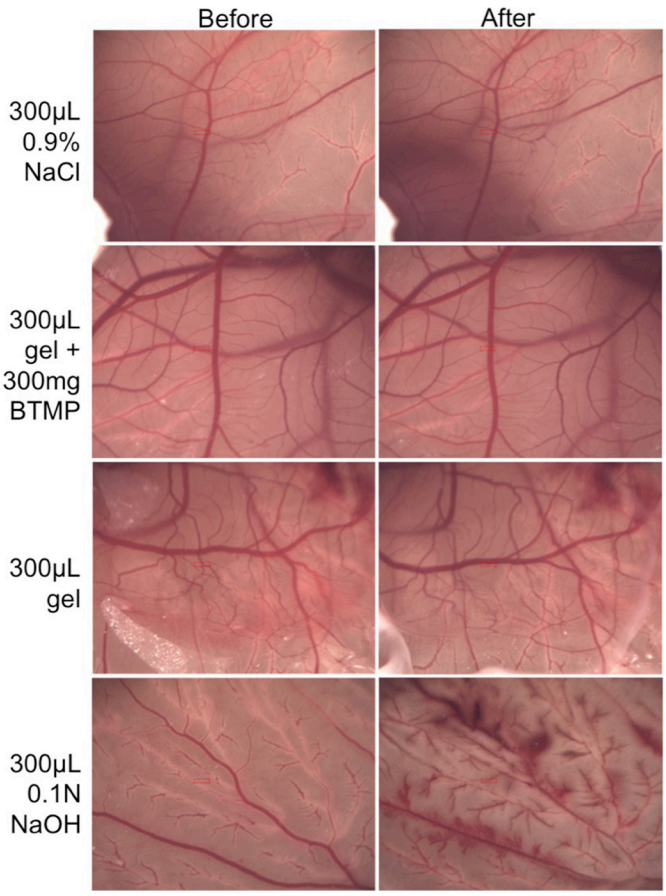
473 Drug delivery II
Wednesday, May 10, 2017 3:45 PM–5:30 PM
Room 301 Paper Session
Program #/Board # Range: 4755–4760
Organizing Section: Physiology/Pharmacology

Program Number: 4755
Presentation Time: 3:45 PM–4:00 PM
Preliminary safety evaluation of a long-term, topical ocular drug delivery platform
Morgan V. Fedorchak[1], Liza A. Bruk[2], Nate Myers[2]. [1]Ophthalmology, University of Pittsburgh, Pittsburgh, PA; [2]Bioengineering, University of PIttsburgh, Pittsburgh, PA.
Purpose: Although topical eye drops are the most common treatment method for many ocular diseases, they are inefficient and inconvenient, often resulting in poor patient adherence and undesirable outcomes. Long-term injections can offer an alternative to eye drops, but are more invasive and have other risks. Previously, we reported on the efficacy of a novel, topical controlled release ocular drug delivery platform, and in this study we seek to expand upon those data with a preliminary safety evaluation.
Methods: The physical properties of the drug delivery system, which comprises a thermoresponsive hydrogel and biodegradable, drug-loaded microspheres, were characterized using the appropriate testing. This includes determination of least critical solution temperature (LCST), viscosity, solid fraction, and swelling ratio. Terminal sterilization was also tested prior to determining in vitro cytotoxicity on conjunctival and corneal epithelial cells using a live/dead assay. The likelihood of ocular irritation was determined using the hen's egg test on chorioallantoic membrane (HET-CAM) and bovine corneal opacity and permeability (BCOP) test. In each case, sodium chloride solution was used as a negative control, and histological evaluation of bovine corneas was used to determine delayed effects, if any. Lastly, *in vivo* safety in a healthy rabbit model was determined by quantifying systemic drug levels and slit lamp examination.
