Besoins et innovations galéniques en ophtalmologie

Frédéric Lallemand

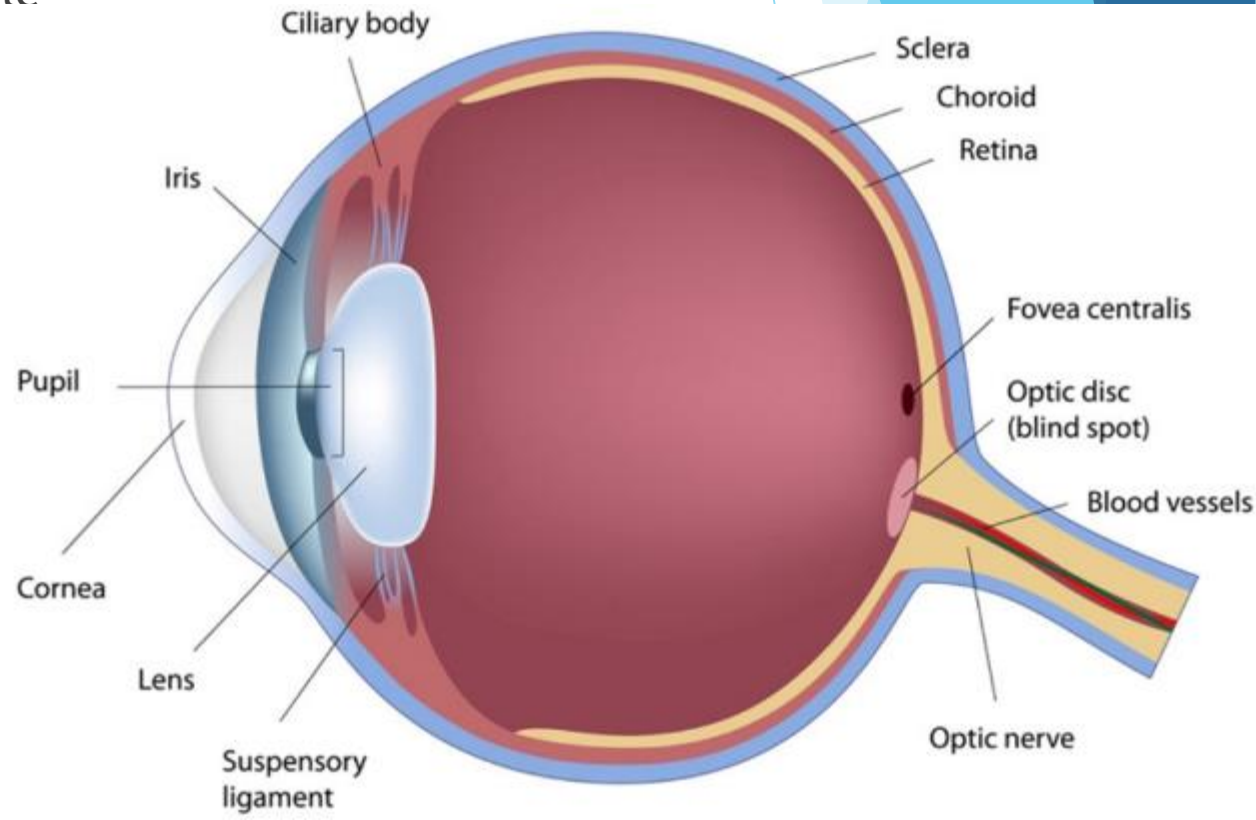
PharmD, PhD

lallemandconseil@gmail.com

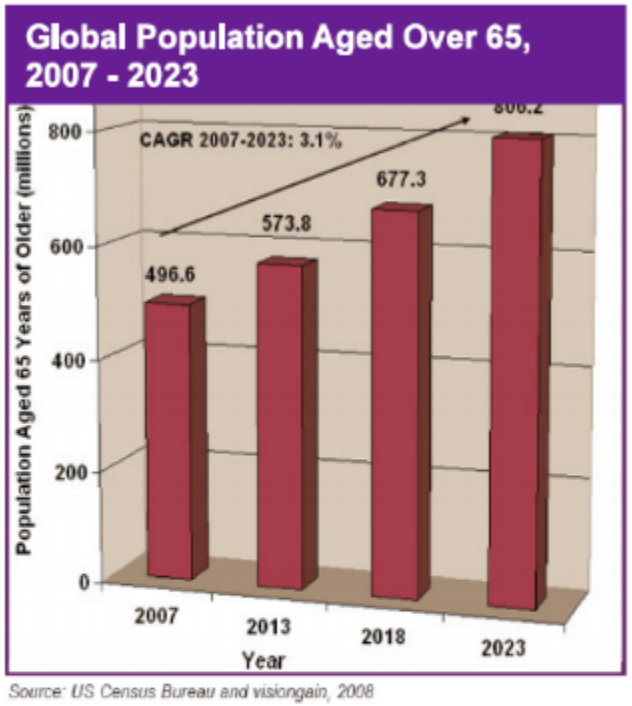
+33 6 60 72 64 03

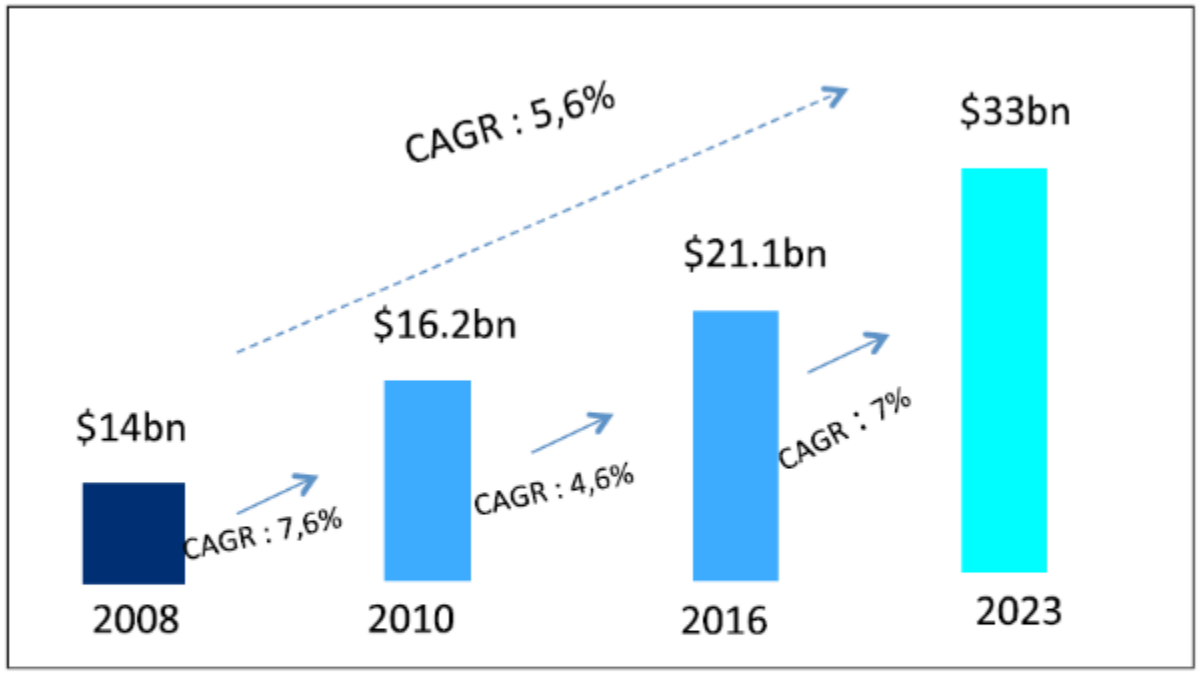
L’œil

- Prolongement du système nerveux central
- Divisé en segment antérieur et postérieur
- Nombreux mécanismes de protection
- Moins de 5 % de la dose administrée atteint sa cible
- Grand nombre de pathologies
- Nombres croissants de patients
  - Vieillissement
  - Diagnostic



Un marché en très forte croissance





taux de croissance annuel composé

- **The global ophthalmic market accounts for $16.2 billion in 2010 and is expected to reach $33 billion in 2023 with an annual growth rate of 5.6%.**
- **Pharmaceutical companies are increasingly focusing on niche drug treatments.**

