**A Review of Topical Cyclosporine A Formulations—A Disease-Modifying Agent for Keratoconjunctivitis Sicca**

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Abstract: Keratoconjunctivitis sicca (KCS) is a multifactorial disease characterized by tear hyperosmolarity, inflammation, and ocular surface damage. Cyclosporine A (CsA) is used as an effective disease-modifying agent to improve the signs and symptoms of KCS by reducing inflammation, which interferes with tear production. This review provides an overview of efficacy, safety, and limitations of currently marketed topical CsA formulations—including CsA ophthalmic emulsion, cationic nanoemulsion, and aqueous nanomicelles—and highlights newer technologies for controlled ocular delivery of CsA and their clinical implications. Long available emulsion formulations of CsA are oil-based and have several limitations, including slow onset of efficacy and low intraocular penetration and bioavailability. Aqueous CsA nanomicelle carriers produce rapid improvement in objective signs of KCS such as corneal and conjunctival staining as early as 4 weeks and have acceptable safety profiles. CsA formulations using semifluorinated alkanes or polyaphrons are currently in clinical development, having recently completed Phase 2 studies. Other carriers for CsA currently in the preclinical phase include microemulsions, polymeric aqueous and lyophilized micelles, and hydrogels; these novel formulations have yet to undergo clinical trials. Formulations that improve tissue availability of CsA may be beneficial in clinical practice by providing faster onset of relief and improving patient adherence.

Keywords: cyclosporine A, keratoconjunctivitis sicca, emulsion, nanomicelles, OTX-101

**Introduction**

Keratoconjunctivitis sicca (KCS) is a complex ocular surface disorder and represents the most common reason for patients needing medical eye care.¹ ² KCS is a multifactorial condition, characterized by a loss of homeostasis of the tear film, inflammation, and ocular symptoms such as discomfort, visual disturbance, and foreign body sensation.¹ ² Prevalence varies globally with known risk factors such as advancing age and Asian race, and assessments of prevalence range approximately from 5% to 33% depending on disease definition used and examined populations.¹ Notably, prevalence of KCS is rising in the younger population potentially due to increased digital screen time.¹ Overall, KCS is associated with reduced work productivity and represents a significant cost burden.¹

**Pathophysiology of Keratoconjunctivitis Sicca**

The central mechanism of KCS is a vicious cycle where inflammation—stimulated by desiccating or hyperosmolar stress—leads to ocular surface damage.³ ⁴ Hyperosmolarity...
can be caused by a number of factors, including lacrimal gland destruction due to Sjögren syndrome; age-related degeneration of the lacrimal gland, conjunctiva, and meibomian glands; damage to sensory nerves during refractive surgery; reduced tear production due to systemic medications; and meibomian gland disease.\(^3\)

Irrespective of the etiology of KCS, chronic inflammation—especially T-cell mediated immune response—and tear hyperosmolarity are common perpetuating factors.\(^3\)-\(^5\) At the onset of the inflammatory response, levels of mitogen-activated protein kinases (MAPKs) and nuclear factor xB increase on the ocular surface.\(^6\),\(^7\) Activation of MAPK cascades triggers secretion of various inflammatory mediators, including interleukin-1β (IL-1β) and tumor necrosis factor α, which mediate activation of resident dendritic cells and T-cell recruitment to the ocular surface.\(^6\),\(^7\) Additional inflammatory mediators released from recruited T-cells along with tear hyperosmolarity further accentuate cellular damage and loss of epithelial and goblet cells leading to a vicious cycle of tear film instability and chronic inflammation.\(^3\),\(^6\) The cascade of events results in loss of ocular homeostasis that leads to the ocular symptoms and signs.\(^3\)

