An ion-paired moxifloxacin nanosuspension eye drop provides improved treatment and prevention of ocular infection

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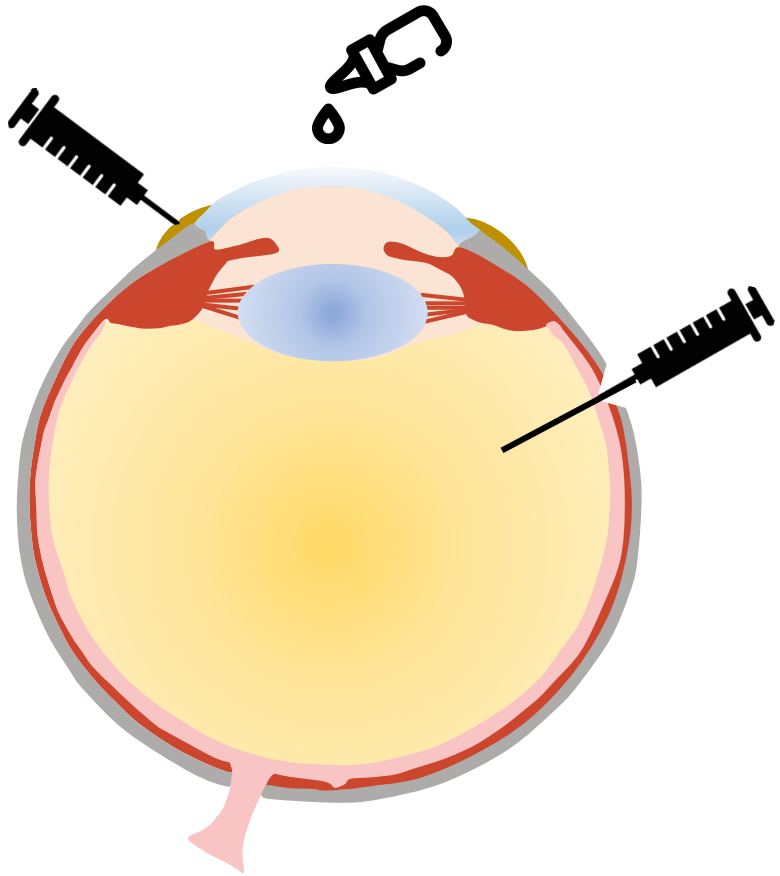
Advanced Delivery Science

Routes of ocular drug delivery



Topical Administration (90%):
Advantages: High patient compliance, self-administrable, non-invasive
Disadvantages: Precorneal clearance, corneal barriers, frequent

Subconjunctival Injection:
Advantages: Delivery to anterior and posterior segment, local depot
Disadvantages: Conjunctival and choroidal circulation

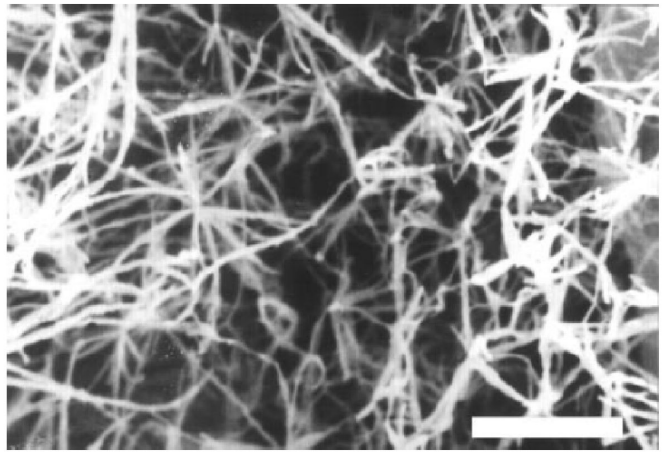
Intravitreal Administration:
Advantages: Directly vitreous and retina, prolonged therapeutic drug levels
Disadvantages: Retinal detachment, hemorrhage, cataracts

Implants:
Advantages: Sustained drug release
Disadvantages: Surgery required

Ocular bacterial infections are common and treatable, but can have serious complications

- Antibiotic eye drops are frequently used in the treatment and prevention of bacterial keratitis (1 million/year), conjunctivitis (4 million/year) and post-surgical endophthalmitis (0.5% of surgeries)
- If not properly treated, can result in corneal scarring, vision impairment and blindness
- Topical moxifloxacin hydrochloride (Vigamox®) is administered via eye drop at least 3x daily for the treatment of ocular infection

