5690 - A0409
Session 516

A Bioavailable, Sustained Release Nanocore (OcuSurf™) Brinzolamide Drug Product for Glaucoma Therapy, Compared to Azopt™

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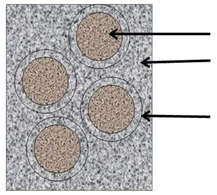
Introduction

One of the leading causes for blindness among the elderly is glaucoma. Brinzolamide, 1% ophthalmic suspension is available commercially as Azopt™ and indicated as a treatment for glaucoma. Glaucoma is a chronic disease, requiring lifelong management of disease.

Azopt is a commercially available ophthalmic suspension eye-drop formulation, requiring thrice-daily dosing. it can be used as a first line medication, as well as an adjunct to other therapies to manage chronic glaucoma. For drug suspensions to absorb, they would need to dissolve first. In the ocular space, rapid fluid turnover and loss *via* the naso-lacrimal duct results in just 5% of the drug being absorbed. Additionally, frequent administration of eye-drops result in missed doses due to patient non-compliance. **Thus, clinical need exists for a delivery system that offers more of a sustained release profile, while offering bioavailability of drug to the target tissue**.

We have invented a delivery system OcuSurf™ (for Ocular Surface), that can be delivered with ease to the ocular surface for bioavailable and sustained delivery of Brinzolamide.

OcuSurf™-Brinzolamide



- **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-BRINZOLAMIDE:
A biphasic nano-dispersion was prepared using both hydrophobic and hydrophilic GRAS excipients. The API was 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 LC ordered structures—that act as one of the mechanisms that enable sustained release.** Process techniques enable control of particle size. We have encapsulated multiple drugs in OcuSurf, demonstrating its platform utility including Brinzolamide.

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 droplet 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 at 5℃/min and images captured every 5 minutes (Triclinic Labs)

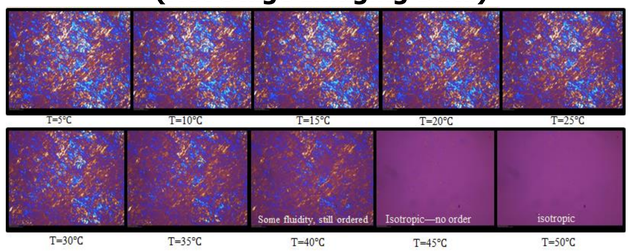
○***In-Vitro* Release, 37ºC, pH 7.4:**
1g of formulation was transferred into a Spectra/Por Float-A-Lyzer G2 Dialysis Device (50kD), which was then placed into a 50 mL tube containing 40 grams of phosphate buffer pH 7.4, 37ºC. The entire assembly was loaded onto a Robbins Scientific Model 400 rotating incubator. At each time point, 1 mL of sample was retrieved and fresh buffer replaced. Samples were measured for drug content using HPLC.

○***Ex-Vivo* Corneal Permeability:**
Six fresh bovine calf corneas were obtained from Research 87, Inc., and mounted onto Franz diffusion cells, maintained at 37ºC. The donor chambers contained either Ocusurf-Brinzolamide (n=3) or Azopt; the receptor chamber was filled with 5mL of Phosphate buffer, pH 7.4. Corneal permeation of drug and drug content in cornea was measured by LC/MS/MS (TSQ Quantum Ultra).

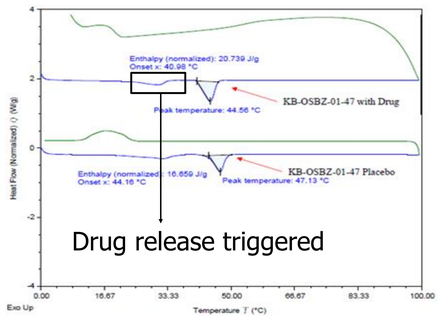
○**Differential Scanning Calorimetry:**
The drug-containing phase was characterized in hermetically sealed pans, using a DSC25 (TA Instruments), by heating at 5℃/min to 100℃.

Results

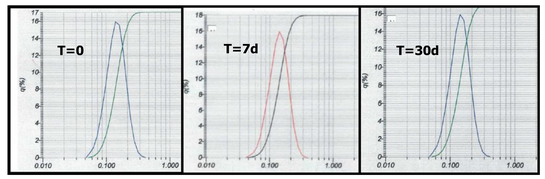
OcuSurf-Brinzolamide Drug Product becomes fluid at physiological temperature, slowly releasing drug from the nano-core matrix (Hot Stage Imaging Data)



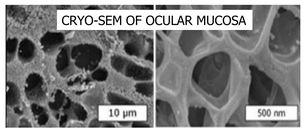
Drug Release is triggered at ~37℃; LC-Ordered state enables sustained release (DSC)



OcuSurf-Brinzolamide is nano-sized (mean: 190-200 nm), allows physical transport through pores of the ocular mucosa



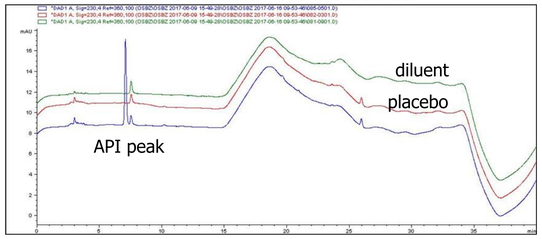
Time	D10 (µm)	D50 (µm)	D90 (µm)
T=0	0.089	0.142	0.215
T=7d	0.086	0.138	0.209
T=30d	0.088	0.140	0.213



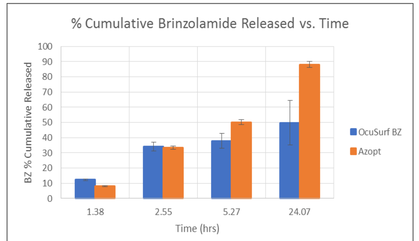
Polymers 2016, 8, 71: doi:10.3390/8030071

Results

Brinzolamide is Encapsulated Intact into OcuSurf Nanocores



Brinzolamide encapsulated in OcuSurf Demonstrates Sustained Release



Sustained Release of Brinzolamide—near linear rates of release from OcuSurf matrix.

Constant rate of Brinzolamide permeation through cornea for OC-BZ group

Conclusions

- Ongoing work include optimization of the Ocusurf-Brinzolamide formulation to **maximize ordered state at 37C and maximize retention on the ocular surface**, through development of a viscous, extrudable LC gel.

Acknowledgements

The authors would like to thank their Integral BioSystems colleagues, past and present, for their contributions to the work presented herein.

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