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A Biomimetic Dissolvable Artificial Tear Insert to Replenish Lipid and Aqueous Tear Components

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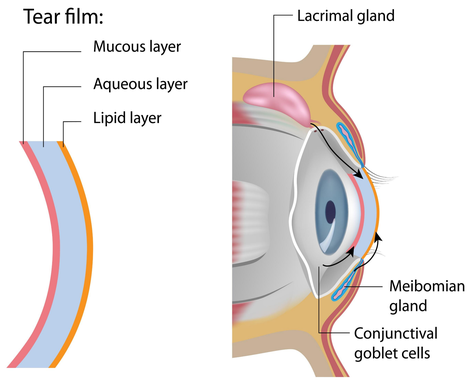
Dry Eye: Lipid and Aqueous Misbalance of the Tear Film

Dry eye is a definable disease characterized by inflammation, loss of integrity of the protective tear film and loss in tear volume caused by deficiencies in the balance of the lipid to aqueous parts that comprise the tear film. Numerous artificial tear brands (Systane® series, Refresh Optiva®) have been developed and commercialized as artificial tears to alleviate symptoms of dry eye disease, *via* replenishment of lubrication of the ocular surface.



We have envisioned that a dissolvable wafer ocular insert (NanoM-Wafer technology) can be constructed for the primary purpose of generating a surface-spreading aqueous-lipid interface to create a long-lasting biomimetic tear film. We have developed dissolvable "biomimetic" tear film wafer constructs that are tolerable to the eye, dissolves within a pre-determined time, to generate a robust air-water interface with low surface energy. The dissolution time can be modulated.

We demonstrate characteristics of the dissolvable wafer technology with measured surface energy, dissolution times, thickness and sterilizability. Tolerability of wafers were tested *in-vivo,* in New Zealand White Rabbits.

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

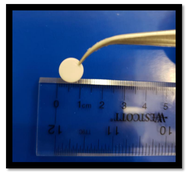
Fabrication : NanoM Wafer prototypes were fabricated by a proprietary process, using combinations of aqueous polymers and lipids. **Thickness:** Fabricated NanoM wafers were measured (n=3) by a Mitutoyo Screw Gauge. **Surface Tension:** The surface energy (SE) of a liquid is directly correlated to surface tension (ST). The surface tension of pre-prototype solutions were measured by a Nanoscience Surface Tensiometer, in Nm/m. **Dissolution Time:** Dissolution time of the prototype films were tested on 8 mm, 200 micron wafers by placing 40 microliters of distilled water, and placed in an incubator at 37°C. Dissolution were also measured *in-vivo*. **Flexural Modulus:** of a film measures its ability to be able to withstand stresses of fabrication, handling thereof and blinking. Flex modulus was tested by "folding of a wafer insert" by the index finger and the thumb. **Safety and Tolerability:** of the prototypes were measured by assessment of ocular tissue, after placement of the prototypes. Animals were evaluated at wafer dissolution. Tolerability of the wafers were assessed by a SPOTS scoring system (Eaton, et. al. 2017). **Feasibility of Sterilizability** was tested by exposing foil-packaged wafer prototypes to sterilizing radiation. The wafers were tested for visual signs of degradation (yellowing) and dissolution time.

NanoM-Wafers in the Rabbit Eye Demonstrate no Adverse Effects at Dissolution (Single Use)

These wafers dissolved in < 30 minutes

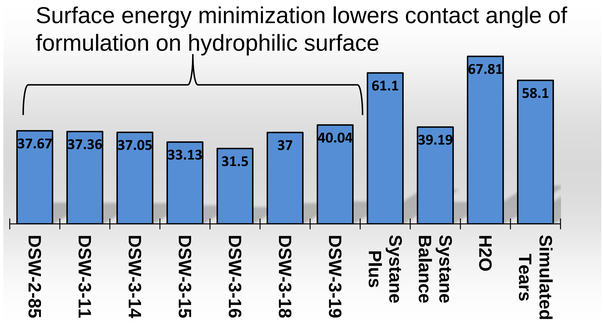
Measures of Tolerability	Average Score (n=4 eyes)
Lid Swelling (Normal/Abnormal)	N
Discharge (0-3)	0
Conjunctival Hyperemia (0-3)	0
Iris Hyperemia (0-3)	0
PLR (0-3)	0
Corneal Opacity Severity (0-4)	0
Corneal Opacity Percent (0-4)	0
Corneal Vascularization (0-2)	0

NanoM Wafer: Applied without Clinical Intervention, Biocompatible

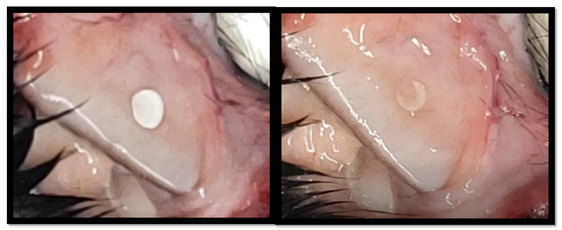


- ✓Dimensions : fits comfortably under lower eyelid
- ✓Turns into a translucent hydrogel upon hydration
- ✓Fluids permeable (O_2, CO_2, H_2O)
- ✓>90% H_2O
- ✓Biodegradable

Surface Energy of the Pre-Film Solutions is Minimized to Enable Spreading on Tissue, Post-Dissolution



Dissolution Time of Dissolvable Wafer Can Be Modulated by Composition

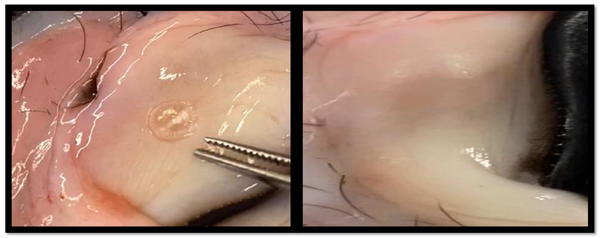


T=0 T=< 5 minutes

All prototypes demonstrated high flexural modulus, with no stress fractures noted upon folding. The wafers adhered to the underlying tissue, upon placement.

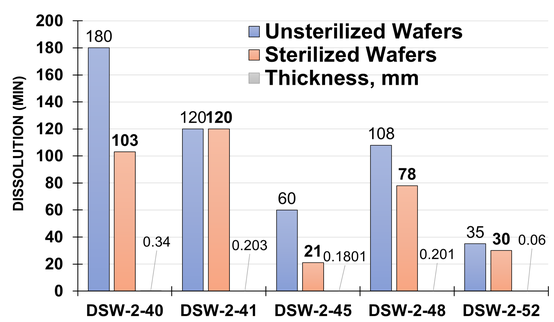
Dissolution Time Can be Extended by *In-Situ* Interlocking with Tissue

Example: Dissolution Time *ex-vivo* : 4-5 hours



T= 60 minutes T= 240 minutes

NanoM-Wafers can be Terminally Sterilized, although Decrease in Dissolution Times are Noted



No discoloration noted, upon sterilization.

Conclusions

This work-in-progress presentation demonstrates feasibility of a versatile, tolerable wafer insert that can be suitably self-administered within the conjunctival fornix, and form a film on the surface of the eye, that:

(a) Can be used as an ophthalmic medical device (no drug) to replenish the three-tier components of the human tear film, (b) Can be modulated in terms of dissolution time to be rapid-dissolving, or longer-lasting.

References

Eaton, et. al. 2017. The SPOTS System: An Ocular Scoring System Optimized for Use in Modern Preclinical Drug Development and Toxicology, J Ocul . Pharmacol. Ther. 33(10):718-734.

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