Polymeric nanomicelles for cyclosporine ocular delivery

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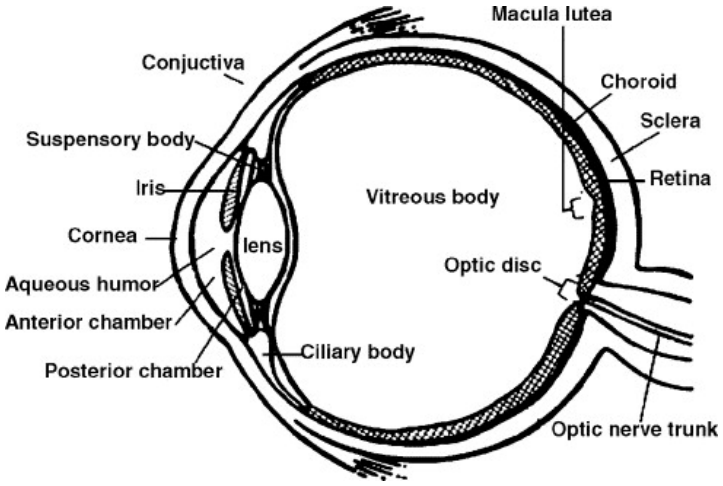
Conference & Exhibition

Nanocarriers and ocular drug delivery

- **Increase residence time on ocular tissues**
  - **ocular surface**
  - **subconjunctival space**
  - **suprachoroidal space**
  - **vitreous humor**



- **Control drug delivery → sustained release**

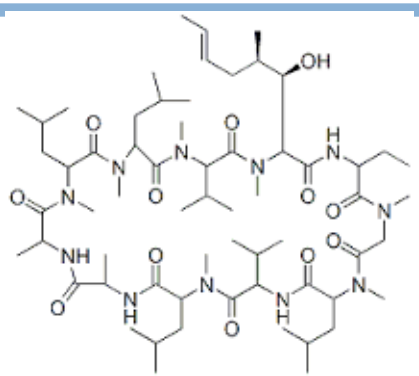
- **Enhance cell uptake (conjunctival and corneal epithelia, RPE)**

- **Low viscosity**

Cyclosporine and eye diseases

Metabolite of fungi

- **Immunosuppressant/antiinflammatory activity**

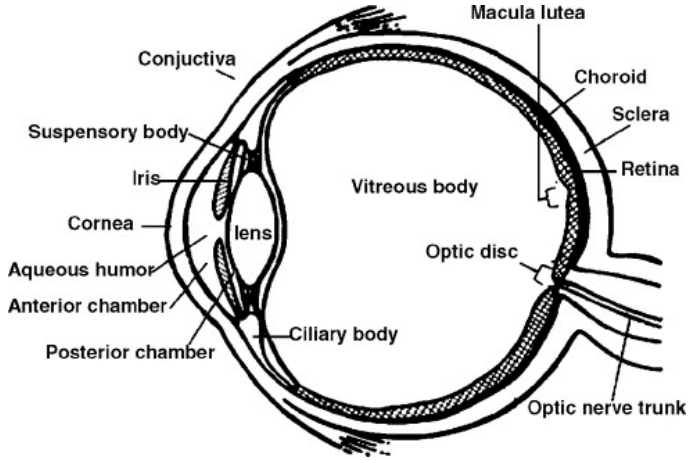


MW: 1201.61 g/mol
LogP: 3
Water sol. 0.03 mg/ml

Topical delivery:

- **<u>Keratoconjunctivitis sicca (Dry eye disease)</u>**

- **Atopic keratoconjunctivitis**
- **Vernal keratoconjunctivitis**
- **Allergic conjunctivitis**
- **Posterior blepharitis**
- **Acute corneal graft rejection**
- **Ocular rosacea**
- **Chronic follicular conjunctivitis (CFC)**



Off label

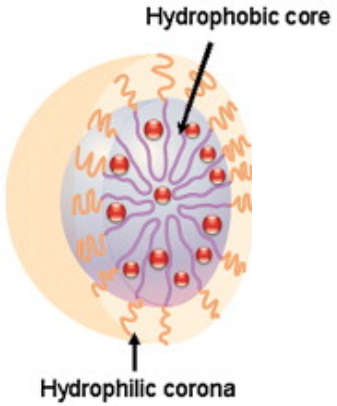
Systemic delivery:

