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Development of a cyclodextrin-based aqueous cyclosporin A eye drop formulations

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ABSTRACT

Cyclosporin A (CyA) is a lipophilic, cyclic polypeptide drug with anti-inflammatory properties. It is used in topical treatment of dry eyes and is now commercially available in oil based surfactant containing eye drops. Surfactants can irritate the eye surface causing burning, itching and irritation of the conjunctiva, and oil-based drops can result in blurred vision. Thus, the aim of this study was to develop surfactant free aqueous 0.05% (w/v) CyA eye drops where the drug is present in an aqueous vehicle containing CyA/cyclodextrin (CyA/CD) nanoparticles. The effects of the natural α-, β- and γ-cyclodextrins (αCD, βCD and γCD), as well as of the water soluble hydroxypropyl derivatives of γCD and αCD (HPγCD, HPαCD) and randomly methylated βCD (RMβCD), were determined in pure water. αCD had the best solubilizing effect increasing the solubility of CyA above 0.05% upon addition of only 5% (w/v) αCD. γCD did not have as good solubilizing effect but was tested further due to its superior ability to form nanoparticles and its favorable toxicological profile. Seven eye drop formulations were prepared and tested. All contained 0.05% (w/v) CyA in addition to polyvinyl alcohol, benzalkonium chloride, disodium edetate and various amounts of CD (αCD, γCD and mixtures thereof). When the formulation contained only αCD most of the drug was dissolved but some small aggregates were formed with hydrodynamic diameter of about 6 and 155 nm. When the formulation contained only γCD negligible CyA/CD complexation occurred with most of the drug present as solid CyA particles. When the formulation contained a mixture of αCD and γCD, where αCD concentration was at least 3% (w/v), the entire drug content was dissolved in the media under formation of relatively large (100–2000 nm) CyA/CD nanoparticles. αCD solubilized the drug while γCD enhanced nanoparticle formation. The effect of polyvinyl alcohol, benzalkonium chloride and disodium edetate on the nanoparticle formation was also investigated and shown to have positive effect on the aggregate formation.

1. Introduction

Dry eye syndrome (DES) is a common ocular disorder caused by decreased tear production that results in discomfort and visual disturbance. DES has multifactorial etiology involving tear film instability, increased osmolality of the tear film and inflammation of the ocular surface, with potential damage to the ocular surface (Anon., 2007b). Few therapies are available for this disease (Yavuz et al., 2012). Appropriate therapy is selected based to the disease severity and can range from artificial tears, that provide palliative relief to eye irritation in patients with tear deficiency, to anti-inflammatory therapies for patients with moderate to severe DES (Anon., 2007a; Calonge, 2001).

Cyclosporin A (CyA) is a cyclic polypeptide drug (Fig. 1) obtained from the fermentation broth of two fungi, *Trichoderma polysporum* and *Cylindrocarpon lucidum* (Laupacis et al., 1982). It has the molecular weight of 1202.6 Da, aqueous solubility of 0.008 mg/ml at ambient temperature (Loftsson and Hreinsdottir, 2006) and Log $P_{octanol/water}$ = 2.92 at 21 °C (Tayar et al., 1993). CyA has a variety of biological activities, including immunosuppressive, anti-inflammatory and antifungal properties (Survase et al., 2011). In ophthalmology CyA has been proven useful for patients with various inflammatory ocular surface disorders, including dry eyes. In 2003 0.05% (w/v) CyA oil based eye drops (Restasis®; Alcon, Texas) became commercially available for topical treatment of DES (Utine et al., 2010). However, using oils and surfactants to deliver CyA topically provides a low drug bioavailability and can cause