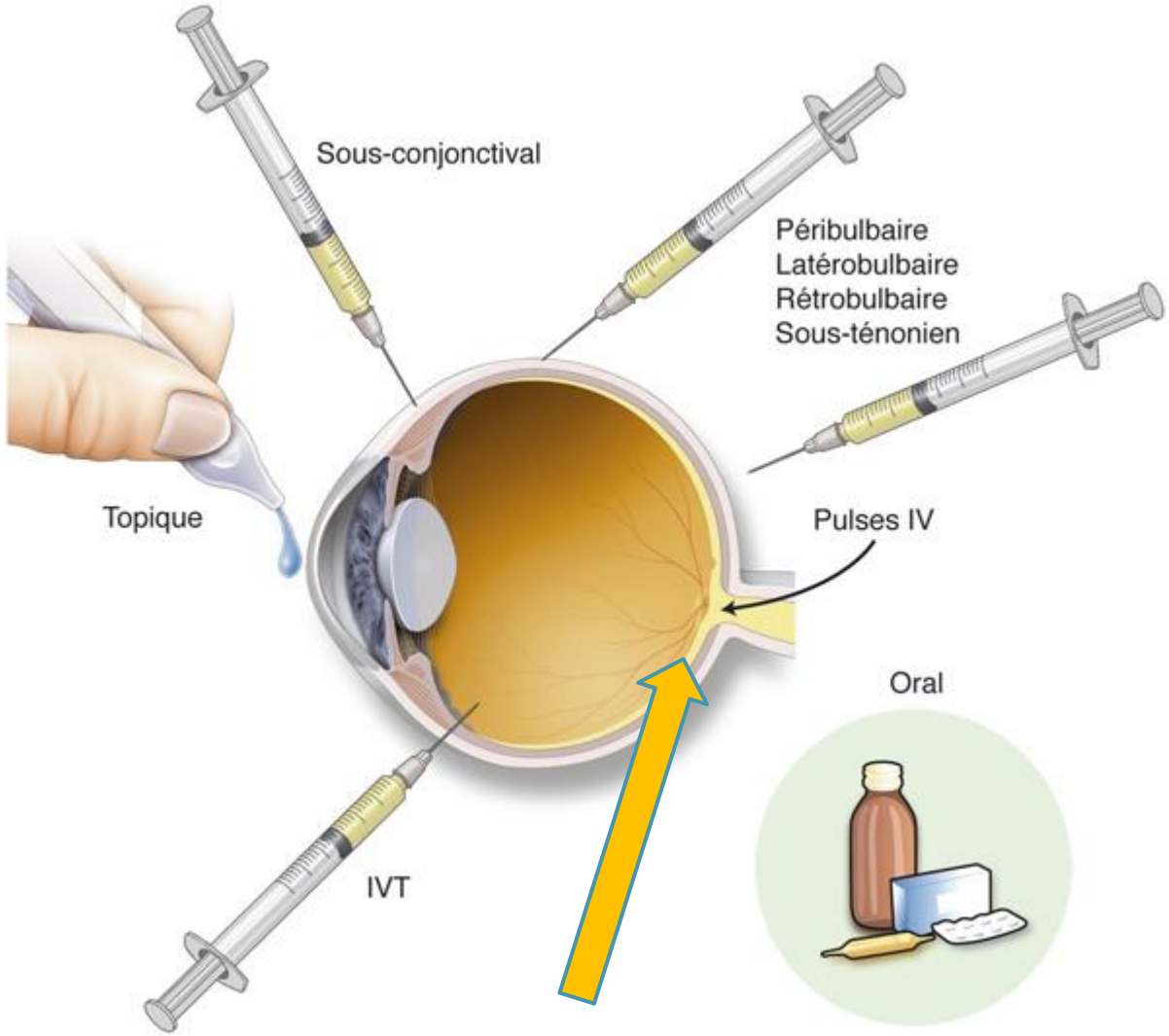
Les pathologies

- Segment antérieur
  - Œil sec
  - Glaucome
  - Allergies
  - Inflammation (surface et uvéites)
  - Infections bactériennes

  et fongiques
  - Maladies rares

- Segment postérieur
  - DMLA sèche et humide
  - Œdème maculaire diabétique
  - Occlusion veineuse rétinienne
  - Inflammation (uvéite postérieure)
  - Maladies rares : dystrophies rétiniennes etc.

Les voies d'administration



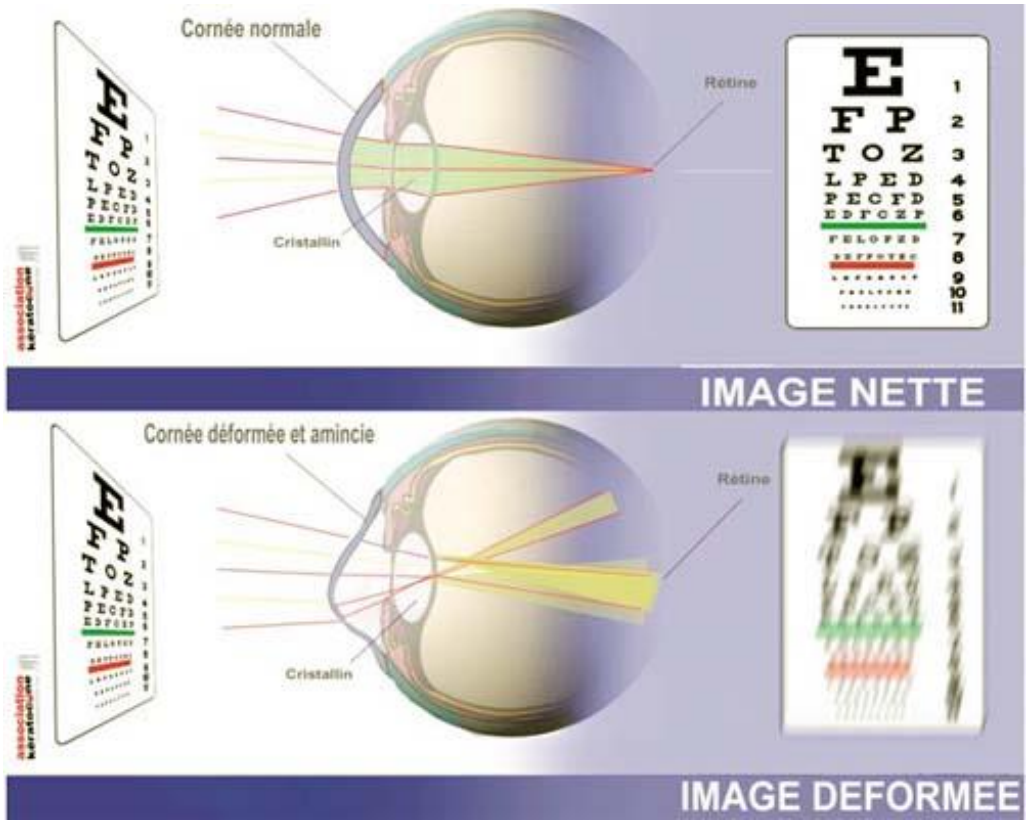
Sous rétinien

Besoins : exemples

- Segment antérieur
  - Formes à libération prolongée : glaucome, antibiotique et antifongique
  - Diminution des effets secondaires liés aux molécules ou aux conservateurs
  - Œil sec : traitement curatif des glandes lacrymales
  - Kits de diagnostic biomarqueurs des larmes
  - Myopie
  - Modèles in vitro / in vivo/ modèles mathématiques
- Segment postérieur
  - Formes retards anticorps monoclonaux antiangiogéniques
  - Administration topique pour l'arrière de l'oeil
  - Thérapie génique vecteur non-viraux, injection intravitréenne
  - Traitement de l'uvéite postérieure
  - Traitement de la DMLA sèche