Noninfectuous uveitis

Aim of the work

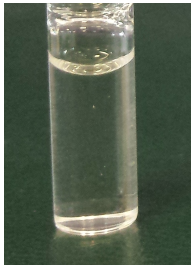
- Preparation and characterization of cyclosporine-loaded micelles for ocular delvery
  - Drug solubilization without oily phase
  - Enhance tissue permeation/retention

- Polymeric micelles: self-assembling colloidal systems
  - non-ionic surfactants
  - ease of preparation



Micelles preparation

- Surfactants dissolution in water
- Cyclosporin addition (EtOH solution)
- Stirring overnight at 25°C (EtOH evaporation)
- Filtration (0.2 µm)

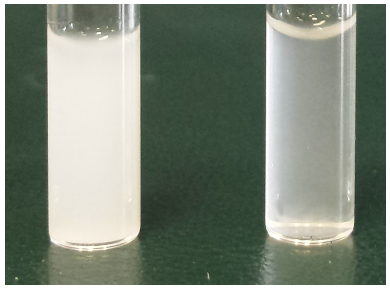


- Cyclosporin solubility
  - Excess amount of drug
  - Centrifugation step

Saturated formulation are opalescent

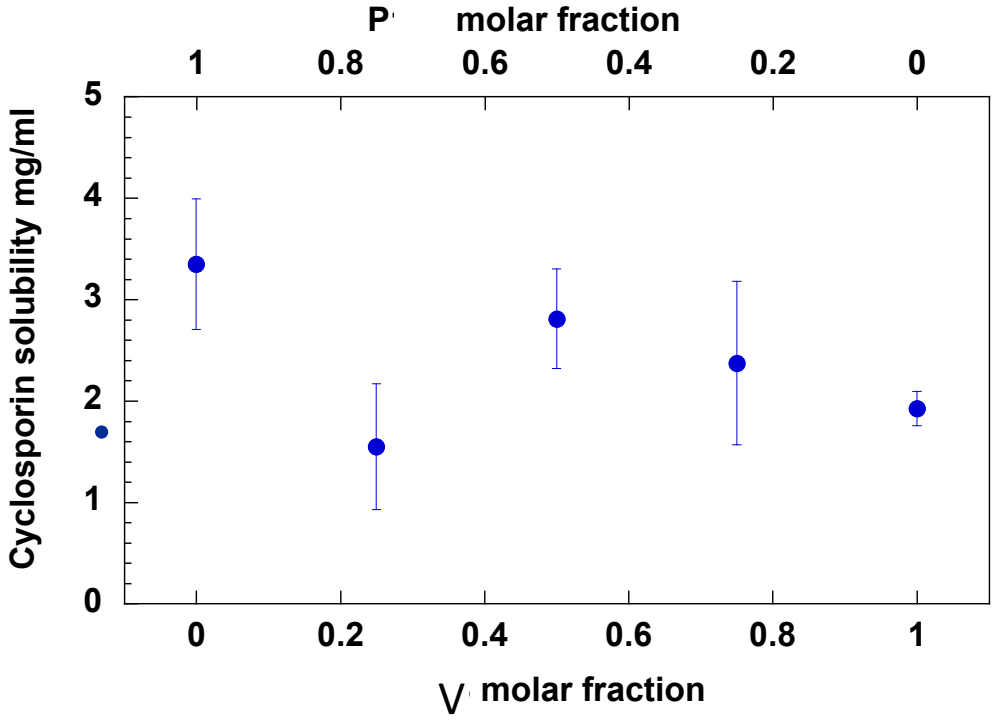
Pre-centrifugation

Post-centrifugation and filtration



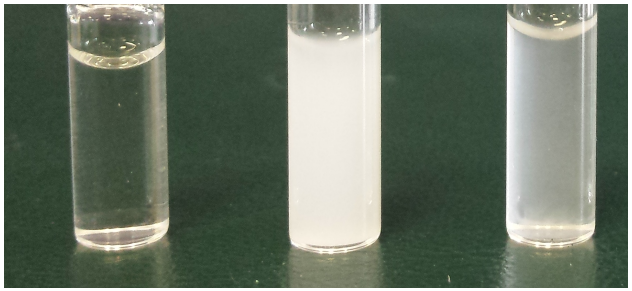
Cyclosporin solubility - P : V molar ratio

