Heather Sheardown

MUCOADHESIVE MICELLES FOR ANTERIOR SEGMENT DRUG DELIVERY

20|20 OptimEyes Technologies

C20|20

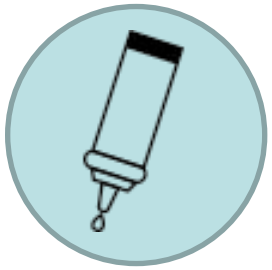
SHEARDOWNLAB

McMaster University

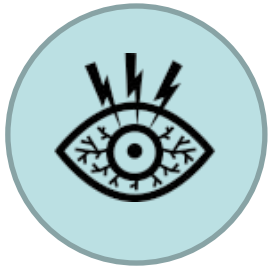
The Problems with Eye Drops

90% of Ophthalmic Pathology is treated with eye drops, but drops simply DO NOT WORK VERY WELL!
Can we make a drop that is better?

95% is lost after the first blink



Wasteful, systemic exposure; Low bioavailability



Uncomfortable and irritating when given multiple times per day

Poor patient compliance

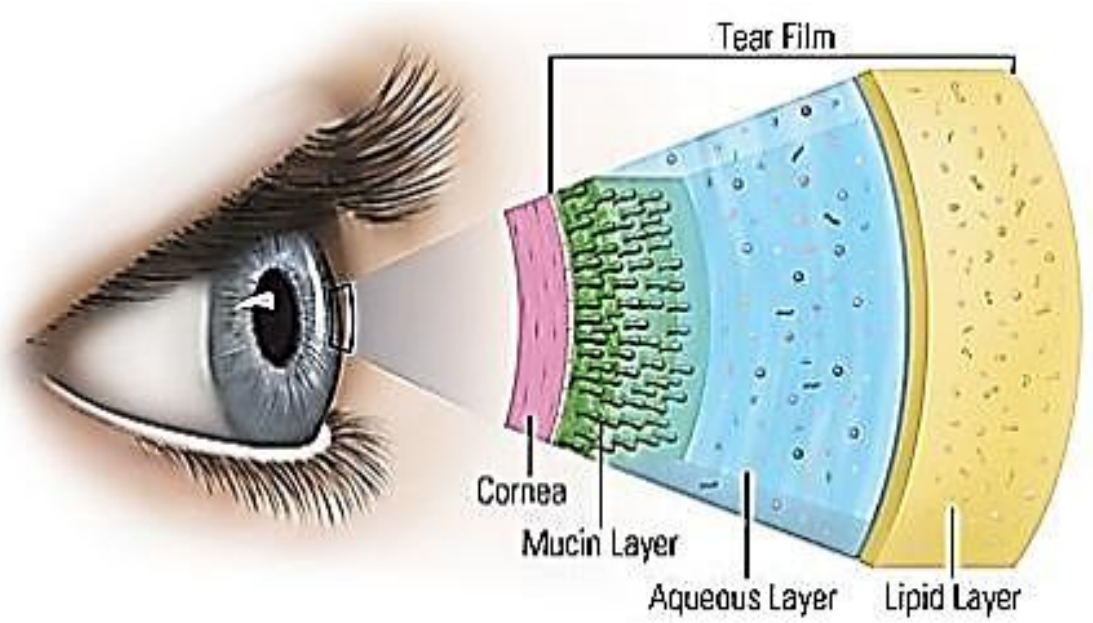
20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

Mucoadhesive Materials for Drug Delivery



- Eyedrops are well accepted but ineffective
- Increase the residence time on eye by increasing contact with the ocular surface
- Mucin layer on the surface of cornea shown to bind to a variety of different natural and synthetic materials
- Use this layer to facilitate interactions with the corneal layer over a prolonged period of time

20|20 OptimEyes Technologies

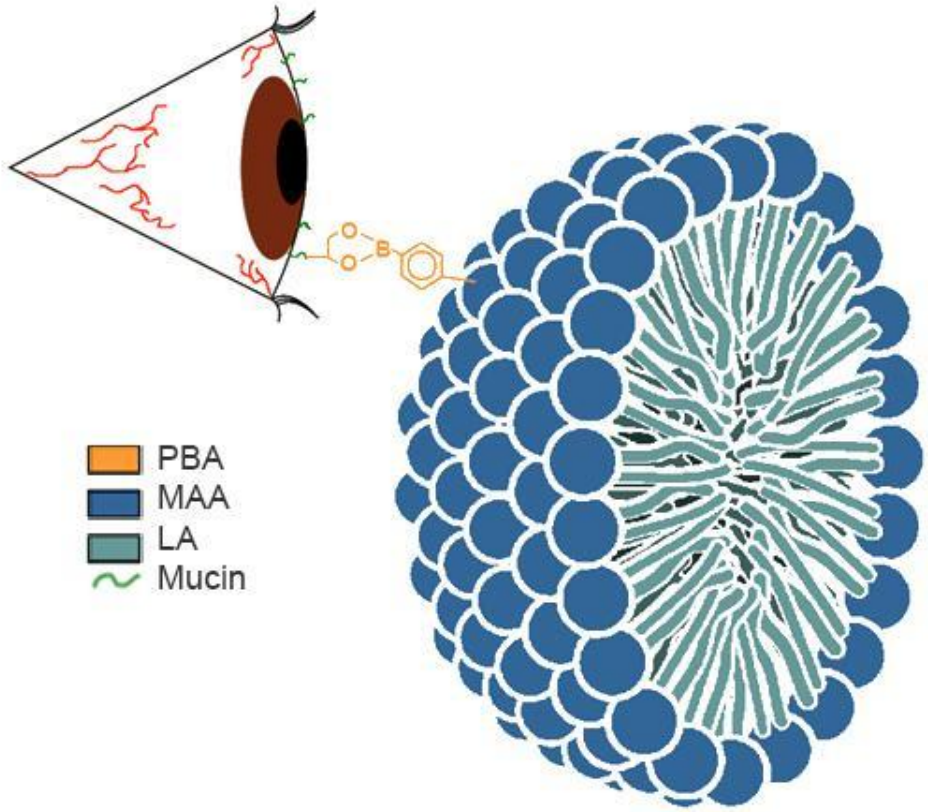
C 20 | 20

SHEARDOWNLAB

McMaster University

Mucoadhesive Micelles for front of the Eye Formulations

- To improve clinical efficacy of pharmacological treatments, a mucoadhesive micelle drug delivery platform for controlled, sustained, and target delivery has been developed
- Particles are uniform with sizes on the order of 200 nm
- Prepared by RAFT and FRP
- In aqueous solution, particles are transparent when PBA content is low (<20%)



20|20 OptimEyes Technologies

C 2 0 | 2 0

OptimEyes
Micelle Technology

- Drug encapsulation improves solubility and decreases irritation
- Sustained release
- Binds to the ocular surface
- Increased ocular residence time gives greater bioavailability