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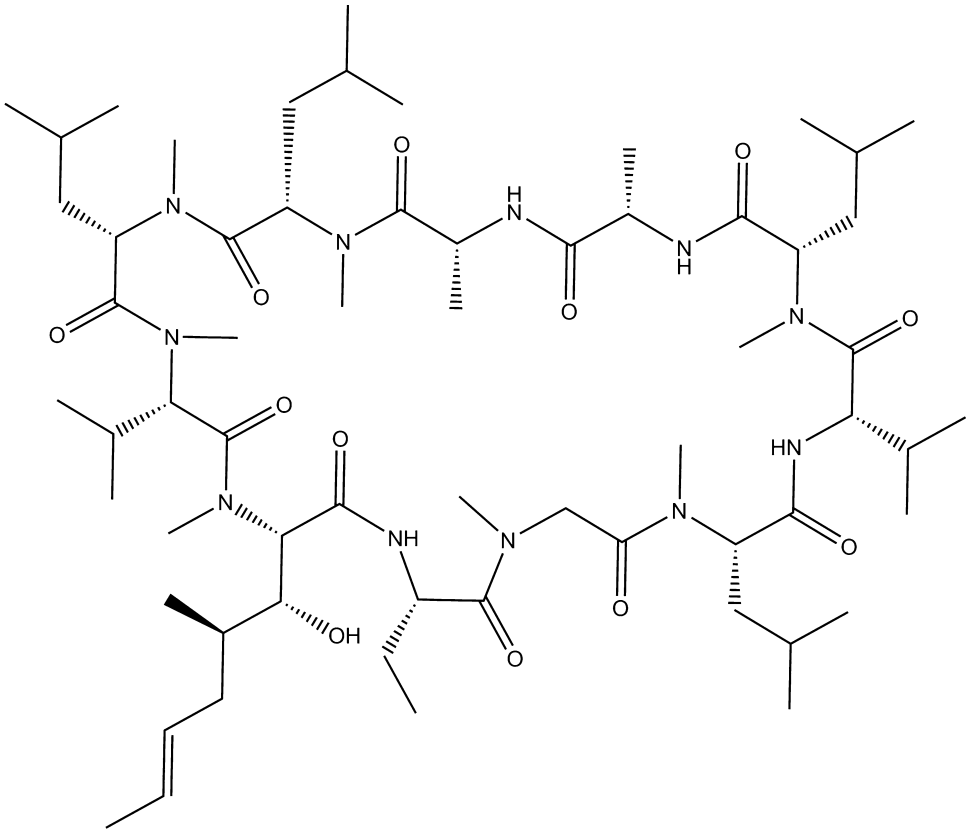

Fig. 1. Chemical structure of cyclosporin A.

blurry vision, burning sensation, itching and irritation of the conjunctiva. A better approach would be to use water based CyA eye drops. Then again, the hydrophobic nature of CyA presents significant formulation challenges (Donnenfeld and Pflugfelder, 2009; Lallemand et al., 2003). One way to overcome these obstacles is to increase the aqueous solubility of CyA through cyclodextrin (CD) complexation and enhance the drug contact time with the eye surface through formation of nanoparticles.

CDs are useful solubilizing excipients that are receiving increasing attention in the pharmaceutical field. They are cyclic oligosaccharides derived from starch containing six (αCD), seven (βCD), eight (γCD) or more (α-1,4)-glucopyranose units. CD molecules are shaped like cones with primary hydroxyl groups extending from the narrow edge of the cone and the secondary groups from the wider edge. In aqueous solutions these hydroxyl groups form hydrogen bonds with surrounding water molecules resulting in hydrophilic outer surface. The central cavity of the CDs is lined with skeletal carbons and ethereal oxygen, which gives the cavity a somewhat hydrophobic character. In aqueous solutions suitably sized lipophilic drug molecules, or lipophilic moieties of larger molecules, can enter the CD cavities to form water-soluble inclusion complexes (Fig. 2) (Brewster and Loftsson, 2007; Loftsson and Brewster, 1996). No covalent bonds are formed or broken during the complex formation and in aqueous solutions drug molecules located within the CD cavities are in dynamic equilibrium with free drug molecules (Stella et al., 1999). CDs and drug/CD complexes are able to self-assemble in aqueous solutions to form nano-sized aggregates and micellar-like structures that are also able to solubilize poorly soluble drugs through non-inclusion complexation and micellar-like solubilization (Brewster and Loftsson, 2007; Loftsson and Duchêne, 2007; Messner et al., 2010). CDs are known to solubilize CyA in aqueous solutions and aqueous CyA eye drop solutions have been described (Kanai et al., 1989; Takano et al., 1992). Previously we have developed and

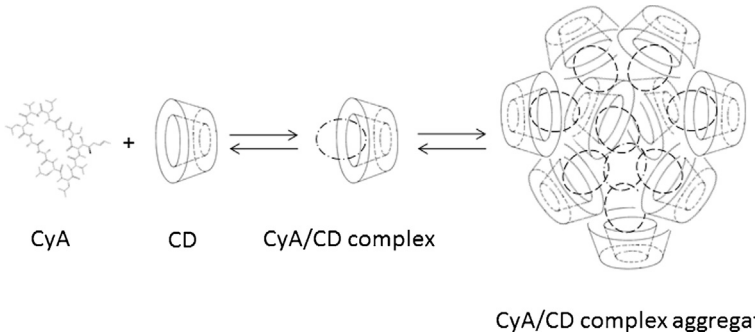

Fig. 2. Formation of CyA/CD complex and complex aggregates. First inclusion complexes are formed between CD and CyA. These complexes can then interact with each other, self-assemble to form aggregates.