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Development of a Highly Bioavailable, Sustained Release Nanocore-based (OcuSurf™) Ophthalmic Formulation for the Treatment of Blepharitis

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Blepharitis: Disease and Clinical Need

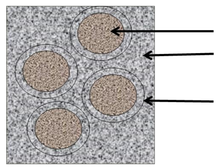
Blepharitis is an inflammation of the eyelids in which they become red, irritated and itchy and dandruff-like scales form on the eyelashes. It is a chronic disorder and prevalent globally. Causative factors attributed to blepharitis are Meiobian gland disorder, Seborrhoeic gland dysfunction of eyelash hair follicles, inflammation caused by the presence of follicular mites and bacterial infection caused by a combination of these factors. Anterior blepharitis is characterized by itching, flaking and crusting on the eyelid margin and the base of the eyelash follicles, while posterior blepharitis is characterized by redness, itching and burning caused by infection on the ocular surface and under the eyelid. There are no FDA-approved pharmacological treatments for blepharitis. The market size for blepharitis is ~$500-700 million.

Picture credit : emedicine.health.com

We have utilized our platform delivery system OcuSurf™ to develop a drug product that targets both anterior and posterior blepharitis.

The product (OcuSurf-FP/MOX) is a combination product of 0.01% Fluticasone Propionate (a potent anti-inflammatory) and 0.5% Moxifloxacin (a potent antimicrobial).

OcuSurf™: Description of Delivery System



- **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**

Materials & Methods

PREPARATION OF OCUSURF-Fluticasone Propionate/ Moxifloxacin:

A biphasic nano-dispersion was prepared using both hydrophobic and hydrophilic GRAS excipients. The APIs were dissolved in the phase that forms the dispersed "cores" of the nanostructure. The cores are suspended in a aqueous hydrophilic continuous phase which keep the cores dispersed and suspended. **The dispersed cores form liquid crystalline (LC) ordered structures, enabling one mechanism of sustained release.**

CHARACTERIZATION:

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

Particle sizing was carried out using a laser diffraction method. Approximately 20µL of formulation was dispersed in a 0.1% w/w surfactant solution. PSD of the nano-dispersion was measured using a Laser Diffraction Particle Sizer, at 25ºC.

○**Imaging:**

A 20µL sample of the drug-containing phase was placed on a microscope slide hot stage and covered with a glass coverslip. Sample was examined under crossed polarizers, on an Olympus BX51P Polarizing Light Microscope. The samples were heated from 5℃ to 55℃ at 5℃/min and images captured every 5 minutes (Triclinic Labs).

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

1g of formulation was transferred into a Spectra/Por Float-A-Lyzer G2 Dialysis Device (50kD), which was then placed into a 50 mL tube containing 35 grams of phosphate buffer (+ solubilizer) 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.

○***Ex-Vivo* Corneal Permeability:**

Six fresh bovine calf corneas were obtained from Research 87, Inc., and mounted onto Franz diffusion cells, maintained at 37ºC. Each donor chamber contained 0.2g Ocusurf-FP/MOX (n=6); the receptor chamber was filled with 5mL of Phosphate buffer (+ solubilizer), pH 7.4. Corneal permeation of drug and drug content in cornea were measured by LC/MS/MS (TSQ Quantum Ultra).

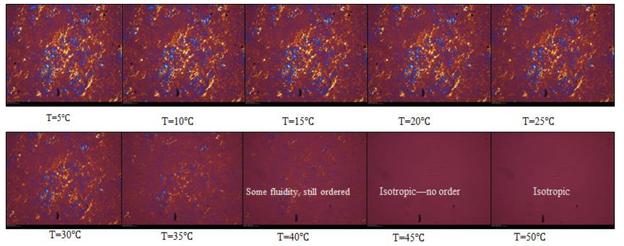
○**Differential Scanning Calorimetry:**

The drug-containing phase was characterized in hermetically sealed pans, using a DSC25 (TA Instruments, Inc.), by heating at 5℃/min to 100℃.

