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OcuSurf™: A Nanostructured, Membrane-Interactive, Biphasic Ocular Drug Delivery System for Once/Day Administration of Water-Insoluble Ophthalmic Medications

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Abstract

OcuSurf™ is a membrane-interactive, biphasic drug-containing delivery system that can be administered to ocular tissues, both for front-of-the-eye and back-of-the-eye indications. For ocular surface indications, therapies that can benefit from OcuSurf range from treatments for bacterial conjunctivitis to blepharitis, post-operative inflammation and glaucoma.

The delivery system is nano-sized, with sufficient fluidity to be applied as eye-drops. Ocusurf is membrane-interactive, with components that interact and adhere to the proteins present on the ocular surface, enabling long-term presence of both small molecule and macromolecule drugs at the disease site. Additionally, the delivery system "melts" on the ocular surface, releasing its payload in a sustained manner.

OcuSurf as a delivery system, is most beneficial for insoluble drugs. For ophthalmics that utilize insoluble compounds, the most common dosage forms are suspensions, in the form of ointments or gels. OcuSurf enhances the bioavailability of these compounds, by absorbing into the ocular tissue first, then releasing by dissolution and diffusion-derived mechanisms. For water-soluble drugs, OcuSurf nano-emulsions act to provide sustained release.

For the studies described herein, we show that this delivery system is nano-sized, has an unique molecular morphology that is visible under polarized light microscopy, has excellent release characteristics and permeates the cornea. **We show characterization of dexamethasone-containing OcuSurf (OcuSurf-DX).**

Attributes and Therapeutic Benefits of OcuSurf™

- *Platform Technology, enabled for multiple small molecule drugs.*
- *Liquid crystalline, ordered structures, characterized by polarized light microscopy. This enables sustained release due to entrapment of molecules in the nanostructures.*
- *Sustained release enabled by following mechanisms: LC state, fast absorption into cornea, membrane interaction.*
- *High bioavailability enabled by presence of dissolved drug in nanostructure cores.*
- *High permeability enabled by the use of membrane-interactive permeation enhancers.*
- *Scaleable*
- *Protected by IP.*

Materials & Methods

PREPARATION:

A biphasic nano-emulsion was prepared using both hydrophobic and hydrophilic GRAS excipients, well below allowable FDA limits. The API is dissolved in the phase that forms the "cores" of the nanostructure. The cores are suspended in a aqueous hydrophilic continuous phase which keep the cores emulsified and suspended. The emulsified cores, in conjunction with the continuous phase form LC ordered structures—that act as one of the mechanisms that enable sustained release. Process techniques enable control of particle size. To date, we have encapsulated multiple drugs in OcuSurf, demonstrating its platform utility.

CHARACTERIZATION:

- **Particle Size Distribution** (PSD):

Particle sizing was carried out during the process of formulation production. Approximately 20µL of formulation was dispersed in a 2% w/w glycerin, 0.1 % w/w sodium pyrophosphate decahydrate solution . PSD of the nano-emulsion was measured using Horiba LA-950V2 at room temperature (22-25ºC).

- **Imaging:**

A 20µL droplet of the emulsion was placed on a microscope slide and covered with a glass coverslip, taking care to maintain the integrity of the emulsion. The emulsion was examined under crossed polarizers, under an Olympus BX51P Polarizing Light Microscope, under a oil-drop 100X objective. Both drug-containing and placebo emulsions were examined.

- **Encapsulation (mg/G)**:

1.0 g of formulation was transferred into a 1.5 mL centrifuge tube, then centrifuged at 6000 rpm for 10 minutes using Eppendorf Centrifuge 5145D at room temperature. 100 µL of this centrifuge was transferred into an HPLC vial containing 900 µL diluent (75% Acetonitrile/25% water). The samples were measured for concentration (mg/mL) at λmax = 239 nm. The concentration was re-calculated into mg API/g formulation.

- ***In-Vitro* Release, 37ºC, pH 7.4:**

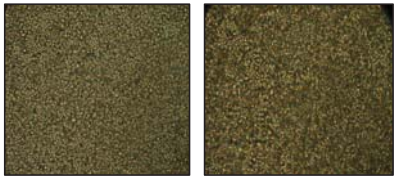
1g of formulation was transferred into a Spectra/Pore Float-A-Lyzer G2 Dialysis Device, which was then placed into a 50 mL locking centrifuge tube. This contained 40 grams of 1% Hydroxylpropyl-β-cyclodextrin in phosphate buffer pH 7.4, 37ºC. The entire assembly was loaded onto a Robbins Scientific Model 400 rotating incubator. At each time point, 1 mL of sample was retrieved and fresh buffer replaced. Samples were measured for drug content using HPLC at λmax = 239 nm.

- ***Ex-Vivo* Corneal Permeability:**

Five fresh bovine calf corneas were obtained from Research 87 and mounted onto Franz diffusion cells, maintained at 37ºC. The donor chamber contained 200 µL of formulation; the receptor chamber was filled with 5mL of 1% HPCD /Phosphate buffer, pH 7.4. Corneal permeation of drug and drug content in cornea was measured by HPLC at λmax = 239 nm.

Results

OcuSurf™ Delivery System is Liquid Crystalline

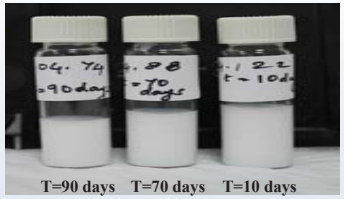


OcuSurf-Placebo OcuSurf-Dexamethasone

OcuSurf ™ Delivery System is Platform

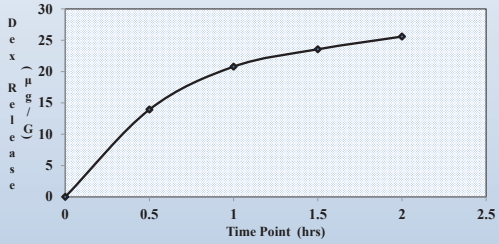
API	Particle Size (D50/D90)	Encapsulation (mg/G)	In vitro Burst (%) at 0.5 hrs
Dexamethasone	0.139/0.170	0.845	34.85
Glucocorticosteroid#2	0.134/0.197	NA	NA
Glucocorticosteroid #3	0.141/0.181	NA	NA
Glucocorticosteroid #4	0.161/0.191	NA	NA

OcuSurf ™ Delivery System is Stable



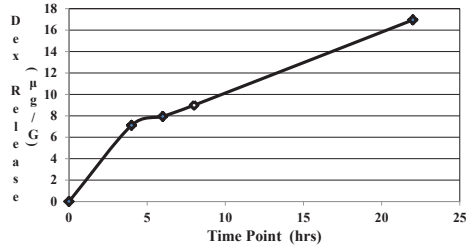
T=90 days T=70 days T=10 days

***In-Vitro* Release**



Results

Corneal Permeability (n=2)



Dexamethasone Content in Cornea after 24hrs

API	Study 1 (%drug cornea/total)	Study 2 (%drug cornea/total)
Dexamethasone in cornea	36	33

Conclusions and Next Steps

- OcuSurf-DX demonstrated enhanced bioavailability, as demonstrated by in-vitro release and corneal permeability data.
- OcuSurf-DX is nano-structured, with dissolved drug in the "cores" of the delivery system.
- A significant portion of drug was extracted from corneas, demonstrating fast and efficient absorption.
- Next steps will include optimization of OcuSurf with multiple drug molecules, to build its platform portfolio.

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