Evaluation of the Pharmacokinetic Profile of a Novel Ophthalmic Formulation of Loteprednol Etabonate

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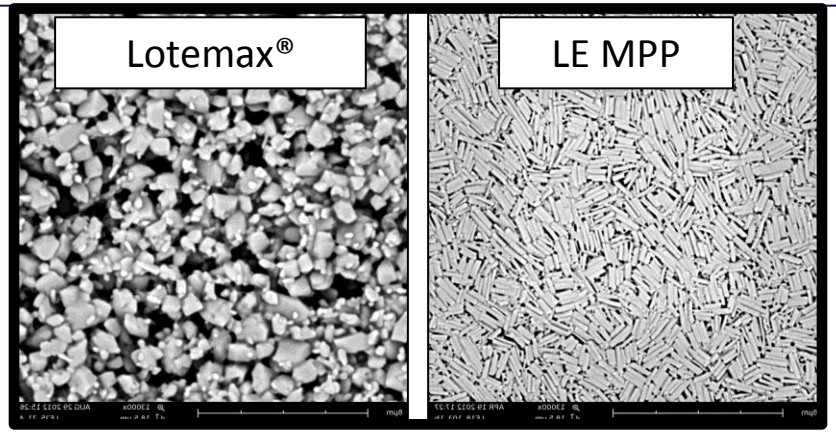
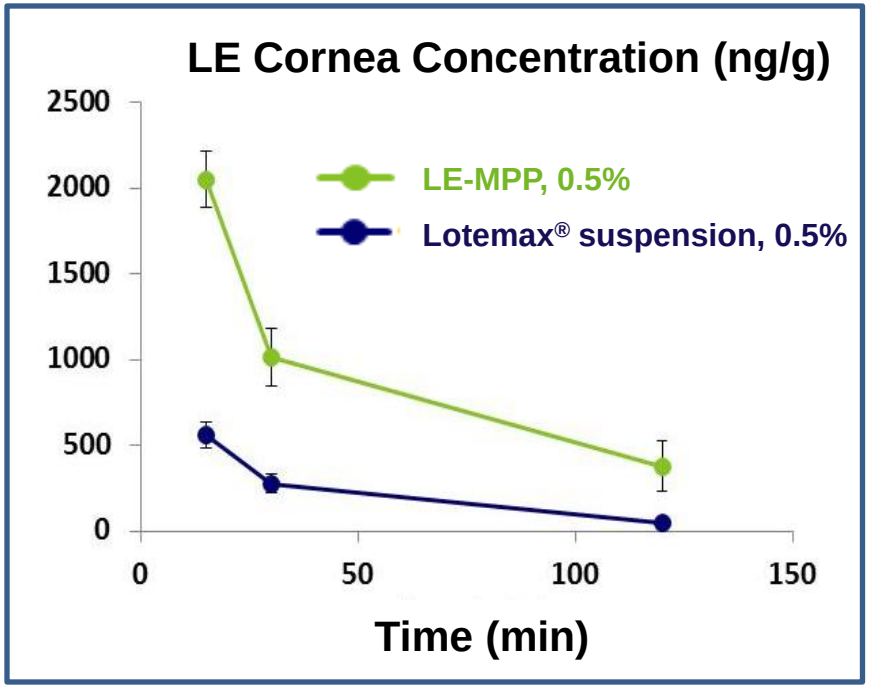
Loteprednol Etabonate Mucus Penetrating Particles (LE-MPP)

- Nano-suspension of loteprednol etabonate (LE) with particle size of 200-500 nm
- Formulated with Kala proprietary coating to allow penetration through mucus of tear film
- Can provide increased penetration and duration in ocular tissues

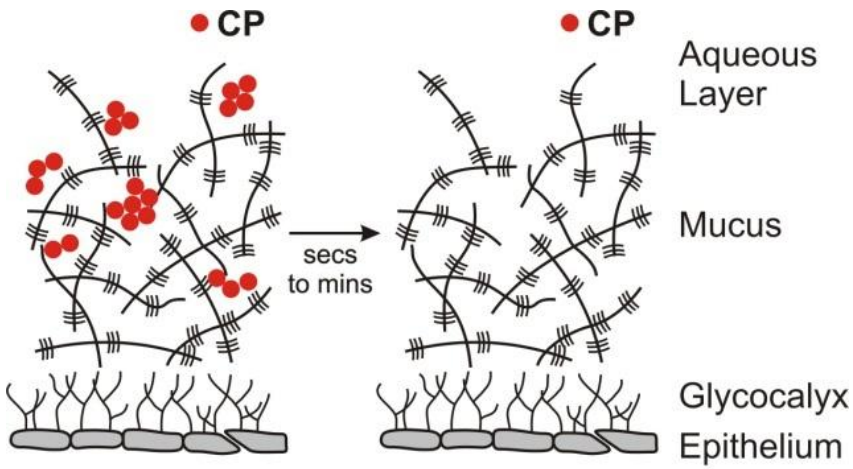




How do MPPs work?