**Management of Keratoconjunctivitis Sicca**

The treatment guidelines for KCS recommend a step-wise approach with various treatment options based on disease severity.\(^8\) Initial steps are patient education, lid hygiene, modification of environmental factors, and ocular lubricants.\(^8\) Although ocular lubricants are a mainstay of KCS, they offer only palliative relief and have no disease-modifying potential.\(^8\) If these initial strategies are ineffective, next steps include nonpharmacological therapies such as tear conservation through punctal occlusion, pulsed light therapy, and moisture goggles, as well as pharmacological therapies such as macrolide antibiotics (which may have anti-inflammatory potential in dry eye associated with meibomian gland disease or blepharitis), corticosteroids, cyclosporine A (CsA), and lymphocyte function-associated antigen-1 antagonists.\(^8\) Surgical approaches such as surgical punctal occlusion, tarsorrhaphy, and salivary gland transplantation may also be considered.\(^8\) Management of meibomian gland dysfunction is an important aspect of overall KCS management and may include warm compresses and device-assisted physical heating therapies to remove the blockage from the meibomian glands, as well as ω-3 essential fatty acid supplementation.\(^8\) This review discusses the emergence of topical CsA as a disease-modifying treatment for KCS, provides an overview of the currently marketed topical CsA emulsion and its limitations, and highlights novel CsA formulations.

**Cyclosporine A and Its Mechanism of Action**

Cyclosporine A is a cyclic polypeptide and a widely used immunosuppressant, with inhibitory action of both cell-mediated and humoral immunity.\(^9\) Systemic CsA is indicated to prevent graft rejection and treat autoimmune conditions.\(^8\),\(^9\) Topical CsA was developed to increase tear production in patients with KCS and its disease-modifying and anti-inflammatory action in KCS is well established.\(^8\),\(^10\) Benefits of using CsA in KCS include improvement of subjective symptoms and objective ocular signs such as improved tear production, tear break-up time, and corneal and conjunctival staining scores.\(^11\) Other indications of topical CsA include meibomian gland dysfunction, viral keratitis, punctate and neurotrophic keratopathy, vernal keratoconjunctivitis, and prevention of graft rejection following ocular surgeries.\(^12\) Topical administration of CsA allows for lower systemic absorption, and thereby reduces the risk of systemic adverse events (AEs) such as nephrotoxicity, hypertension, anemia, and hyperesthesia.\(^13\)

Cyclosporine A is a calcineurin inhibitor and acts by blocking T cell infiltration, activation, and the subsequent release of inflammatory cytokines as illustrated in Figure 1.\(^12\),\(^14\),\(^15\) In addition, CsA has an antiapoptotic and protective action on human conjunctival epithelial cells, unlike corticosteroids.\(^8\),\(^14\) Topical CsA use is associated with fewer complications than steroids, long-term use of which is associated with cataract development, increased intraocular pressure, and opportunistic infections.\(^8\),\(^12\)

This review examines the challenges to topical CsA delivery for the treatment of KCS, and presents currently available formulations, both marketed and in development.

**Challenges to Topical Delivery of CsA**

Ocular targets for drug delivery in KCS include cornea, conjunctiva, tear film, and lacrimal and meibomian glands.\(^3\) Amount of drug available for intraocular tissue penetration largely depends on the physiochemical properties of the delivery vehicle.\(^16\) Ocular drug delivery and optimal tissue bioavailability have been a continued challenge due to the presence of dynamic and static ocular barriers.\(^17\) Static barriers include anatomic structures such as corneal epithelium, stroma, and blood-aqueous barrier. Various dynamic factors, such as tear turnover rate,
dilution with tear, blinking, and lacrimation, shorten the residence time of topically administered drugs. Drug permeability into the conjunctiva is further limited due to extensive vascular and lymphatic drainage. Loss of drug volume can also occur due to gravity and nasolacrimal drainage. Rapid tear film turnover time of 2 to 3 mins washes topically applied drug solutions in just 15 to 30 s after administration. These ocular barriers and defense mechanisms limit the bioavailability of topically administered drugs to less than 5%. High hydrophobicity and poor aqueous solubility of CsA make it extremely difficult to formulate as conventional eye drops. The release and subsequent intraocular penetration of CsA from a lipophilic carrier, such as an emulsion, are generally low. Although emulsions have the advantage of rapid ocular spreading upon application, lower bioavailability of lipophilic drugs from emulsions limits the amount of CsA available in an already challenging aqueous ocular environment. Clinical results show that the time to onset of efficacy with CsA emulsions is 6 months on average. Such long lead times to initial efficacy may interfere with patient adherence to treatment in KCS. Given the chronic nature of KCS, repeated and continued usage is important to attain therapeutic levels of CsA in ocular tissues.

