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Delivery of Proteins to the Ocular Surface *via* NanoM-Wafer DDS

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The Problem: Delivering Water-Soluble Proteins to the Ocular Surface

The ocular surface is rich in a diverse array of proteins, each playing a crucial role in maintaining its structural integrity, protecting it from infection, lubricating the eye, and regulating tear production. Macromolecules like lumican, keratocan and mimecan are found in the corneal stroma and help maintain corneal transparency, with suppressed protein expression invariably leading to dysfunction. Therapeutic approaches can be via pharmacologic targeting of receptors with both biologic and small molecule therapies. Protein, peptide or nucleic acid therapies for ocular surface disorders are primarily by eye-drops, which lead to rapid wash-out due to high turn-over of the tear fluid and naso-lacrimal drainage. This leads frequent administration of the eye-drop formulation, often 4-6 times per day to obtain a therapeutic effect. Additionally, protein solutions are inherently unstable long-term, requiring storage of the eye-drop formulation in the frozen state (such as Oxervate®). In envisioning a protein product, it is logical to design a delivery system that can deliver intact protein in therapeutic concentrations on the ocular surface, for multiple days. An ophthalmic insert that maintains integrity of the encapsulated protein at physiological temperature and pH (37°C, pH 7.4), releases functional protein for multiple days, is stable in storage and can be self-administered is a logical design improvement for sustained delivery of proteins. We have developed a protein-containing nanostructured ocular insert (NanoM-Wafer™) that is placed into the lower conjunctival fornix in an elastomeric dry form. The flexural modulus and dimensional stability of the wafer contributes to the biocompatibility at the target site. The delivery system is designed to be matched in flexural modulus to ocular conjunctival fornix. We hypothesized that proteins of various molecular weights can be encapsulated intact in the ocular insert, with >80% integrity, measured by SEC. We demonstrate sustained release of intact protein from the wafer at 37°C, pH 7.4 for > 14 days. Acute tolerability was measured in New Zealand White rabbit eyes.

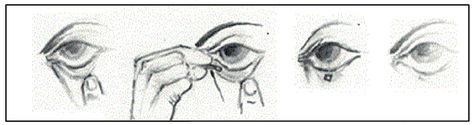
Materials and Methods (Characterization and *In-Vivo*)

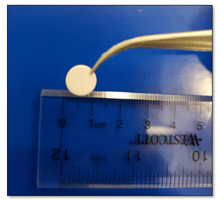
Fabrication : NanoM Wafer prototypes were fabricated by a proprietary process that resulted in an unique layered, intercalated microstructure, which enabled sustained release of the proteins. The wafer contained combinations of polymers and excipients compatible to the proteins. Proteins varied in molecular weight: 10-30 kDa, 60-70 kDa and 110-125 kDa. **Thickness:** Fabricated NanoM wafers were measured (n=3) by a Mitutoyo Screw Gauge. **Encapsulation (µg/mg):** 10 mg of the dry wafer was dissolved in an appropriate organic solvent, to dissolve the wafer polymer, leaving the protein undissolved. The dissolved polymer is removed by centrifugation, and the protein pellet is dried and reconstituted. The solution was analyzed for protein concentration to calculate % encapsulation and assay (mg/g). The chromatograms were analyzed for %HMW species and %monomeric protein. **Stress-Strain studies**: Stress-strain studies were performed using the Shimadzu EZ-tensile tester, to evaluate the elastomeric properties of the wafer. ***In-Vitro* Release (%):** (10 mg) samples were evaluated for in-vitro release at 37ºC, using a low-volume proprietary method. Time point samples were taken over the duration of study and analyzed by SEC HPLC for protein released. **Safety and Tolerability**: of the prototypes were measured by assessment of ocular tissue, after placement of the prototypes. Tolerability of the wafers were assessed by a SPOTS scoring system (Eaton, et. al. 2017). Sterilization of wafers were accomplished by exposing pre-packaged wafers to cold sterilizing radiation.

NanoM-Wafers in the Rabbit Eye are Adherent and Demonstrate no Adverse Effects at Placement

- ✓ Acute Tolerability: No redness, hyperemia, discharge, corneal opacity was noted upon placement of the insert.
- ✓ The wafer was translucent and adherent to underlying tissue.

