Mucosal-Penetrating Particles Enable Topical Delivery to Posterior Segment of the Eye

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ABSTRACT SUMMARY
Kala’s proprietary mucosal-penetrating particle (MPP) technology enables drug delivery to the back of the eye via topical administration and can potentially serve as a therapeutic approach for age-related macular degeneration (AMD). In preclinical studies, topically instilled MPP of sorafenib, a small molecule receptor tyrosine kinase inhibitor (RTKi), resulted in significantly higher drug levels in retina and choroid than those from a non-MPP comparator. Drug exposure at the front of the eye was dependent on MPP release rate and could therefore be minimized.

INTRODUCTION
Rapid drug elimination from the ocular surface is a major obstacle for topical ophthalmic drug delivery. Although eye drops remain the preferred ophthalmic dosage form due to localized action and relative patient comfort, it is well established that conventional solutions and suspensions deliver <5% of a dose to the anterior segment tissues while the remaining portion is cleared from the ocular surface within minutes after application by lachrymation, blinking, and drainage. Topical delivery to the posterior segment is even less efficient due to additional diffusional barriers. As a result, high systemic doses or invasive therapies are currently used to treat conditions in the back of the eye.

Nanoparticles have the potential to improve ocular exposure from topical administration. However, this effort had been undermined by adhesion of virtually all synthetic nanoparticles to the ocular mucus layer, which protects the eye by effectively trapping and rapidly clearing foreign particles from the ocular surface. Ocular residence time of such nanoparticles is, therefore, limited by the turnover rate of the peripheral ocular mucus, typically on the order of seconds to minutes. To enhance topical ocular delivery, drug carriers must avoid entrapment by, and readily penetrate through, the mucus layer of the eye.

Figure 1. Representative 15-second trajectories of conventional nanoparticles (left) and Kala MPP (right) in human cervicovaginal mucus: MPP avoid entrapment and are able to diffuse through mucus.

Kala’s proprietary MPP technology is a novel drug delivery platform that enables drug-loaded nanoparticles to effectively penetrate human mucus secretions (as illustrated in Figure 1), thereby improving drug distribution at mucosal surfaces and facilitating drug release directly to underlying tissues. As a proof of concept, Kala has applied this technology to formulate and topically deliver sorafenib, a small molecule RTKi, that has promising properties as a potential antiangiogenic treatment for AMD.

EXPERIMENTAL METHODS
Sorafenib-loaded MPP with relatively fast drug release kinetics (MPP1) were prepared via a proprietary method of applying an MPP coating on drug in suspension. This method employs excipients approved by the FDA for use in ophthalmic products and produces a stable aqueous nanosuspension of MPP.

Sorafenib-loaded MPP with relatively slow drug release kinetics (MPP2) were prepared by encapsulating sorafenib into a biodegradable polymeric nanoparticle decorated with an MPP-enabling coating. Briefly, a solution containing 10 mg/mL sorafenib free base (LC Labs), 3.5 mg/mL PLA (Polylactide, 100DL7A, Surmodics), and 1.5 mg/mL PLA-PEG (poly(ethylene glycol)-co-polylactide, 100DL-mPEG2K, Surmodics) in tetrahydrofuran was added at a controlled rate to a 40-fold excess of aqueous solution of Pluronic F127 at stirring. The produced particles were stirred at room temperature to remove the organic solvent and crystallize unencapsulated drug. The unencapsulated drug crystals were removed by filtration through 1 um Millipore glass fiber filter. The nanoparticles were isolated from the filtrate by centrifugation at 23,000 RCF ( Sorval Legend, Thermo Scientific) and washed once with 0.5% aqueous Pluronic F127. The final product was resuspended in 0.5% Pluronic F127 and stored under refrigeration.

Sorafenib concentrations in the MPP formulations were confirmed by HPLC. Size was measured by dynamic light scattering, using a Zetasizer Nano ZS90 (Malvern Instruments). In vitro drug release was evaluated at 37°C in 50mM phosphate buffer (pH 7.4) in the presence of 0.5% Tween 80 to ensure sink conditions.

The pharmacokinetics of sorafenib following a single topical administration of MPP or non-MPP comparator was evaluated in New Zealand White rabbits (NZW) at a contract research organization (PharmOptima, LLC). An aqueous suspension of sorafenib was used as the non-MPP comparator. Each animal received a 50 uL topical instillation containing 5 mg/mL sorafenib in both eyes (N=6). Ocular tissues, including cornea and an 8mm punch of choroid and of retina from the back of the eye,
were harvested at various time-points. The punch was used to target the area at the back of the eye where the human macula would be as this is the target for AMD therapy. Sorafenib levels were determined by LC/MS.

RESULTS AND DISCUSSION
MPP1 and MPP2 formulated as described above formed stable nanosuspensions with a Z-average diameter of 187 nm (PDI=0.172) and 222 nm (PDI=0.058), respectively. Since MPP1 was essentially a pure drug suspension, its drug release was driven largely by drug dissolution, resulting in a complete release in less than 1 h \textit{in vitro}. In the case of MPP2, drug was encapsulated into a polymeric core and the maximum achieved drug loading was 20%. The polymeric composition of MPP2, including the molecular weight of PLA, the ratio of PLA to PLA-PEG and the composition of PLA-PEG, was systematically optimized in order to achieve a release rate well-differentiated from MPP1. The optimized MPP2 formulation demonstrated continuous drug release over ~24 h \textit{in vitro}.

In cornea, a single dose of the fast-releasing MPP1 formulation produced drug levels up to 18-fold higher than those from the comparator and sustained a >7-fold enhancement over the comparator for at least 6 h (Figure 2A). In contrast, the slow-releasing MPP2 formulation produced only an approximately 3-fold enhancement over the comparator steadily sustained over the course of 6 h. However, in posterior segment tissues (retina and choroid), both MPP1 and MPP2 produced similarly high drug levels, well-outperforming the comparator (Figure 2B, choroid data not shown). In fact, the retina drug levels produced by the MPP formulations approach or exceed reported cellular IC\textsubscript{50} against VEGFR-2 (14 ng/g) and PDGFR-β (37 ng/g) for sorafenib, a relatively low potency first generation RTKi.\textsuperscript{8,9} Furthermore both MPP formulations were well-tolerated as assessed by Draize scoring. These results not only demonstrate a proof-of-concept that the MPP technology can greatly enhance delivery to the back of the eye via topical administration but also suggest that topical delivery of a small molecule RTKi formulated as MPP could have a potential in the treatment of AMD.

CONCLUSION
Topical delivery of sorafenib, a small molecule RTKi, formulated as MPP greatly enhances drug levels in the retina and choroid. Drug levels in anterior segment tissues depend on the MPP release rate and can be reduced without significantly affecting the back of the eye levels. Our results validate the significant potential of the MPP technology in creating effective topical treatments for a broad range of ocular diseases.

REFERENCES
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Figure 2. Sorafenib levels in cornea (A) and retina (B) of NZW rabbits following a single topical instillation of MPP and non-MPP comparator (N=6, error bars=SEM).