Available Ophthalmic CsA Formulations
An ophthalmic emulsion of 0.05% CsA (Restasis®; Allergan, Inc., Irvine, CA, USA) was the first topical CsA approved by the US Food and Drug Administration (FDA) in 2003 to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS. This conventional CsA 0.05% emulsion is a preservative-free anionic oil-in-water formulation comprising castor oil with polysorbate 80 and carbomer copolymer acting as an emulsifying and stabilizing agent, respectively. In 2 multicenter and randomized Phase 3 trials, twice-daily administration of CsA 0.05% emulsion for 6 months significantly improved corneal staining and anesthetized Schirmer’s tear test values from baseline compared with vehicle (P ≤0.05). Conjunctival staining in temporal and nasal conjunctival zones improved significantly from baseline in both CsA 0.05% emulsion and vehicle groups; however, there was no significant difference between CsA 0.05% emulsion and vehicle treatment. About 80% of enrolled patients completed treatment with CsA 0.05% emulsion and 6.5% patients discontinued treatment due to AEs. In a Phase 4 trial, CsA 0.05% emulsion significantly (P <0.001) improved tear film breakup time from baseline in patients with KCS at month 6.
Table 1  Comparison of Emulsion and Aqueous Formulations of Cyclosporine A

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Composition</th>
<th>Advantages</th>
<th>Limitations</th>
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<tr>
<td>Approved Formulations</td>
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<tr>
<td>Emulsion</td>
<td>Anionic oil in water emulsion 0.05% (Restasis®)</td>
<td>• Improved some subjective symptoms, corneal staining, anesthetized Schirmer’s score and tear breakup time at 6 months compared with vehicle11,22</td>
<td>• Ocular bioavailability of CsA from emulsion is low16</td>
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<td></td>
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<td>• Can readily spread over the ocular surface on instillation13</td>
<td>• High incidence of ocular discomfort and patient dissatisfaction22</td>
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<td></td>
<td>Cationic emulsion 0.1%, 1 mg/mL (Ikervis®)</td>
<td>• Improved corneal staining, global symptom scores from baseline at 6 months25</td>
<td>• Ocular bioavailability of CsA from emulsion is low16</td>
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<td></td>
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<td>• Increased residence time and ocular tissue bioavailability of CsA compared with anionic emulsion13</td>
<td>• Proportion of patients achieving meaningful improvement in OSDI scores and corneal staining were not statistically significant compared with the vehicle group24,25</td>
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<td>OTX-101 0.09% (CEQUA™), aqueous nanomicellar solution27,29,30</td>
<td>• Improved corneal staining at 4 weeks and conjunctival staining at 6 weeks compared with vehicle, with improvement persisting throughout the study29,30</td>
<td>• Effect in severe forms of KCS is unknown29,30</td>
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<td>Formulations in Development</td>
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<td>Nonaqueous solution</td>
<td>Semiﬂuorinated alkanes (CyclASol®)35</td>
<td>• Eliminates the need for water, oils, surfactants, or preservatives</td>
<td>• Effect in patients with meibomian gland dysfunction unknown</td>
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<td></td>
<td></td>
<td>• In a phase 2 study, total corneal staining was significantly improved at 4 and 12 weeks vs CsA 0.05% emulsion</td>
<td>• Phase 3 studies not complete</td>
</tr>
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<td>Emulsion</td>
<td>Polyaphron dispersion (MC2-03)13,37</td>
<td>• Low concentration of surfactant designed to minimize adverse effects</td>
<td>• Further clinical studies are needed to fully determine clinical efficacy and safety</td>
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<td></td>
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<td>• Phase 3 studies not complete</td>
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<tr>
<td>Emulsion</td>
<td>Microemulsion (MiDROPS)20</td>