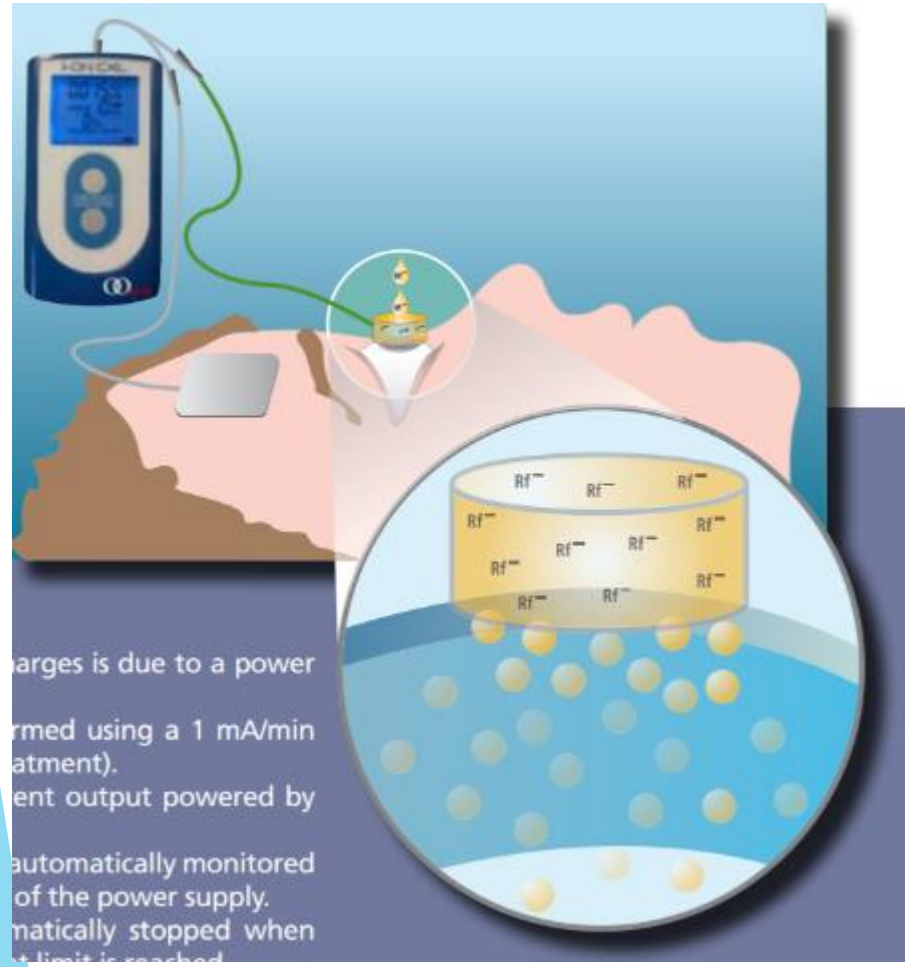
Quelques innovations récentes

le kératocône



- Kératocône correspond à une deformation de la cornée
- Cause probablement génétique
- Touche homme et femme à partir de 10 ans
- Correction par port de lunettes ou lentilles
- Réticulation du collagène par riboflavin
- Greffe de cornée

Iontophorèse pour le kératocône



- Administration de riboflavin dans le stroma par iontophorèse
- Irradation par la lumière
- Réticulation du collagène et rétractation de la cornée
- Développement d'un générateur et d'une formulation adaptée
- Marquage CE en 2013 par la société SOOFT Italia

Novasorb® - la nano-émulsion cationique

- Caractéristiques physico-chimiques
  - Emulsion huile-dans-eau
  - Taille de la nanogouttelette = 150 nm
  - Potentiel zéta = + 40 mV (positif)
  - Viscosité: ν = 1.1 m m^2/s (équivalent à l'eau)
  - Hypotonique à isotonique : 180-300 mOsm
  - Tension de surface : σ=41 mN/m (proche des larmes)

