

Ocular Delivery

CARMEN ALVAREZ-LORENZO



INTEGRATING
Delivery Science
ACROSS DISCIPLINES



Bioinspired contact lenses that deliver antioxidant agents

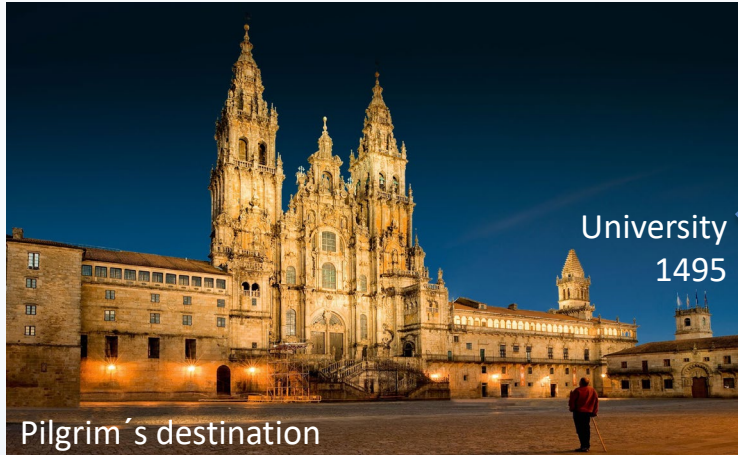
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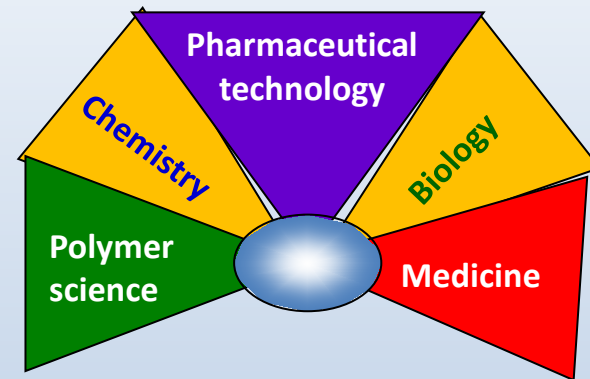
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<https://www.idfarmausc.es/en>

Advanced Drug Delivery Systems and Scaffolds for Regenerative Medicine



- What is a Contact Lens?
- Therapeutic interest
- Contact Lens with antioxidants

What is a Contact Lens?



A thin plastic lens placed directly on the surface of the eye to correct visual defects.

Contact lenses are ocular prosthetic devices used by +150 million people worldwide, and they can be worn to correct vision or for cosmetic or therapeutic reasons.



Sports starts

- Novak Djokovic
- Dwight Howard
- Cristiano Ronaldo
- Phil Mickelson



Martina Navratilova



What is a Contact Lens?



FDA classifies CLs according to the intended use as:

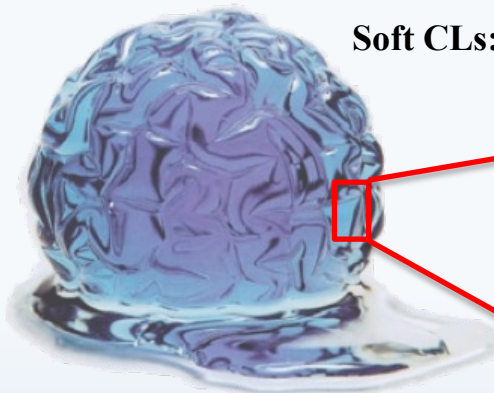
- (1) non-therapeutic CLs (e.g. for correction of refractive ametropia, aphakia, and presbyopia);**
- (2) specialized use CLs (e.g. for the treatment of keratoconus),**
- (3) therapeutic CLs that serve as a tool in the management of a wide variety of ophthalmic disorders refractory to other treatment modalities (e.g. soft (plano) bandage lens)**

- 1. Therapeutic**
 - a. Pain relief**
 - b. Promote epithelial healing**
 - c. Act as a splint in the treatment of lacerations, perforations and ulcerations**
 - d. Protect the cornea from mechanical damage secondary to abnormalities of the eyelid**
 - e. Improve visual acuity by correcting irregular corneal surface**
 - f. Deliver medications**

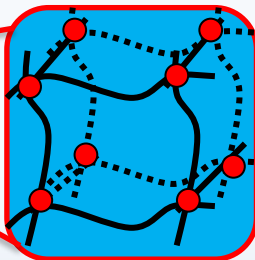
- 2. Clinical**
 - a. Corneal edema**
 - b. Persistent epithelial defects**
 - c. Noninfectious corneal ulcerations or small perforations especially those requiring cyanoacrylate glue**
 - d. Recurrent corneal erosions**
 - e. Filamentary keratitis**
 - f. Keratitis sicca**
 - g. Neurologic conditions leading to exposure**
 - h. Irregular corneal surfaces secondary to anterior corneal dystrophies**
 - i. Corneal scars or opacities**
 - j. Cosmetic tinted and painted lenses**
 - k. Post surgical (such as after Boston Keratoprosthesis)**

A contact lens is a medical device that requires a prescription

What is a Contact Lens?