20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

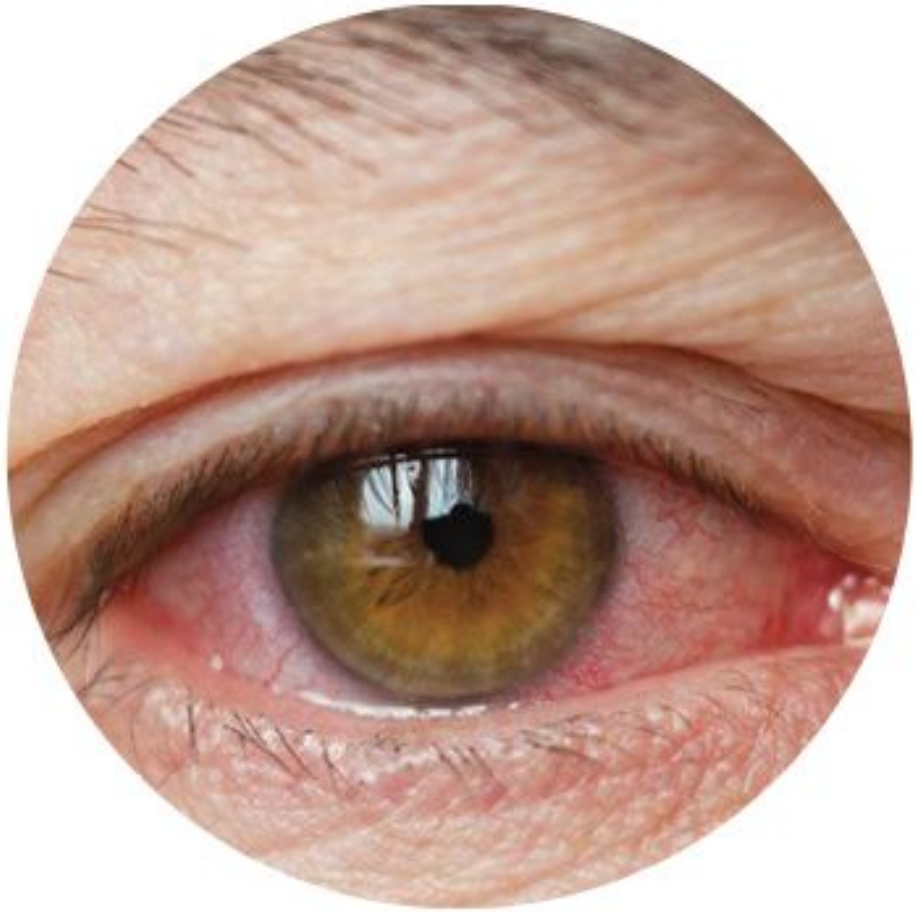
McMaster University

OptimEyes
Micelle Technology

- Patented Technology
- Platform with many potential applications
- Lead Indications = Dry Eye Disease – (High Dose Cyclosporine) and Glaucoma (Latanoprost)

Dry Eye Disease

- Affects millions throughout the world
- Most common reason for visits to eye practitioners
- Characterized by vicious cycle of tear film instability and hyperosmolarity that leads to inflammation and ocular surface damage
- Associated with significant pain, limitations in performing daily activities, reduced general health and depression

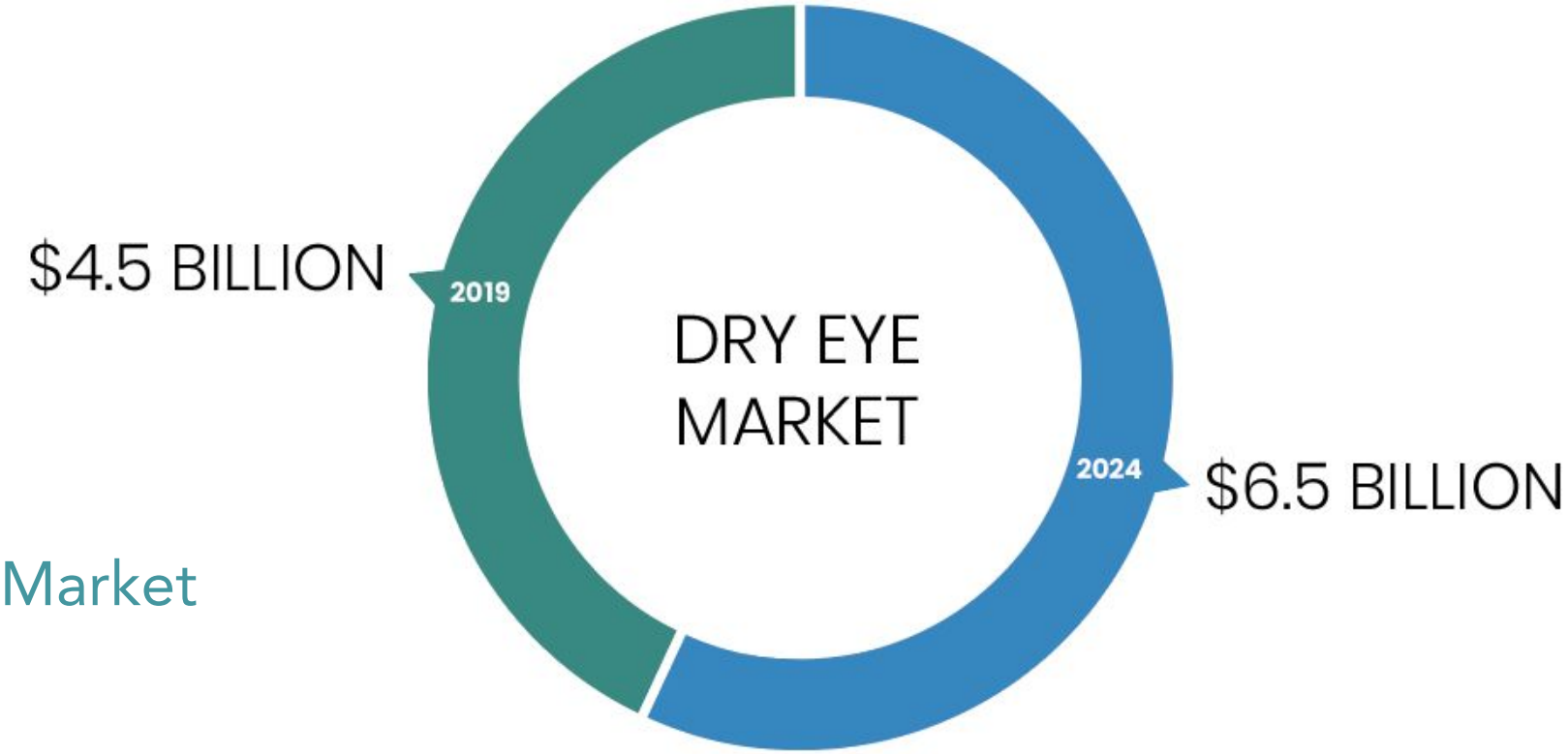


20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University



Growing Dry Eye Market

Treatments – lubricating drops, cyclosporine A, lifitgrast
Estimates 2019; Courtesy Market Scope
Market-scope.com