Topical ocular drug delivery is complicated by biological mucus barriers



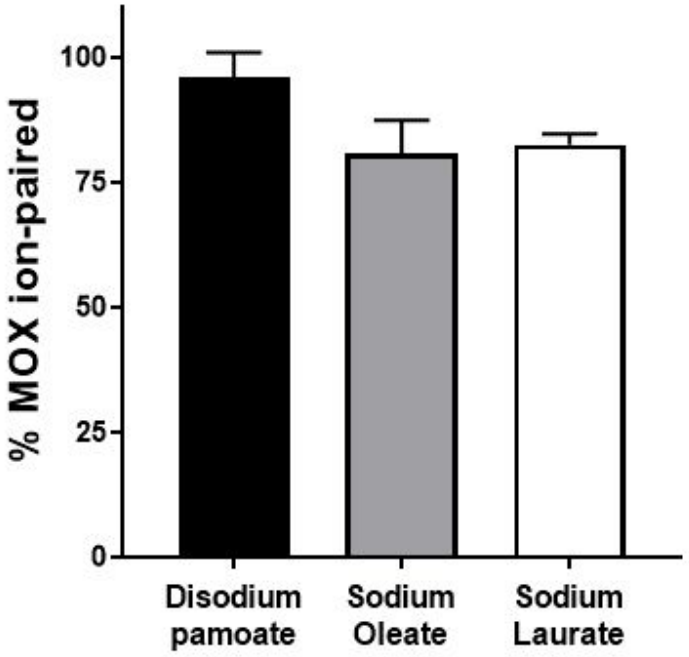
Mucus is a nanoporous meshwork of proteins (mucins) with spacing of ~200 nm

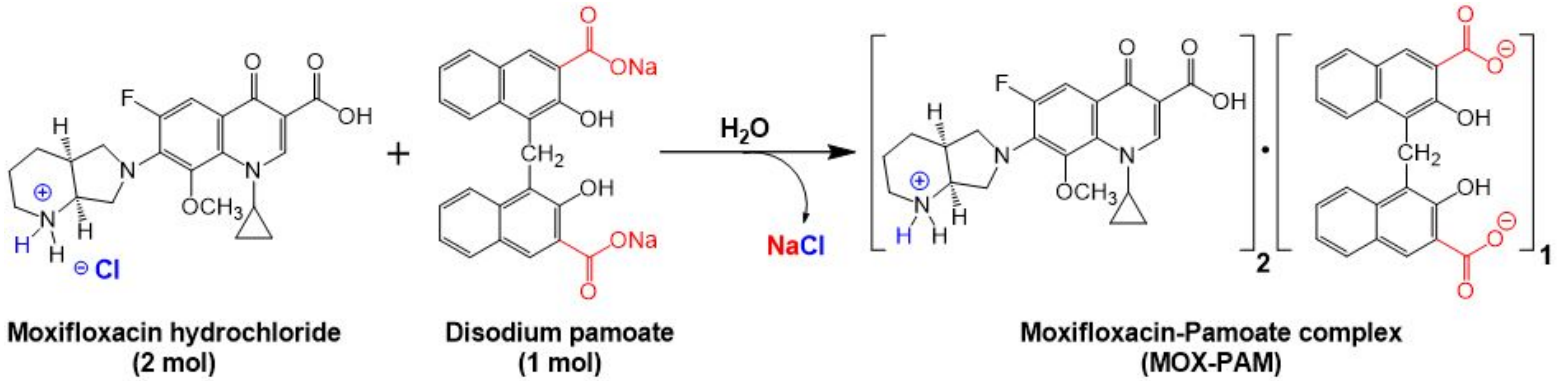
- Ocular tear film is a mucus barrier that protects corneal surface from pathogens and debris
- Mucins are highly adhesive and facilitate clearance from the ocular surface
- Tear production, blinking (12-20/min) and fluid draining limit corneal residence time
- Intraocular drug absorption after topical administration is low, requiring frequent dosing

Ceric, et al. *Jap Soc Microscopy*, 2005
https://www.systane.in/professional/tear-film.aspx

Commercial anionic ion-pairing agents are used to transform hydrophilic drugs

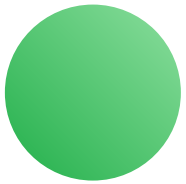
Water-soluble drugs are prone to increased clearance from the ocular surface