- 5mM surfactants concentration
- Determination of cyclosporin solubility
  - Dilution with CH3CN
  - HPLC analysis
- Water solubility: 0.03 mg/ml

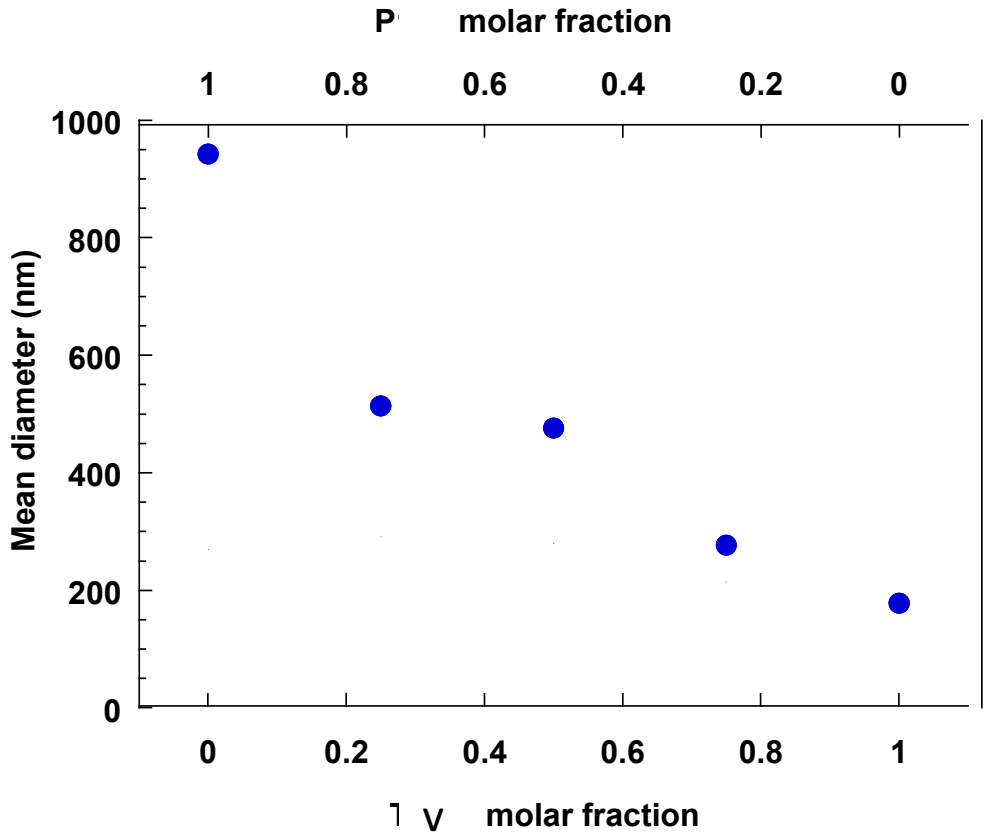


Opalescent formulations

Nanosuspension



DLS analysis - P : v molar ratio



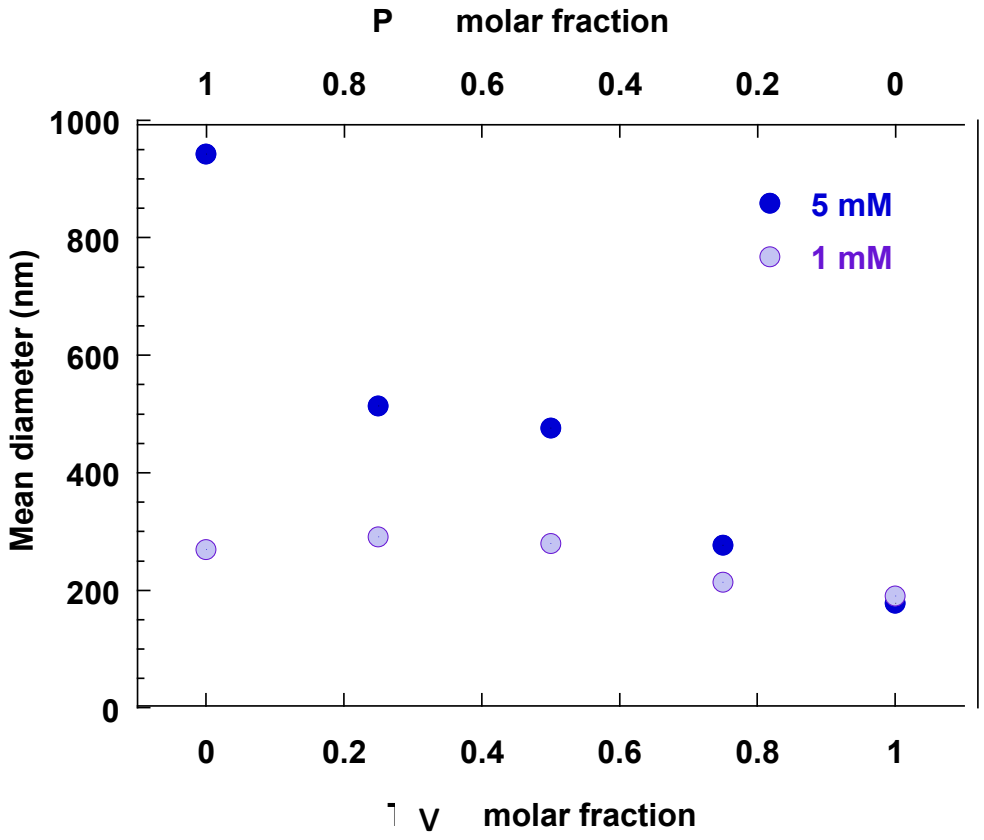
5 mM

All the formulations have been filtered (0.2 µm)

DLS analysis

v	P	5 mM PI
0	1	0.158
0.25	0.75	0.073
0.5	0.5	0.094
0.75	0.25	0.166
1	0	0.183

DLS analysis - P : v molar ratio



5 mM and 1 mM
All the formulations have been filtered (0.2 µm)

