238 - C0049

Sustained Release of Small, Hydrophilic Peptides to the Ocular Surface via NanoM™

Shikha P. Barman, Yang Li, Laura Kaminski, Chunhong Li and Kevin L. Ward
Integral BioSystems, LLC, Bedford, MA

Issues with Peptide Delivery to the Ocular Surface

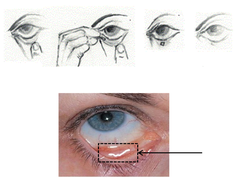
There is increasing interest in the use of therapeutic ophthalmic peptides to develop therapies to address ocular disorders. Clinical trials in dry eye, microbial keratitis and corneal injury are underway. Peptides have high receptor specificity, promising more effective therapy compared to small molecule pharmaceuticals. Peptides can vary in structure and molecular weight resulting in a range of physico-chemical properties. Most peptides have high water solubility, and are susceptible to oxidation and to rapid proteolytic degradation. The synergistic effect of these attributes is a short peptide half-life and fleeting residence time on the ocular surface, compromising their therapeutic effect and requiring dosing as frequently as 5-6 times daily.

A sustained release delivery system is a rational solution to these issues; protection of the peptide from proteolysis can be achieved by encapsulation within a matrix, while releasing the active in a sustained manner. An ocular delivery system that will reside on the surface of the eye has target performance characteristics of comfort, sustained drug release, biodegradability and ease of placement. This requires a bioengineering approach to product design, in order to strike a balance between these critical quality attributes.

NanoM™ Wafer is a novel drug delivery system that effectively encapsulates peptides in an intact fashion, is biodegradable, and is self-administered into the conjunctival fornix. It can be developed to release intact drug in a sustained fashion. The peptide in these studies is a 39 amino acid chain with a molecular weight of ~4200 g/mole, and it is highly soluble in water.

Sterile NanoM Wafer: Applied without Clinical Intervention, Biodegradable, Biocompatible

Method of Placement

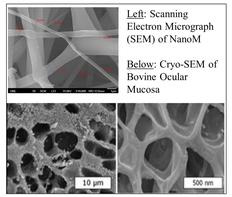


- Dimensions : 8-10 mm length x0.150-0.200mm thickness x 1-2 mm width
- Placement: In lower conjunctival fornix, then hydrated with two drops of a buffering solution.
- Translucent hydrogel upon hydration
- Fluids permeable (O_2, CO_2, H_2O)
- >90% water in hydrogel
- ~45-50 µg/mg loading

Materials & Methods

- Fabrication: The NanoM Wafer was fabricated using a proprietary process that generates an intercalated structure of interstitial pore size ~50-100 nm and containing 45-50 µg/mg of peptide. Post-fabrication, the wafer was dried under vacuum to remove residual solvents.
- Encapsulation (µg/mg): 10-20 mg of the drug product was sonicated in 1mL of an aqueous buffer, to dissolve all contents. Ethanol was added to precipitate the polymer, and the slurry was centrifuged. The supernatant was removed for HPLC analysis (RP C18 column) and analyzed for peptide content.
- Peptide Integrity: The drug product was dissolved as described above for encapsulation, and analyzed for degradation products characterized as % oxidization, etc.
- *In-Vitro* Release (%): (20-40 mg) samples were placed in 1 mL Float-a-lyzer tubes, suspended in 40 g of buffer and rotated at 37ºC. Time point samples were taken over the duration of study and analyzed by HPLC.
- Thickness: was measured (n=3) by a Mitutoyo Screw Gauge.
- Quantification of Mechanical Adhesive Strength of NanoWafer to Tissue: Measurement of Mechanical Adhesive Strength to conjunctival tissue was assessed using a Shimadzu Mechanical Tensile tester. A representative sample of the NanoM wafer was applied to hydrated bovine conjunctival tissue. The force required to pull apart the wafer from the tissue was recorded in N (stress)/mm (strain)(Peel Test).
- EpiOcular Testing: Hydrated wafers were tested for irritation using the Epiocular Corneal Construct Model (Cyptorex, LLC).
- Preliminary In-vivo Irritation Assessment: *In vivo* studies with placebo NanoM wafers were conducted in normotensive New England White rabbits at Pine Acres Rabbitry Farm, Norton, MA. Sterile NanoM are inserted (placebo NanoM wafers) into the conjunctival cul de sac of each eye of the rabbit. Baseline redness of each eye was assessed before and after NanoM placement. The rabbits were assessed for 2-3 hours. General irritation assessments were made.