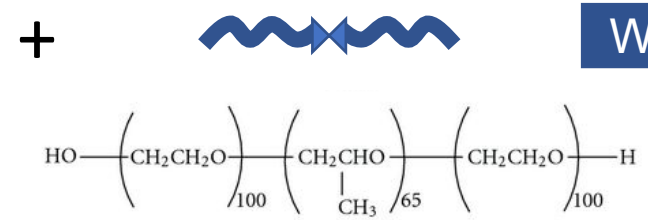


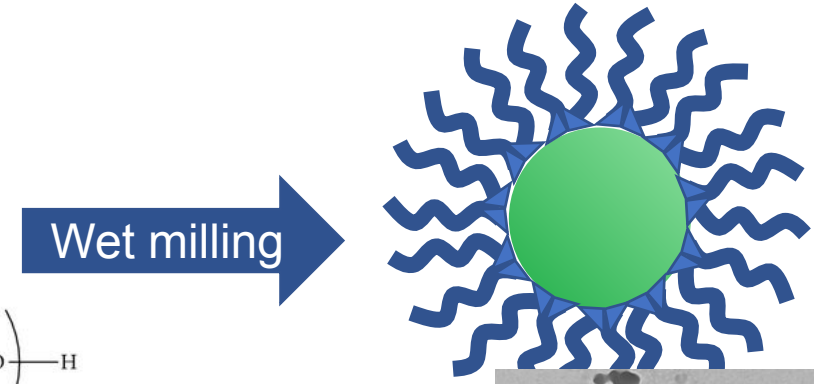
Hydrophobic ion-paired complexes are muco-inert