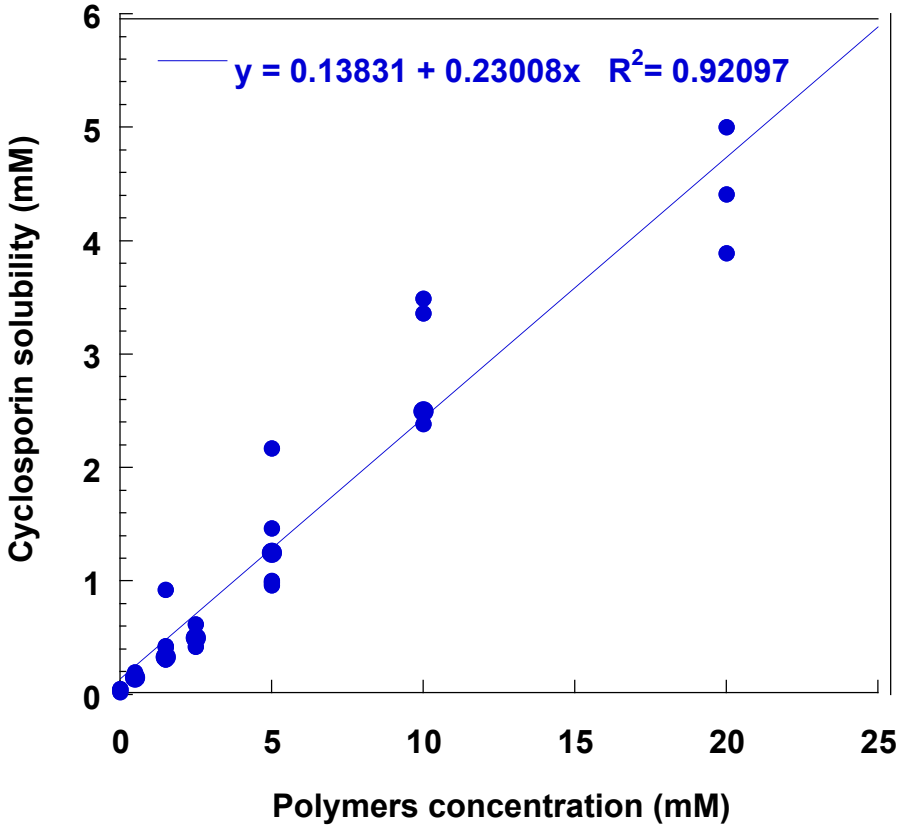
DLS analysis

v	P	5 mM PI	1 mM PI
0	1	0.158	0.123
0.25	0.75	0.073	0.005
0.5	0.5	0.094	0.014
0.75	0.25	0.166	0.096
1	0	0.183	0.065