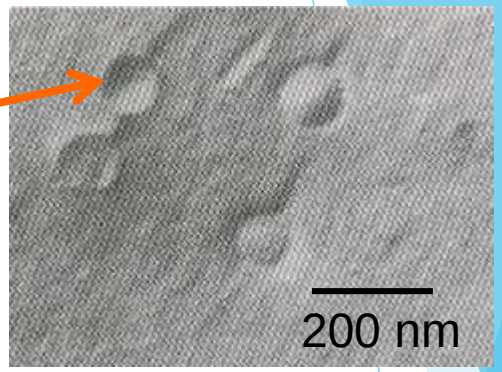
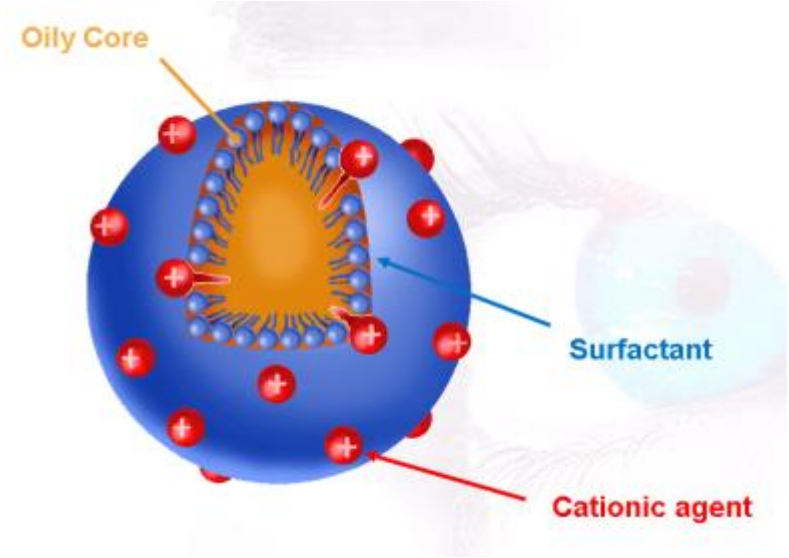
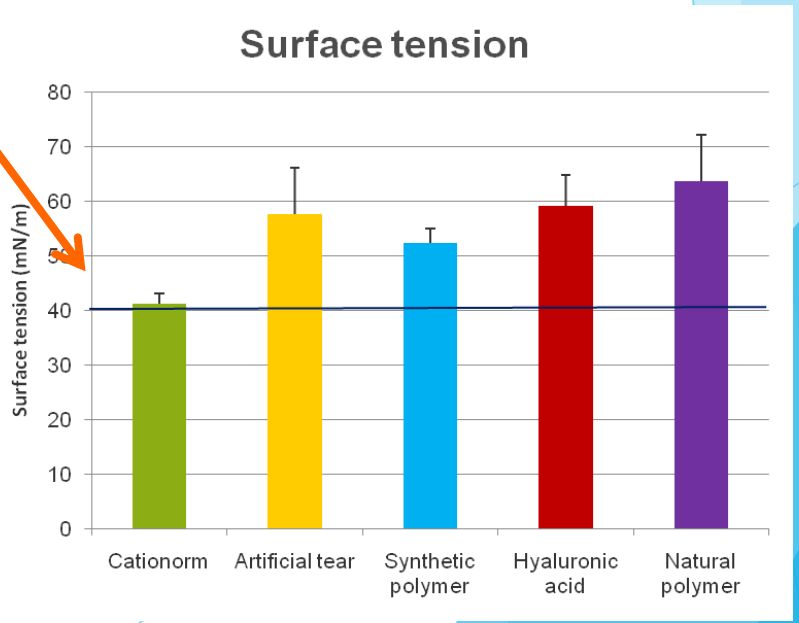
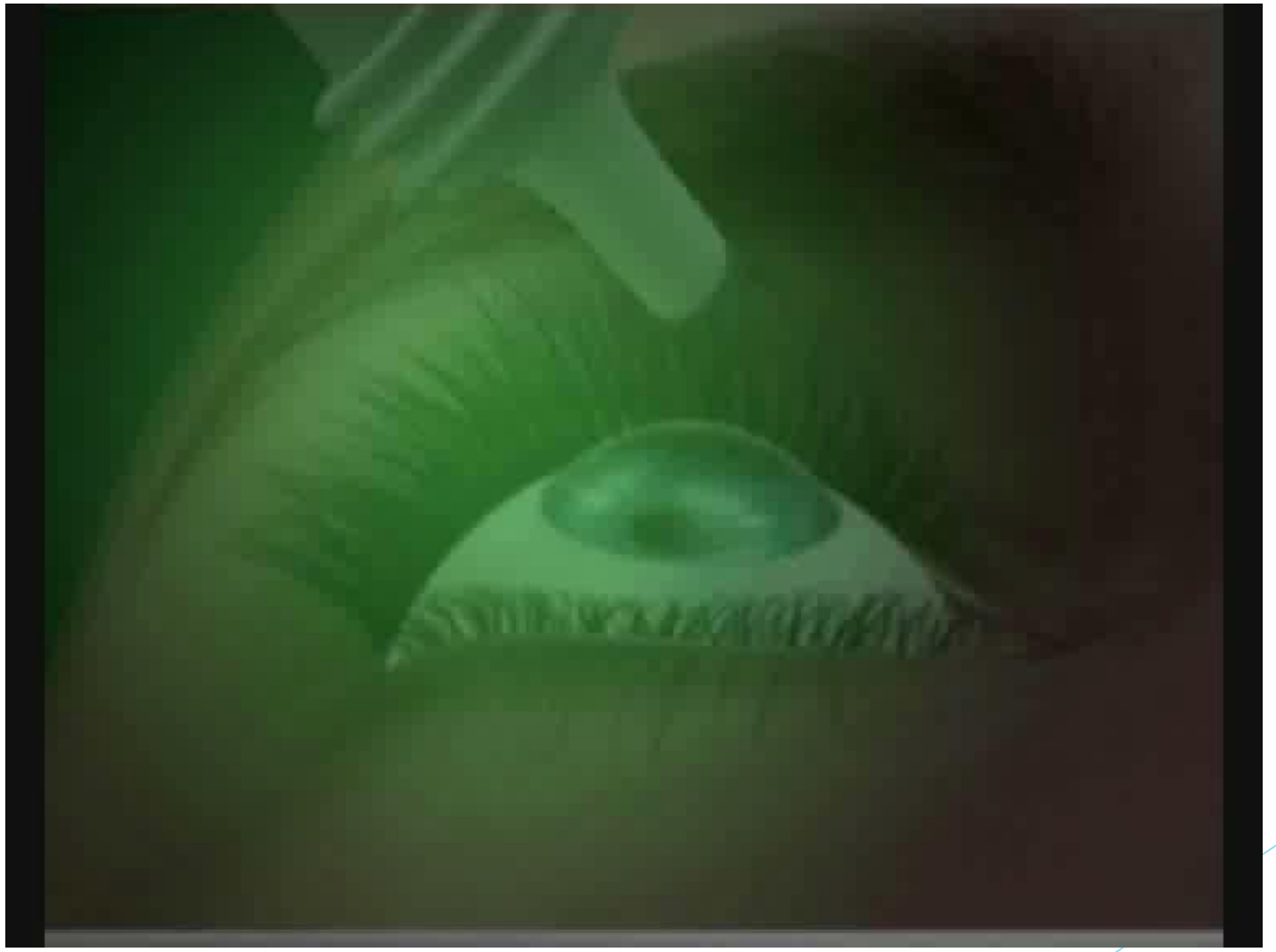