A MOX-PAM nanosuspension can be formulated by wet milling

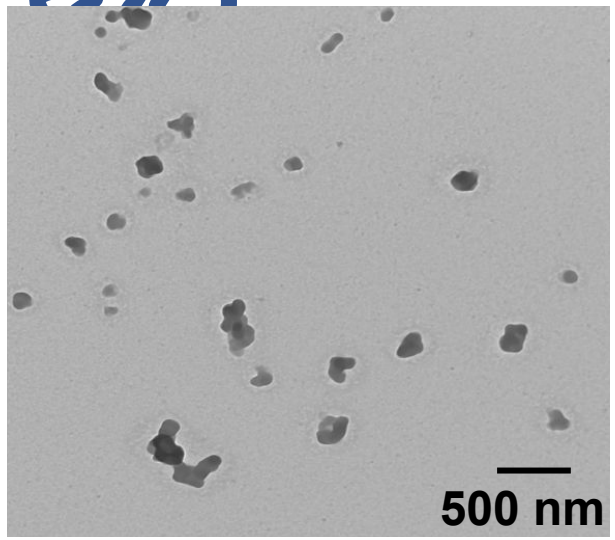


MOX-PAM ion pair

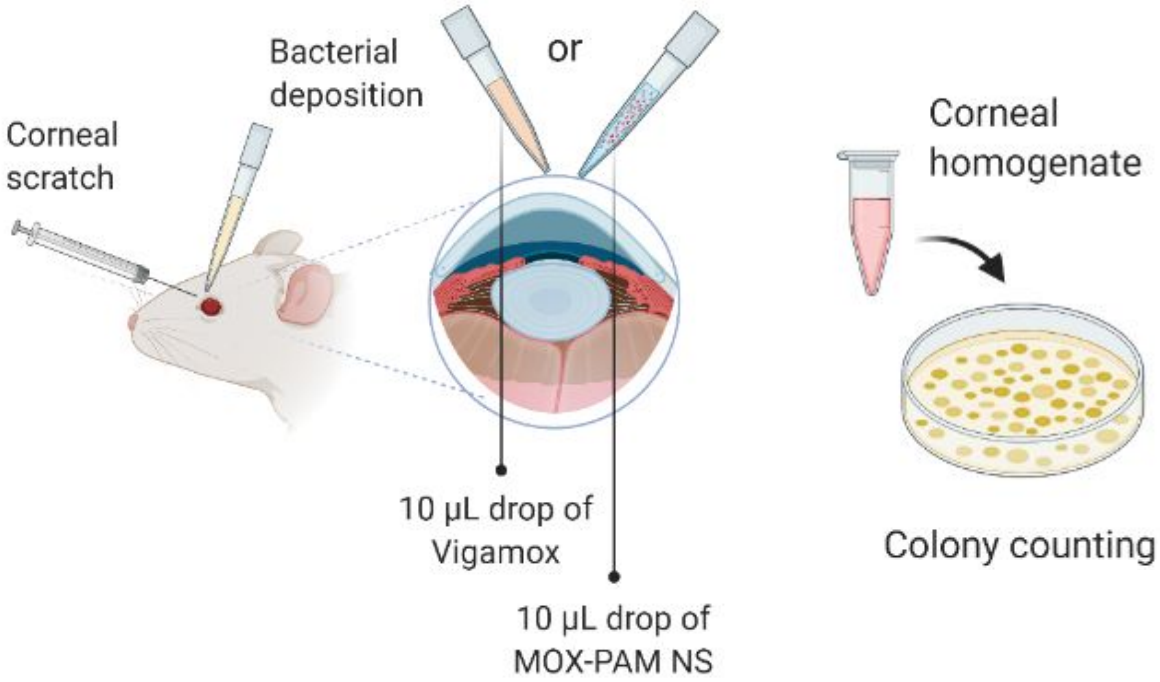


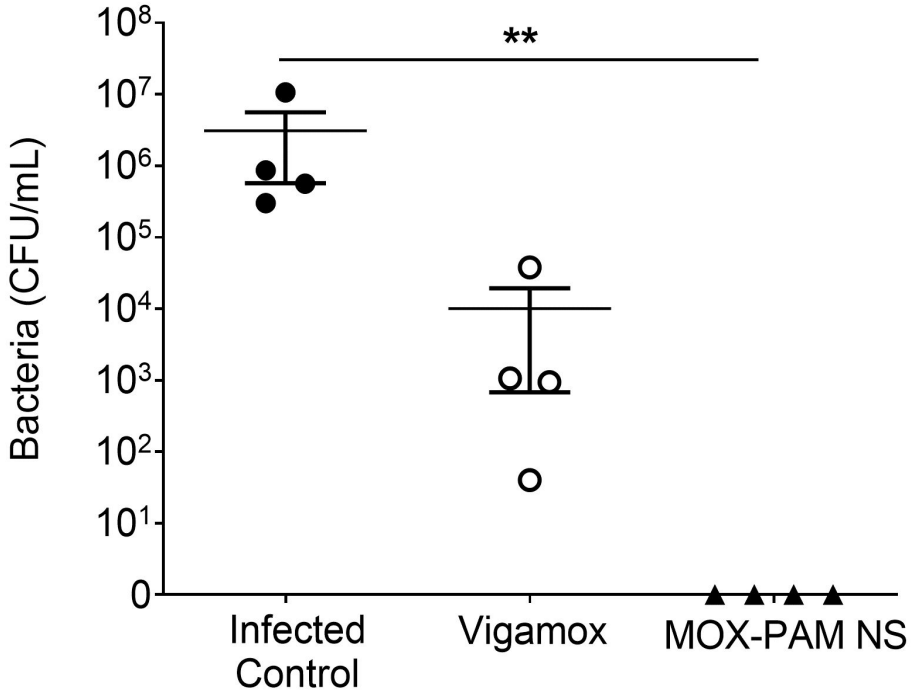


Laboratory scale wet nanomilling



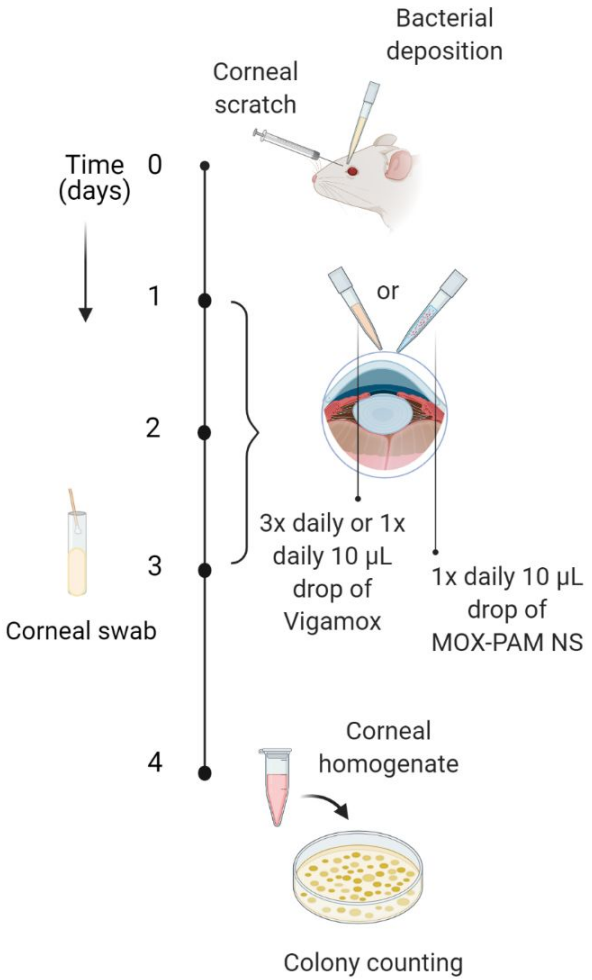
MOX-PAM NS is more effective in preventing ocular infection