NanoM Wafer: Mucosa-Mimetic, Mucosa-Active → High Biocompatibility

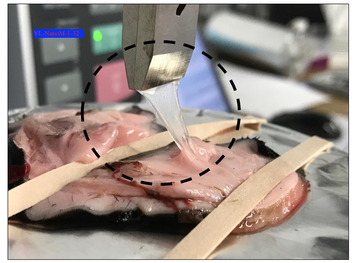


- Structural Porosity of NanoM Wafer is mimetic of ocular mucosa.
- After hydration, consistency of NanoM wafer is similar to ocular mucosa.
- After hydration, bioadhesion of NanoM to tissue occurs.

NanoM Wafer: Rapidly Hydrating and Translucent due to Nano-architecture

NanoM Wafer rapidly hydrates into a flexible hydrogel that adheres to conjunctival mucosa. % hydration = ~75%

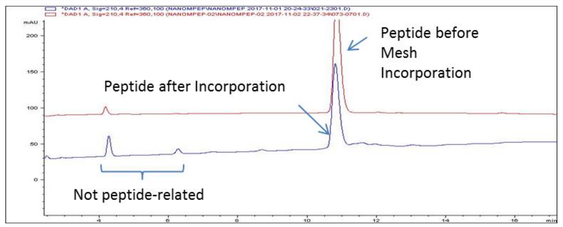
Surface characteristics of NanoM Wafer enable light bonding to conjunctival tissue until it biodegrades



Bonding occurs ~30 minutes after application of wafer and hydrating buffer.

This allows removal of wafer if applied incorrectly.

NanoM Wafer : Encapsulation of Intact Peptide

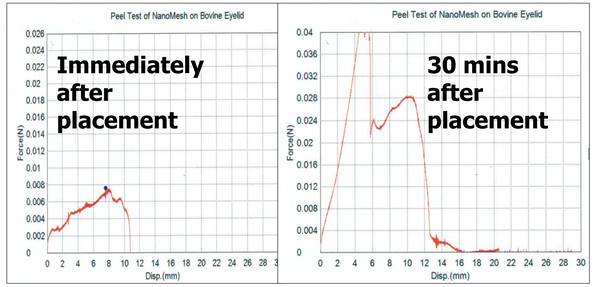


Flexible Pliable NanoM Wafer: Biocompatibility Tests

No redness, animal discomfort or irritation were noted in normotensive rabbit eyes for placebo NanoM of maximum thickness, for the duration of the study. Peptide-NanoM not tested.

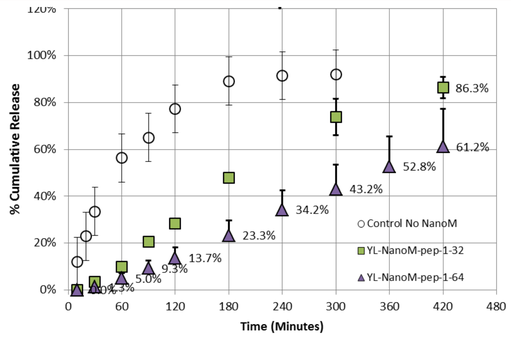
Hydrated placebo NanoM wafers were classified as "non-irritants" in the Epiocular Model, with 0.5% BAK used as control irritant.

Bioadhesion to tissue occurs ~30 minutes after application of NanoM wafer (Peel Test)



Bonding occurs ~30 minutes after application of wafer and hydrating buffer. This allows removal of wafer if applied incorrectly.

Peptide Release Rate is Modulated by NanoM Composition



Control: No NanoM; YL-NanoM-pep-32 (composition 1); YL-NanoM-pep-64 (composition 2)

Conclusions and Future Work

- The feasibility of NanoM as a sustained release platform to deliver water-soluble peptides has been demonstrated. Even for immediate release prototypes, this mode of delivery is more efficient than eye-drops.
- Future work will involve optimization of the product for biodegradability, mucoadhesivity, and flexibility using stress/stain mechanical property testing.
- Irritation testing

Contact Information

sbarman@integralbiosystems.com

2018 ARVO Annual Meeting, Eye and Vision Research, April 29-May 3, 2018, Honolulu, Hawaii