Soft CLs: hydrogel and silicone hydrogel



*3D network of cross-linked polymer chains
 embedded in a liquid phase*



United States Patent Office

3,220,960

Patented Nov. 30, 1965

1

3,220,960

**CROSS-LINKED HYDROPHILIC POLYMERS AND
 ARTICLES MADE THEREFROM**

Otto Wichterle, Václavkova 2, Prague, Czechoslovakia,
 and Drahošlav Lim, No. 57, Senohraby, near Ricany,
 Czechoslovakia

No Drawing Original applications Apr. 24, 1956, Ser.
 No. 580,410, and Apr. 24, 1956, Ser. No. 580,411, now
 Patent No. 2,976,576, dated Mar. 28, 1961. Divided
 and this application Dec. 21, 1960, Ser. No. 77,278
 14 Claims. (Cl. 260—2.5)

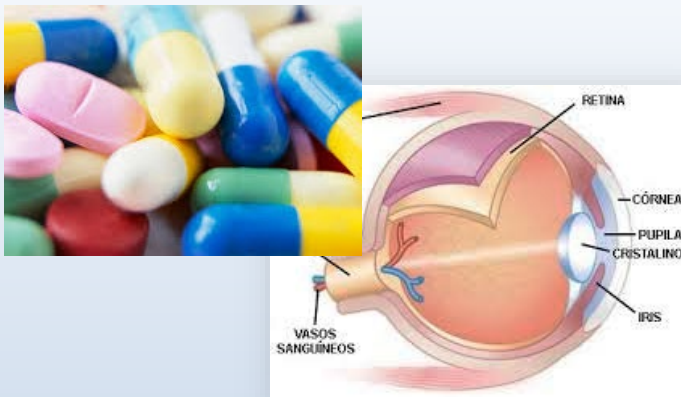
2

**“medicinal active substances such as antibiotics may be
 dissolved in the aqueous constituent of the hydrogels to
 provide medication over an extended period”**

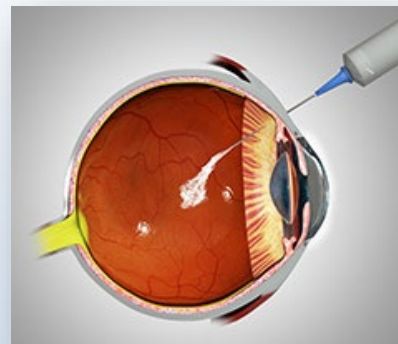
10 base of the invention relates to the use of hydrogels and
 methacrylic acid with alcohols having hydrophilic groups
 which after polymerization impart hydrophilic properties
 to the polymer obtained. A major portion of a mono-
 ester of acrylic or methacrylic acid with a bi-functional

- What is Contact Lens?
- **Therapeutic interest**
- Contact Lens with antioxidants

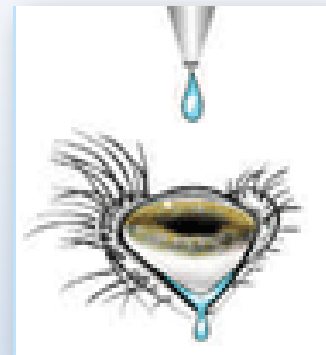
Systemic dosage forms



Intraocular administration

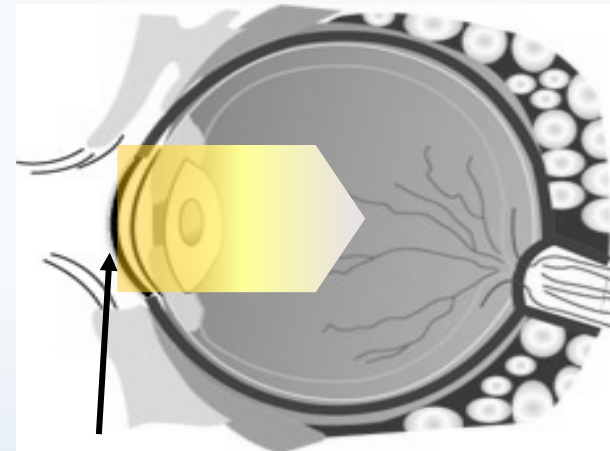
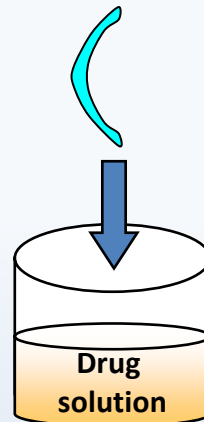
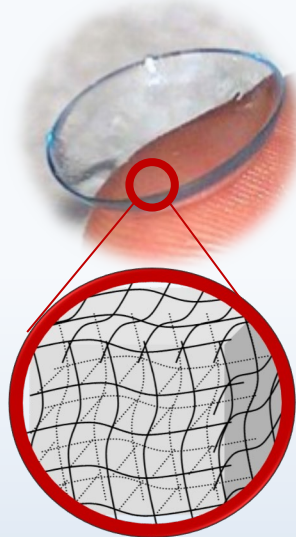


Topical administration



Current ocular treatments are poorly efficient or risky!