20|20 OptimEyes Technologies

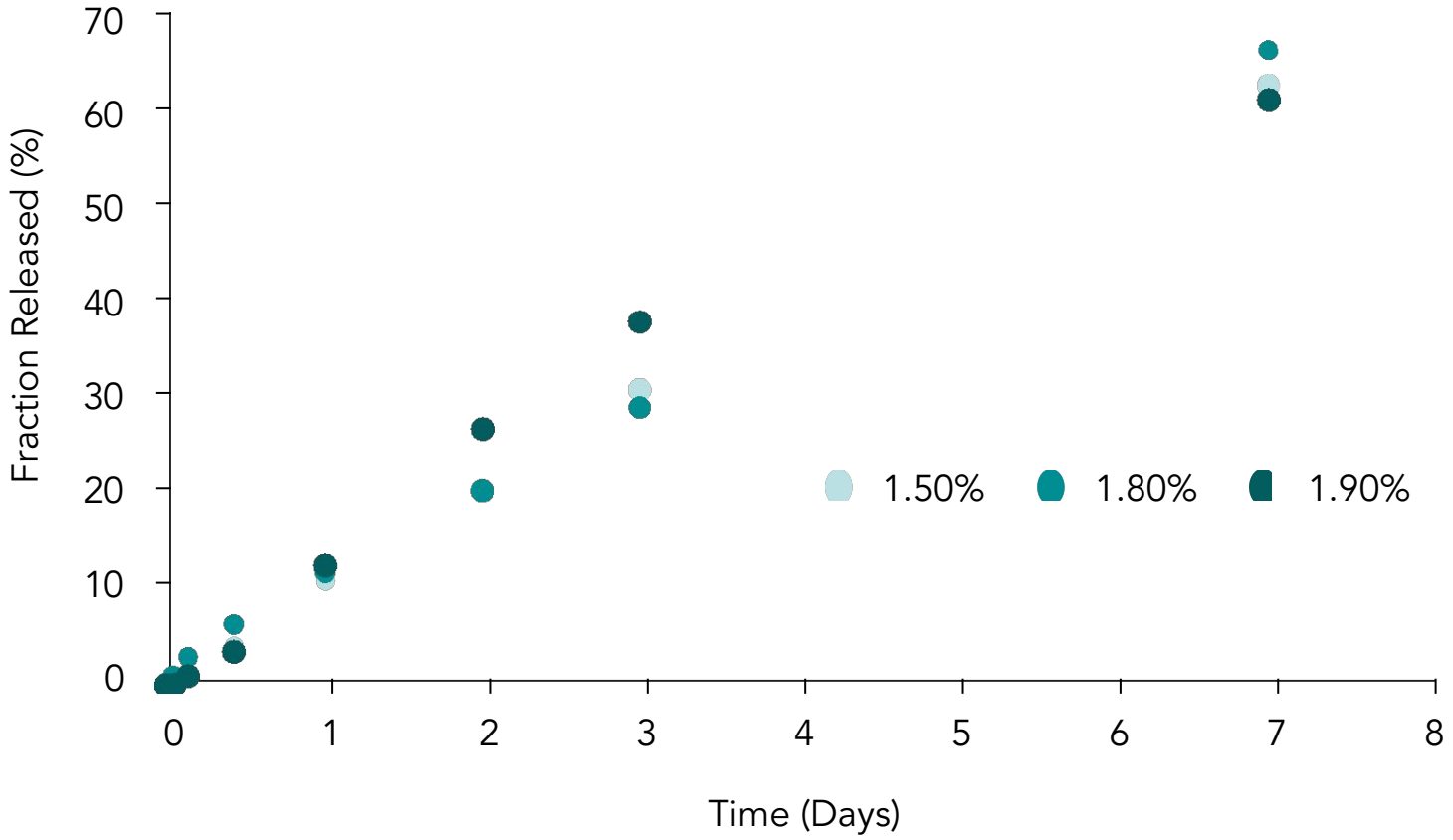
C 20 | 20

SHEARDOWNLAB

McMaster University

In Vitro Drug Release

Cyclosporine A (CycA), a common topical drug used to treat dry eye disease (DED) released over 2 weeks



20|20 OptimEyes Technologies

C 20 | 20

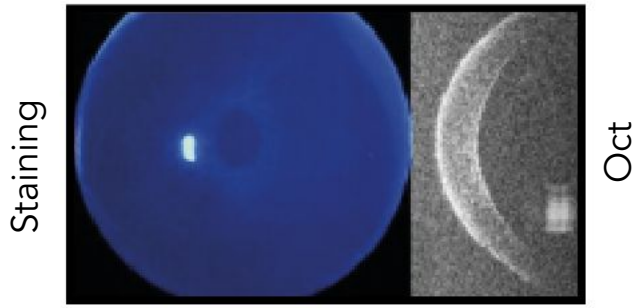
SHEARDOWNLAB

McMaster University

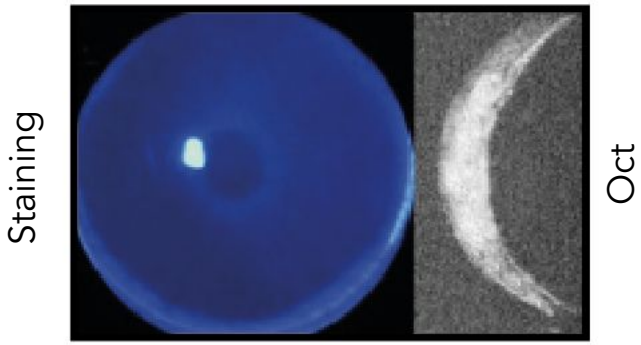
Micelles Appear Safe & Tolerable

- Rabbits & Rats
- No signs of corneal thickening, morphology changes or irritation at various micelle dose levels
- No cell death with polymer incubation

PBS Control



Michelle Formulation



20|20 OptimEyes Technologies

C 20 | 20

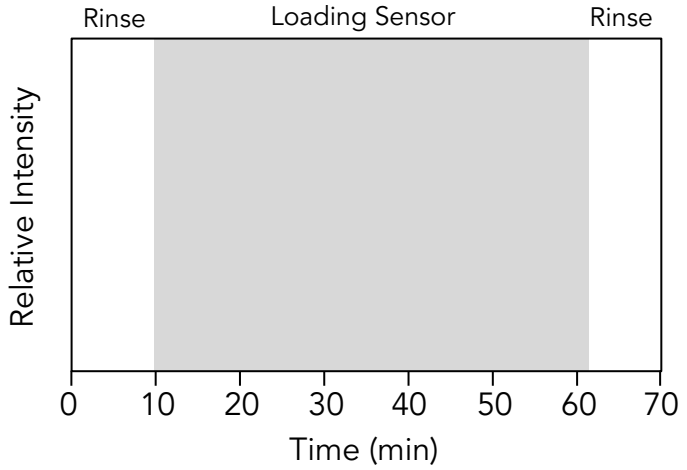
SHEARDOWNLAB

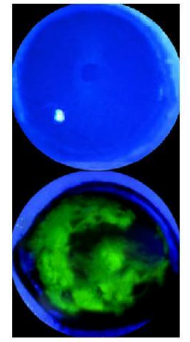
McMaster University

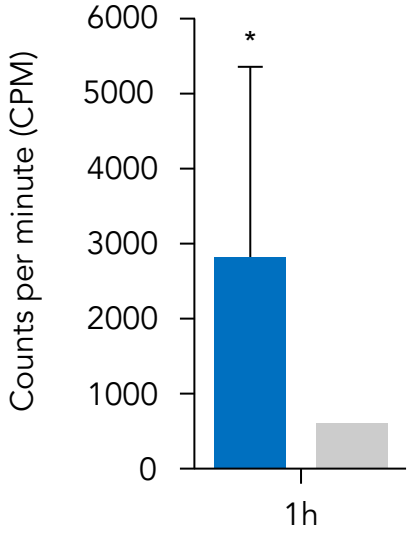
Micelles Appear Safe & Tolerable

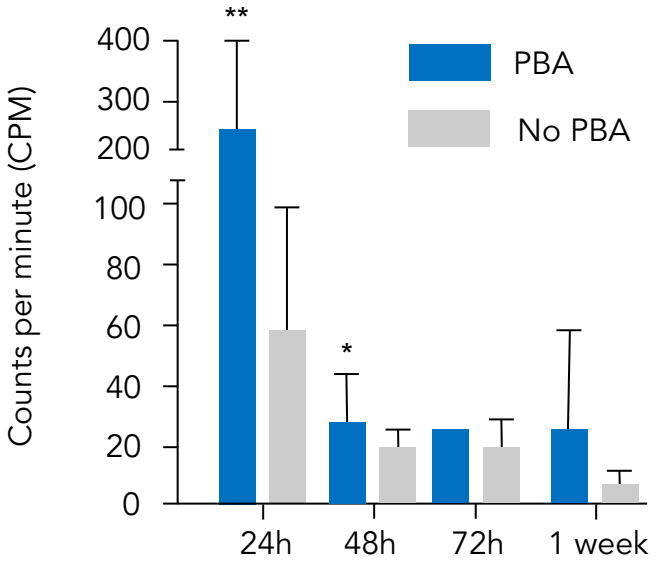
Significantly more mucin binding when PBA is present confirmed:

- In vitro: Surface plasmon resonance (SPR)
- In vivo: 1-125 Radiolabelling









Comparison of Clinical Efficacy to Restasis®

A scopolamine induced dry eye disease rat model

Restasis®

0.05% cyclosporine

- TWICE PER DAY
- EVERY 3 DAYS

OptimEyes Micelle Formulation

0.075% cyclosporine A

- TWICE PER DAY
- EVERY 3 DAYS
- EVERY 5 DAYS

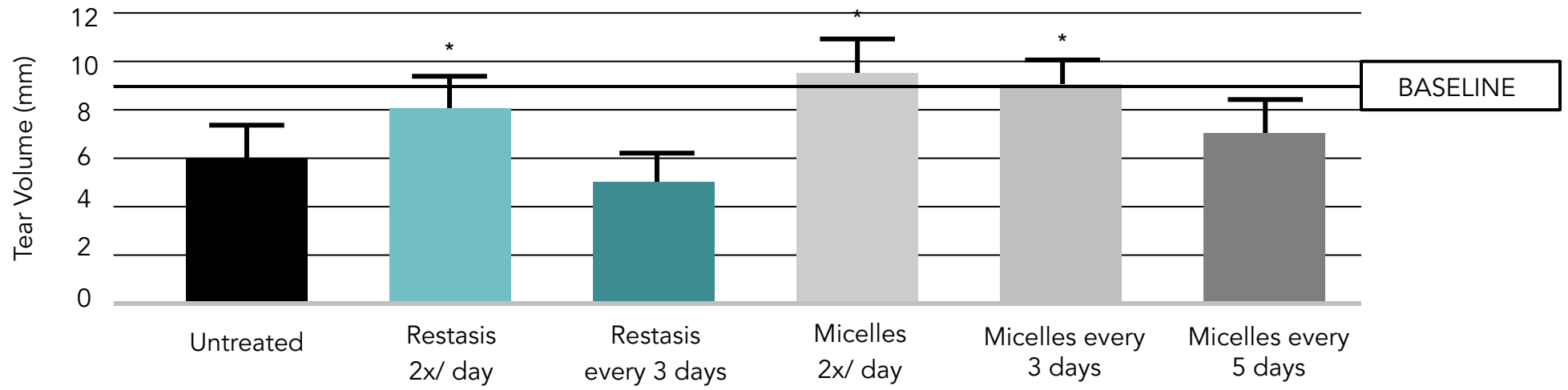
20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