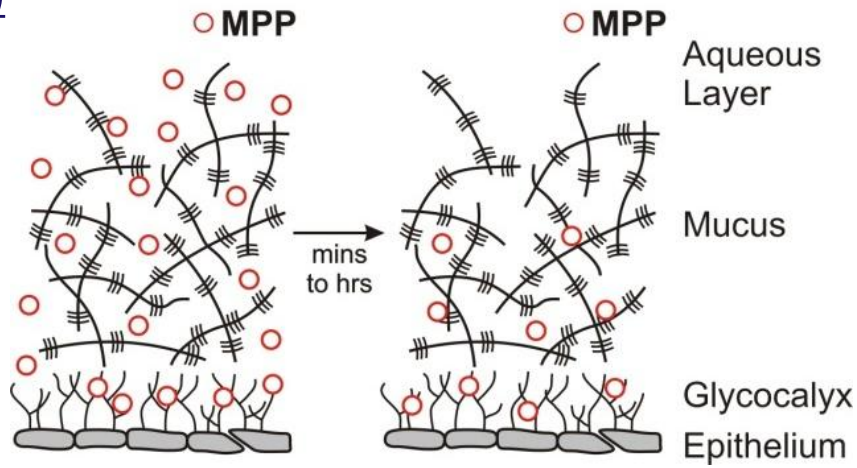
Conventional Particles (CP)

1. Muco-adhesive particles are **rapidly cleared** from mucus through mucus turnover
2. Particle aggregation and mucus adherence leads to **poor distribution**



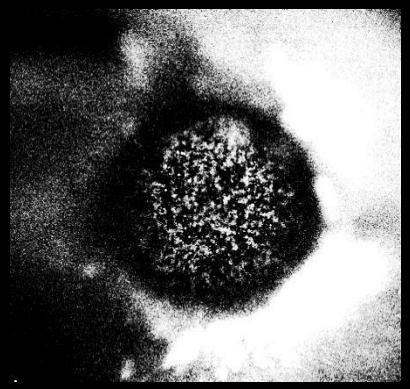
Mucus Penetrating Particles (MPP)

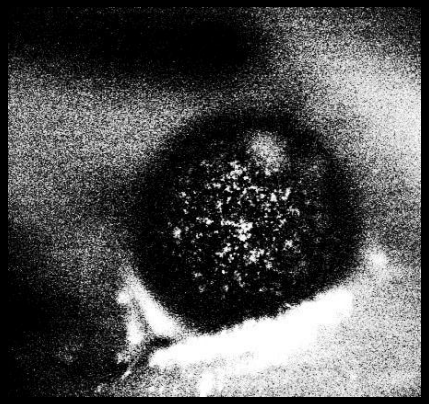
1. Muco-inert particles penetrate through tear film mucus layer
2. Mobility leads to **uniform distribution** across the mucosal epithelia



Previously Demonstrated Significant Corneal Delivery and Duration

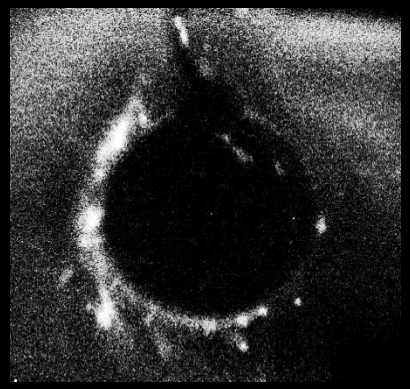
Kala MPPs





1 dose → *2hr* → *4hr*

Control Nanoparticles



MPPs – inert nanoparticles with Kala's proprietary coating

Control nanoparticles - same size and composition as the MPPs but without the proprietary coating

