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Delivery of a PPAR Agonist *via* a Biodegradable Ocular Insert to Achieve Scar-Free Corneal Wound Healing

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Unmet Clinical Need and Overarching Challenge:

For deeper injuries to the cornea such as those caused by thermal, chemical and mechanical injuries, the stroma heals *via* the transformation of keratocytes to fibroblasts and myofibroblasts. There is a critical balance between the events of tissue regeneration and fibrosis. Distortion of this balance can result in fibrotic scar tissue formation leading to corneal opacity and blindness. *This molecular process is triggered by transforming growth factor-beta (TGF-β), a key modulator in corneal wound healing and the fibrotic reaction (Jeon K 2017).* The current solution to restore vision in cases of distorted vision due to corneal opacity is through corneal transplant surgery. This is enormously challenging, due to shortage of transplant-grade, viable donor-matching corneal tissue.

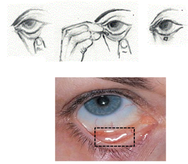
This clinical challenge is yet, unmet. The current pharmacological approach to treat corneal wounds include the use of commercial ophthalmic steroids and antibiotics; while these do result in healing in immuno-competent eyes for superficial wounds, fibrotic scar formation (and resultant corneal opacity) can occur from deep, invasive wounds leave no recourse, other than corneal transplantation. *Thus, while there are medications address infection and inflammation, there are NO ophthalmic treatments on the restoration of remodeled, organized tissue that is scar-free. One additional barrier is the achievement of therapeutic drug concentrations, via eye-drops.*

Goals of Program: This development program stems from a previously demonstrated basic, research premise that inhibition of myo-fibroblast differentiation by regulation of TGF-β expression by a peroxisome proliferator-activated receptor gamma (PPARγ) agonist OS300 (structure undisclosed at this time) can regulate the wound healing to achieve organized tissue structure (undisclosed publication). **The program defined herein proposes development of OS300 into its sustained administration on the ocular surface *via* Integral BioSystems' proprietary sustained release delivery platform, NanoM™.**

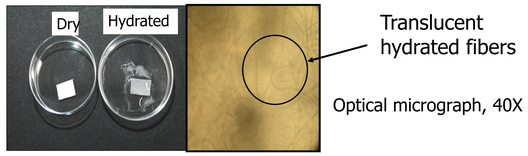
Selection of PPAR-Ɣ Agonist: OS300 is a tissue-permeable, highly specific PPAR-Ɣ agonist, as a potentially promising pharmacological agent to regulate the process of wound healing and tissue modeling. **This molecule has been shown to not only downregulate TGF-β expression, but also other immunological markers for inflammation** (undisclosed research). OS300 delivered at a concentration of 10μM *via* eye-drops formulated in DMSO, has been demonstrated to affect wound healing without a fibrotic healing response by downregulating the TGF-β expression in an alkali corneal burn model (undisclosed research). Additionally, OS300 has been shown to be highly cell-permeable, with an oral bioavailability of >95%. With a log P of 2.4, OS300 is expected to adequately permeate the cornea and other adjoining tissues.

NanoM Wafer is Placed Under Lower Eyelid

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



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 0.17-0.20 microg/mg. 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 drug content.

○Drug Integrity: The drug product was dissolved as described above for encapsulation, and analyzed for degradation products characterized as % oxidization, etc.

○Incubation Studies: OS300/NanoM wafers were incubated for 14 days at 37℃ in phosphate buffer at pH 7.4. The drug was extracted and tested for integrity by HPLC analysis.

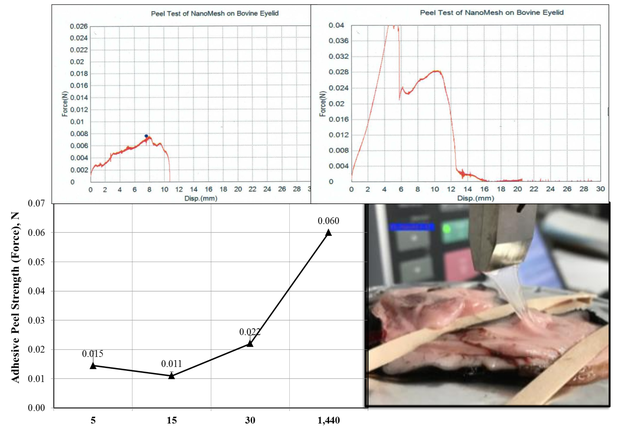
○% Hydration: Water uptake by NanoM wafers were measured gravimetrically, by incubation in buffer at 25C for 3 hours.

○*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).

Bioadhesion to Tissue Occurs ~30 Minutes After Application of NanoM Wafer

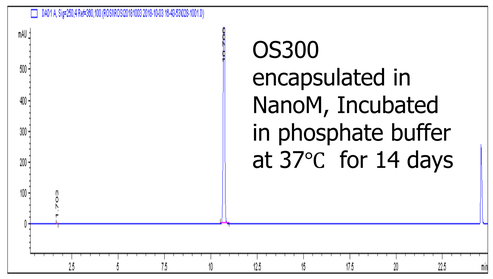


Bonding occurs ~30 minutes after application of wafer and hydrating buffer. This allows removal of wafer if applied incorrectly.

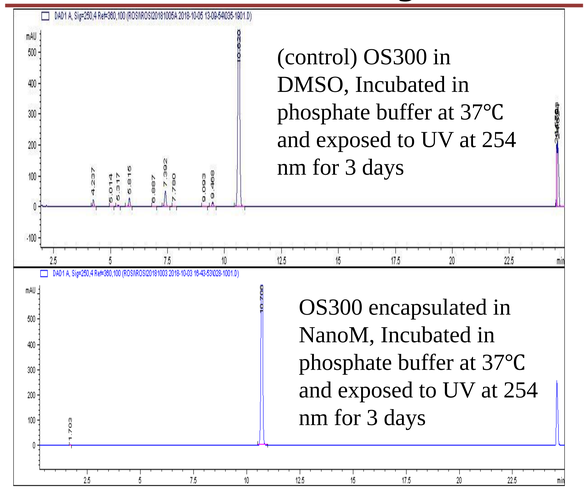
Physico-chemical Characterization of OS300-NanoM

OS300 Loading in NanoM	0.17 μg/mg
% Hydration	>100%
Dimensions of NanoM wafer	0.1±0.05 mm (thickness), 1±0.5 mm (width) x 5±0.5 mm (length)

OS300 Extracted from NanoM after Incubation for 14 days in Phosphate Buffer at 37℃ Maintains Chemical Integrity

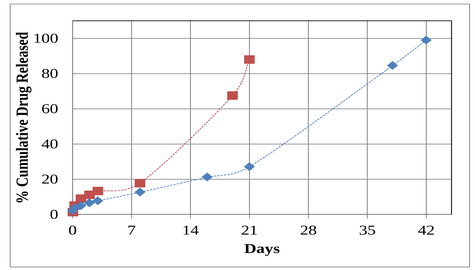


OS300 Encapsulated in NanoM is Protected from UV Degradation



Conclusion : OS300, an UV-sensitive compound is protected from UV degradation. This is an important attribute for an insert applied on the ocular surface.

OS300-NanoM: Drug Release Is Modulated by Modulation of Matrix



Next Steps

- Dose Response in an Alkali Burn Rat Model (PD)
- Pharmacokinetics in a Rat Model
- Irritation Studies Rabbit—Multi-day administration

References

1. Jeon KI, 2017. Am. J. Pathol. 187(8); 1660-1669

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