Therapeutic interest



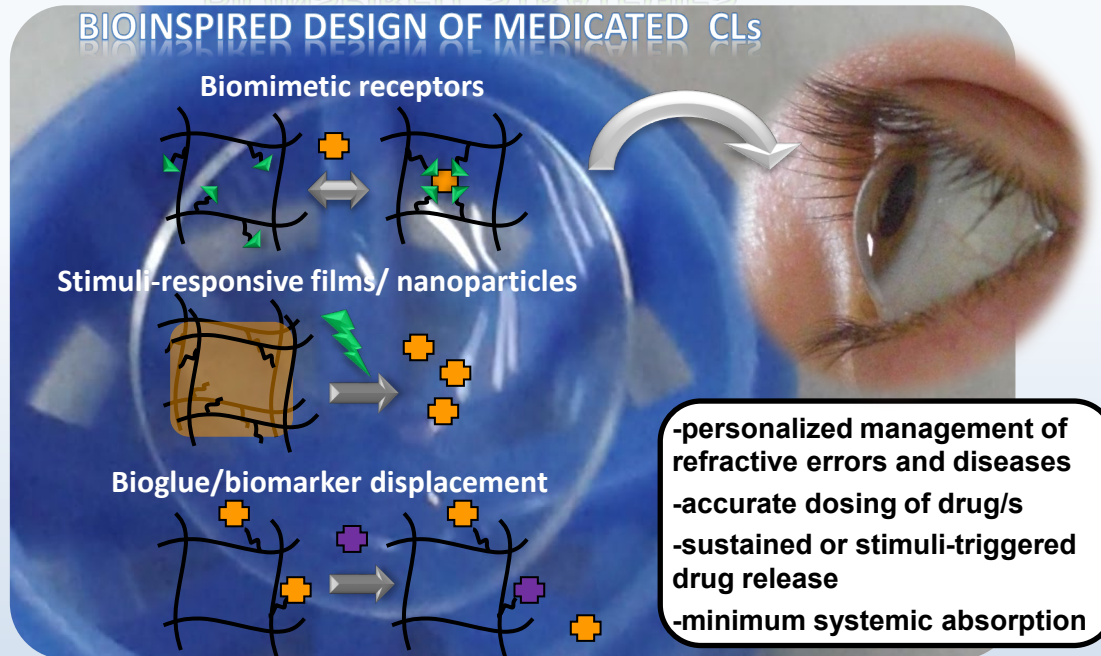
Post-lens lachrymal fluid

- ✓ Turnover of the postlens tear film occurs slowly, and the greater drug concentration attained should promote the pass through the cornea.
- ✓ The release towards the external surface of the CL is minimized by the dry periods during the blinking interval (5-times smaller diffusion).
- ✓ Prolonged stay of the drug on the cornea leads to higher intraocular concentration, which in turn results in remarkable improvements in pharmacological response.

C. Alvarez-Lorenzo et al. *Acta Biomaterialia* 84, 49-62 (2019).

BIOINSPIRED STRATEGIES

BIOINSPIRED DESIGN OF MEDICATED CLs



C. Alvarez-Lorenzo et al. *Acta Biomaterialia* 84, 49-62 (2019).

A.F. Pereira-da-Mota et al. *Journal of Controlled Release* 343, 672-702 (2022).

A.F. Pereira-da-Mota et al. *Journal of Controlled Release* 348, 431-443 (2022).

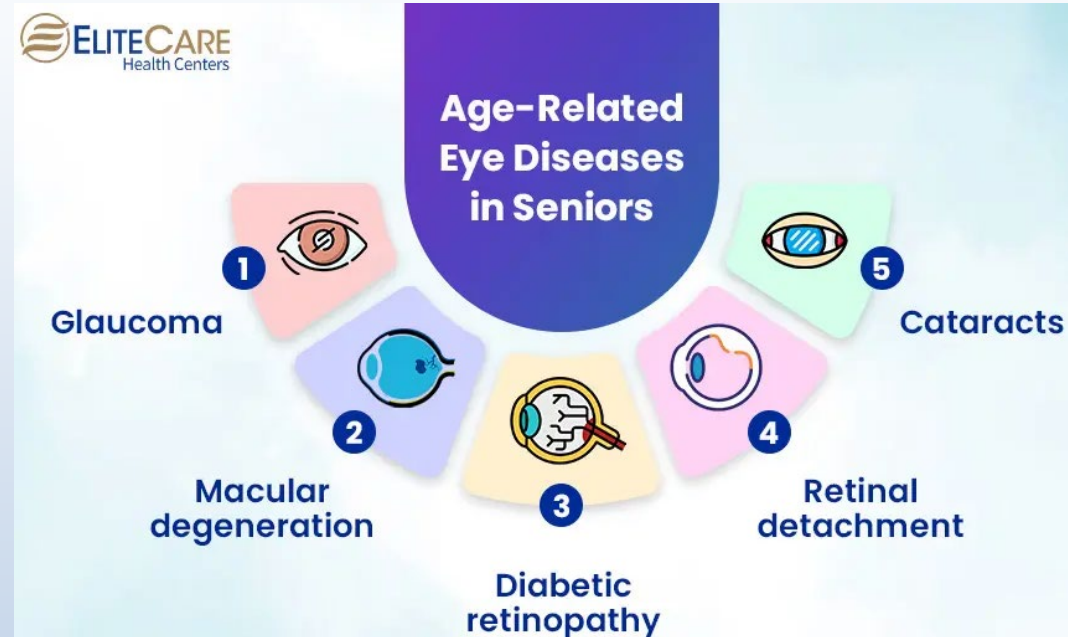
M. Vivero-Lopez et al. *ACS Applied Materials & Interfaces* 14, 55431-55446 (2022).

A.F. Pereira-da-Mota et al. *Drug Delivery and Translational Research* 13, 1116-1127 (2023).

- What is a Contact Lens?
- Therapeutic interest
- Contact Lens with antioxidants

✓ **Preservation of ocular health through prevention and treatment of**

- **Light-related damage**
- **Age-related diseases**

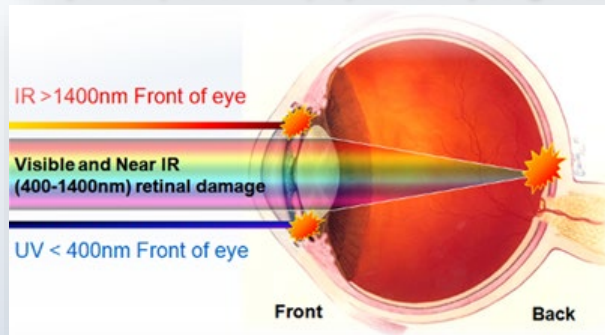


Contact Lens with antioxidants

Light-related damage & Age-related diseases

Retina damage by lasers

("retinal hazard spectral region" 400 to 1,400 nm; the green laser pointer (490-575 nm) is particularly dangerous)



Night-time artificial light exposure linked to increased risk of age-related macular degeneration

