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The effect of hydroxypropyl methylcellulose on the release of dexamethasone from aqueous 2-hydroxypropyl-β-cyclodextrin formulations

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Abstract

The effect of hydroxypropyl methylcellulose on the complexation of dexamethasone with 2-hydroxypropyl-β-cyclodextrin (HPβCD) was investigated. The aqueous solubility of dexamethasone was significantly increased by formation of a water-soluble dexamethasone-HPβCD (1:1) inclusion complex. The complexation was increased when hydroxypropyl methylcellulose was added to the aqueous complexation medium. Addition of 0.1% (w/v) hydroxypropyl methylcellulose resulted in a 26% increase in the stability constant of the complex. The release of dexamethasone from aqueous HPβCD vehicles was affected by the hydroxypropyl methylcellulose induced complexation increase. Also, the effect of HPβCD on the permeability of dexamethasone from an aqueous solution through the cornea into the aqueous humor was investigated in vivo in rabbits.

Key words: Cyclodextrin; Dexamethasone; Hydroxypropyl methylcellulose; Permeability; Release; Solubility; Topical formulation

Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic cavity in the center. In aqueous solutions CDs are able to form non-covalent inclusion complexes with various types of lipophilic drugs. Encapsulation of a drug molecule will affect many of its physicochemical properties and can result in increased aqueous solubility and stability (Szejtli, 1988). These effects of CD encapsulation have been utilised in pharmaceutical formulations to improve bioavailability of drugs, for example, after topical application of dexamethasone to the eye (Usayapant et al., 1991). However, other vehicle additives can have a significant effect on the drug-CD complex formation. Thus, lipophilic preservative molecules have been shown to displace drug molecules from the CD cavity (Loftsson et al., 1992) and small lipophilic molecules such as ethanol and propylene glycol are also known to reduce the extent of complexation (Pitha and Hoshino, 1992; Loftsson et al., 1993). The purpose of this study was to investigate the effect

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of a commonly used water-soluble polymer, i.e., hydroxypropyl methylcellulose, on the CD complexation and permeability of dexamethasone. The effect of cyclodextrin on the trans-corneal permeability of dexamethasone was also investigated.

Dexamethasone was obtained from Sigma Chemical Co. (St. Louis, MO), 2-hydroxypropyl-β-cyclodextrin of molar substitution 0.6 (HPβCD) from Wacker-Chemie (Munich, Germany), and hydroxypropyl methylcellulose 4000 from Mecobenzon (Copenhagen, Denmark). Maxidex® eye drops were obtained from Alcon Laboratories Inc. (Fort Worth, TX). All other chemicals used were of pharmaceutical or special analytical grade. Semi-permeable cellophane membrane (Spectrapore® membrane tubing no. 2) was obtained from Spectrum Medical Industries (Los Angeles, CA).

The quantitative determination of dexamethasone was performed on a HPLC component system from Milton Roy consisting of a ConstaMetric 3200 solvent delivery system operated at a flow rate of 1.50 ml/min, a Rheodyne 7125 injector, a Beckman Ultrasphere ODS 5 mm (4.6 × 150 mm) column and a Spectro Monitor 3200 UV/Vis variable-wavelength detector operated at 263 nm. The mobile phase consisted of acetonitrile, tetrahydrofuran and water (35:1:64) and the retention time was 4.4 min. The aqueous humor samples from the eye were injected directly into the column without any pre-treatment. The drug recovery from aqueous humor samples which had been spiked with dexamethasone was estimated to be about 100%.

The solubility of dexamethasone in various vehicles was determined by adding excess amounts of the drug to water or aqueous HPβCD solutions, containing no or 0.1% (w/v) hydroxypropyl methylcellulose 4000, and heating the suspensions in sealed containers in an autoclave (120°C for 20 min). After equilibration at room temperature (about 23°C) for at least 3 days the suspensions were filtered through a 0.45 μm nylon membrane filter, diluted with a mixture of methanol and water (7:3) and analysed by HPLC. The 3 day equilibration was considered sufficient, since further equilibration of the suspensions for up to 10 days did not result in any further drug precipitation. The apparent stability constant of the dexamethasone-HPβCD complex was calculated from the slope of the phase-solubility diagrams and the determined solubility of dexamethasone in pure water (2.8×10^{-4} mol/l), assuming a 1:1 stoichiometric ratio (Higuchi and Connors, 1965).