Results: In vitro characterization tests show favorable properties for use of this drug delivery system on the ocular surface. Viscosity was measured to be 0.248±0.005 Pa*s and LCST was 34.5°C, indicating suitability as a liquid drop that forms a solid depot. UV/Vis absorbance confirms opacity of the solid gel, a requirement for visibility during use. Solid fraction measurements over 28 days demonstrate that the gel is non-degradable over time. Results of irritation and cell viability studies demonstrate acceptable results, with no observable irritation during HET-CAM (Figure 1) and BCOP testing. Finally, systemic drug levels were not detectable and no irritation was noted during in vivo testing.
Conclusions: The results suggest that the materials tested are non-irritating and retain the necessary properties for their intended use. These data represent an important step toward translatability of the system.



HET-CAM results (from top): negative control, gel, gel plus microspheres, positive control.
Commercial Relationships: Morgan V. Fedorchak, University of Pittsburgh (P); **Liza A. Bruk**, None; **Nate Myers**, None
Support: Wallace H. Coulter Foundation, P30 EY008098, Unrestricted grant from Research to Prevent Blindness

Program Number: 4756
Presentation Time: 4:00 PM–4:15 PM
Evaluation of PTS*sol* for sustained topical ocular drug delivery
Sara M. Smith[1], Jacklyn H. Salmon[1], Santhi Abbaraju[2], Rasidul Amin[2], Sidney L. Weiss[3], Poonam Velagaleti[3], Ulrich Grau[3], Brian C. Gilger[1]. [1]Department of Clinical Sciences, North Carolina State University, Raleigh, NC; [2]Symmetry Biosciences, Durham, NC; [3]i-novion, Randolph, NJ.
Purpose: Thermosensitive pentablock copolymers have previously shown to provide sustained drug release following subcutaneous, intracameral, and intravitreal injection. This study evaluated the release characteristics of brinzolamide (BRZ) from liquid pentablock copolymers (PTS*sols*) when applied topically through measurement of ocular residence time and reduction of intraocular pressure (IOP) in dogs.
Methods: Corneal retention time was evaluated by applying PTS*sols* containing NIR-labeled IgG (IRDye800CW, LICOR Biosciences, Lincoln, NE) to the corneal surface of mice and monitored by in vivo imaging (IVIS, Xenogen, Alameda, CA). The PTS*sol* with the longest corneal retention time was used as the vehicle for BRZ. Following measurement of baseline IOP for 5 days, normotensive dogs were dosed 3 consecutive days, with 4 untreated days between treatments: BRZ 1% in PTS*sol* once daily, PTS*sol* (blank polymer) once daily,

and commercial BRZ 1% (Azopt) three times daily (tid). The right eye remained untreated. IOP was measured at 7am and 4pm for each treatment day and at 7am for two days following treatment. Ocular exams were performed daily to monitor tolerability.
Results: PTS*sol* provided sustained ocular surface retention of NIR IgG. NIR IgG in saline was retained less than 3 hours, while PTS*sol* designated 1-0GH remained on the ocular surface for up to 21 hours and used to create a 1% BRZ PTS*sol* formulation. Topical PTS*sol*, PTS*sol* with BRZ 1%, and Azopt were all well tolerated, without signs of inflammation at any time point. For Azopt tid, percent reduction in IOP between the left (treated) and right (untreated) eye was significantly greater compared to baseline at the 4pm time points on each treatment day ($p<0.030$). Percent reduction in IOP after once daily BRZ 1% in PTS*sol* 1-0GH at the PM timepoints was significantly greater than at baseline for treatment days 2 and 3 ($p=0.020$). Although not significant, percent reduction in IOP was also greater at the AM time points each day including untreated days suggesting a sustained effect of BRZ 1% in PTS*sol* on IOP.
Conclusions: BRZ in PTS*sol* was well tolerated. Once daily BRZ 1% in PTS*sol* 1-0GH resulted in a significant IOP reduction in treated compared to untreated eyes on most treatment days. Sustained IOP lowering 24 hours post-dosing suggests that a PTS*sol* of BRZ at a suitable concentration may allow once/day dosing in glaucoma. Higher BRZ concentrations in PTS*sols* are currently being evaluated.