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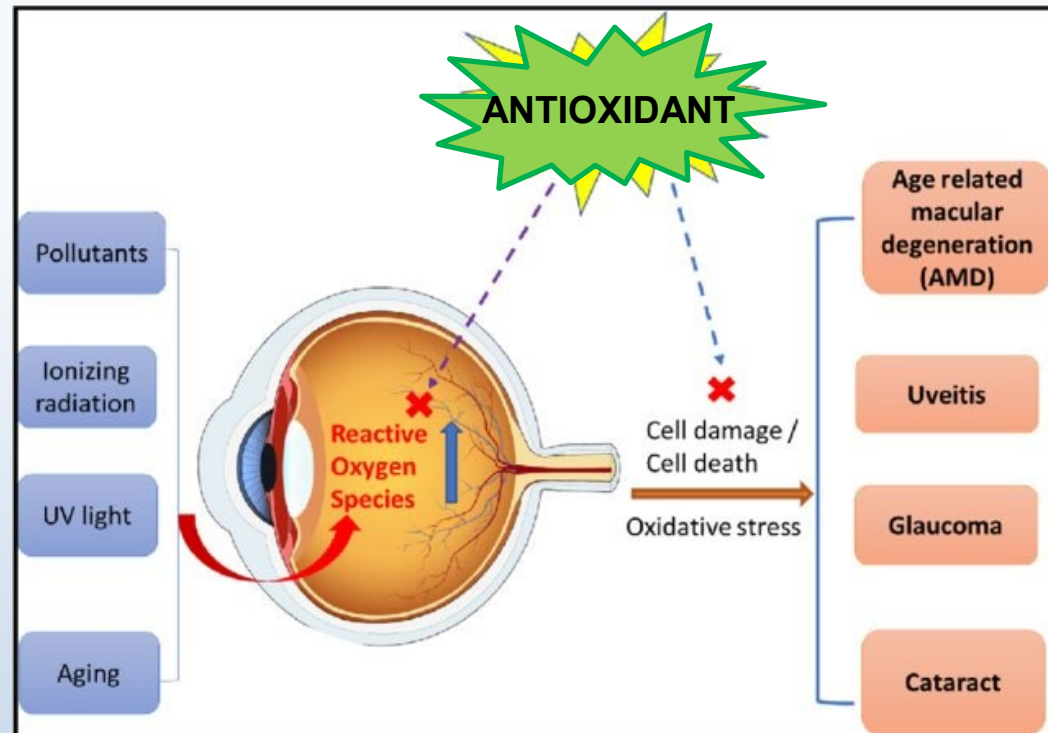


By Dr. Sanchari Sinha Dutta, Ph.D.

Jan 16 2024



A recent study published in *JAMA Network Open*, reveals that higher levels of exposure to outdoor artificial light at night can increase the risk of incident exudative age-related macular degeneration.



Adapted from Sharma et al. *Journal of the Indian Chemical Society* 99, 100387 (2022).

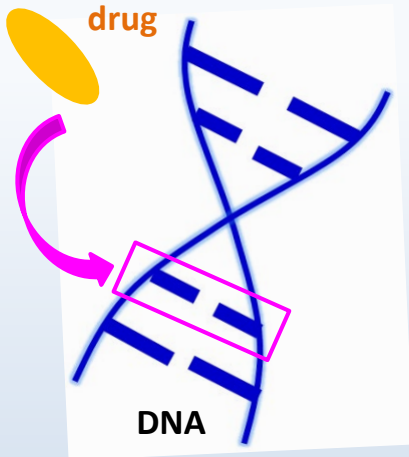
The aim was to develop CLs with receptors for antioxidant agents using two different bioinspired strategies:

a) mimicking DNA-binding drugs: using nucleotides as monomers with affinity for transferulic acid (TA), a very efficient radical scavenger;

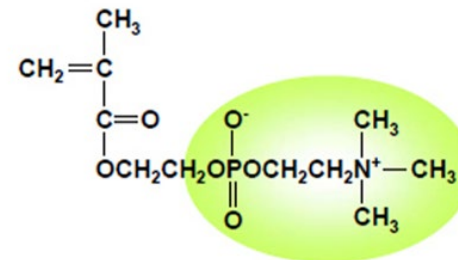
and b) mimicking cell membrane components (phospholipids, MPC) to promote hydrophobic interactions to bind resveratrol while increasing overall hydrophilicity, and thus comfort, of CLs

a)