Photo microscope électronique





Novasorb® - instillation à la surface de l’œil



Emulsion cationique

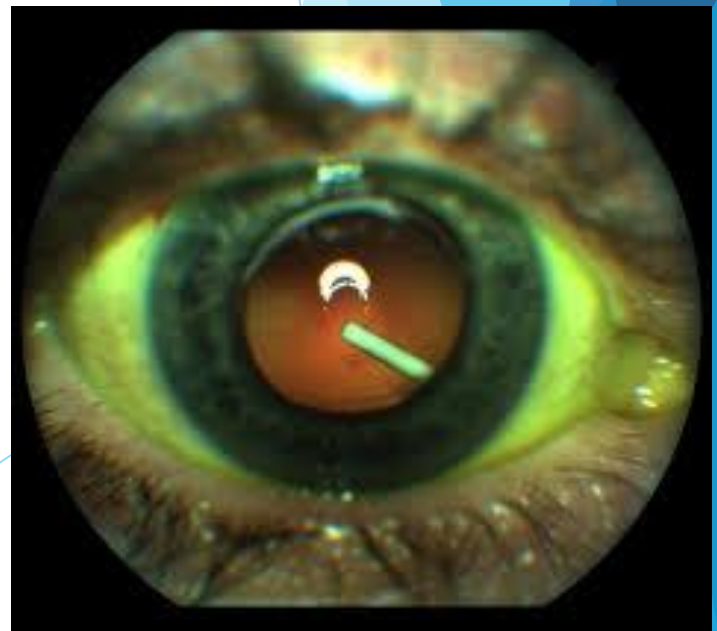
Occlusion de la veine centrale de la rétine

- Accumulation de liquide dans la macula entraînant son épaississement
- Liée aux problèmes de circulation induits par le diabète
- Troubles de la vision puis lésions irréversibles sur la rétine

- Traitements :
  - Collyres ou injections intravitréennes et périoculaires de corticoides ou d'antiangiogénqiues
  - Photocoagulation au laser

Implant ophtalmique Ozurdex

- OZURDEX 700 microgrammes, implant PLGA intravitréen avec applicateur
- AMM centralisée en Europe en 2010
- Libération jusqu'à 6 mois
- Problème du PLGA proinflammatoire, problème résidu de polymère



Solution autoconservée : SofZia™

- Solution sans conservateur mais passant les tests d'efficacité antimicrobienne
- Mélange en faible quantité de

borate, sorbitol, propylene glycol,

et zinc

Meilleure tolérance

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Ophthalmology Management GLAUCOMA SofZia preservative system meets United States Pharmacopoeia standards