Tear Volume Returns to Baseline



Micelles dosed once every three days is equivalent to Restasis twice daily

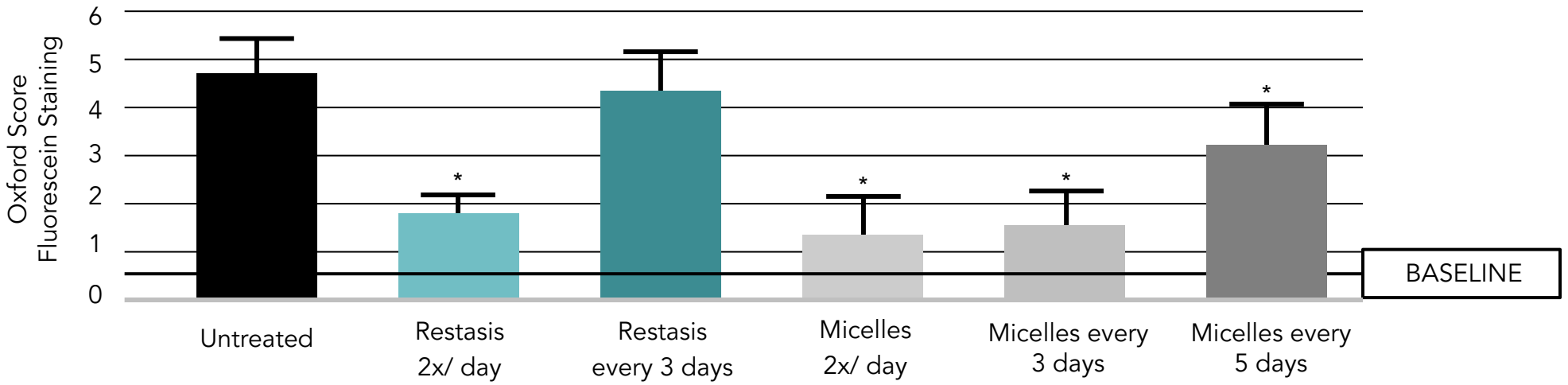
20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

Staining Returns to Baseline



Micelles dosed once every three days is equivalent to Restasis twice daily

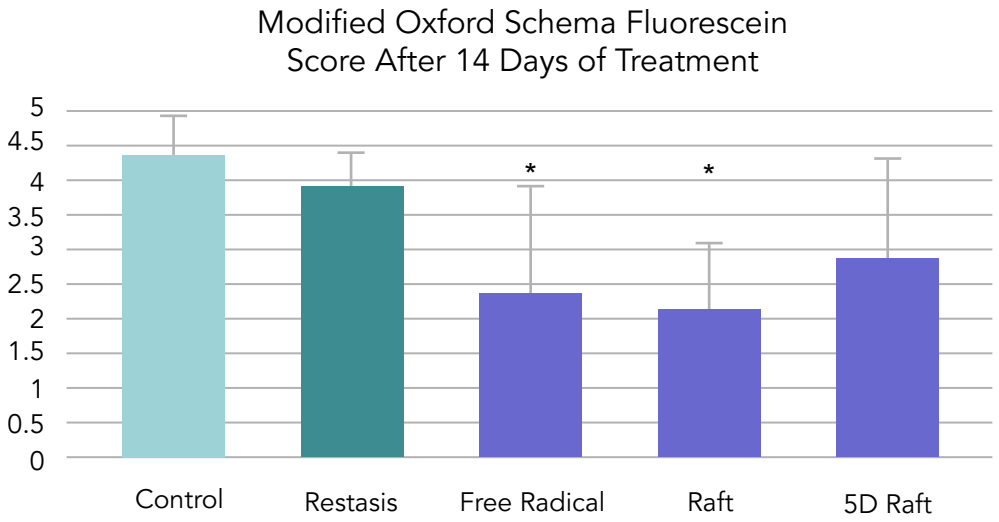
20|20 OptimEyes Technologies

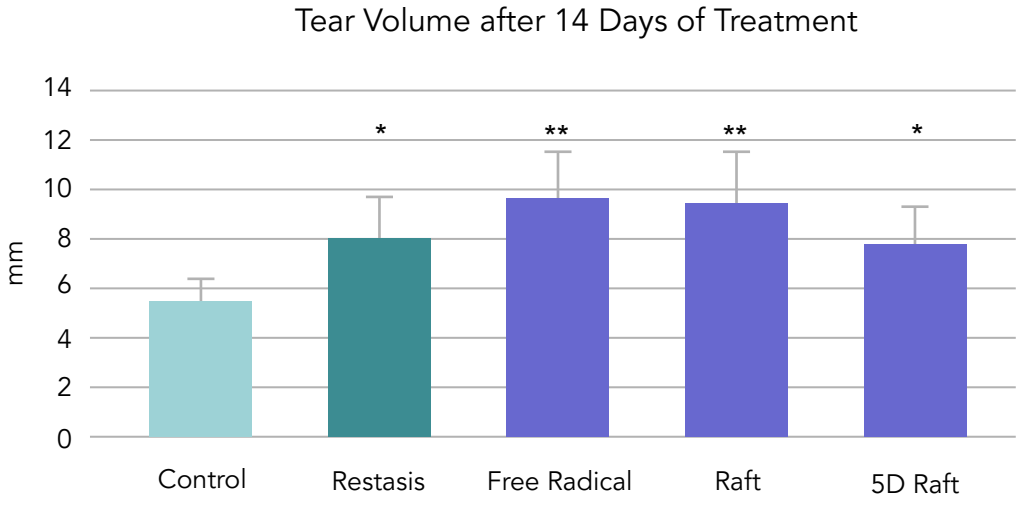
C 20 | 20

SHEARDOWNLAB

McMaster University

Higher Concentration Micelles Prepared by Free Radical Polymerization





20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

Comparison of Corneal Bioavailability

Results after 15 days in New Zealand White Rabbits

Restasis®

0.05% cyclosporine A

TWICE PER DAY

OptimEyes Micelle Formulation

0.15% cyclosporine A

TWICE PER DAY

EVERY 3 DAYS

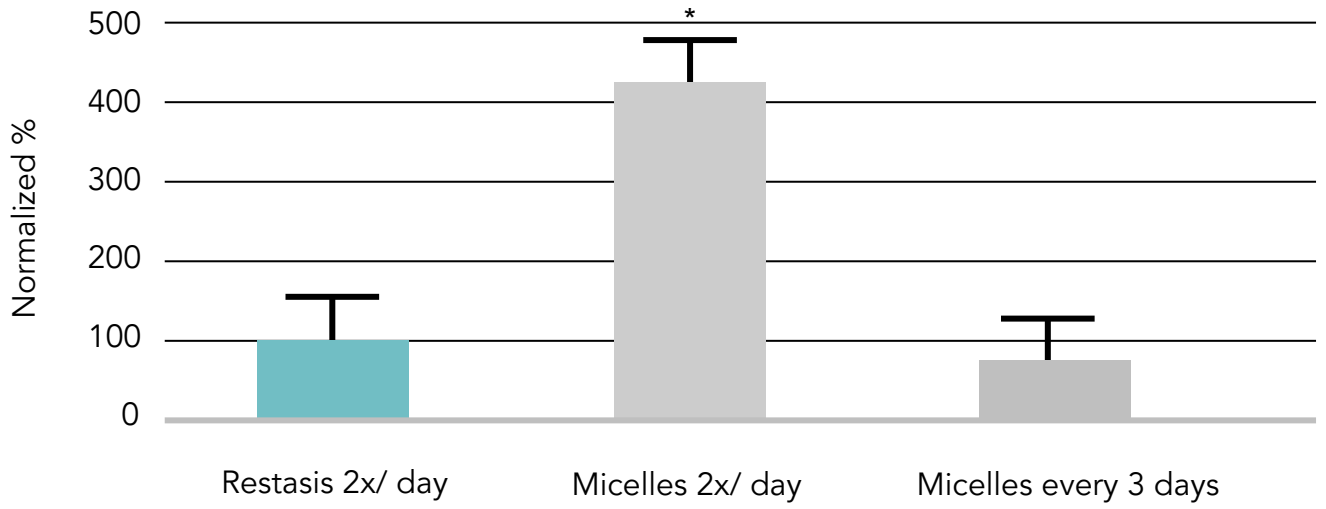
20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

