Introduction

Millions of people suffer from a variety of ocular diseases which in some cases lead to vision impairment and eventually blindness. Topical administration of drugs, for treatment of ocular inflammations and infections, through cornea is the preferred method for drug delivery, but cornea’s barriers makes delivery of a sufficient amount of therapeutic drugs a challenging task. Ultrasound has been shown to enhance delivery of lytic agents into thrombi and anticancer drugs into cells. Further, application of ultrasound for delivery of drugs into skin has been one of extensive investigated research areas with promising results. Our research describes applying ultrasound for increasing corneal permeability for several ocular drugs while generating some changes in corneal structure. We have worked on developing procedures to determine effectiveness and safety of ultrasound application in enhancing ocular drug delivery.

Materials

**Adult New Zealand white rabbit cornea:** standard model for ocular drug delivery

**Drug Solutions**
- Sodium Fluorescein, 0.25%
  - Used for diagnosis of corneal abrasions, corneal ulcers and herpetic corneal infections
  - Hydrophilic
  - Maximum absorption @ 490 nm
- Tobramycin, 0.3%
  - Ophthalmic antibiotic formulation for topical therapy of external infections
  - Hydrophilic
  - Maximum absorption @ 278 nm
- Dexamethasone Sodium Phosphate, 0.1%
  - Topical steroid solution used to suppress inflammatory response to different conditions
  - Hydrophilic
  - Maximum absorption @ 242 nm

**Spherical Diffusion Cell**
- Transducer (Unfocused circular transducers with 15 mm active diameter at frequencies of 400 KHz, 600 KHz, 800 KHz, and 1 MHz)
- Thermometer
- Ophthalmic solution
- Eye cup
- Cornea

**Histology**
- Cornea were dissected after both in vitro and in vivo study, kept in formalin and used for histology slides.
- Damages observed in epithelium were categorized in four different groups based on the geometrical width of epithelial layer including all the five biological sub-layers:
  - None of the layers are damaged or missing (class 0).
  - Some cells are missing or first layer of epithelium is removed (class 1).
  - Two layers are missing or damaged (class 2).
  - All three layers are missing or epithelium is severely damaged (class 3).

**Conclusion**
- Corneal permeability increase was highest at 400 KHz, both in vitro and in vivo study, and appeared to be higher at higher ultrasound frequencies.
- Ultrasound application provided enhancement of trans-corneal delivery of clinically relevant compounds.
- One of the main mechanisms of the ultrasound-induced penetration may be cavitation-induced production of pits on the surface of cornea which will be further investigated using Passive Cavitation Detection.
- Future studies involve establishing a stimulating model using PZFlex to investigate safety of this application and validating in vitro and in vivo results for temperature increase in cornea.

**Figure:**
- In vitro study: Dissected cornea was placed over the spherical joint of diffusion cell, between donor and receiver compartments.
- In vivo study: Animals were anesthetized before starting the experiment.
  - The eye cup was placed on the eye filled with Dexamethasone.
  - Transducer was placed on a metal stand and submerged inside solution.

**Corneal Permeability**
- \[ \frac{V(C_a - C_r)}{(A(1-t/C_p))} = \frac{V(C_a)}{A(t/C_p)} \]
  - \( p \): permeability, cm/sec
  - \( V \): volume of the receiver compartment
  - \( C_a \): concentration in donor compartment
  - \( C_r \): concentration in receiver compartment

**Drug Solutions**
- Tobramycin
  - Concentration: 0.3%, 0.5%, 0.8%, and 1 W/cm²
  - Application duration: 5 min

**Results**
- For Tobramycin, no statistically significant changes were observed in the corneal permeability.

**Figures:**
- Changes in corneal permeability for Tobramycin at different frequencies (400 KHz, 600 KHz, 800 KHz, and 1 MHz).
- Changes in corneal epithelium for Dexamethasone Sodium Phosphate at different frequencies (400 KHz, 600 KHz, 800 KHz, and 1 MHz).
- Chromatography was used to investigate the amount of drug penetrated through cornea into aqueous humor.