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Sustained Release of Peptides to the Ocular Surface *via* NanoM™ Wafer

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Peptide Delivery to the Ocular Surface

Therapeutic peptides offer certain advantages as ocular drugs; these include their high biological activity, high specificity and low toxicity. Therapeutic peptides have found applications in chronic dry eye disease, glaucoma and corneal wound healing. Most of the peptides are less than 100 amino acids and range in physiochemical properties such as log P, pka and cell permeability. However, most of the peptides demonstrate low half lives in-vivo, either by high rates of metabolism, or high rates of proteolytic cleavage causing inactivation. Additionally, peptides that are highly water soluble are rapidly cleared from the ocular surface, requiring dosing as frequently as 5-6 times daily. A sustained release delivery system is a logical 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.

We have developed a novel drug delivery system (DDS), the NanoM Wafer, that can effectively encapsulate peptides in an intact fashion, is biodegradable, is self-administered into the conjunctival fornix, and which can be developed to release intact drug over 1 day to 1 week. The properties of the DDS were matched to the tissue to maximize biocompatibility and minimize a foreign-body response to the device. As a model compound, we have selected a 39-mer poly (amino acid) with a molecular weight of 3900 g/mole and with high solubility in water.

We present characterization data that demonstrates encapsulation of intact drug peptide, % water sorption, biodegradation time and modulation of peptide release, from the NanoM™ Wafer.

NanoM Wafer is Self-Applied to the Conjunctival Fornix

Intercalated Nanostructure and Proprietary Excipient Composition of NanoM Wafer contributes to bioadhesion to tissue, biodegradability and sustained release.

Materials & Methods

Characterization:

○**Fabrication:** The NanoM Wafer was fabricated using a proprietary process that generates an intercalated structure of interstitial pore size ~50-100 nm. Post-fabrication, the wafer was dried in vaccum to remove residual solvents.

○**Encapsulation (mg/G)**: 20 mg of the drug product was dissolved in 1mL of a dissolution solvent, to dissolve all contents. 1 mL of an aqueous solution was added to precipitate the polymer. 1mL of the slurry was centrifuged and the supernatant was removed for HPLC analysis (RP C18 column) and analyzed for peptide content. Peptide encapsulation is expressed in µg peptide/mg product.

○**Peptide Integrity:** The drug product was dissolved in an organic solvent and analyzed for degradation products characterized as % oxidization, etc.

○***In-Vitro* Release and 1 hr burst (%):** (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.

○**Bovine Bioadhesion Studies**: Prototypes were tested for ex-vivo bioadhesion by applying the meshes onto fresh bovine eyelid conjunctival tissue and incubated in phosphate buffer containing glutathione (2-5℃). The meshes were periodically tested for delamination from the tissue, at least once per day. The following scoring system was used. 0=delaminated at T=0, 1=delaminated after 4 hours, 2=delaminated after 1 day, 3=delaminated after 2 days, 4=did not delaminate in 3 days. The tissue could not be maintained after 3 days.

○**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 using the Epiocular Corneal Construct Model (Cyptorex, LLC).

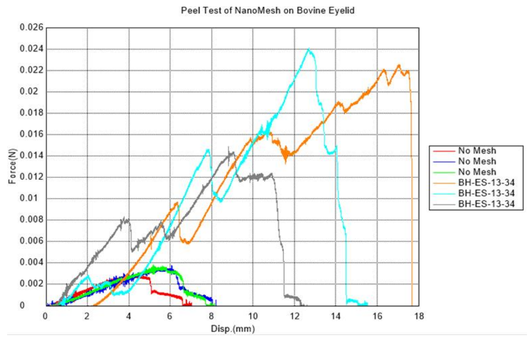
○**Preliminary In-vivo Irritation Assessment**: *In vivo* studies with placebo NanoM wafers were conducted in normotensive New England White rabbits at Toxikon Corp, Bedford, MA. Sterile NanoM are inserted (blank nanomesh into the conjunctival cul de sac of each eye of the rabbit. Baseline redness of each eye was assessed before and after mesh placement. The rabbits were assessed for 2-3 hours. No peptide-containing NanoM were tested.

Results

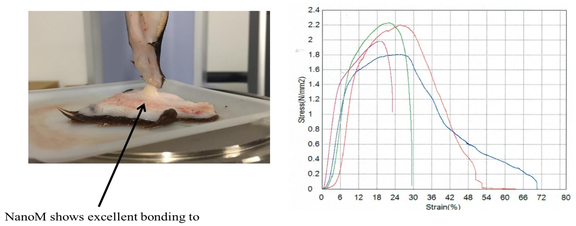
Nano-engineered NanoM Critical Product Attributes

Attributes	Results
NanoM-Peptide Dimensions	0.250mm (thickness) x 0.5 mm (depth) x 5 mm (length)
Encapsulation (mg/g)	~10 microgram/mg
% Burst	Varies based on composition
% hydration in 30 seconds	~116%-~145%

Nano-engineered NanoM Wafer adheres to bovine conjunctival tissue, *ex-vivo: Stress-Strain Curves*



NanoM Wafer is bonded to tissue (no delamination) after 3 days in PBS, pH 7.4, 37℃



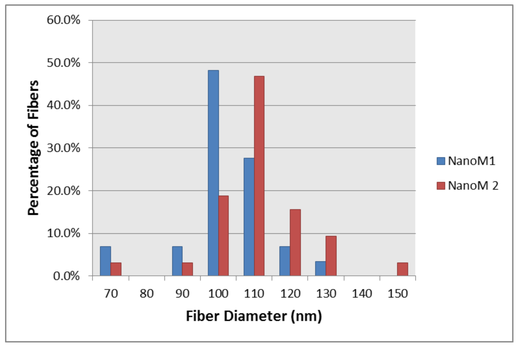
Placebo NanoM Wafer Irritation Testing

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.

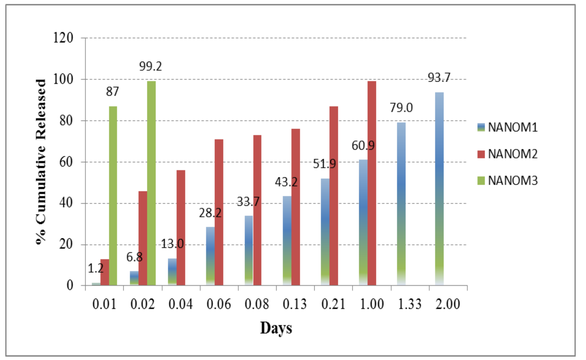
Hydrated placebo meshes were classified as "non-irritants" in the Epiocular Model, with 0.5% BAK used as control irritant.

Results

Peptide-Containing Intercalated Polymers have diameters between 100-120 nm: Thickness is a parametric variable that controls drug release rate



Formulation Variants of NanoM Wafer can modulate release of peptide from 1 day to 5 days



-NanoM-1 : PLGA-based; NanoM-2: Aqueous polymer-based; NanoM-3: Aqueous polymer-based

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, flexibility using stress/stain mechanical property testing.
- Irritation testing
- Ex-vivo perfusion drug release

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