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Review article

Cyclosporine A delivery to the eye: A comprehensive review of academic and industrial efforts

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ABSTRACT

Local ocular delivery of cyclosporine A (CsA) is the preferred method for CsA delivery as a treatment for ocular inflammatory diseases such as uveitis, corneal healing, vernal keratoconjunctivitis and dry eye disease. However, due to the large molecular weight and hydrophobic nature of CsA and the natural protective mechanisms of the eye, achieving therapeutic levels of CsA in ocular tissues can be difficult. This review gives a comprehensive overview of the current products available to clinicians as well as emerging drug delivery solutions that have been developed at both the academic and industry levels.

Contents

Abbreviations: Aq-CsA, CsA in a micellar solution; AUC, area under the curve; BAK, benzalkonium chloride; bid, twice daily; CKC, cetalkonium chloride; CMC, critical micellar concentration; CsA, cyclosporine A; DDS, drug delivery system; DED, dry eye disease; EDTA, ethylenediaminetetraacetic acid; Em-CsA, CsA in an oil-in-water emulsion; EU, European Union; EVEIT, *Ex Vivo* Eye Irritation Test; HA, hyaluronic acid; HEMA, 2-hydroxyethyl methacrylate; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; KCS, keratoconjunctivitis sicca; MCT, medium-chain triglyceride; MD, multi-dose container; mPEG-hexPLA, methoxy poly(ethylene)glycol-hexyl substituted poly(lactides); NA, not available; NaCl, sodium chloride; NaOH, sodium hydroxide; Oil-CsA, CsA in a castor oil solution; PLGC, poly(lactide-*co*-glycolide-*co*-caprolactone); p-HEMA, poly-HEMA; PLGA, poly(lactic-*co*-glycolic acid); qd, once daily; SCF-CO_2, supercritical fluid of carbon dioxide; SFA, semifluorinated alkane; TBC, to be confirmed; TFLL, tear film lipid layer; tid, three times daily; TJ, Taejoon; UD, unit-dose container; US, United States; VKC, vernal keratoconjunctivitis; WW, worldwide.

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1. Introduction

Cyclosporine A (CsA) is a cyclic undecapeptide of 1202.6 Da that was discovered in the 1970s by Sandoz [1]. Given its strong immunosuppressive potency, it was first developed to counter graft rejection following organ transplantation [2]. Its large molecular weight and hydrophobic nature (Log P = 1.4–3.0; solvent dependent) are responsible for its low aqueous solubility (6.6–106 μg/mL; temperature dependent) [3,4], necessitating the development of drug delivery strategies to maximize its bioavailability. CsA was initially marketed as an injectable ethanolic solution in the mid-1980s and then as an oily solution from the early 1990s, under the trade name Sandimmune® [5]. In the mid-1990s, the formulation was modified to improve its systemic bioavailability. Since then, CsA has been developed as a self-microemulsifying drug delivery system marketed under the trade name Neoral® as an oral solution and as soft gel capsules. In liver-transplanted patients, CsA area under the curve (AUC) and maximum serum concentration (C_{max}) were 50% and 90% higher, respectively, following Neoral® treatment compared with Sandimmune® treatment [6].

In ophthalmology, CsA use was investigated as early as 1981, initially for administration after corneal graft transplantation [7]. CsA also showed interesting activity in uveitis, corneal healing, vernal keratoconjunctivitis and other inflammatory diseases of the eye [4,8]. Initially, CsA was administered orally for the treatment of ophthalmic diseases. Although CsA was able to reach therapeutic levels in different ocular tissues [9], the non-ocular administration led to occurrence of systemic adverse events such as nephrotoxicity, hypertension, anemia, paresthesia and hyperesthesia [10]. Therefore, local (ocular) administration of CsA-loaded products became the preferred method of delivery for treatment of ophthalmic pathologies.

Given that the eye is essentially an extension of the central nervous system, ocular drug delivery is particularly challenging, especially for the local delivery of poorly water-soluble and/or large molecules. The eye possesses a multitude of protective mechanisms against external threats such as dust, xenobiotics and pathogens. These defense mechanisms (e.g. blinking, tearing and tear film turnover) are extremely efficient in clearing foreign elements from the ocular surface [11]. However, they also lead to very poor drug penetration for topically applied ocular drugs, typically below 5% [12]. Over the past two decades, several drug delivery strategies have been investigated that enhance the ocular bioavailability of CsA following topical instillation to achieve and improve disease management without the CsA-induced systemic adverse effects associated with oral administration (Fig. 1). These efforts finally led to the commercialization of several eye drops based on various drug delivery systems. The first ophthalmic product on the United States (US) market was Restasis®, approved in 2002 [13] and launched in 2003 by Allergan, whereas Santen (Novagali) became the first company to reach the European Union (EU) market with CsA eye drops (Ikervis®) in 2015 [14]. Both products utilize nanoemulsion drug delivery systems and are intended for the treatment of dry eye disease (DED).

In 2003, Lallemand et al. [4] published a comprehensive review on CsA ocular delivery. At that time, Restasis® was the only

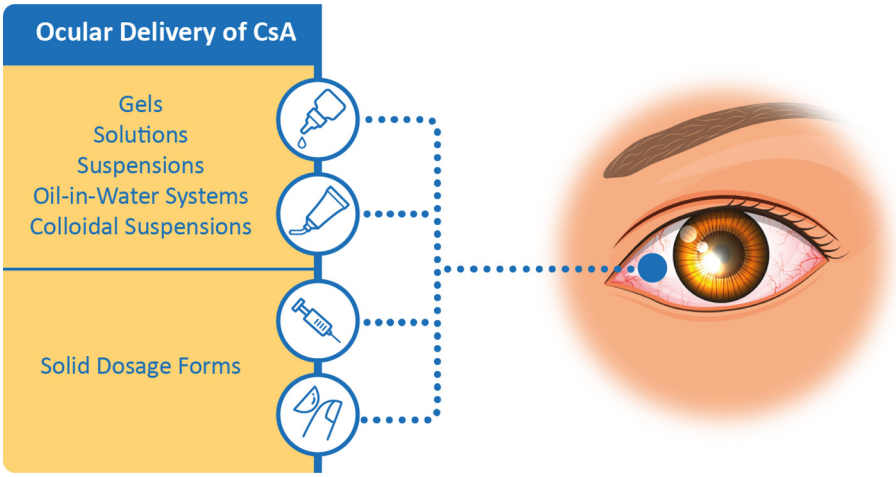

Fig. 1. Pharmaceutical forms for cyclosporine A ocular delivery.