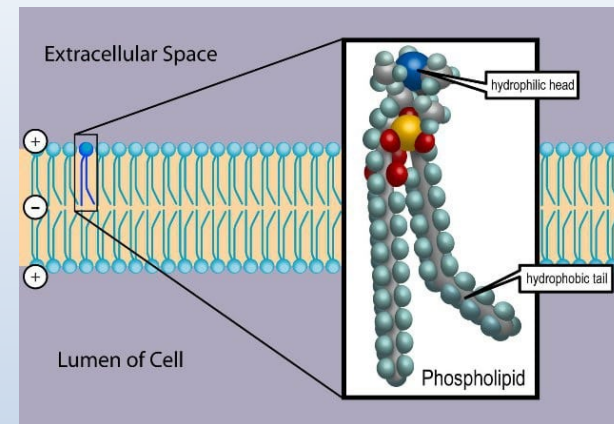
DNA-binding
drug



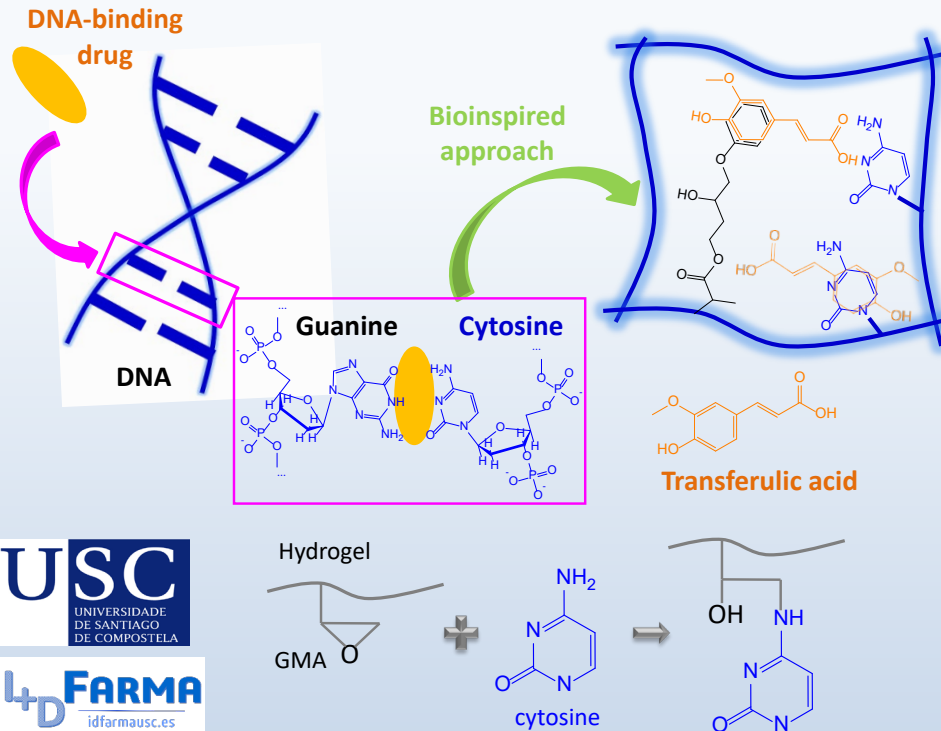
b)



2-Methacryloyloxyethyl Phosphorylcholine



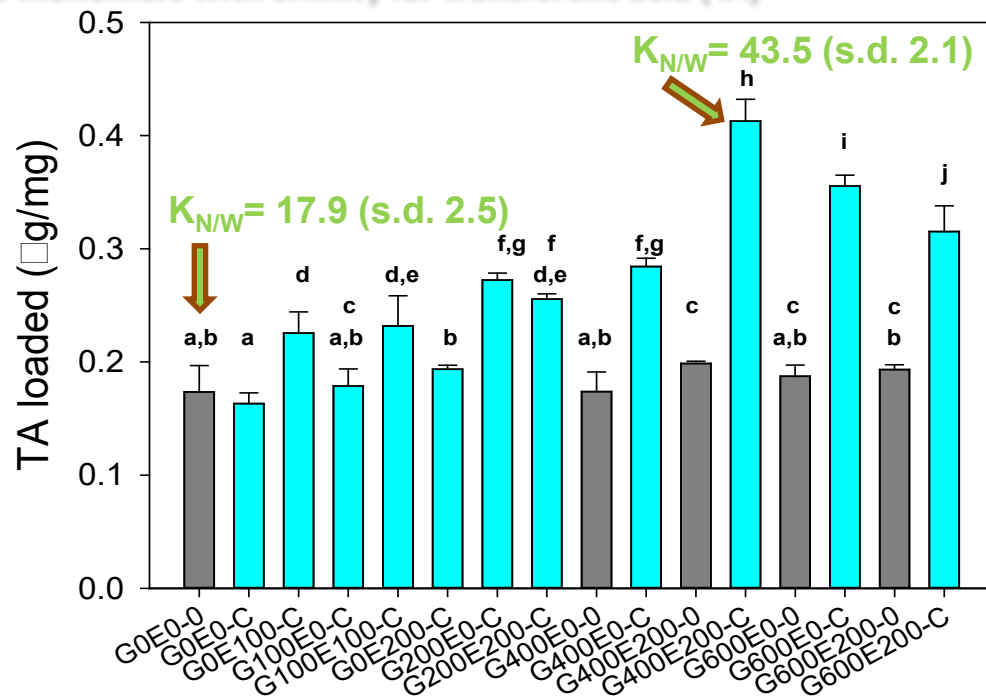
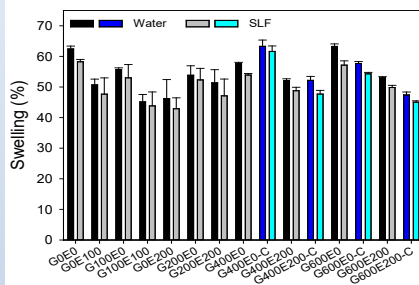
a) mimicking DNA-binding drugs: using nucleotides as monomers with affinity for transferulic acid (TA)



Hydrogel	HEMA (mL)	EGDMA (μ L)	GMA (μ L)	EGPEM (μ L)
G0E0	8	12.1	0	0
G0E100	8	12.1	0	150
G100E0	8	12.1	110	0
G100E100	8	12.1	110	150
G0E200	8	12.1	0	300
G200E0	8	12.1	220	0
G200E200	8	12.1	220	300
G400E0	8	12.1	430	0
G400E200	8	12.1	430	300
G600E0	8	12.1	640	0
G600E200	8	12.1	640	300

Varela-Garcia et al. *Biomaterials Science* 8, 1171-1180 (2020).

