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INFLUENCE OF PEG CHAIN LENGTH ON THE PROPERTIES OF TPGS MICELLES FOR OCULAR DRUG DELIVERY

UNIVERSITÀ DI PARMA

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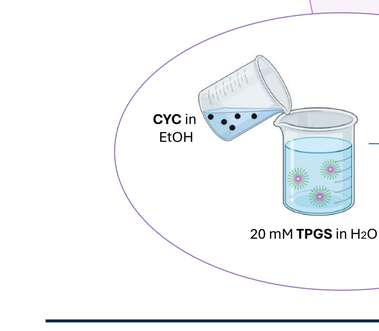
BACKGROUND

Globally, at least 2.2 billion people suffer of vision impairments or **blindness**. Forecasts for 2030 estimate an **increase in the incidence** for **chronic retinopathies**, such as glaucoma, age-related macular degeneration and diabetic retinopathy [1].



The administration of **neuroprotective compounds** could help to preserve the patient's visual function by promoting neuronal survival [2].

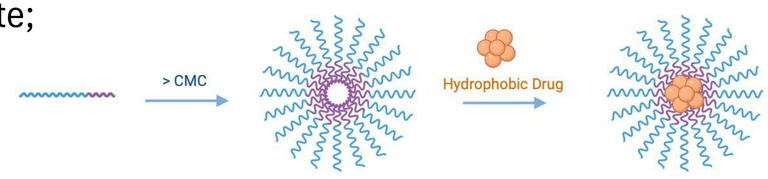
However, the anatomical, physiological and metabolic **barriers of the eye**, together with the **physico-chemical properties** of the active compounds, hinder the administration of drugs, especially to the posterior segment [3].

A possible strategy is the use of **nanocarriers**, such as **polymeric micelles**, to solubilize hydrophobic drugs and promote their penetration into ocular tissues.

PURPOSE

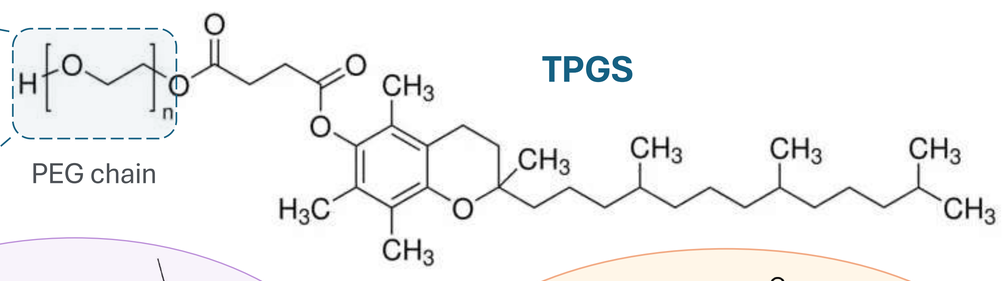
Formulation of **D-α-tocopheryl polyethylene glycol succinate (TPGS) micelles** with **different PEG length** and investigation of its influence on:

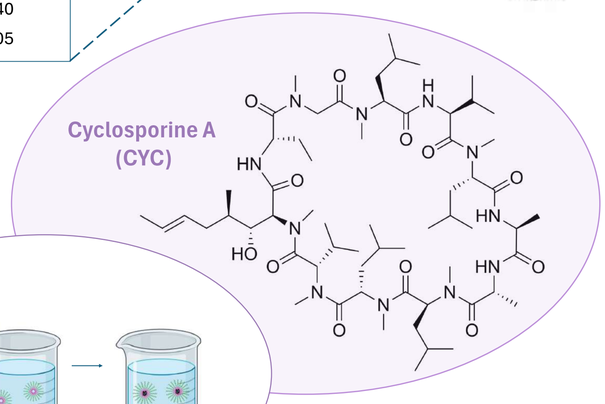
1. the size and structure of the micelles;
2. the loading capacity of hydrophobic neuroprotective compounds;
3. TPGS hydrolysis rate;
4. micelles diffusion.