Commercial Relationships: Sara M. Smith, None; **Jacklyn H. Salmon**, None; **Santhi Abbaraju**, None; **Rasidul Amin**, Symmetry Biosciences (C); **Sidney L. Weiss**, i-novion (I); **Poonam Velagaleti**, i-novion (P), i-novion (I); **Ulrich Grau**, i-novion (P), i-novion (I); **Brian C. Gilger**, i-novion (C)

Program Number: 4757
Presentation Time: 4:15 PM–4:30 PM
Coefficient of friction between carboxymethylated hyaluronic acid (CMHA-S) films and the ocular surface
Brittany Coats[1], Jourdan Colter[1], Hee-Kyoung Lee[2], Brenda Mann[2], Barbara Wirostko[2, 3]. [1]Mechanical Engineering, University of Utah, Salt Lake City, UT; [2]Eyegate Pharma, Waltham, MA; [3]Department of Ophthalmology and Visual Sciences, University of Utah, Salt Lake City, UT.
Purpose: A novel hyaluronic acid polymer film, CMHA-S, is currently being developed as an ocular drug-delivery vehicle. Film retention in the inferior fornix for extended periods of time remains a challenge. Previous work by our group shows this obstacle can be overcome by careful control of the frictional interface between the CMHA-S film and the globe/eyelid. In this experimental study, we designed a custom tribometric system to quantify the coefficient of friction (COF) of CMHA-S on the eye, and evaluate the increase in friction when methylcellulose is added to the formulation.
Methods: CMHA-S films with (n=5) and without (n=15) methylcellulose were tested against ovine and human sclera. Scleral annuli and CMHA-S films were attached to a stress-controlled rheometer modified with custom fixtures. Blink Tears lubricating eye drops (Abbott Laboratories) were applied to a surrounding well to maintain lubrication throughout testing. Testing was carried out at axial loads of 0.3, 0.5, and 0.7 N. At each load, four positive and negative revolutions were applied at effective velocities of 0.3, 1.0, 10.0, and 30.0 mm/s, with a 12 second relaxation time between each set of revolutions. Loads and rates selected are replicative of physiological conditions in the eye. Two-way ANOVAs with repeated measures were used to evaluate the effect of sliding velocity and formulation (CMHA-S+/-methylcellulose) and sliding velocity and species (ovine, human) on friction.
Results: Static and kinetic COFs of the CMHA-S film relative to ovine sclera were found to be 0.29±0.1 and 0.15±0.1, respectively. Static COF was significantly dependent on rate ($p<0.0001$), especially for CMHA-S with methylcellulose ($p=0.0002$). Kinetic COF was not affected by rate. CMHA-S with methylcellulose had 1.6 and 1.8 higher static and kinetic COFs, respectively, than CMHA-S, but damaged quicker at high loads and rates. CMHA-S tested against human sclera was not statistically different from CMHA-S tested against ovine sclera.
Conclusions: CMHA-S with methylcellulose had a higher frictional interaction with the globe, but it was prone to wear. This suggests that methylcellulose can be used to tailor CMHA-S frictional interaction with the globe surface and eyelid, but careful consideration of potential increased degradation must be considered.
Commercial Relationships: Brittany Coats, EyeGate (F); **Jourdan Colter**, EyeGate (F); **Hee-Kyoung Lee**, EyeGate (E), EyeGate (I); **Brenda Mann**, EyeGate (E), EyeGate (I); **Barbara Wirostko**, EyeGate (E), EyeGate (I)
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Program Number: 4758
Presentation Time: 4:30 PM–4:45 PM
Ocular and Plasmic Dexamethasone Distribution following Controllable Continuous Sub-Tenon Drug Delivery in rabbit
Ding Lin, Xuetao Huang, Yezhen Yang, Yiqin Duan, Manqiang Peng, Kuanshu Li. Changsha Aier hospital, Changsha, China.
Purpose: To examine the distribution of dexamethasone in ocular and plasmic samples following CCSDD of dexamethasone disodium phosphate in rabbit, and to compare that with two traditionally routes: subconjunctival injection and intravenous injection.