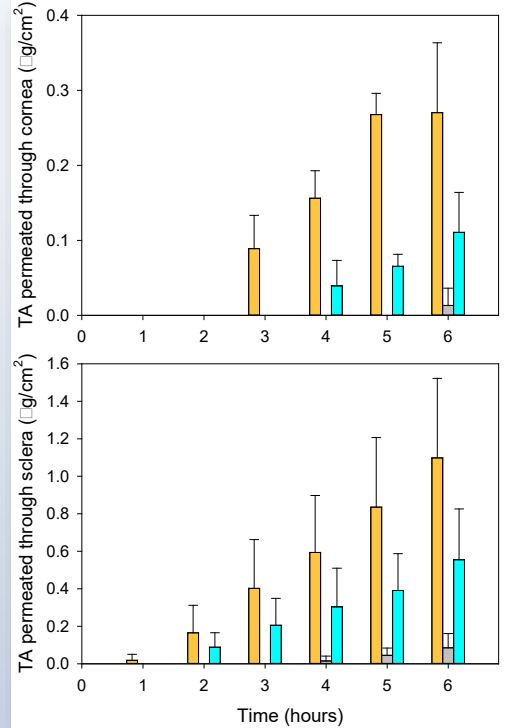
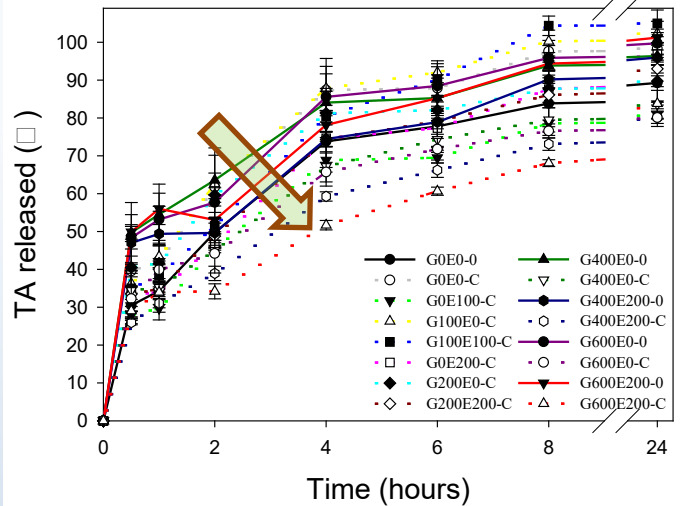
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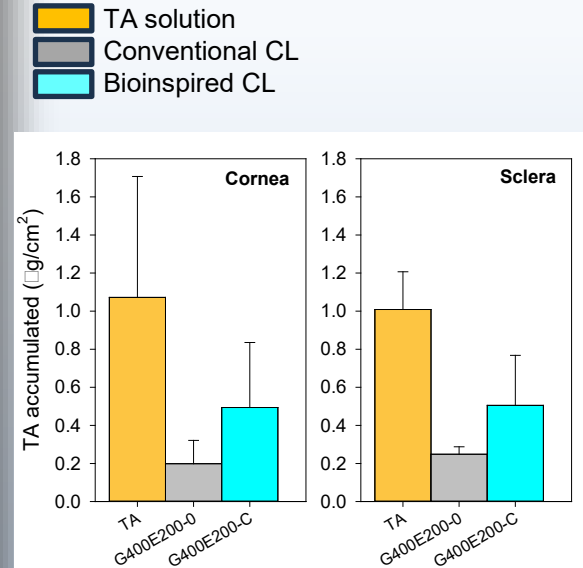
Varela-Garcia et al. *Biomaterials Science* 8, 1171-1180 (2020).

a) mimicking DNA-binding drugs: using nucleotides as monomers with affinity for transferulic acid (TA)

Drug release



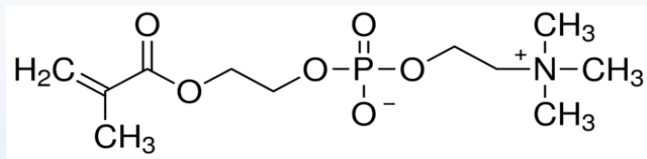
Cornea and sclera permeability



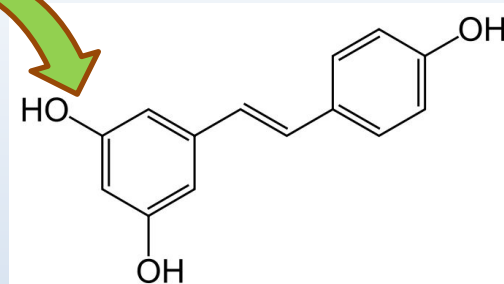
Varela-Garcia et al. *Biomaterials Science* 8, 1171-1180 (2020).

b) mimicking cell membrane components (phospholipids, MPC) and binding of resveratrol

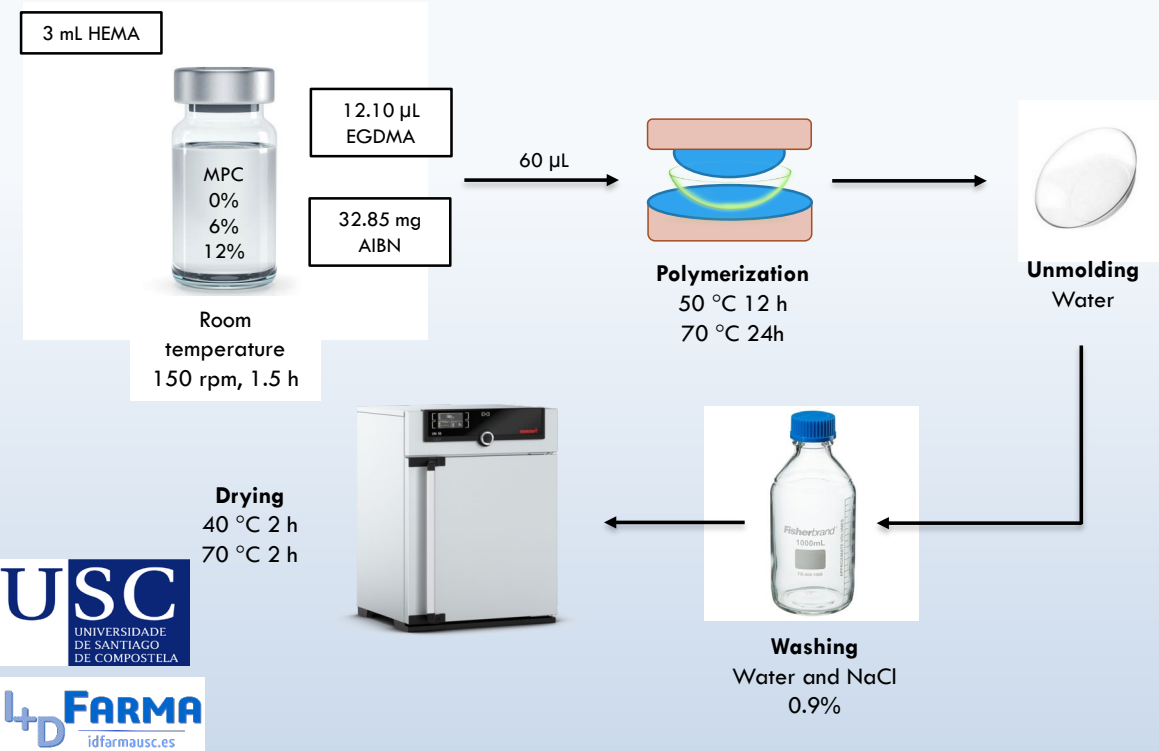
Antibiofouling phosphorylcholine (MPC) + antioxidant resveratrol