Corneal Bioavailability



Micelles ocular adherence and sustained release provide greater corneal drug amounts relative to Restasis®

20|20 OptimEyes Technologies

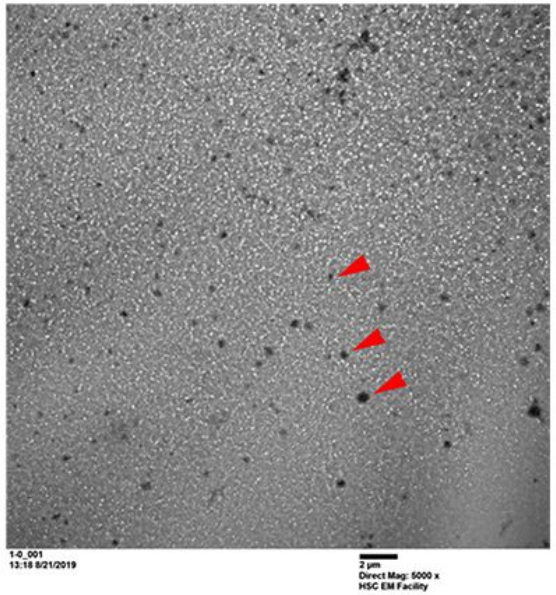
C 20 | 20

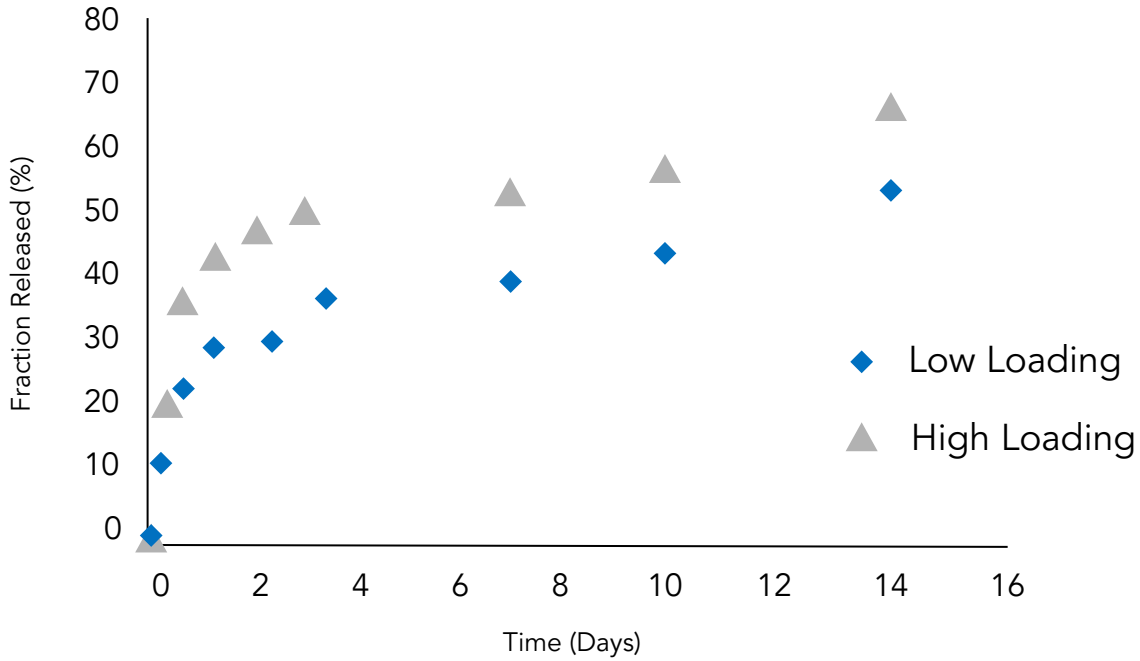
SHEARDOWNLAB

McMaster University

Latanoprost as an Alternate Therapeutic

A) Transmission electron micrographs of the micelles (arrowheads). Scale bars, 2μm. B) % release of latanoprost from micelle-latanoprost conjugate





20|20 OptimEyes Technologies

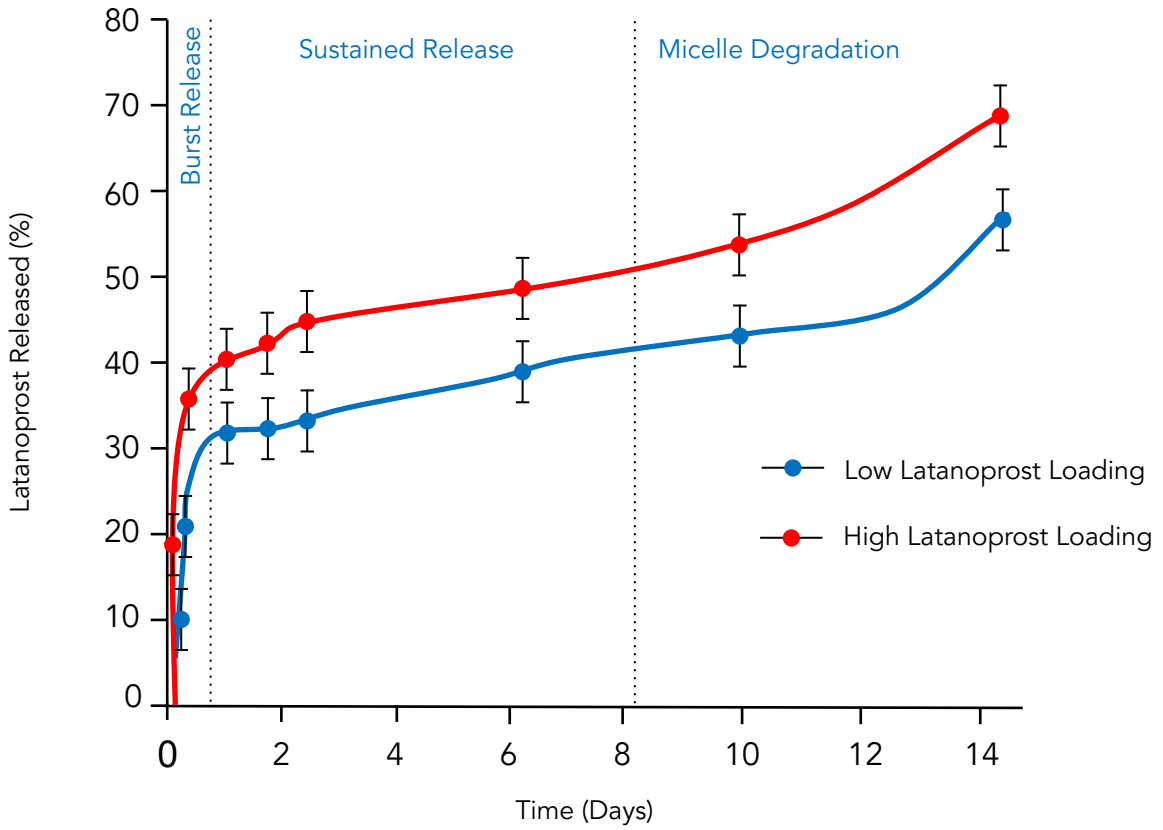
C 20 | 20

SHEARDOWNLAB

McMaster University

Release can be Tailored by Loading

- Higher loading gives a similar release profile but more drug release
- Micelle degradation seems to occur after about 12 days, with a second burst following this