The effect of HPβCD on the permeability of dexamethasone through a semi-permeable cellophane membrane was investigated. The membrane was placed in a Franz diffusion cell (Vangard International Inc., Neptune, NJ) containing 10 ml of an aqueous 5% (w/v) HPβCD solution as a receptor phase. The donor phase (the drug vehicle) consisted of a 0.5% (w/v) suspension or solution of dexamethasone in an aqueous HPβCD solution, or in an aqueous solution containing both HPβCD and 0.1% (w/v) hydroxypropyl methylcellulose 4000, which had been heated in an autoclave (120°C for 20 min). After equilibration for 3 days 2.0 ml of the donor phase were applied to the membrane surface (area 3.1 cm^2). The assembled diffusion cells were kept at room temperature (about 23°C) and samples (30 μl) were removed from the donor phase every 10 min, up to 2 h, and analysed immediately by HPLC. Each experiment was repeated at least three times and the results reported are the mean values ± standard error of the mean (SE) in mg dexamethasone min^{-1} cm^{-2}.

The permeability of dexamethasone through the cornea was determined in vivo in English brown rabbits (0.5–1.5 years old) of either sex. The dexamethasone eye drop solution contained 1.3% (w/v) dexamethasone in an isotonic vehicle consisting of 20% (w/v) HPβCD, 0.1% (w/v) hydroxypropyl methylcellulose 4000, 0.02% (w/v) benzalkonium chloride and 0.1% (w/v) EDTA in water. The solution was sterilised in an autoclave (heating to 120°C for 20 min). The rabbits were placed in restraint boxes, to which they had been habituated, and anaesthetised with an intramuscular injection of ketamine (10 mg/kg). A single 50 μl dose of the 1.3% dexamethasone solution was administered to the lower conjunctival fornix of one eye and, as a reference, a 50 μl dose of Maxidex® (containing 0.1% dexamethasone alco-

holic suspension) was administered in the same manner to the other eye. At 30, 60, 90, 120, 180 or 320 min after the administration approx. 0.1-ml samples of the aqueous humor was withdrawn from the eyes through 25-gauge needles. The samples were kept frozen until analysed by HPLC. Three animals were used for each time point and the results reported are the mean values ± SE.

The phase-solubility diagrams of dexamethasone in aqueous HPβCD solution are shown in Fig. 1. The solubility increased linearly as a function of the HPβCD concentration with a slope of less than unity and, thus, formation of a 1:1 complex could be assumed. The solubility increase was notably larger when hydroxypropyl methylcellulose was present in the solution. The stability constant of the dexamethasone-HPβCD inclusion complex was determined to be 1230 M^{-1} when no hydroxypropyl methylcellulose was present in the aqueous HPβCD solution as compared to 1550 M^{-1} when 0.1% hydroxypropyl methylcellulose was present, representing a 26% increase.

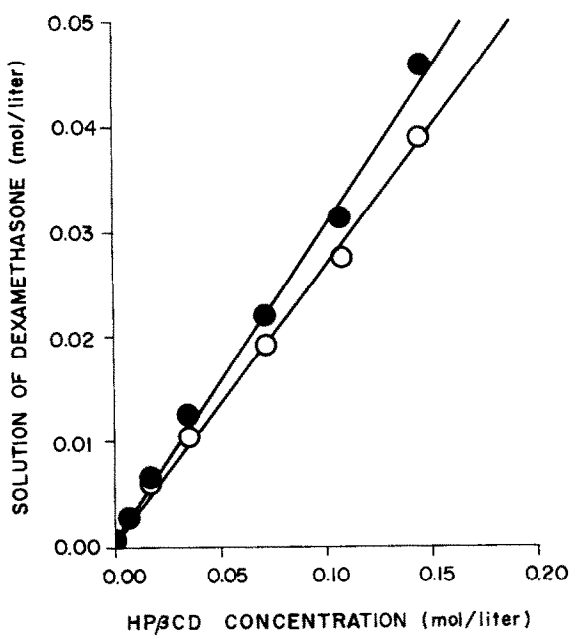

Fig. 1. Phase-solubility diagrams of dexamethasone in aqueous HPβCD solutions containing 0.0 (○) and 0.1% (●) hydroxypropyl methylcellulose at room temperature (23°C).

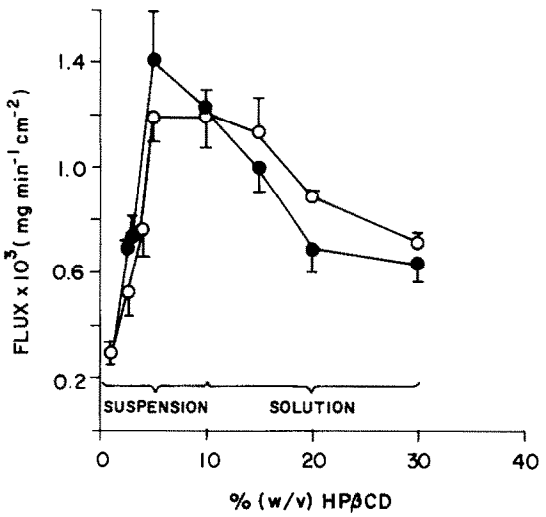

Fig. 2. Relationship between the HPβCD concentration and the mean flux of dexamethasone from an aqueous HPβCD solution containing 0.5% dexamethasone in a suspension or a solution through a semi-permeable cellophane membrane at room temperature. No hydroxypropyl methylcellulose present in the aqueous HPβCD vehicle (○) and 0.1% hydroxypropyl methylcellulose present (●).

