater. Res. A* **73**: 437–444

Degenring, R. F., Jonas, J. B. (2005) Photodynamic therapy in combination with intravitreal triamcinolone for myopic choroidal neovascularization. *Acta Ophthalmol. Scand*. **83**: 621

Geroski, D. H., Edelhauser, H. F. (2001) Transsclera drug delivery for posterior segment disease. *Adv. Drug Deliv. Rev*. **52**: 37–48

Hämäläinen, K. M., Kananen, K., Auriola, S., Kontturi, K., Urtti, A. (1997) Charaterization of paracellular and aqueous penetration routes in cornea conjunctiva, and slera. *Invest. Ophthalmol. Vis. Sci*. **38**: 627–633

Higuchi, T., Connors, K. A. (1965) Phase-solubility techniques. *Adv. Anal. Chem. Instrum*. **4**: 117–212

Hosoya, K., Lee, V. H. L., Kim, K.-J. (2005) Roles of the conjunctiva in ocular drug delivery: a review of conjunctival transport mechanisms and their regulation. *Eur. J. Pharm. Biopharm*. **60**: 227–240

Jaffe, G. J., Martin, D., Callanan, D., Pearson, P. A., Levy, B., Comstock, T. (2006) Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study. *Ophthalmology* **113**: 1020–1027

Jonas, J. B. (2005) Intravitreal triamcinolone acetonide for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol. Scand*. **83**: 645–663

Jonas, J. B., Spandau, U. H., Kamppeter, B. A., Harder, B. (2006) Follow-up after intravitreal triamcinolone acetonide for exudative age-related macular degeneration. *Eye* **20**: 566–572

Loftsson, T., Hreinsdóttir, D. (2006) Determination of aqueous solubility by heating and equilibration: a technical note. *AAPS PharmSciTech* 7: www.aapspharmscitech.org

Loftsson, T., Järvinen, T. (1999) Cyclodextrins in ophthalmic drug delivery. *Adv. Drug Deliv. Rev*. **36**: 59–79

Loftsson, T., Stefánsson, E. (1997) Effect of cyclodextrins on topical drug delivery to the eye. *Drug Devel. Ind. Pharm*. **23**: 473–481

Loftsson, T., Stefánsson, E. (2002) Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye. *Acta Ophthalmol. Scand*. **80**: 144–150

Loftsson, T., Stefánsson, E. (2007) Cyclodextrins in ocular drug delivery. *J. Drug Del. Sci. Tech*. **17**: 3–9

Loftsson, T., Fridriksdottir, H., Thorisdottir, S., Stefansson, E. (1994) The effect of hydroxypropyl methylcellulose on release of dexamethasone from aqueous 2-hydroxypropyl-β-cyclodextrin formulations. *Int. J. Pharm*. **104**: 181–184

Loftsson, T., Hreinsdóttir, D., Másson, M. (2005a) Evaluation of cyclodextrin solubilization of drugs. *Int. J. Pharm*. **302**: 18–28

Loftsson, T., Jarho, P., Másson, M., Järvinen, T. (2005b) Cyclodextrins in drug delivery. *Expert Opin. Drug Deliv*. **2**: 335–351

Loftsson, T., Konrádsdóttir, F., Másson, M. (2006a) Influence of aqueous diffusion layer on passive drug diffusion from aqueous cyclodextrin solutions through biological membranes. *Pharmazie* **61**: 83–89

Loftsson, T., Sigurdsson, H. H., Hreinsdóttir, D., Konrádsdóttir, F., Stefánsson, E. (2007) Dexamethasone delivery to posterior segment of the eye. *J. Incl. Phenom. Macroc. Chem*. In press

Merkus, F. W. H. M., Verhoef, J. C., Marttin, E., Romeijn, S. G., van der Kuy, P. H. M., Hermens, W. A. J. J., Schipper, N. G. M. (1999) Cyclodextrin in nasal drug delivery. *Adv. Drug Deliv. Rev*. **36**: 41–57

Myles, M. E., Neumann, D. M., Hill, J. M. (2005) Recent progress in ocular drug delivery for posterior segment disease: emphasis on transsclera iontophoresis. *Adv. Drug Deliv. Rev*. **57**: 2063–2079

Nivaggioli, T., Shiah, J. G., Lin, Q. (2005) *Extended release biodegradable ocular implants*. US patent appl. no. 2005/0244467. Allergan Inc., US

Prausnitz, M. R., Noonan, J. S. (1998) Permeability of cornea, sclera, and conjunctiva: a literature analysis for drug delivery to the eye. *J. Pharm. Sci*. **87**: 1479–1487

Raghava, S., Hammond, M., Kompella, U. B. (2004) Periocular routes for retinal drug delivery. *Exp. Opin. Drug Deliv*. **1**: 99–114

Rudnick, D. E., Noonan, J. S., Geroski, D. H., Prausnitz, M. R., Edelhauser, H. F. (1999) The effect of intraocular pressure on human and rabbit sclera permeability. *Invest. Ophthalmol. Vis. Sci*. **40**: 3054–3058

Sasaki, H., Yamamura, K., Nishida, K., Nakamura, J., Ichikawa, M. (1996) Delivery of drugs to the eye by topical application. *Prog. Ret. Eye Res*. **15**: 583–620

Shell, J. W. (1982) Pharmacokinetics of topically applied ophthalmic drugs. *Surv. Ophthalmol*. **26**: 207–218

Shiah, J.-G., Bhagat, R., Nivaggioli, T., Peng, L., Chou, D., Weber, D. A. (2005) *Ocular implant made by a double extrusion process*. US patent appl. no. 2005/0048099. Allergan Inc., USA

Sigurdsson, H. H., Konrádsdóttir, F., Loftsson, T., Stefánsson, E. (2007) Role of topical versus systemic absorption in delivery of dexamethasone to the anterior and posterior segments of the eye. *Acta Ophthalmol. Scand*. In press

Sigurðsson, H. H., Stefánsson, E., Guðmundsdóttir, E., Eysteinsson, T., Thorsteinsdóttir, M., Loftsson, T. (2005) Cyclodextrin formulation of dorzolamide and its distribution in the eye after topical administration. *J. Control. Release* **102**: 255–262

Slakter, J. S., Bochow, T. W., D'Amico, D. J., Marks, B., Jerdan, J., Sullivan, E. K., Robertson, S. M., Slakter, J. S., Sullins, G., Zilliox, P. (2006) Anecortave acetate (15 milligrams) versus photodynamic therapy for treatment of subfoveal neovascularization in age-related macular degeneration. *Ophthalmology* **113**: 2–13

Van Ooteghem, M. M. M. (1993) Formulation of ophthalmic solutions and suspensions. Problems and advantages. In: Edman, P. (ed.) *Biopharmaceutics of ocular drug delivery*. CRC Press, Boca Raton, pp 27–42

Washington, N., Washington, C., Wilson, C. G. (2001) *Physiological pharmaceutics; barriers to drug absorption*. 2nd edn, Taylor & Francis, London

Yang, T., Hussain, A., Paulson, J., Abbruscato, T. J., Ahsan, F. (2004) Cyclodextrins in nasal delivery of low-molecular-weight heparins: in vivo and in vitro studies. *Pharm. Res*. **21**: 1127–1136

Yasukawa, T., Ogura, Y., Sakurai, E., Tabata, Y., Kimura, H. (2005) Intraocular sustained drug delivery using implantable polymer devices. *Adv. Drug Deliv. Rev*. **57**: 2033–2047