Methods: New Zealand white rabbits (n=6/time/group) were included in the experiments. There are three groups including controllable continuous sub-tenon drug delivery system (CCSDD) group, intravenous injection (IV) group and subconjunctival injection (SC) group. Under general anesthesia, tube were implanted on the scleral surface in the CCSDD group. After implantation, trickled 0.3 ml initial doses of 5 mg/ml dexamethasone disodium phosphate, and start timing, and then constantly perfused at a rate of 0.1 ml/h for 10 hours using a pump. We administrated 1mg/Kg dexamethasone disodium phosphate intravenously in IV group and 0.3ml of 5mg/ml dexamethasone disodium phosphate into sub-conjunctive in SC group. At different time point within 24h, the blood samples and eye samples were collected in labeled polypropylene vials, sealed, and immediately stored at -20 °C until analysis. The dexamethasone concentration was analyzed by Shimadzu LC–MS 2010 system.
Results: In the CCSDD group, high levels of DEX were observed in the ocular tissue immediately after the administration and was maintained at 12 hours. Even at 24 h, the mean DEX concentration was 31.72 ng/ml and 22.40 ng/ml in aqueous and vitreous respectively. The maximum DEX in plasma was 321.81 ng/ml, 1798.44 ng/ml and 8441.26 ng/ml respectively in CCSDD, SC and IV group. Each ocular tissue peak DEX level is higher in CCSDD and SC group than IV group. Although there are a similar Cmax levels in ocular tissues in CCSDD and SC, the ocular tissues exclusion of iris exposure ($AUC_{0\text{-}24}$) to DEX is higher and plasma exposure is lower in CCSDD than SC.
Conclusions: Controllable continuous sub-tenon drug delivery diffusion of dexamethasone resulting in high levels in the ocular tissue and low levels in the plasm. This procedure provides a new approach that can optimize delivery of agents to the ocular while minimizing the potential for systemic toxicity owing to large drug.

Thus CCSDD is an effective method of delivering dexamethasone into both the anterior and posterior segments of the eye.
Commercial Relationships: Ding Lin; **Xuetao Huang**, None; **Yezhen Yang**, None; **Yiqin Duan**, None; **Manqiang Peng**, None; **Kuanshu Li**, None

Program Number: 4759
Presentation Time: 4:45 PM–5:00 PM
Production and characterization of a sustained release system of dasatinib to prevent proliferative vitreoretinopathy
Shigeo Tamiya[1], Rajat Chauhan[2], Rayeanne Balgemann[2], Hidetaka Noma[1, 3], Kevin McDonald[1], Henry J. Kaplan[1], Martin O'Toole[2]. [1]Ophthalmology & Visual Sciences, University of Louisville, Louisville, KY; [2]BioEngineering, University of Louisville, Louisville, KY; [3]Ophthalmology, Tokyo Medical University Hachioji Medical Center, Hachioji, Japan.
Purpose: Traction retinal detachment (TRD) associated with proliferative vitreoretinopathy (PVR), which is caused by the formation and contraction of fibrotic scar tissue on the vitreoretinal surface, remains the major complication following surgical correction for retinal detachment and/or ocular trauma. Whilst we have previously demonstrated that dasatinib, a tyrosine kinase inhibitor currently used for the treatment of chronic myeloid leukemia, can prevent TRD in an in vivo model of PVR, multiple intravitreal injections were required. We hypothesized that a sustained release system of dasatinib can prevent TRD with a single injection; the purpose of this project was to produce and characterize a sustained release system of dasatinib in vitro.
Methods: Spray drying method was utilized to produce dasatinib-incorporated poly(lactic-co-glycolic acid) (PLGA) particles (Das-PLGA). Particle size was measured by SEM. Release profile was determined by suspending Das-PLGA in PBS, and measuring dasatinib content daily. The effect of Das-PLGA on PVR-related cell function was determined using the type I collagen contraction assay, in which contraction of a collagen matrix by cultured porcine retinal pigment epithelial (RPE) cells was examined.