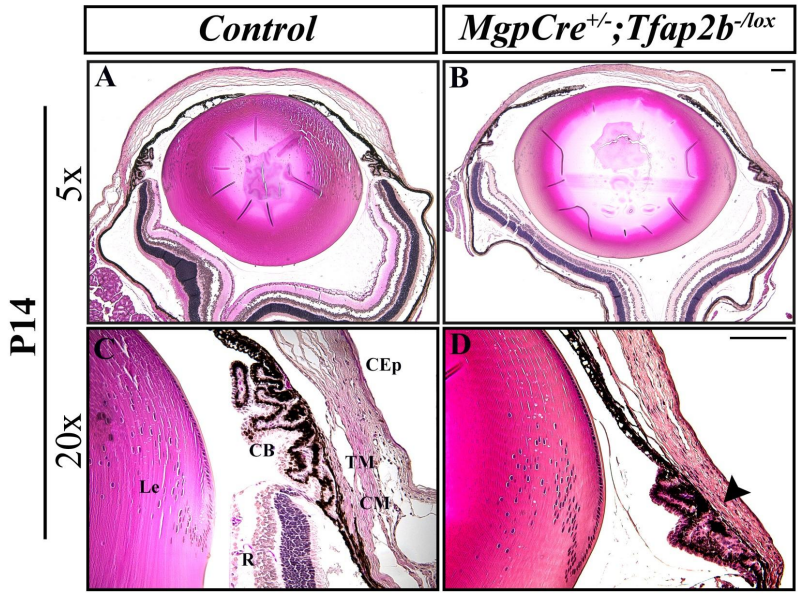
20|20 OptimEyes Technologies

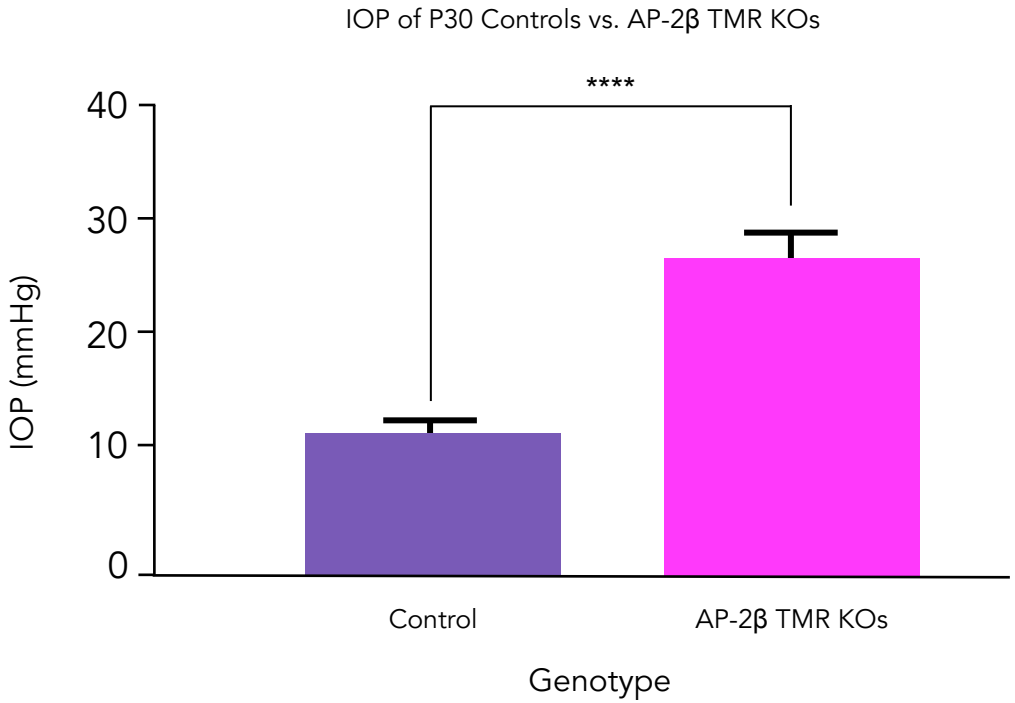
C20|20

SHEARDOWNLAB

McMaster University

Testing in a Novel Glaucoma Model





20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

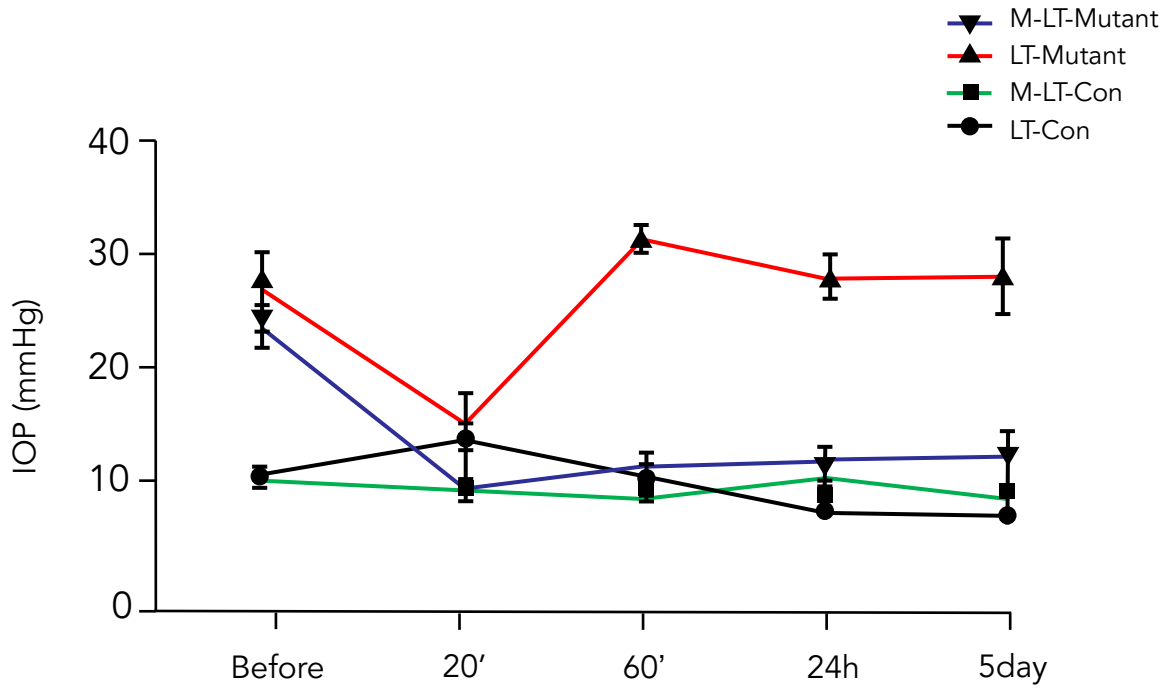
Treatment Protocol

Mutant and wild-type littermates were used for the experiments.

5 mL of blank micelle, 0.005% Latanoprost (50ng/mL) or micelle loaded with 0.05% Latanoprost was administered in the mouse eyes every 5 days.

IOPs were taken before and after administering the drops.