Schopf, L et. al.,
Poster Presentation ARVO 2013

Study Design

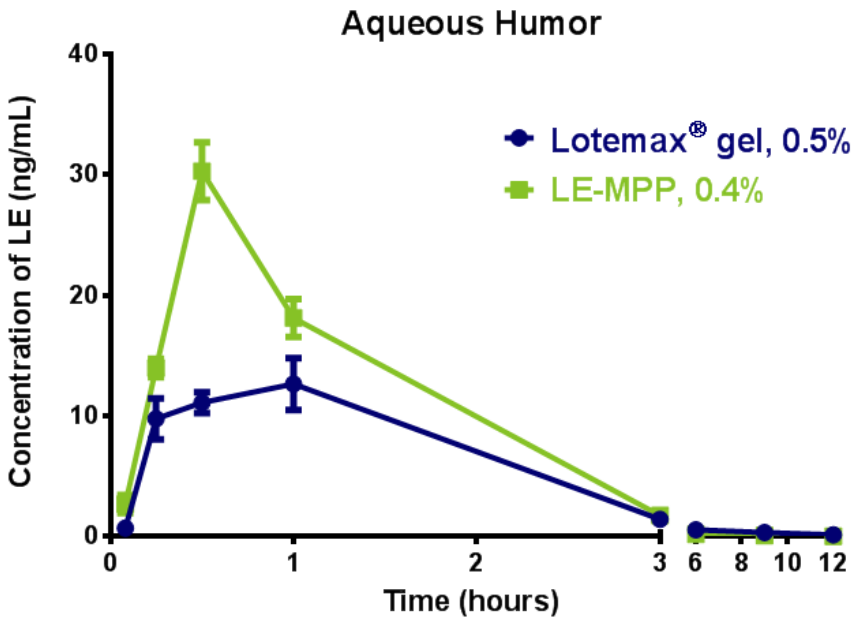
Number of NZW Rabbits	Test Article	Dosing	Terminal Time Points (Post-dose)	Tissues and Fluids
3 per time point (n=6 eyes)	Lotemax® Gel (0.5% LE)	35 µL -QD	0.083, 0.25, 0.5, 1, 3, 6, 9, and 12hr	Cornea Aqueous humor
	LE Test Formulation (0.4% LE-MPP)			

- The test formulations were well tolerated. No abnormal observations were noted in any rabbits following administration of the test formulations.
- Animals were euthanized by intravenous barbiturate overdose post-dose
- Both eyes were harvested with the collection of aqueous humor and dissection of cornea

T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were determined using Pharsight's Phoenix WinNonlin software (v.6.2.1) for all collected matrices. The log-linear trapezoidal rule was used for calculating AUC. $T_{1/2}$ was calculated using the "best-fit" or a minimum of the three last data points. If the calculated r^2 for the regression was <0.6, the value was not reported. Prior to the calculation, any mean data points with a %CV >100 were checked for outliers at the $p<0.01$ level using the Grubbs' Test. If indicated as an outlier, the value was excluded prior to calculating any pharmacokinetic parameter.

Comparison of Lotemax gel, 0.5% and LE-MPP, 0.4%

LE-MPP 1.6-fold greater AUC_{0-3} Compared to Lotemax Gel in Aqueous Humor



In this study, at a 20% lower dose strength, LE-MPP provided equal or better drug levels than Lotemax® gel formulation

Comparison of Lotemax gel, 0.5% and LE-MPP, 0.4%

Loteprednol Pharmacokinetic Parameters	Aqueous Humor (Lotemax® gel, 0.5%)	Aqueous Humor (LE-MPP, 0.4%)
T_{max} (hours)	1.0	0.5
C_{max} (ng/g or ng/mL)	12.7	30.3
$t_{1/2}$ elimination (hours)	2.9	2.6
$AUC_{0\text{-last}}$ (ng*h/g or ng*h/mL)	28.7	42.6