APRIL 2007

GLAUCOMA

SofZia preservative system meets United States Pharmacopoeia standards

by Robert J. Noecker, M.D. EyeWorld Guest Editorial

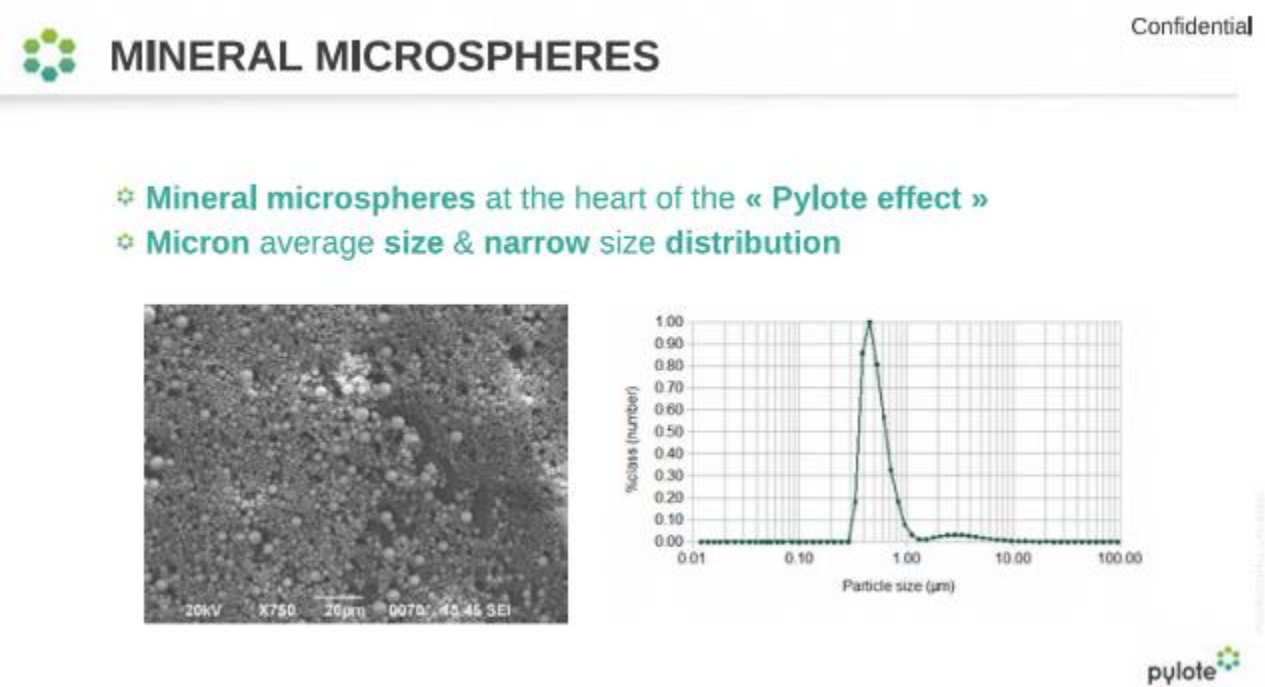
Introduction

Glaucoma medications supplied in multi-dose containers are subject to repeated use by the patient and carry a risk of becoming contaminated by a variety of microorganisms.1,2 Multi-dose ophthalmic preparations are required to utilize some form of antimicrobial system.3,4 Benzalkonium chloride (BAK), the most widely employed preservative in topical ophthalmic preparations, is an effective preservative, yet its use over time can result in damage to the ocular surface.5,6 In response to the negative effects associated with chronic BAK exposure, alternative preservatives are needed in glaucoma medications. The SofZia preservative system in Travatan Z (Alcon Labora-tories, Fort Worth, Texas) is one new approach. This article will evaluate the SofZia preservative system versus United States Pharmacopeia (USP) standards for antimicrobial effectiveness when used in

Figure 1

Flacon sans conservateur

- Intrégration de microsphères de oxyde de zinc dans la paroi des flacons ophtalmiques
- Conservation 15 jours après ouverture sans conservateurs dans le liquide
- Brevet « Utilisation de matériaux incorporant des microparticules pour éviter la prolifération de contaminants » WO 2015197992 A1
- Société Pylote à Toulouse : PYCLEAR PROTECTION



Modèles

Drug Deliv. and Transl. Res. (2016) 6:660–675
DOI 10.1007/s13346-016-0330-y

REVIEW ARTICLE

Human corneal cell culture models for drug toxicity studies

Seppo Rönkkö[1] · Kati-Sisko Vellonen[1] · Kristiina Järvinen[1] · Elisa Toropainen[1] · Arto Urtti[1,2]

Published online: 9 September 2016

Abstract In vivo toxicity and absorption studies of topical ocular drugs are problematic, because these studies involve invasive tissue sampling and toxic effects in animal models. Therefore, different human corneal models ranging from simple monolayer cultures to three-dimensional models have been developed for toxicological prediction with in vitro models. Each system has its own set of advantages and disadvantages. Use of non-corneal cells, inadequate characterization of gene-expression profiles, and accumulation of genomic aberrations in human corneal models are typical drawbacks that decrease their reliability and predictive power. In the future, further improvements are needed for verifying comparable expression profiles and cellular properties of human corneal models with their in vivo counterparts. A rapidly expanding stem cell technology combined with tissue engineering may give future opportunities to develop new tools in drug toxicity studies. One approach may be the production of artificial miniature corneas. In addition, there is also a need to

Introduction

Cornea is an effective absorption barrier for topically applied ocular drugs, but at the same time it is the most significant route for drug permeation to the anterior chamber [1]. Therefore, isolated animal corneas and cultured corneal epithelia have been used to study drug permeability in the cornea [2–4]. In vivo biodistribution studies require sacrification of at least 20 animals (e.g., 5 time points, 4 eyes/point, 2 drugs or formulations compared), typically rabbits, because non-invasive sampling is not possible and many animals must be killed at each time point in order to generate the concentration curves [5–7]. The role of corneal cell models in permeability testing has been reviewed previously [8, 9].