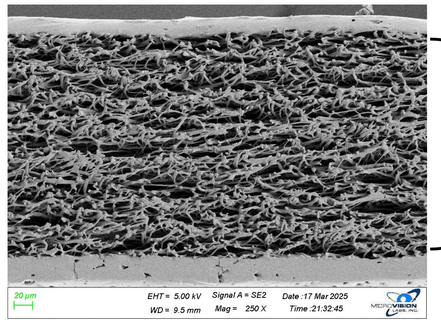
NanoM Wafer: Applied without Clinical Intervention, Biocompatible



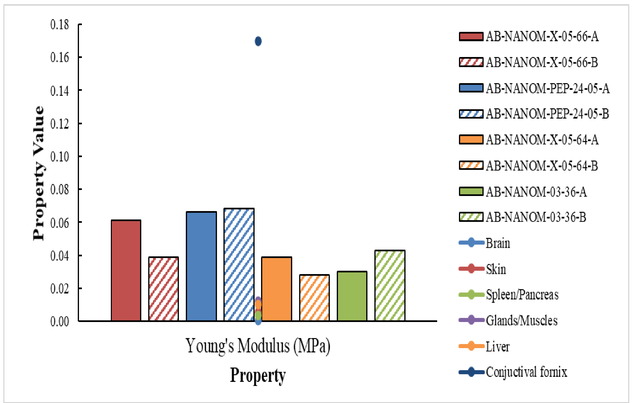


- ✓Thickness : 150-250 microns
- ✓% Hydration : 110-125%
- ✓% Strain at break : > 300 mPa
- ✓ Encapsulation (mg/g) : 3-50 micrograms/wafer (as needed)
- ✓Residual Solvent : < 0.5%

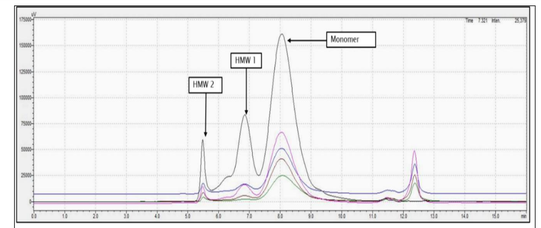
Scanning Electron Micrographs (SEM) of Protein-Containing NanoM Wafers (Cross-sectional View)



Young Modulus of the Hydrated NanoM Wafer Inserts are Comparable to Underlying Soft Tissue



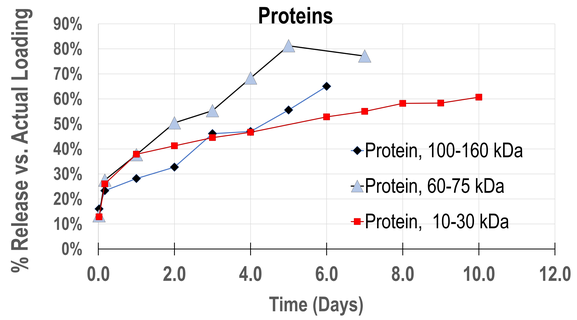
Intact Protein is Released at Every Timepoint



RRT		1mg/g IgG Standard	T= 0.5h	T= 24h	T=120h	T=192h
1	% Monomer	69.39	79.3	82.6	86.5	91.2
0.85	% HMW 1	25.3	16.2	12.9	9	5.2
0.69	% HMW 2	5.31	4.5	4.5	4.5	3.6
N/A	% LMW	0	0	0	0	0

Timepoint (hour)	Buffer Removed (g)	AUC	%IgG	mg/g	Adj. (IgG)	Total mg	% Release
0.5	0.2588	335907	0.0078	0	0.0117		29.19
1.5	0.2512	317784	0.0074	0.0020	0.0132		22.72
2	0.2534	304635	0.0071	0.0039	0.0146		25.25
4	0.2587	251806	0.0061	0.0057	0.0149		25.65
22	0.2603	250682	0.0061	0.0073	0.0164		28.31
72	0.2589	353389	0.0083	0.0088	0.0211		36.32
120	0.2515	544954	0.0119	0.0109	0.0289		49.78
168	0.2534	812925	0.0172	0.0139	0.0399		68.71

Terminally Sterilized Wafers Demonstrate Sustained Release of Proteins at Different Molecular Weights



Conclusions and Considerations

This work-in-progress presentation demonstrates feasibility of a versatile, tolerable wafer insert that can be suitably self-administered within the conjunctival fornix, to form an adherent film wafer. The wafer:

(a) Can be utilized to deliver proteins, peptides and nucleic acids,

(b) Can be utilized as a delivery system for other indications such as glaucoma.

(c) Can be sterilized and scaled up.

Acknowledgments

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