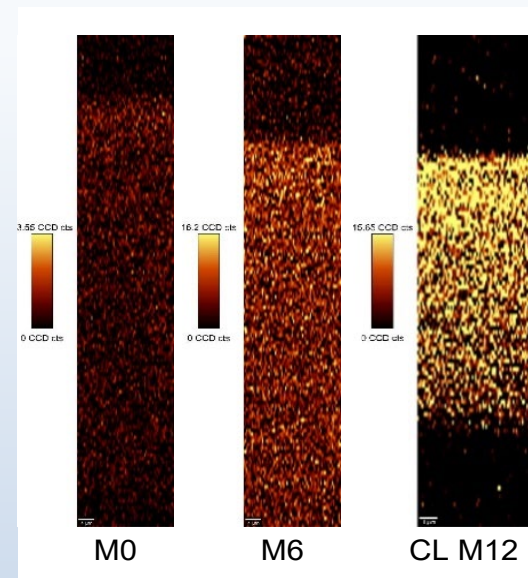
2-methacryloyloxyethyl
 phosphorylcholine
MPC



b) mimicking cell membrane components (phospholipids, MPC) and binding of resveratrol



Raman microscope images of CLs (along the depth) recorded with a filter at 717 cm^{-1}

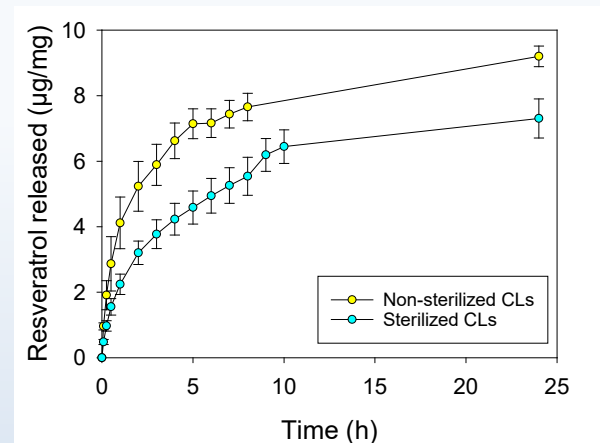


Vivero-Lopez et al. *ACS Applied Materials & Interfaces* 14, 55431-55446 (2022).

b) mimicking cell membrane components (phospholipids, MPC) and binding of resveratrol

- ✓ The total amount loaded was 20% higher than for previously developed silicone or HEMA-based hydrogels.

CLs	Resveratrol loaded (mg/g)
Non-sterilized	10.73 ± 0.96
Sterilized 24 h	10.56 ± 0.20
Sterilized 48 h	11.45 ± 0.78

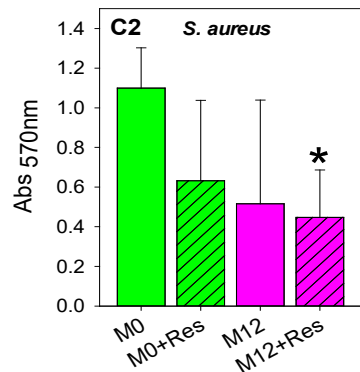
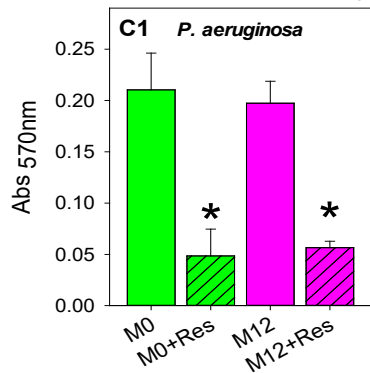


- ✓ Resveratrol release profiles in NaCl 0.9% protected from light at 36 °C and 180 rpm from non-sterilized and sterilized CL M12.

Vivero-Lopez et al. *ACS Applied Materials & Interfaces* 14, 55431-55446 (2022).

Contact Lens with antioxidants

✓ Antibiofilm activity



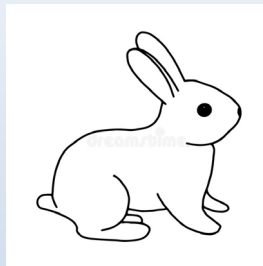
✓ In vivo tests



In vivo experiments
(n = 10)

Eye drops group
(n = 4)
Euthanized after 8 h

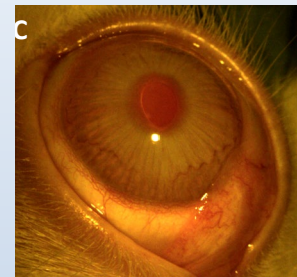
CLs group
(n = 6)