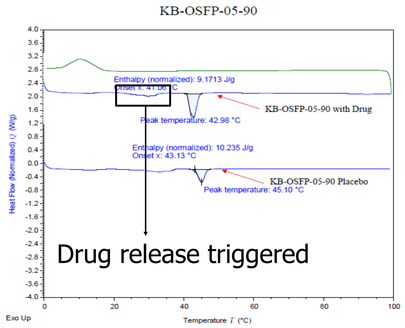
OcuSurf™-FP (0.01%)/MOX (0.5%)

- Fluticasone Propionate, 0.01% : High potency glucocorticosteroid; commercial approved dermal product is Cutivate®, 0.05% FP.
- Moxifloxacin Free Base, 0.5% : Same concentration as commercial Moxifloxacin, free base selected due to higher tissue permeability.

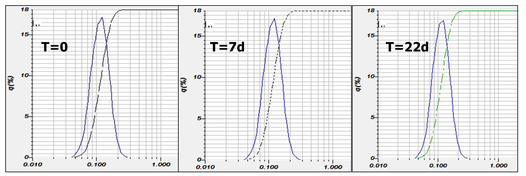
OcuSurf becomes fluid at physiological temperature, slowly releasing drug from the nano-core matrix (Hot Stage Imaging Data)



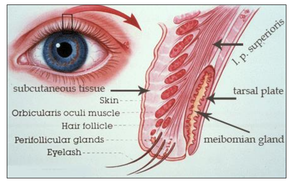
Drug Release is triggered at ~37℃; liquid crystalline (LC) ordered state enables sustained release (DSC)



OcuSurf-FP/MOX is nano-sized (mean: 110-120 nm), allows deep physical transport into follicles and lipid membranes



Time	D10 (µm)	D50 (µm)	D90 (µm)
T=0	0.076	0.114	0.167
T=7d	0.076	0.115	0.168
T=22d	0.075	0.112	0.165

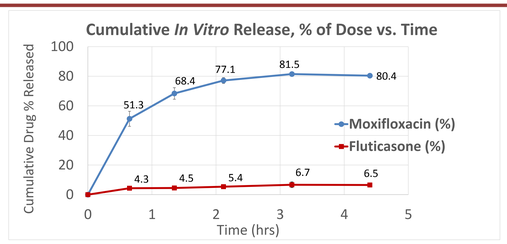


Picture credit : eyelabs.wordpress.com

Fluticasone Propionate does not permeate cornea (avoids steroid-induced side effects), high corneal permeation of Moxifloxacin Free Base

Time (hours)	Moxifloxacin Free Base: Ave. µg Mox-FB permeated (Dose%)	St. Dev.	Fluticasone Propionate: Ave. µg FP permeated	St. Dev.
1 h	**2.1 (0.2%)**	0.1	BLOQ	n/a
3 h	**5.2 (0.5%)**	1.7	BLOQ	n/a
5 h	**10.1 (0.9%)**	3.2	BLOQ	n/a
7 h	**17.5 (1.6%)**	4.3	BLOQ	n/a
19 h	**105.3 (9.6%)**	28.5	BLOQ	n/a
Cornea	**12.5 (1.1%)**	3.1	**0.54 (2.5%)**	0.1
Total (Cornea +19h perm.)	**117.8 (10.8%)**	30.3	*LOQ ~ 50 ng/mL*	

In Vitro Concomitant Release of Fluticasone Propionate and Moxifloxacin Free Base



Physicochemical Properties of Fluticasone Propionate and Moxifloxacin Free Base render them ideal for penetration of eyelash hair follicles

Fluticasone Propionate:
- Log P : 3.73 (high penetration into eyelid)
- Lipid Soluble—soluble in gland lipids and oils
- Potent glucocorticosteroid

Moxifloxacin Free Base:
- Log P : 2.03
- Lipid Soluble—soluble in gland lipids and oils
- Broad-based Antimicrobial (gram positive and gram negative)

Conclusions

Design feasibility of a combined anti-inflammatory/anti-microbial product for blepharitis was demonstrated.

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