P: v 1:1 Ratio

Cyclosporin solubility – surfactants concentration

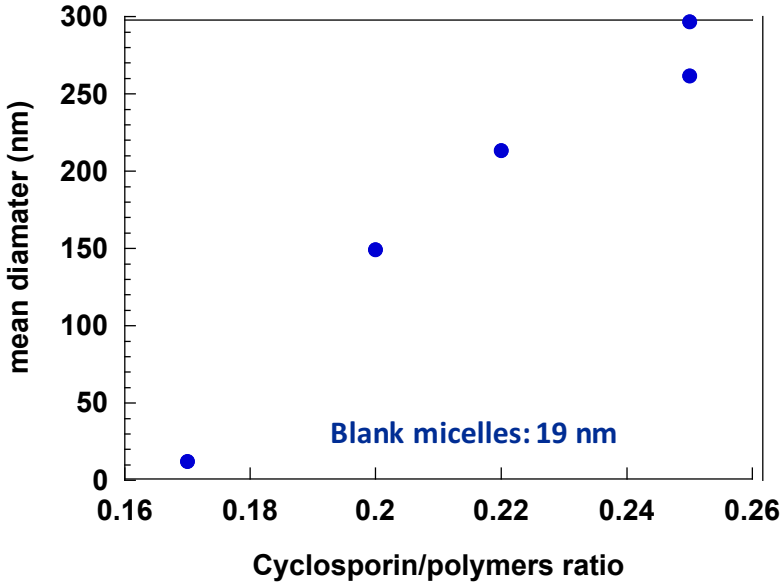
P : v 1:1



Formulation pH : 6.6 – 7.1

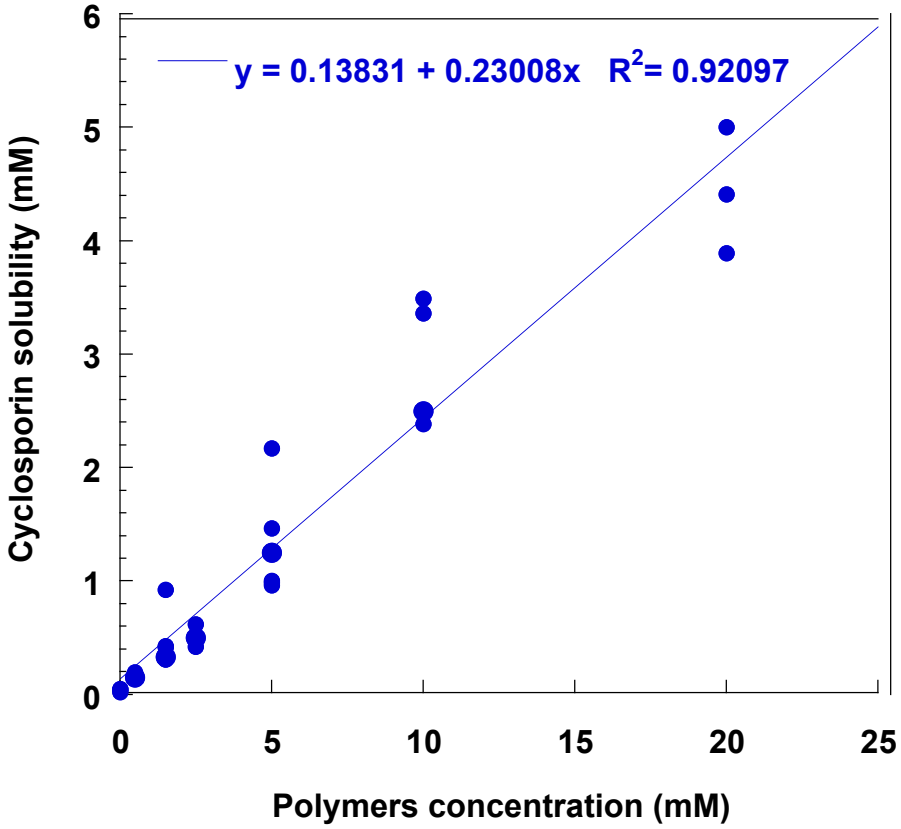
0.9% NaCl addition

DLS analysis