Effect of Latanoprost Micelles on IOP in Glaucomatous Mice



20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

Micelle Properties with Alternate Drugs

Drug	Solubility (Water)	Uses	Dosage Form	Drug Loading	Release character	Micelle Size (nm)
Cyclosporine A	0.08 mg/mL	Tear modulator	0.05% Emulsion 500 µg/mL	1.95 mg/mL	Prolonged release over 10 days	131.5 ± 1.00
Latanoprost	0.05 mg/mL	Glaucoma	0.005% Solution 50 µg/mL	2.5 mg/mL	Biphasic release over 14 days	92 ± 3.42
Hydroxy-chloroquine	20 µg/mL	Anti-malarial	400 mg (oral)	751 µg/mL	Complete release within 72 hours	

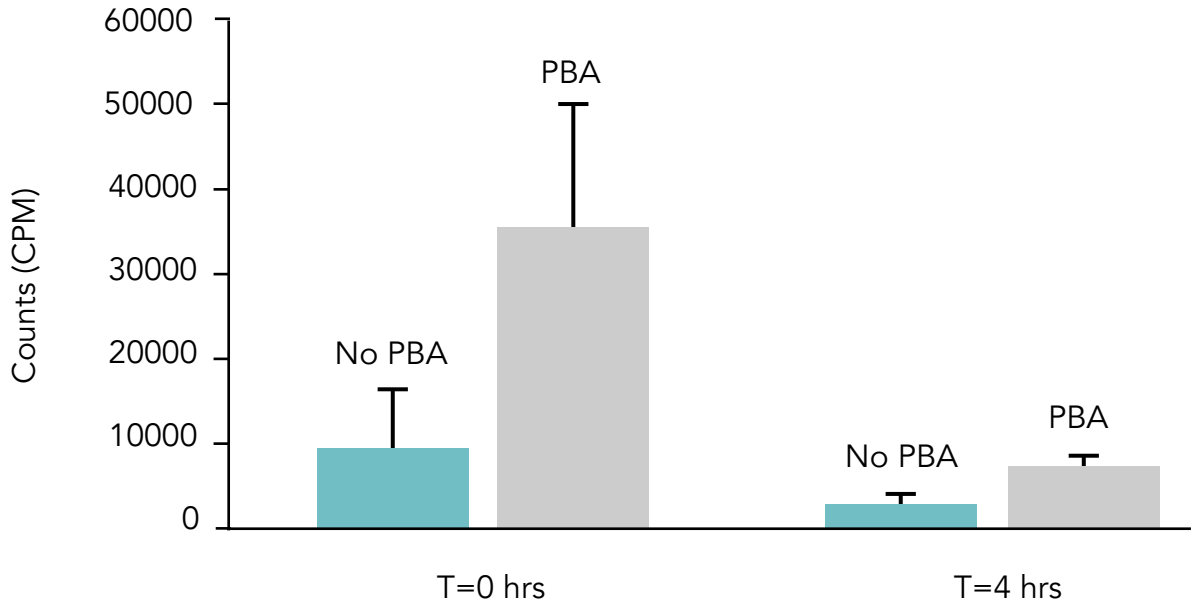
20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

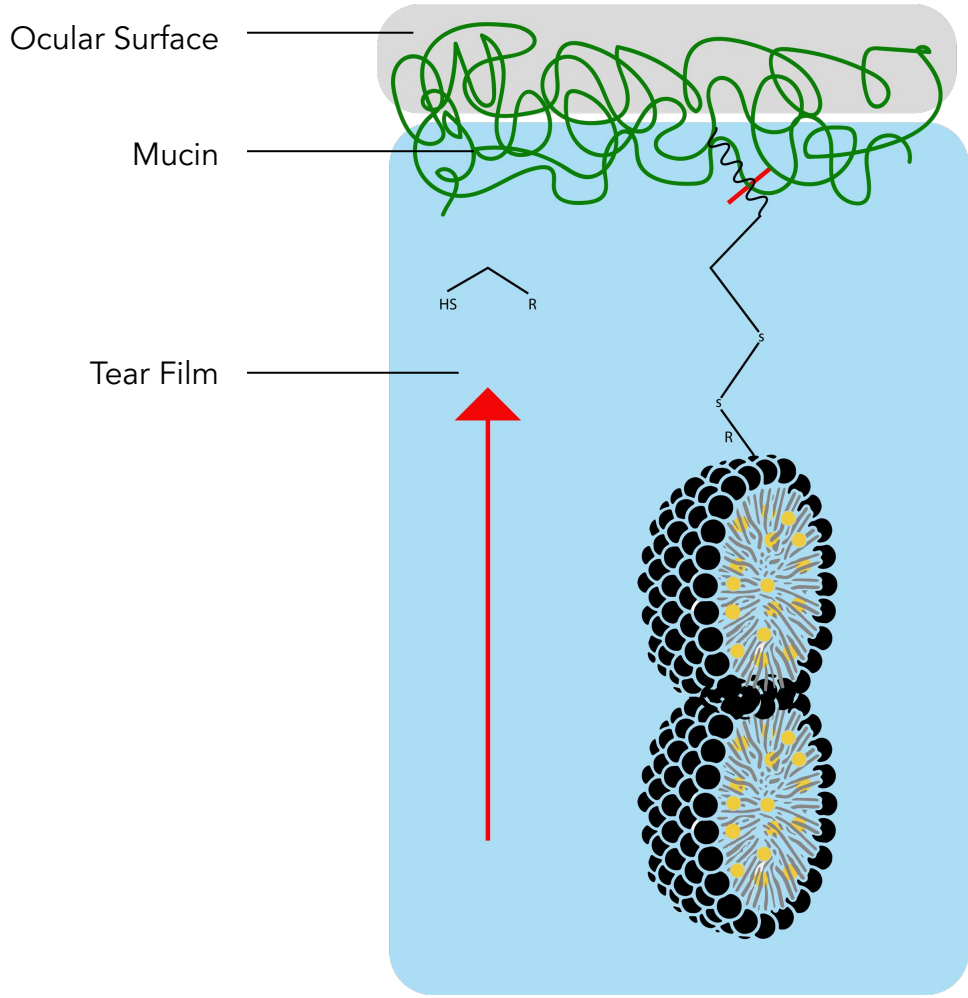
McMaster University

Nasal Administration of Micelles



Alternative Formulations – Thiol Binding

- Nanoparticle travels through tear film to mucin-layer
- Thiol-disulfide exchange occurs, binding the nanoparticle to the mucin-layer
- Small thiol molecule leaving group provides secondary benefits



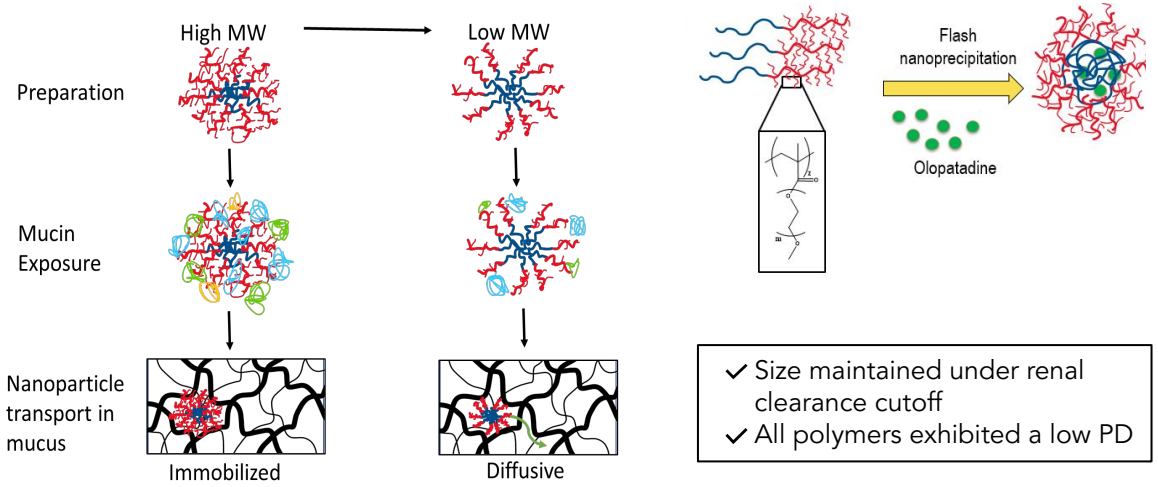
R = Small Thiol Molecule

Alternative Formulations: Mucoadhesive/Mucopenetrative Nanoparticles

(1) Mucoadhesive nanocarriers – adhere to the tear film mucin proteins to allow for localization of drug at the site of absorption

(2) Mucopenetrative nanocarriers – penetrate through the tear film mucins to directly reach the underlying epithelium for localized drug delivery

- Linear-brush copolymers based on polylactic acid (PLA) and poly(oligo(ethylene glycol) methacrylate) (POEGMA), a brush polymer derivative of PEG:
- Offers the capacity of easy functionalization of PEG-based polymer
- Facilitates tunable molecular weight distributions
  - Offers potential to balance mucopenetration/ mucoadhesion
- Incorporation of a poorly soluble drug (i.e. olopatadine for treatment of allergic conjunctivitis) during NP synthesis via flash nano precipitation