<td>• Delivers approximately 2–3 times higher CsA than CsA 0.05% emulsion in vivo</td>
<td>• Clinical studies not complete</td>
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<tr>
<td></td>
<td></td>
<td>• Thermodynamically stable, smaller size droplets, longer shelf life</td>
<td>• Uses high amounts of surfactant (can be associated with tolerability issues)</td>
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<td></td>
<td></td>
<td>• Can be manufactured easily</td>
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<td></td>
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<td>• Exists in single phase</td>
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<tr>
<td>Aqueous micelles</td>
<td>Mixed polymeric micelles with poloxamer and watersoluble derivative of vitamin E39</td>
<td>• May increase ocular penetration of CsA</td>
<td>• Clinical studies not complete</td>
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<td></td>
<td></td>
<td>• Temperature-dependent self-assembly of poloxamer</td>
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<td>• Potential antioxidant properties of this formulation can be beneficial</td>
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<tr>
<td>Lyophilized micelles</td>
<td>Lyophilized CsA-loaded polymeric nanocarrier38</td>
<td>• Higher stability and shelf life38</td>
<td>• Clinical studies not complete</td>
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<tr>
<td></td>
<td></td>
<td>• Higher retention time and controlled delivery of CsA in vivo38</td>
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Abbreviations: CsA, cyclosporine A; KCS, keratoconjunctivitis sicca; MiDROPS, Microemulsion Drug Ocular Penetration System; OSDI, Ocular Surface Disease Index.
43% of enrolled and treated patients experienced AEs and the most frequent ocular AEs were installation site reactions including burning and pain. A cationic nanoemulsion (Ikervis®; Santen SAS, Evry, France) (Table 1) was developed and approved by the European Medical Agency in 2015 for use in severe keratitis that has not improved despite the use of artificial tears. The cationic nanoemulsion was expected to have improved bioavailability and residence time compared with anionic emulsions, potentially due to the electrostatic interactions between the positively charged oil droplets and negatively charged mucins in the corneal epithelium. In a phase 3 study, treatment with cationic emulsion for 6 months significantly improved corneal staining compared with vehicle ($P = 0.037$). There was a higher proportion of patients with a combined result of $\geq 2$ grades improvement in corneal staining and $\geq 30\%$ improvement in the ocular surface disease index after 6 months of treatment with cationic emulsion (28.6%) vs vehicle (23.1%). However, these improvements were not significant compared with the vehicle. Moreover, the percentage of patients (29.2%) that experienced ocular discomfort following instillation was higher than in the vehicle group (8.9%). There was a discontinuation rate of about 10% with cationic emulsion treatment.

OTX-101 0.09% (CEQUA™; cyclosporine A 0.09%; Sun Pharmaceutical Industries, Inc., Princeton, NJ, USA) (Table 1) is a clear aqueous nanomicellar formulation approved by the FDA in 2018 to increase tear production in patients with KCS. Nanomicelles are amphiphilic molecules that self-assemble into typical supramolecular aggregates above the critical micelle concentration in the aqueous medium. Hydrophobic interactions of core-forming units drive the micelle formation with a water-insoluble or hydrophobic core and an outer water-soluble or hydrophilic shell. Nanomicellar technology allows the encapsulation of hydrophobic CsA within its hydrophilic core that, in turn, favors better dispersion and solubility of CsA into the precorneal tear film. When the temperature of the medium rises above dissociation temperature, nanomicelles disassemble into monomers and release the drug into surrounding aqueous tissue. Nanomicelles are thermodynamically stable even at higher dilutions and exhibit a reversible association with CsA (Figure 2). Their small size (10–80 nm; average of 22 nm) may allow nanomicelles to easily diffuse through scleral aqueous pores (20–80 nm in size).