surfactants conc: 1 mM



Cyclosporin solubility – surfactants concentration

P : v 1:1



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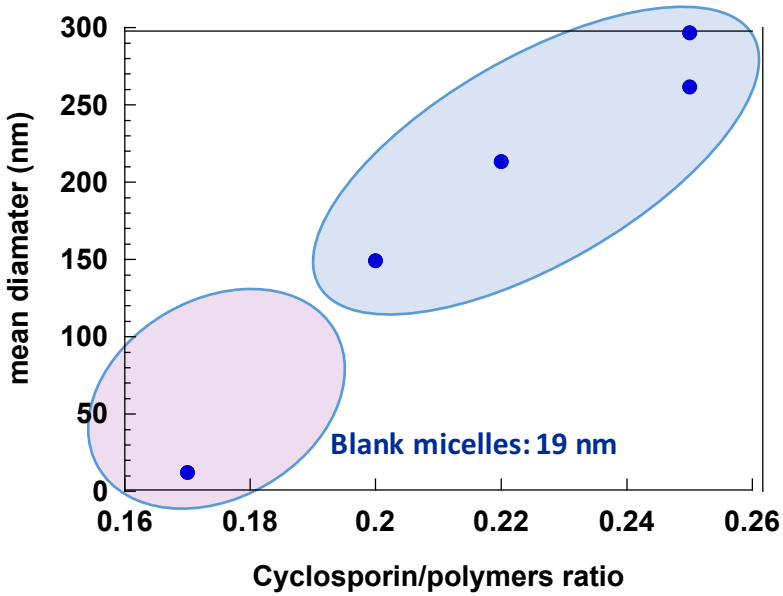
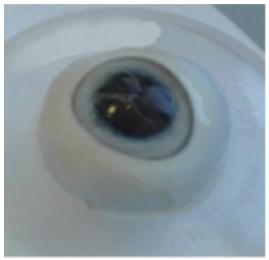


