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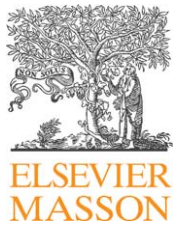

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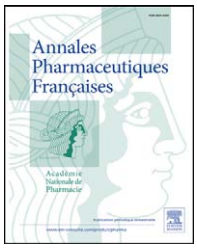

THEMATIC SESSION: MÉDICAMENTS EN OPHTALMOLOGIE

Colloidal systems for the delivery of cyclosporin A to the anterior segment of the eye☆

Systèmes colloïdaux pour la délivrance de la ciclosporine A dans le segment antérieur de l'œil

C. Di Tommaso[a], F. Behar-Cohen[b,c], R. Gurny[a], M. Möller[a,*]

[a] *School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, 30, Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland*
[b] *Inserm, UMRS 872, centre de recherches des Cordeliers, 15, rue de l'École de médecine, 75006 Paris, France*
[c] *UMRS872, université Paris Descartes-Paris 5, 75005 Paris, France*

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Summary Due to the eye's specific anatomical and physiological conformation, the treatment of eye diseases is a real challenge for pharmaceutical therapy. The presence of efficient protective barriers (i.e., the conjunctival and corneal membranes) and protective mechanisms (i.e., blinking and nasolachrymal drainage) makes this organ particularly impervious to local drug therapy. To overcome these issues, numerous strategies have been envisioned using pharmaceutical technology. Many formulations currently on the market or still under development are emulsions or colloidal systems intended to enhance precorneal residence time and corneal penetration, causing a consequent increase in drug bioavailability after instillation. After a review of some recent developments in the field of cyclosporin A formulations for the eye, a novel micellar formulation of cyclosporine A based on a diblock methoxy-poly(ethylene glycol)-hexysubstituted poly(lactides) (MPEG-hexPLA) is described.

MOTS CLÉS
Systèmes colloïdaux ;
Biodisponibilité ;
Ophtalmologie

Résumé La particulière conformation anatomique et physiologique de l'œil fait de cet organe un réel défi pour la technologie pharmaceutique. La présence de barrières protectrices très efficaces (les membranes conjonctivale et cornéenne) et de mécanismes protecteurs (clignement, drainage nasolacrymal) rend cet organe particulièrement inaccessible pour la

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* Corresponding author.
E-mail address: Michael.Moeller@unige.ch (M. Möller).

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Délivrance des médicaments ;
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thérapie locale. Pour faire face à ces problèmes, plusieurs stratégies ont été développées. Certaines formulations sur le marché ou encore en développement clinique sont composées d'émulsions ou de systèmes colloïdaux qui ont le but d'améliorer le temps de résidence précornéenne et la pénétration de la cornée. De cette façon, la biodisponibilité du principe actif peut être augmentée après instillation. Après avoir fourni une vue d'ensemble des développements les plus récents dans la formulation de la ciclosporine A, une nouvelle formulation micellaire de ciclosporine A pour les applications ophtalmiques obtenue par l'utilisation du copolymère méthoxy-poly(éthylène glycol)-hexylsubstituted poly(lactides) sera présentée.

Introduction

Cyclosporin A (CsA) is a potent immunosuppressant widely used in ophthalmic applications for the prevention of corneal graft rejection or the treatment of diseases involving cytokines, such as dry eye syndrome and autoimmune uveitis [1,2]. Due to its hydrophobicity and poor solubility, its pharmaceutical formulation is a challenge, especially for topical ocular applications. Due to its particular anatomy and physiology, the eye is extremely impervious to foreign substances and, consequently, to drugs as well. Classically, the eye is divided into two different segments: the anterior and the posterior segment [3]. In this paper, some of the most recent CsA colloidal formulations developed during the last decade for anterior segment treatment will be reviewed, and a novel CsA formulation based on the methoxy-poly(ethylene glycol)-hexylsubstituted poly(lactides) (MPEG-hexPLA) will be presented as a promising novel carrier for ophthalmic therapy.

Topical ocular administration

In ophthalmic therapy, to be effective for most indications, the drug has to overcome the anatomical and physiological barriers that protect the eye from foreign substances that could be harmful or toxic. The necessity of overcoming these natural ocular barriers for disease treatments is a real challenge for the development of pharmaceutical formulations. A schematic illustration of the barriers that the drug has to overcome after topical instillation is presented in Fig. 1.

Classically, the eye is divided into two different segments: the anterior and the posterior segment. The anterior segment consists of the cornea, the conjunctiva, the sclera and the anterior uvea [3]. These structures surround the anterior chamber, which is filled with aqueous humor. Diseases affecting this part of the eye are normally treated with eye drops or special inserts. The frequent instillation allows the achievement of therapeutic drug concentrations in the cornea, in the aqueous humor and in the iris/ciliar body [4], although most of the applied drug is rapidly drained off, limiting the drug absorption to less than 5% [5].

However, topical drug administration has many drawbacks [4,6,7]:

- limited drug absorption due to the presence of conjunctival and corneal barriers;
- the presence of lachrymal fluid, which constantly washes the surface of the eye and protects it from the external environment;
- short contact time between drug and ocular tissues due to the protective mechanisms of the eye, such as nasolachrymal drainage, tear turnover, and protein binding;
- necessity of formulations of an amphiphilic nature to increase corneal penetration;
- necessity of frequent instillations of the product to reach therapeutic levels;
- poor compliance and peak-valley effect of drug concentration;
- the presence of preservative agents in many commercial eye drops that have a certain surface toxicity.

Cyclosporin A in ophthalmic applications

The typical pathologies of the anterior segment of the eye are dry eye syndrome, glaucoma, inflammations, infections, or corneal diseases. For some of these diseases, treatment with CsA is suggested.

The cyclic undecapeptide CsA is a potent immunosuppressant that interacts with cyclophillin A by forming a complex that inhibits a phosphatase calcineurin. In response to particular stimuli, related to the intracellular concentration of calcium, calcineurin dephosphorylates the nuclear factor for T-cell activation (NF-AT). In the nucleus, the NF-AT promotes the transcription of interleukin 2, which leads to T-cell activation. The inactivation of calcineurin by CsA avoids the dephosphorylation of NF-AT, preventing its transportation into the nucleus and, consequently, blocking the gene expression of IL-2 and other genes necessary for T-cell activation [8,9]. The immune suppression is reversible when the treatment is stopped. The calcineurin/NF-AT is also present in other cell types, and the systemic administration of CsA thus has several serious side effects, especially high blood pressure and kidney problems.

The use of CsA in dry eye syndrome treatment began when there was a better understanding of the disease etiology. In fact, classical dry eye disease is considered to be provoked by a constant drying of the sclera and conjunctiva and by a decrease in tear production associated with modifications of the tear film. Studies suggested that an inflammatory response mediated by T-cells contributed to the disease pathology, as did lymphocytic infiltration of the lachrymal gland. Due to the inflammatory-autoimmune nature of dry eye, the administration of CsA suppresses the