Results: Spray drying produced Das-PLGA with relatively narrow size distribution, with the average size being consistently between 1.0-1.4μm. Das-PLGA had an extended release profile with dasatinib being released beyond three weeks. Compared to PLGA control (without dasatinib), Das-PLGA significantly prevented the contraction of a collagen matrix by cultured RPE cells.
Conclusions: Spray drying reliably produced Das-PLGA with a narrow size distribution and an extended dasatinib release profile. Incorporated dasatinib remained functional as demonstrated by the inhibition of PVR-related function of cultured RPE cells.
Commercial Relationships: Shigeo Tamiya, None; **Rajat Chauhan**, None; **Rayeanne Balgemann**, None; **Hidetaka Noma**, None; **Kevin McDonald**, None; **Henry J. Kaplan**, None; **Martin O'Toole**, None
Support: DoD BAA Award#W81XWH-15-1-0298; Research to Prevent Blindness Unrestricted Award; KY Lions Eye Foundation

Program Number: 4760
Presentation Time: 5:00 PM–5:15 PM
A novel minimally invasive adjustable-depth blunt injector for delivery of therapeutics into the extravascular spaces of the choroid
Ygal Rotenstreich[1, 2], Adi Tzameret[1, 2], Sapir Kalish[1, 2], Ettel Bubis[1, 2], Michael Belkin[2, 1], Iris Moroz[1], Mordechai Rosner[1, 2], Itay Levy[3], Shlomo Margel[3], Ifat Sher-Rosenthal[1]. [1]Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel; [2]Goldschleger Research Institute, Tel Aviv University, Tel Aviv, Israel; [3]Department of Chemistry, Bar-Ilan Institute of Nanotechnology and Advanced Materials, Ramat Gan, Israel.
Purpose: To investigate the feasibility and safety of a novel minimally-invasive adjustable-depth blunt injector for pharmaceuticals and cell therapy delivery into the extravascular spaces of the choroid (EVSC).
Methods: An adjustable-depth blunt injector for delivery of therapeutics into the EVSC was developed. Two hundred and fifty microliters containing Indocyanine Green (ICG), sodium fluorescein, iron oxide nanoparticles (IONPs) or 15 million human bone marrow mesenchymal stem cells (hBMSCs) were injected into the EVSC of New Zealand rabbits using the novel injector, 3.5 mm posterior to the limbus. No immunosuppressants were used. Spectral Domain Optical Coherence Tomography (SD-OCT), fundus imaging, electroretinography (ERG) and histology analysis were performed for assessment of injection safety and efficacy.
Results: ICG, fluorescein, IONPs and stem cells were detected across the EVSC in rabbit eyes, covering over 80 percent of the posterior eye surface. Injected IONPs were retained in the EVSC for at least two weeks following injection. Stem cells were retained in the EVSC for 10 weeks following transplantation. No retinal detachment, choroidal hemorrhage or inflammation were detected in any of the injected eyes or contralateral control eyes. No reduction in retinal function was recorded by electroretinogram up to 10 week following cell transplantation.
Conclusions: This novel minimally invasive delivery system may be used to safely inject large volumes of pharmaceuticals and cell therapies into the EVSC from the same location used for intravitreal injections. Therapeutics are introduced into a new treatment reservoir compartment -the EVSC which can serve as a depot, in close proximity to the retinal pigment epithelium (RPE), throughout the surface of the RPE. This system is predicted to enhance the therapeutic effects of treatments for posterior eye disorders. Furthermore, this study demonstrates the safety of hBMSC transplantation in the EVSC compartment and is expected to directly lead to phase I/II clinical trials for hBM-MSC transplantation in retinal degeneration patients.
Commercial Relationships: Ygal Rotenstreich, Sheba Medical Center (P); **Adi Tzameret**, None; **Sapir Kalish**, None; **Ettel Bubis**, None; **Michael Belkin**, None; **Iris Moroz**, None; **Mordechai Rosner**, None; **Itay Levy**, None; **Shlomo Margel**, None; **Ifat Sher-Rosenthal**, None