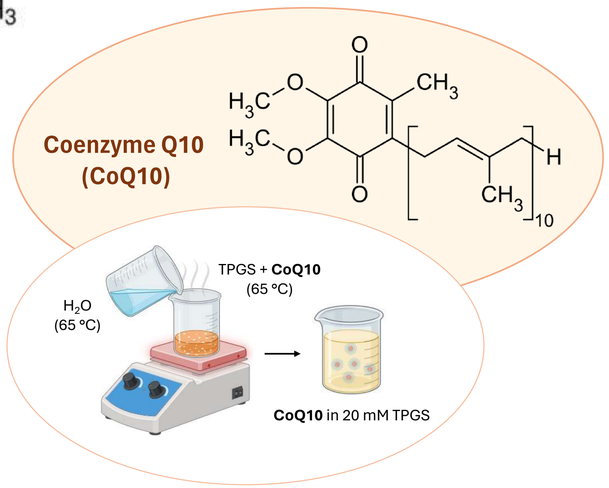


METHODS

TPGS	n	MW (Da)
400	8 – 9	905
600	12 – 14	1105
750 M	16 – 17	1260
1000	22	1513
1500	33	1983
2000	44	2471
3000	66	3440
4000	88	4405







- **Loading capacity** of neuroprotective drugs *(CoQ10 and CYC)*
- **Size measurement** of blank and loaded micelles *(SAXS and DLS analysis)*
- **Stability** of the micelles in terms of size and drug loading
- In vitro **degradation** kinetics of TPGS *(hydrolysis studies)*

Experimental conditions (37 °C)	
TPGS	2.5 mM
Porcine esterases	50 UI/mL
PBS	775 µL
Final volume = 1 mL	

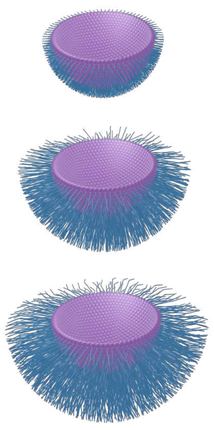
100 µL withdrawal
Time: 0, 1, 2, 4, 6, 8, 24, 30, 48 h
1:10 dilution with MeOH

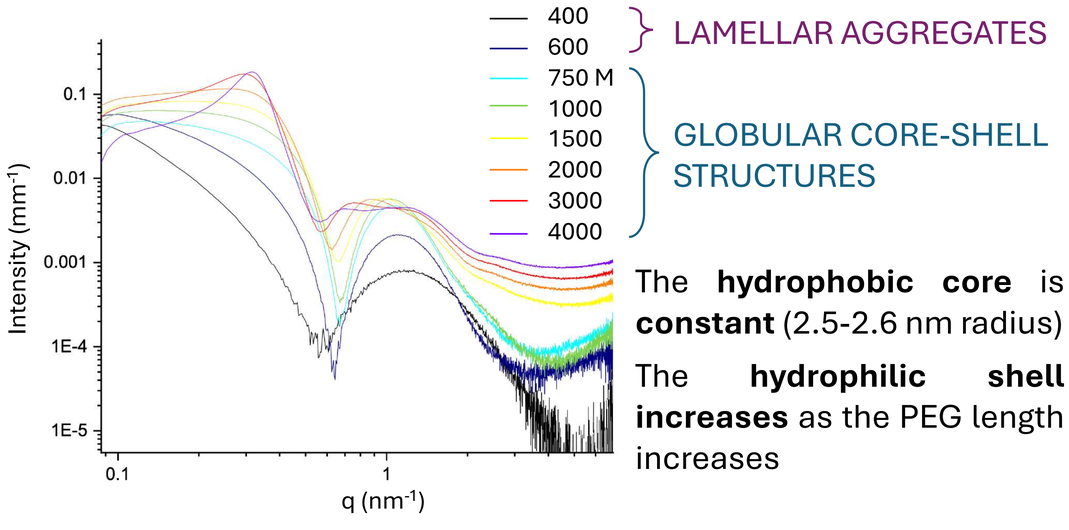
- In vitro **diffusion** studies in a model of the vitreous body