- ✓ Formulation in the right eye
- ✓ No formulation in the left eye

8 h wear CLs group
(n = 3)
Euthanized after 8 h

10 h wear CLs group
(n = 3)
Euthanized after 24 h

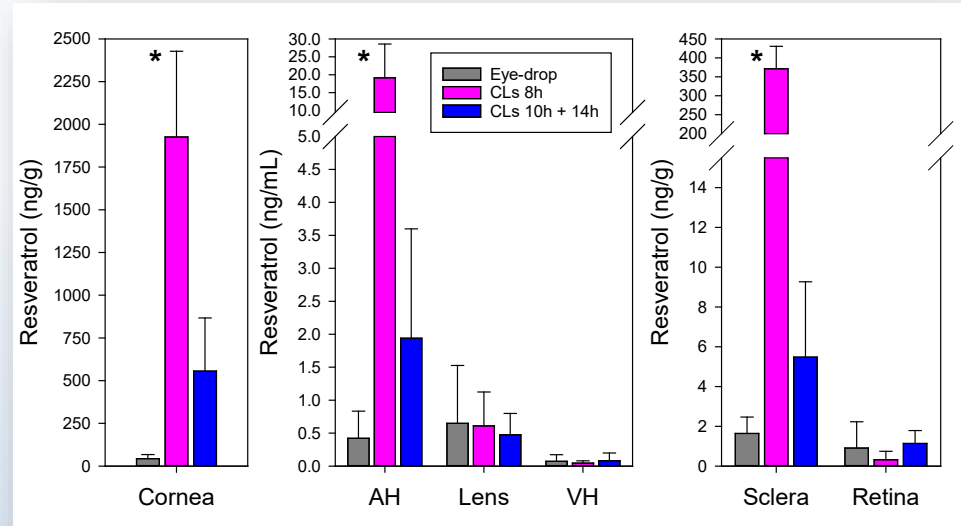
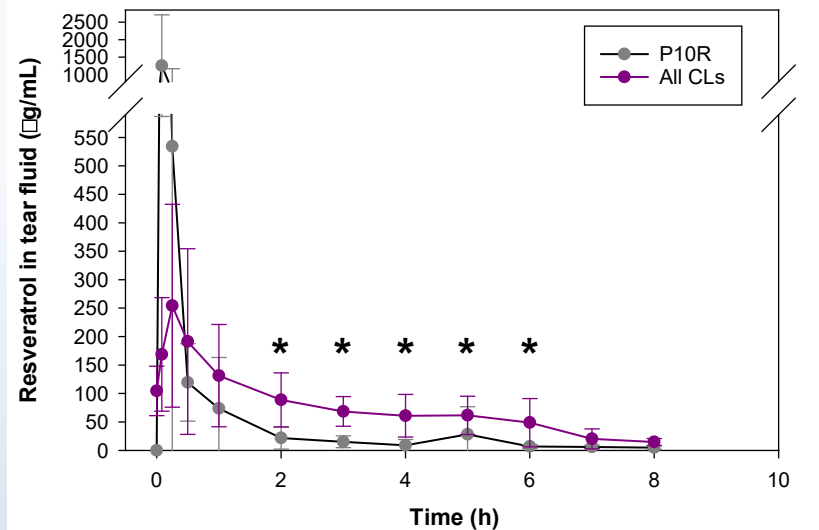


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b) mimicking cell membrane components (phospholipids, MPC) and binding of resveratrol



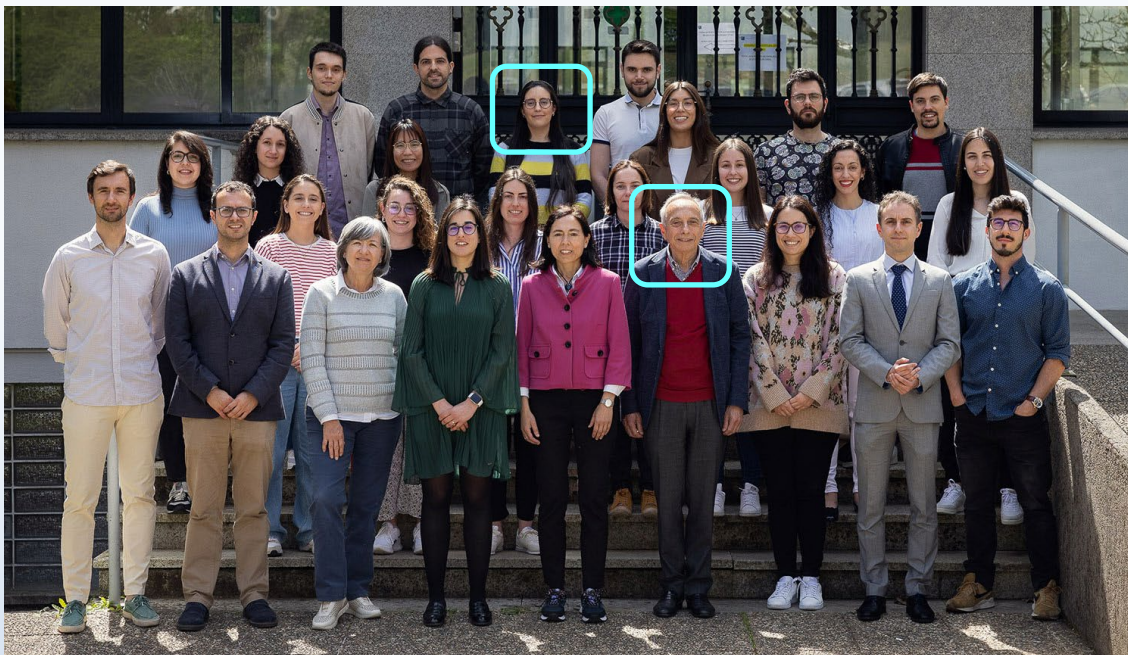
- ✓ All formulations tested allowed resveratrol to reach the cornea, aqueous humor, lens, vitreous humor, sclera and retina. However, the levels achieved in the cornea, aqueous humor and sclera after eight hours of contact lens insertion were much higher than those obtained with the micellar dispersion.
- ✓ No resveratrol in the control eye.

Vivero-Lopez et al. *ACS Applied Materials & Interfaces* 14, 55431-55446 (2022).

- **Material design of CLs applying bioinspired strategies opens a wide range of possibilities to transform these medical devices into efficient ocular drug delivery platforms.**
- **CLs can provide therapeutic treatments to the eyes of people requiring vision impairment correction and also to normal vision patients as transparent bandages.**
- **Advances in materials science and technology may help preparing CLs that can deliver the drug needed by each patient, contributing to personalized medicine strategies.**



ACKNOWLEDGEMENTS



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Thank you!