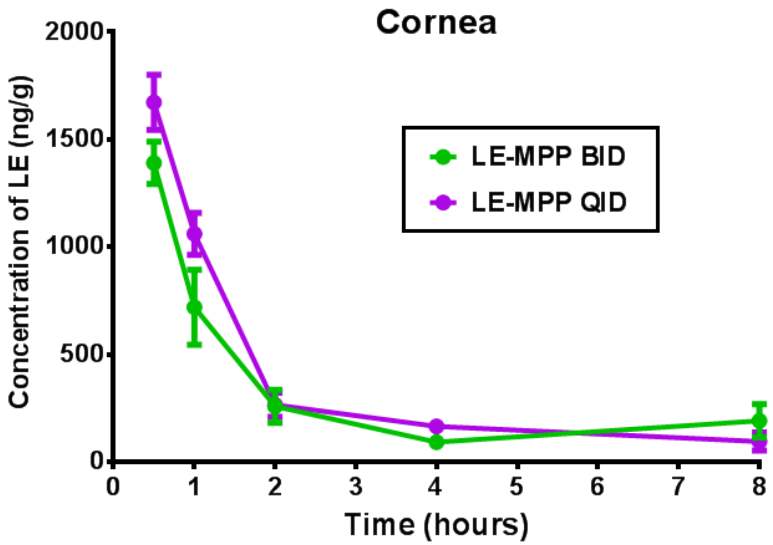
Study Design

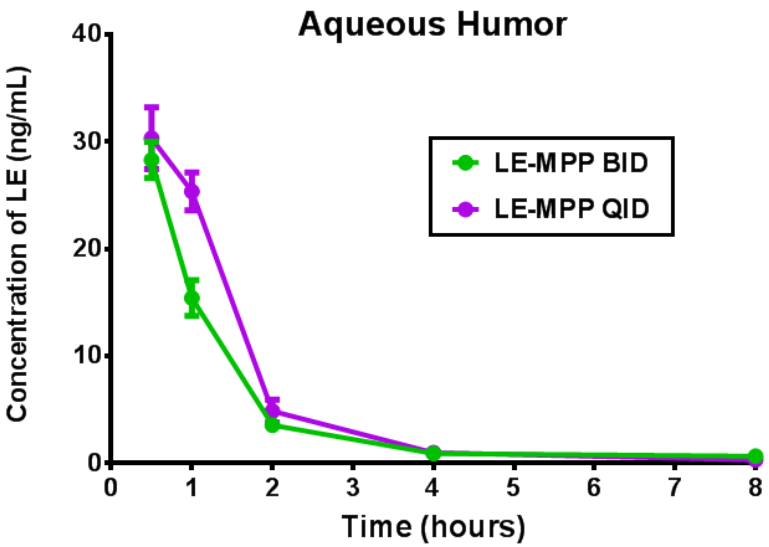
Number of NZW Rabbits	Test Article	Dosing	Terminal Time Points (Post-dose)	Tissues and Fluids
3 per time point (n=6 eyes)	LE-MPP	50 µL-QID	0.5, 1, 2, 4, and 8hr	Cornea Aqueous humor
	LE-MPP	50 µL-BID		

- The test formulations were well tolerated. No abnormal observations were noted in any rabbits following administration of the test formulations.
- Animals were euthanized by intravenous barbiturate overdose post-dose
- Both eyes were harvested with the collection of aqueous humor and dissection of cornea

T_{max}, C_{max}, $t_{1/2}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were determined using Pharsight's Phoenix WinNonlin software (v.6.2.1) for all collected matrices. The log-linear trapezoidal rule was used for calculating AUC. $T_{1/2}$ was calculated using the "best-fit" or a minimum of the three last data points. If the calculated r^2 for the regression was <0.6, the value was not reported. Prior to the calculation, any mean data points with a %CV >100 were checked for outliers at the $p<0.01$ level using the Grubbs' Test. If indicated as an outlier, the value was excluded prior to calculating any pharmacokinetic parameter.

LE-MPP: Twice-a-day (BID) compared to Four-times-a-day (QID)





Loteprednol Pharmacokinetic Parameters	Cornea LE-MPP, 0.5% BID	Cornea LE-MPP, 0.5% QID	Aqueous Humor LE-MPP, 0.5% BID	Aqueous Humor LE-MPP, 0.5% QID
T_{max} (hours)	0.5	0.5	0.5	0.5
C_{max} (ng/g or ng/mL)	1392	1672	28	30
$AUC_{0\text{-last}}$ (ng*h/g or ng*h/mL)	2279	2713	35	45

- Tmax and Cmax values were similar regardless of dose frequency
- $AUC_{0\text{-last}}$ values were greater from the QID group than that of BID dosed group

Conclusions

- In this study, LE-MPP provides equal or better drug levels in both the cornea and aqueous humor compared to Lotemax® gel even at a 20% lower dose strength
- In a rabbit PK study comparing dose frequency of LE-MPP, 0.5%, four-times-a-day versus twice-a-day increased total drug exposure by only 15-20%
- This works supports the premise that mucus penetrating particle (MPP) technology can be used to enhance ocular exposure for topically applied therapeutics
- Further studies to assess the clinical efficacy and safety of LE-MPP are warranted

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