TPGS solution (200 µL) loaded with Nile red (20 µL)
+ 1.5 mL HA_{1000} 0.45 gel (H_2O:PBS)
The diffusion process was investigated at 37 °C → Image J

RESULTS

SAXS ANALYSIS OF BLANK MICELLES

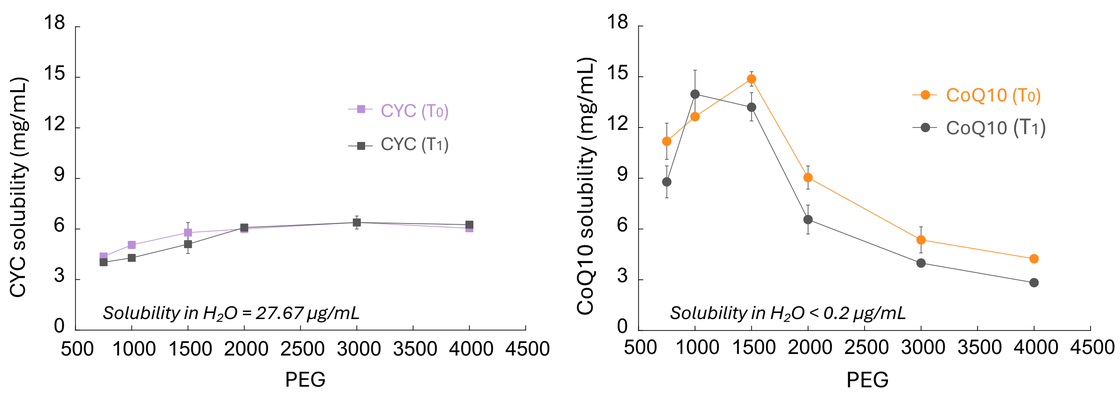




The **hydrophobic core** is **constant** (2.5-2.6 nm radius)

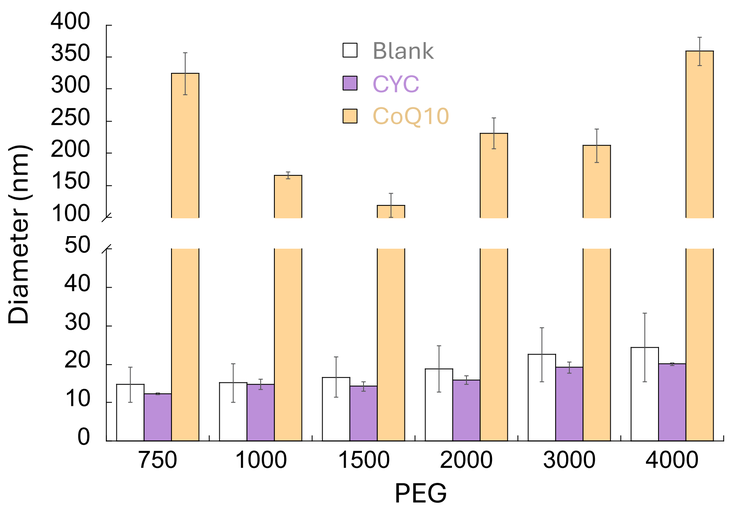
The **hydrophilic shell increases** as the PEG length increases