The effect of HPβCD on the flux of dexamethasone from an aqueous vehicle through a semi-permeable cellophane membrane was investigated (Fig. 2). The dexamethasone concentration was kept constant at 0.5% but the HPβCD concentration was increased from 1 to 30% and this was carried out both when no hydroxypropyl methylcellulose was present in the vehicle and when 0.1% hydroxypropyl methylcellulose was present. At low HPβCD concentrations, when dexamethasone was in suspension, the flux increased with increasing HPβCD concentration but when all dexamethasone was in solution, at HPβCD concentrations equal to or above 10%, the flux decreased with increasing HPβCD concentration. When dexamethasone was in suspension increasing the HPβCD concentration resulted in increasing amounts of dissolved drug and, since the rate of drug release from the dexamethasone-HPβCD complex was much faster than that of drug dissolution, this increase in solubility led to greater flux through the membrane. On the other hand, when all dexamethasone was in solution increasing the HPβCD con-

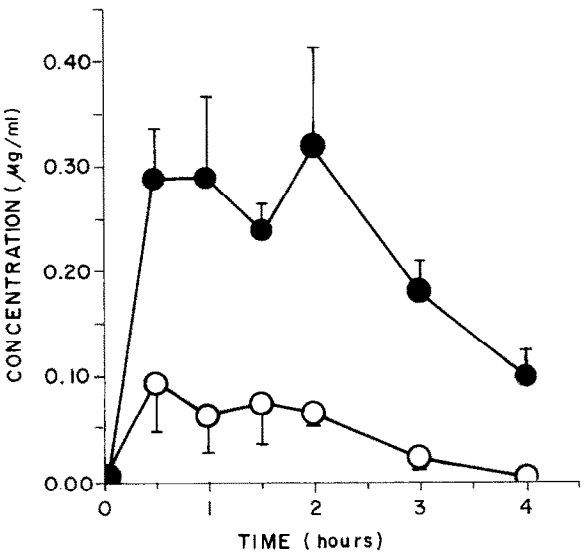

Fig. 3. Mean dexamethasone concentration in the aqueous humor of rabbits after administration of 1.3% dexamethasone in an aqueous HPβCD solution (●) or a 0.1% dexamethasone alcoholic suspension (Maxidex®) (○).

centration led to increased HPβCD complexation of the drug molecules and since the hydrated dexamethasone-HPβCD complex permeates the membrane at a much slower rate than the free drug molecules this increased complexation resulted in a decrease in flux (Loftsson et al., 1991). Maximum flux through the membrane was obtained when just enough HPβCD was used to keep all dexamethasone in solution.

When hydroxypropyl methylcellulose was added to the aqueous HPβCD vehicle the stability constant of the dexamethasone-HPβCD complex was increased, resulting in a leftward shift of the HPβCD concentration-flux profile (Fig. 2). The larger stability constant resulted in increased complexation of the drug and, thus, at each given HPβCD concentration a greater fraction of the drug molecules was bound to the HPβCD molecules.

The effect of HPβCD on the permeability of dexamethasone from an aqueous solution through the cornea into the aqueous humor was investigated in vivo in rabbits. The drug was solubilised in the isotonic vehicle by HPβCD complexation and in this way it was possible to obtain a significantly higher concentration of dissolved drug. However, an increase of about 13-fold in the total dexamethasone concentration only resulted in an increase of about 4-fold in the intra-ocular concentration (Fig. 3).

In conclusion, our results show that it is possible to achieve effective trans-ocular delivery of lipophilic drugs, like dexamethasone, from aqueous eye drop formulations. During drug formulation it is important to investigate the effect of other vehicle excipients on the drug-cyclodextrin complexation. Various lipophilic additives can reduce the extent of complexation while others, such as hydroxypropyl methylcellulose, can enhance complexation. Drug release from the aqueous cyclodextrin containing vehicle is affected by both the addition of too much and too little cyclodextrin to the vehicle. Maximum release is obtained when just enough cyclodextrin is added to the vehicle to keep all the drug in solution.

1. Acknowledgements

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