CyA cornea accumulation

- **Freshly explanted porcine eye-bulbs**

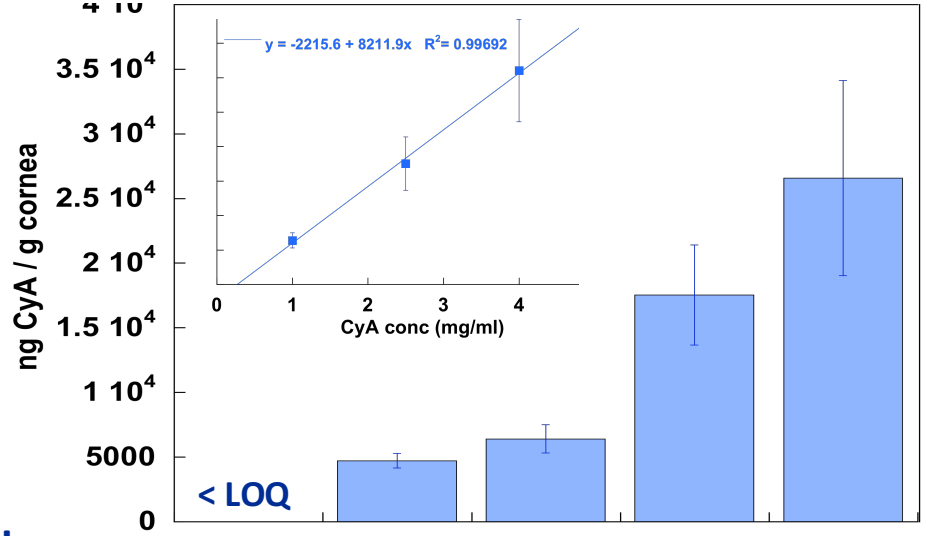


- Formulation application (200µl)

- 3h contact

- **Careful ocular surface cleaning**
- **Aqueous sampling and analysis**
- **Cornea dissection**
- **Extraction**
- **Concentration under N_2**
- **HPLC analysis**
- **Method validation for specificity and recovery (92± 5 %)**

References:
- coarse emulsion
- positively charged nanoemulsion (commercial) cetalkonium chloride



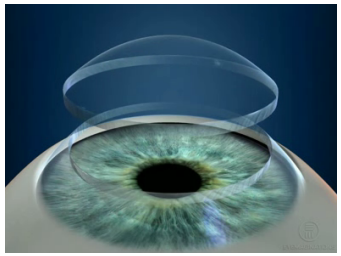
Coarse emulsion 1 mg/ml

Comm.formulation 1 mg/ml

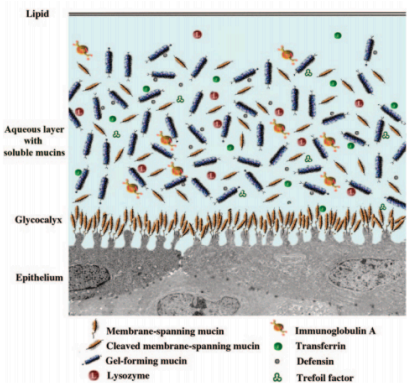
1	2.5	4	CyA mg/ml
0.25	0.25	0.17	CyA/Surf ratio
200	200	20	Size nm