SOLUBILITY AND STABILITY STUDIES

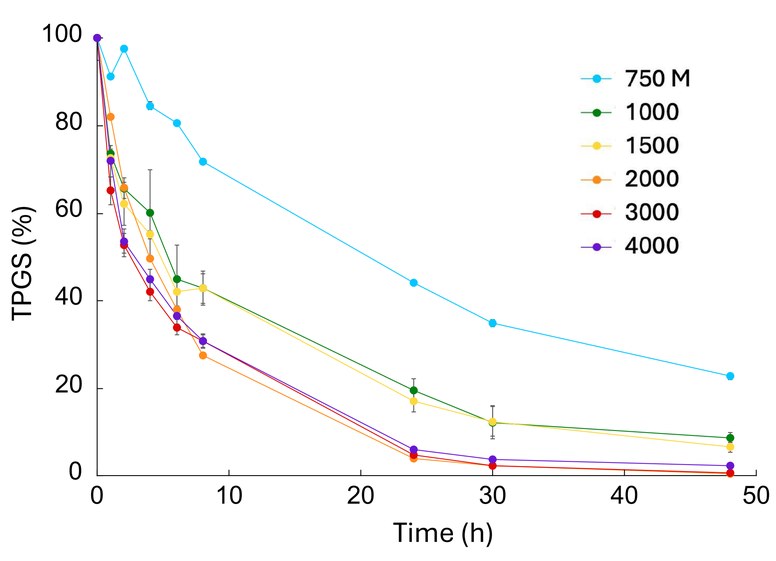


TPGS micelles (20 mM) **increase the solubility of CYC and CoQ10 in water**, with stability at 15 days (T_1) depending on the TPGS involved

DLS ANALYSIS OF BLANK AND LOADED MICELLES

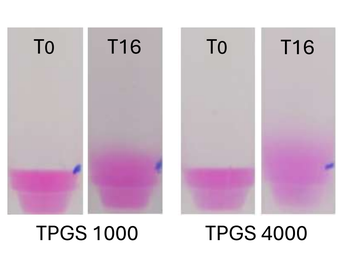


- The **size** of the blank micelles **increases** as the **PEG length increases**
- Compared with blank micelles, CYC loading does not lead to an increase in size, while **CoQ10 loading has a significant impact**



HYDROLYSIS KINETICS STUDIES

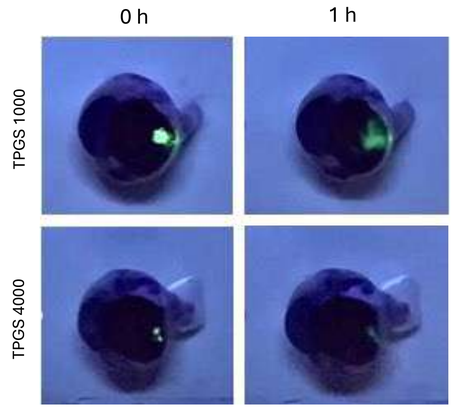
As the length of the **PEG chain increases**, **degradation** by esterases is **accelerated**



DIFFUSION STUDIES

PEG length impacts on diffusion: TPGS 4000 diffuses two-times faster than TPGS 1000

ON GOING EVALUATIONS



- SAXS analysis of loaded micelles
- Ex vivo diffusion studies on porcine eyes

CONCLUSIONS

TPGS micelles with different PEG chain lengths have important solubilizing and stabilizing capabilities on hydrophobic drugs. Due to their diffusional and hydrolysis properties, they are proposed for the controlled drug delivery to the posterior segment after intravitreal administration.

[1] W. Health Organization, *"World report on vision", Geneva, Switzerland: World Health Organization, 2019.*

[2] M. T. Pardue and R. S. Allen, *"Neuroprotective strategies for retinal disease,"* Prog Retin Eye Res, vol. 65, pp. 50–76, Jul. 2018, doi: 10.1016/J.PRETEYERES.2018.02.002.

[3] Q. Qi *et al.*, *"Challenges and strategies for ocular posterior diseases therapy via non-invasive advanced drug delivery,"* Journal of Controlled Release, vol. 361, pp. 191–211, Sep. 2023, doi: 10.1016/J.JCONREL.2023.07.055.