- ✓ Size maintained under renal clearance cutoff
- ✓ All polymers exhibited a low PD

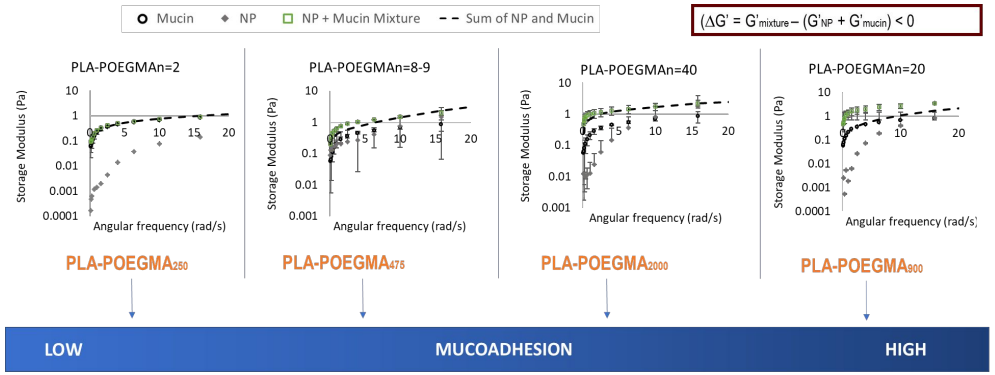
Name	#OEGMA monomer repeat units	Synthesis Time (min)	Mn (g/mol)	Mw (g/mol)	Đ
PLA-POEGMA250	4	180	18800	25200	1.34
PLA-POEGMA475	7-9	45	17500	24700	1.41
PLA-POEGMA900	20	40	30800	42900	1.40
PLA-POEGMA2000	40	15	27300	34100	1.25

20|20 OptimEyes Technologies

C20|20

SHEARDOWNLAB

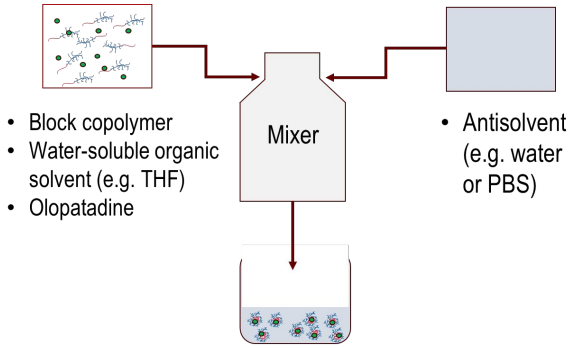
McMaster University



Nanoparticle Fabrication:

Nanoparticles fabrication through flash nanoprecipitation:

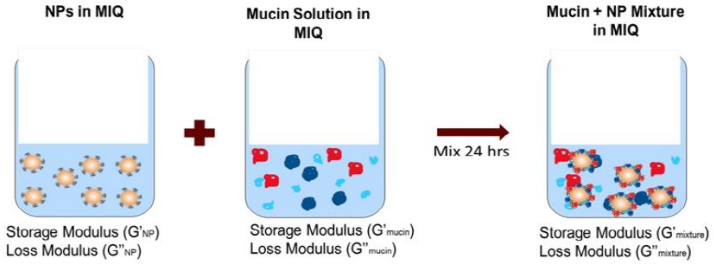
- Nanoparticle size can be tuned through (1) choice of organic solvent and (2) injection flow rate through mixer.



Rheology:

Assessing mucoadhesive properties of PLA-POEGMA NPs through Rheology:

- The Rheological response of the NP-mucin mixture should be greater than the contributions from the NPs and mucin alone for mucoadhesive polymers.



	Average Eff Diameter	Average Polydispersity
PLA-POEGMA 250	217 ± 1.37	0.15 ± 0.04
PLA-POEGMA 475	56 ± 0.55	0.24 ± 0.01
PLA-POEGMA 900	80 ± 0.99	0.16 ± 0.01
PLA-POEGMA 2000	82 ± 0.67	0.15 ± 0.02

20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University

Conclusions

OptimEyes Therapeutics

Internal Product Development

1-2 per week high-dose Cyclosporine A

Once per week latanoprost

Other Potential Once-Per-Week Therapeutics

20|20 OptimEyes Technologies

Strategic Partnership

External Collaborations

Wide Spectrum of small molecules

Feasibility Studies & Licensing Agreements

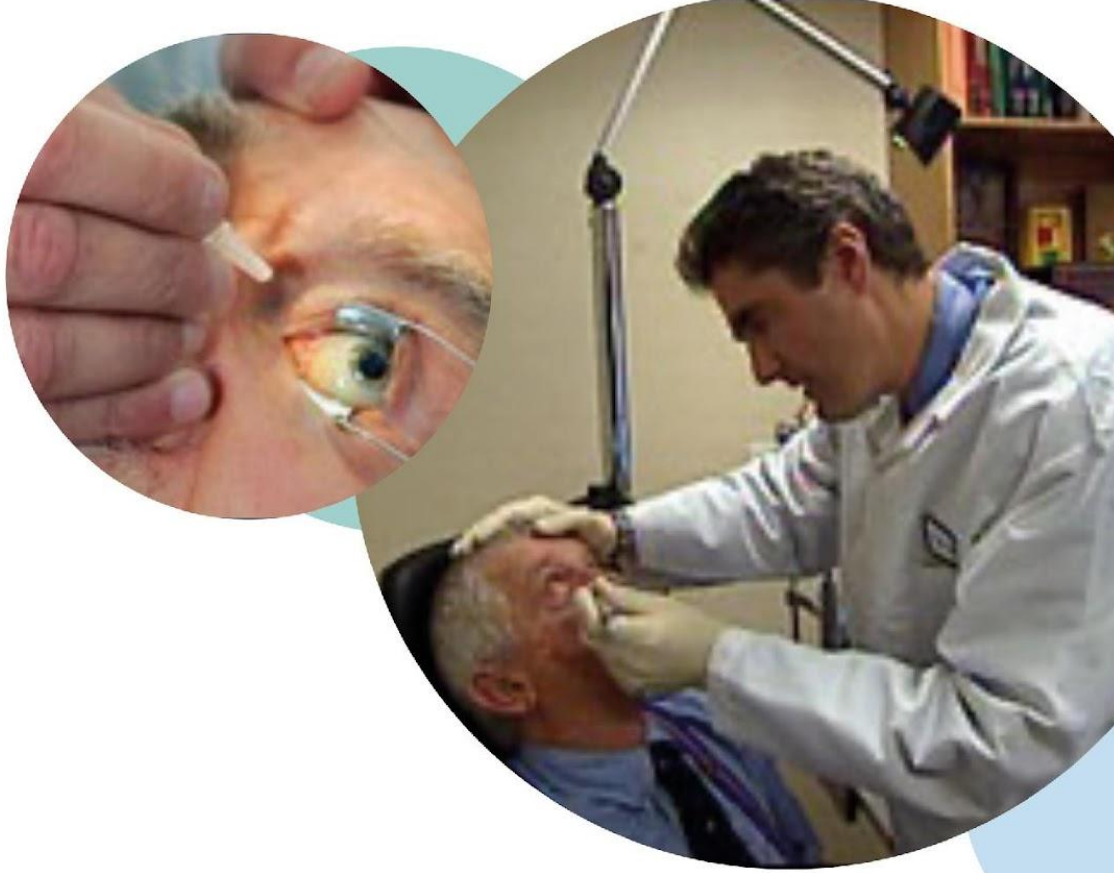
20|20 OptimEyes Technologies

C20|20

SHEARDOWNLAB

McMaster University

Acknowledgements



Sheardown lab group – Graeme Prosperi-Porta, Lina Liu, Talena Rambarran, Karim Soliman, Ben Muirhead, Taylor Goostrey, Ridhdhi Dave, Aftab Taiyab, Fran Lasowski

West-Mays group

Andy Whitlock

Afecta Pharmaceuticals

Funding – NSERC, CIHR, ORF

20|20 OptimEyes Technologies

C 20 | 20

SHEARDOWNLAB

McMaster University