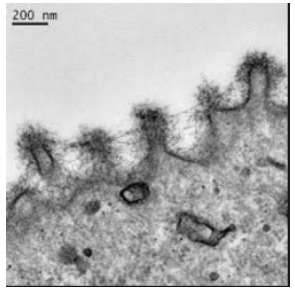
Mucoadhesion

Freshly explanted porcine eye bulbs

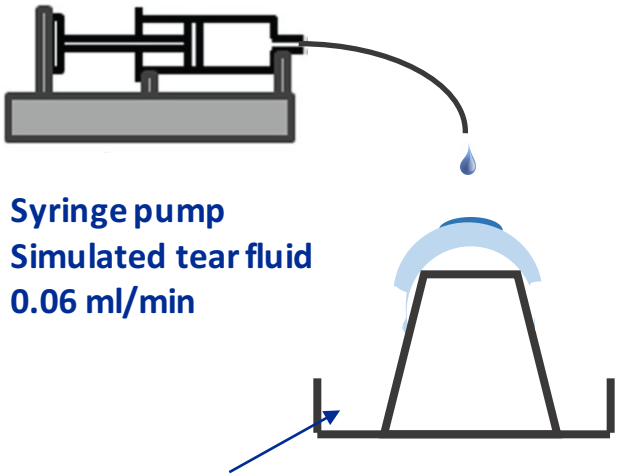


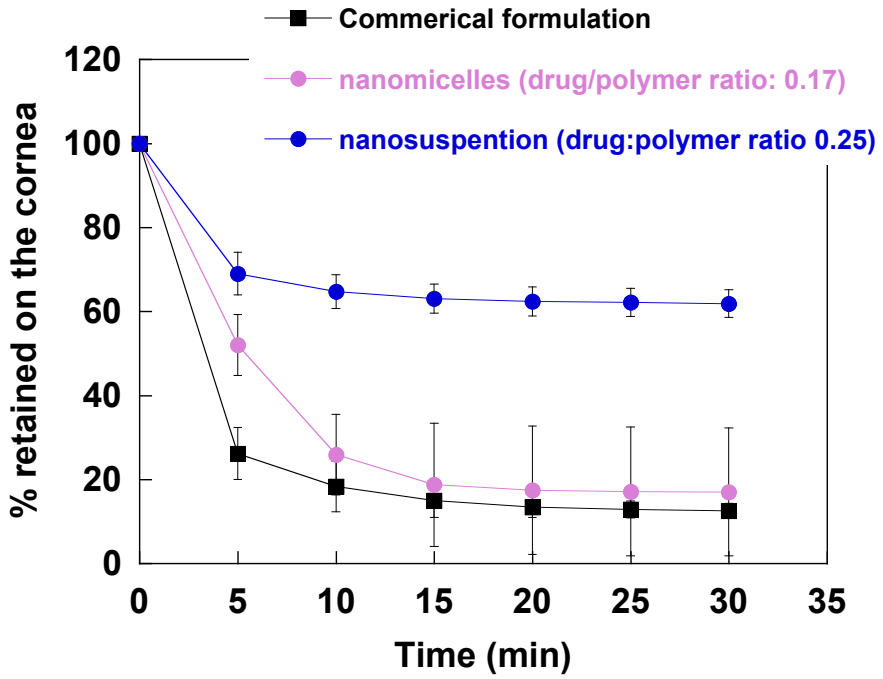
- cornea dissection
- 20 µl of formulation
- 5 minutes waiting





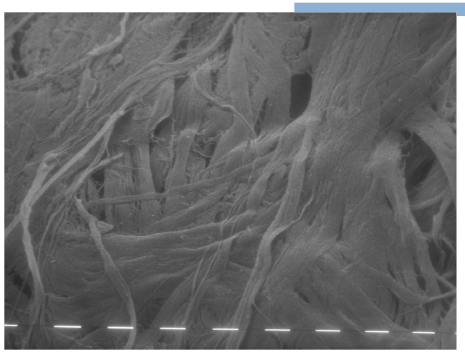
From University of Houston Tear Film Structure and Function; Rachel Redfern, OD, PhD, FAAO September 14, 2015



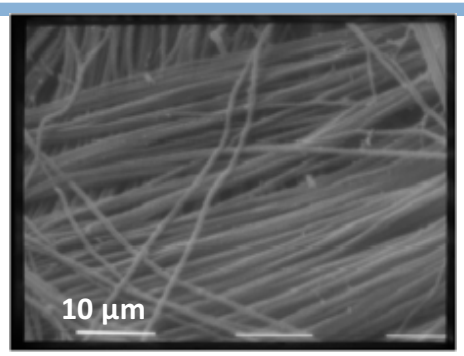


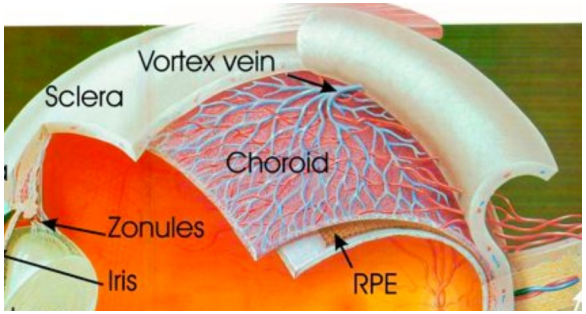
CyA transcleral delivery

SEM 5000 X



SEM 20000X





CyA 4 mg/ml
20 mM surfactants (P:v 1:1)
Micelles size approx. 20 nm

Sclera pore size: 20-80 nm

Application time	Amount retained (µg/cm²)	Amount Permeated (µg/cm²)
6 h	12 ± 5	0
22h	50.6 ± 9	2 - 20

Conclusion & Perspectives

- **Polymeric mixed micelles of P and V**
  - **Ease of preparation**
  - **Good cyclosporine solubility**
  - **Good performance on tissue**

  - **Stability**
  - **Tolerability (in vivo test)**
  - **Further characterization**

Acknowledgement

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