As a drug permeation route, the corneal cells are exposed to the potential toxic effects of the applied drugs. Traditionally, the corneal and other ocular toxicity has been studied in animal experiments, but such experiments (e.g., Draize test) have

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Nanomedicine (Lond). 2013 Dec;8(12):1955-68. doi: 10.2217/nnm.12.202. Epub 2013 Feb 26.

Measuring the intravitreal mobility of nanomedicines with single-particle tracking microscopy.

Martens TF[1], Vercauteren D, Forier K, Deschout H, Remaut K, Paesen R, Ameloot M, Engbersen JF, Demeester J, De Smedt SC, Braeckmans K.

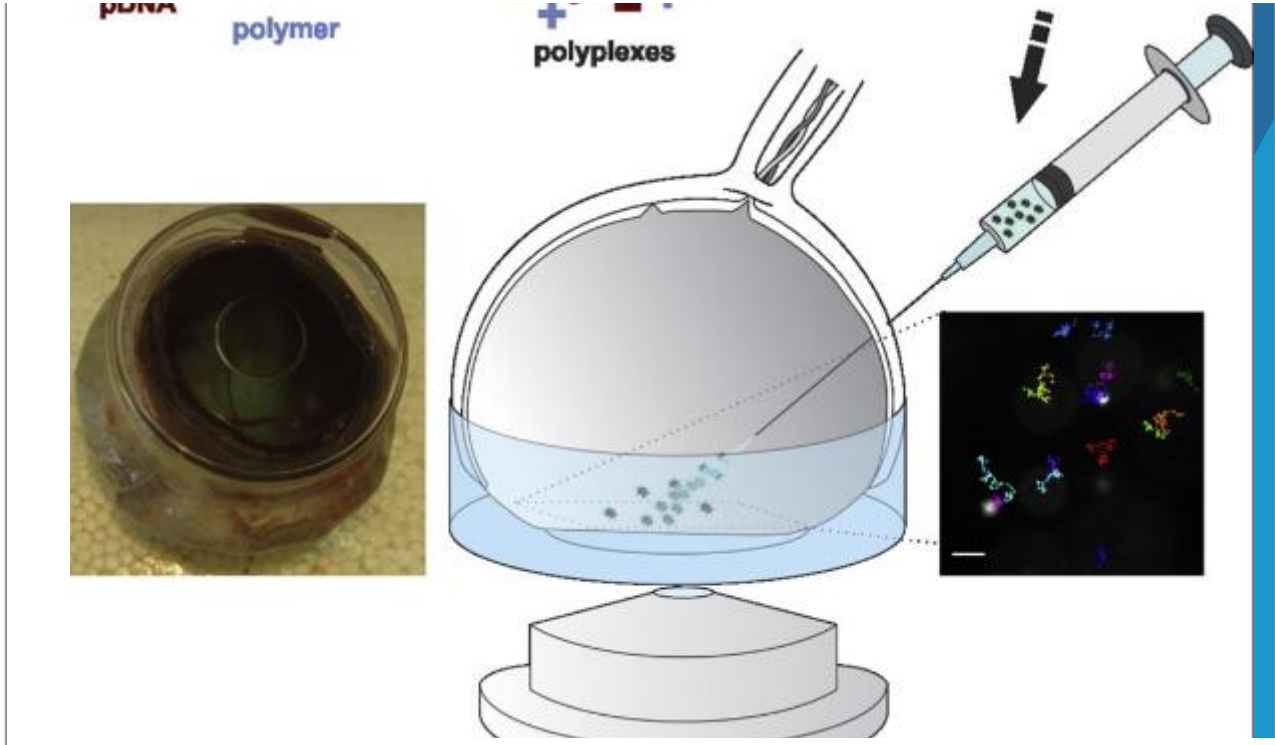
⊕ Author Information

Abstract

AIM: To develop a robust assay to evaluate and compare the intravitreal mobility of nanoparticles in the intact vitreous body.

MATERIALS & METHODS: Excised bovine eyes were prepared to preserve the fragile structure of the vitreous humor, while permitting high resolution fluorescence microscopy and single-particle tracking analysis of intravitreally injected nanoparticles. This assay was validated by analyzing polystyrene beads and further employed to evaluate gene nanomedicines composed of poly(amido amine)s and plasmid DNA.

RESULTS: The assay was able to distinguish immobilized cationic nanoparticles from mobile PEGylated nanoparticles. PEGylation of the polyplexes resulted in a drastic improvement of their mobility.



fluorescence single particle tracking (fSPT) microscopy

Freins à l'innovation académique

- Secteur peu connu
- Peu de discussions entre galénistes et ophtalmologues/ hôpitaux
- Certains produits sont couteux notamment les anticorps monoclonaux, les peptides, ADN etc.
- Souvent les académiques ne brevètent pas ou pas accompagnés par les organismes de transfert
- Manque de connaissance des prérequis réglementaires de l'industrie

Mais…

- Marché en croissance
- Il reste des marchés de niche à prendre
- La plupart des besoins reposent sur
  - le drug delivery
  - L'amélioration de la biodisponibilité
  - La réduction de la fréquence d'administration

⇒ Du travail pour les galénistes