Figure 2 Suspension of cyclosporine A in emulsion vs nanomicelles.
A preclinical study compared the ocular distribution and tolerability of OTX-101 and CsA 0.05% emulsion in New Zealand white rabbits. Following a single dosing, there was a higher CsA concentration with OTX-101 0.05% compared with CsA 0.05% emulsion in most ocular tissue samples, including the cornea (2.18-fold) and superior bulbar conjunctiva (1.76-fold) with minimal systemic exposure. There was a dose-related increase in CsA with repeat dosing of OTX-101 0.05% and this also resulted in higher concentrations of CsA in ocular tissues and aqueous humor than CsA 0.05% emulsion.

Phase 2b/3 and 3 clinical studies showed that twice-daily administration of OTX-101 0.09% was superior to vehicle in increasing tear production and improving ocular signs from baseline, including conjunctival and corneal staining in patients with KCS. Importantly, improvement in these objective signs was seen at and after 4 weeks of therapy. In a pooled analysis of phase 2b/3 and 3 trials, least square mean change from baseline for total corneal staining on day 28 was −0.9 and −0.5 for OTX-101 0.09% and vehicle, respectively (P = 0.0008). Similarly, there was a significant reduction in total conjunctival staining from baseline (P = 0.0316) on day 28 compared with the vehicle. It is important to note that the degree of conjunctival staining correlates with the severity of KCS. Moreover, clearing of conjunctival and corneal staining implies an improvement in ocular surface integrity and resolution of underlying pathology. On day 84, there was a significantly higher proportion of patients with an increase in Schirmer’s scores from baseline of ≥10 mm in the OTX-101 0.09% group vs vehicle (16.6% vs 9.0%, respectively, P <0.0001).

About 93% of enrolled patients on OTX-101 0.09% completed phase 2b/3 and 3 studies, and the withdrawal rate due to AEs was less than 4%. Most of the treatment-emergent AEs that occurred with OTX-101 0.09% during the 3-month treatment period were mild or moderate in nature and resolved without any treatment. Instillation site pain was the most frequent AE (21.8% in OTX-101 0.09% group and 4.0% in vehicle group) and there were no serious AEs considered related to treatment.

Formulations of Cyclosporine A Under Development

A CsA nonaqueous formulation (CyclASol, Novaliq, Heidelberg, Germany) uses semifluorinated alkanes as a water-free solvent. Liquid semifluorinated alkanes are amphiphilic compounds that are colorless, chemically and physiologically inert and laser-stable. Their low surface tension allows them to spread rapidly over the ocular surface, minimizing visual disturbance. Efficacy and safety of CsA nonaqueous solution were evaluated in an exploratory phase 2, randomized, vehicle-controlled study. Treatment with 0.1% cyclosporine nonaqueous solution significantly improved total corneal staining at 4 and 12 weeks—but not 16 weeks—vs CsA 0.05% emulsion (open-label active comparator; P ≤0.05). Improvements in total corneal staining vs vehicle (double-masked comparator) were not statistically significant. Adverse events were reported in 31.4% of patients; 1.2% of patients withdrew from the study due to AEs.

MC2-03 (MC2 Therapeutics, Hørsholm, Denmark) (Table 1) uses polyaphrons dispersed in carbomer hydrogel as carriers for CsA. Polyaphrons are lipid-based formulations characterized by a high concentration of the dispersed oil phase and a surfactant-to-oil ratio much lower than emulsions. Preliminary results from a phase 2 study in patients with dry eye and moderate to severe keratitis showed 6 months of treatment with MC2-03 0.06% led to a significantly higher percent of patients with a clinically relevant response (defined as 2-grade improvement in corneal staining on the modified Oxford scale) in both eyes vs ocular lubricant (43.1% vs 22.8%, P = 0.0289). The most common AEs included eye pain and eye irritation, and no serious AEs were reported to be related to study drugs.

