2-HYDROXYPROPYL-ß-CYCLODEXTRIN IN EYE DROPS.
EVALUATION OF ARTIFICIAL TEAR-DROPS IN HUMAN PATIENTS

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ABSTRACT:
Relatively little is known about the effects of cyclodextrins (CDs) on the human eye, especially in patients with dry eyes. In an effort to gain more knowledge on the effects of CDs on the human eye we designed a 2-hydroxypropyl-ß-cyclodextrin (HPßCD) containing eye drop preparation with cholesterol, which is a natural tear ingredient. A pilot study in rabbits and human patients was followed by an open trial and then a double masked study in patients with mild dryness. All these patients reported that they felt better in both eyes. One patient complained of crusts on the eyelid margin and this was related to the HPßCD containing artificial tears. No changes were observed in visual acuity or intraocular pressure, nor on the ocular surface or anterior eye structure.

1. INTRODUCTION

Human tears contain three main components, an aqueous portion, a lipid and a mucus component. However, treatment of tear deficiency, i.e. dry eyes, depends mainly on saline tear substitutes, and disregards the lipid and mucus components. In this study we develop and test a tear substitute that attempts to mimic human tears and contains saline, and cholesterol dissolved with the aid of 2-hydroxypropyl-ß-cyclodextrin. Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface, and therefore they are usually soluble in water. The molecule has a central lipophilic cavity and cyclodextrins are capable of forming inclusion complexes with a wide variety of hydrophobic drug molecules (1). ß-Cyclodextrin, is the one most practical to use in pharmaceutical formulations but it has a relatively low aqueous solubility, haemolytic activity and nephrotoxicity which limits its use (2,3). A ß-cyclodextrin derivative, 2-hydroxypropyl-ß-cyclodextrin also forms inclusion complexes with various hydrophobic drugs (4,5,6). This results in the improvement of solubility, dissolution rate, bioavailability and unlike ß-cyclodextrin and its methyl derivatives, it is without toxicity (7,8,9,10) such as to the corneal epithelium. The properties of this ß-cyclodextrin derivative makes it a desirable vehicle in ophthalmic eye-drop formulations of poorly water soluble drugs. It has previously been reported that this compound is non-toxic to the rabbit eye (8,11).
2. MATERIALS AND METHODS

Artificial tear drops containing 2-hydroxypropyl-β-cyclodextrin and cholesterol were formed. A short term study (single application, one week) and an intermediate-term study (up to one month) were performed in people with dry eyes. The effect of this artificial tear solution on the structures of the eyes was evaluated with slit lamp biomicroscopy and a measurement of the visual acuity and intraocular pressure. The study was approved by the Landakot hospital ethics board and, before entering the study, all patients were informed of its nature and risks.

Cholesterol was obtained from Sigma Chemical company (USA), 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution 0.9 from Wacker-Chemie (Germany), and hydroxypropyl methylcellulose from Mecobenzon (Denmark). A commercially available tear substitute, Isoptonaturale® was obtained from Alcon Laboratories (USA). All other chemicals used were of pharmaceutical or special analytical grade. Concentration of chemicals in the formulation is given in per cent (%) to indicate weight-in-volume (% w/v).

An aqueous solution was created with HPβCD (20%), cholesterol (0.05%), hydroxypropyl methylcellulose (0.1%), benzalkonium chloride (0.01%), sodium edetate (0.05%) and sodium chloride (0.14%). The solution was sterilised in an autoclave (120°C for 20 min). The isotonicity was monitored with an automatic osmometer from Knauer (Germany) and the pH of the final solution was about 5.

2.1. Mild dry eye syndrome

Human patients were eligible for the trial if they had mild dryness of eyes, and fulfilled all of the four following criteria: (1) complained of dryness in one or both eyes; (2) had not previously been treated for dry eyes; (3) had Schirmer’s test, under topical anaesthesia, less than 5 mm in 5 minutes in one or both eyes; and (4) a slit lamp examination revealed no pathological changes on the surface of the eye other than mild punctate staining with fluorescein dye. Four patients entered the single application part of the study. The visual acuity and the intraocular pressure were measured, as was done in all study groups, and the surface of the eyes and cornea examined with a slitlamp microscope, before one drop of the cyclodextrin-cholesterol teardrop was instilled to one eye, the other eye serving as untreated control. Identical examinations were repeated 30 and 60 minutes after the installation and patients were asked to report any discomfort in their eyes. In the next phase patients were examined as above and given a 15 ml bottle containing cyclodextrin-cholesterol tear drops and asked to administered the drops three times a day in one eye. Six patients participated in this part of the study and they returned for examination after one week.

A group of 8 patients, who complained of mild dryness and met the same criteria as the patients above were given two identical bottles, one containing the cyclodextrin-cholesterol eye drop solution and the other Isoptonaturale®. The bottles were labelled 1-R, 1-L, 2-R and 2-L and so on for use in right (R) and left (L) eye. The patients administered the eye drop solution three times a day for four weeks and returned for examination (as above) one and four weeks from the start of the trial.