Other novel carriers under development include Microemulsion Drug Ocular Penetration System (MiDROPS) of CsA (Table 1). Droplets in this system are <10 nm in diameter and are thermodynamically stable with longer shelf life. Unlike conventional emulsions, MiDROPS are in a single phase and can be easily manufactured at a lower cost. This microemulsion was developed to safely deliver higher amounts of CsA to ocular tissue than existing formulations. A preclinical study in Dutch-belted rabbits that compared MiDROPS and conventional CsA 0.05% emulsion showed MiDROPS delivered amounts of CsA into ocular tissue 2 to 3 times greater than CsA 0.05% emulsion. Both twice daily 0.05% and once-daily 0.1% CsA-MiDROPS in mice significantly reduced corneal permeability, T cell infiltration, and conjunctival goblet cell loss compared with CsA 0.05% emulsion.

Another novel formulation under development loads lyophilized CsA into polymeric micelles (Table 1).
similar to MiDROPS, instillation
2017
Cornea
which may interfere with
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and better patient compliance may result
Further clinical studies are needed to
On examination,
In addition, studies are
(Cyclosporine capsules and oral solution, USP) MODIFIED.
Ocul Surf
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Ocul Surf
(Cyclosporine ophthalmic emulsion) 0.05% for topical
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<0.05) higher CsA concentrations in cornea of rabbits
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Clinically, KCS is often described as chronic and
availability of effective and well-tolerated treatments.
impurity and permeability in addition to bene
ments may provide the advantage of enhanced drug solu-
tion containing poloxamer 407 and a water-soluble deri-
vant of vitamin E as excipients to enhance CsA
ability and permeability in addition to beneficial
antioxidant effect from vitamin E.
On examination,
these CsA loaded micelles demonstrated stability upon
dilution and increased CsA solubility and delivery to
ocular tissues.
Another approach to increase bioavailability and resi-
dence time of drug is by using contact lenses with hydro-
gel-loaded drug particles. A recent study has explored
monomeric gels loaded with high concentrations of CsA
for in situ formation of drug particles, to bypass tolerabil-
ity issues associated with excipients. However, scattering
of light by the drug particle can cause decreased transpar-
ency of lenses. Further clinical studies are needed to
evaluate the clinical efficacy and safety of these novel
carrier systems.

Implications for Clinical Practice
The growing prevalence of KCS stresses the need for
availability of effective and well-tolerated treatments.
Clinically, KCS is often described as chronic and
progressive, and better patient compliance may result
in improved long-term outcomes and potentially reduced
use of therapy. Currently available CsA emulsions have
several limitations including low bioavailability of CsA
and slow onset of action, which may interfere with
patient adherence. Novel formulations for opthalmic use,
including aqueous nanomicellar technology, may help
overcome these challenges by enhancing and maximizing
tissue availability of CsA for rapid efficacy, potentially
improving patient compliance and clinical outcomes in
KCS.

Abbreviations
AE, adverse event; CsA, cyclosporine A; CyP, cyclophilin;
FDA, US Food and Drug Administration; IkBα, nuclear factor
of k light polypeptide gene enhancer in β-cells inhibitor, alpha;
IL-2, interleukin 2; KCS, keratoconjunctivitis sicca; MAPK,
mitogen-activated protein kinase; MiDROPS, Microemulsion
Drug Ocular Penetration System; MPTP, mitochondrial per-
meability transition pore; NFAT, nuclear factor of activated
T cells; NFKB, nuclear factor of κB; P, phosphorylated; OSDI,
Ocular Surface Disease Index.

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