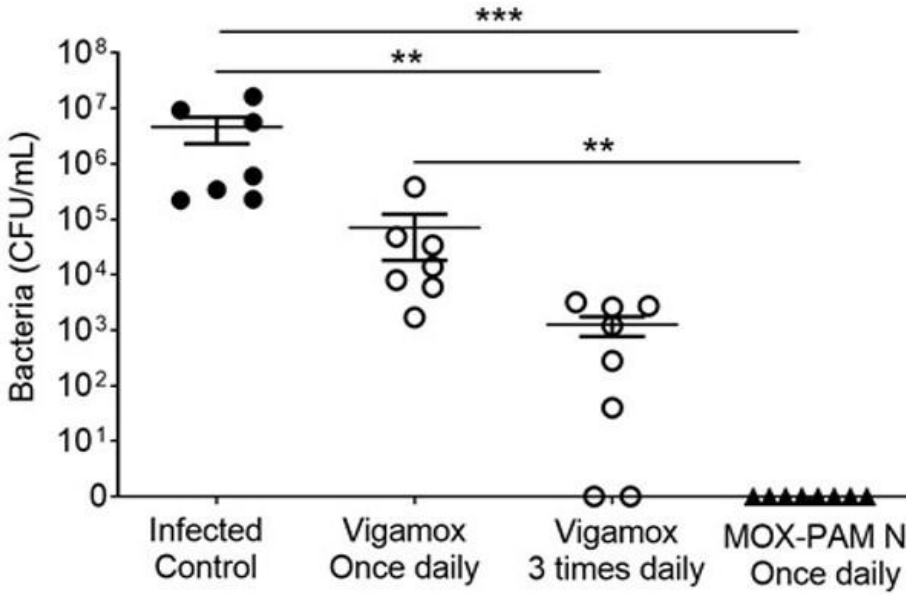


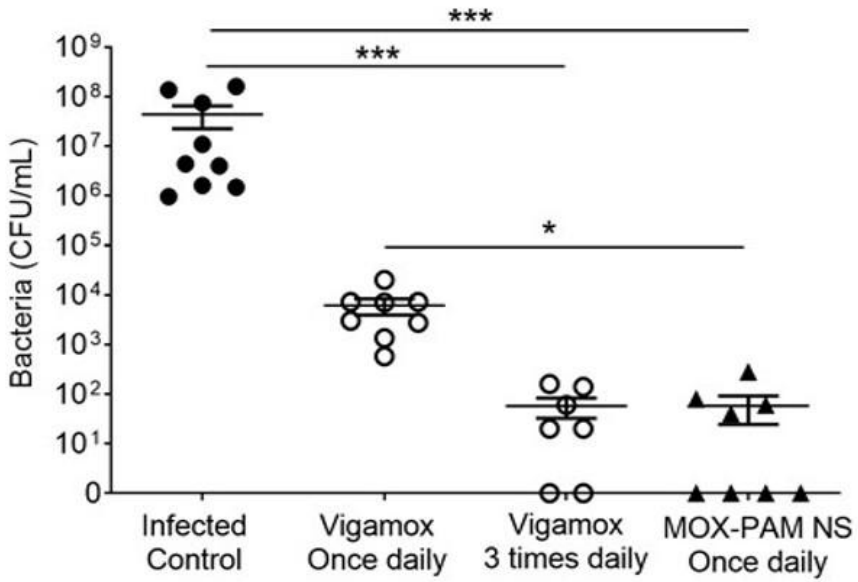


MATRIX	MOX-PAM NS			VIGAMOX		
	C_{max} (µg/g)	t_{max} (h)	AUC_{0-24h} (µg*min/g)	C_{max} (ng/g)	t_{max} (h)	AUC_{0-24h} (µg*min/g)
CORNEA	106.5 ± 66.7	1.5	961.9 ± 269.2*	99.4 ± 31.4	0.25	555.2 ± 66.8
AQUEOUS	153.3 ± 41.7	0.25	780.6 ± 404.5*	98.5 ± 27.8	0.5	175.9 ± 27.6

MOX-PAM NS is more effective in treating ocular infection







Conclusions

- Topical eye drops are the most common dosage route, though drug delivery efficiency is low
- To increase ocular bioavailability, rapid penetration of the tear film mucus barrier is key
- Hydrophobic ion pairing can be used to transform hydrophilic drugs into a complex that can be further formulated into a muco-inert nanosuspension
- MOX-PAM NS is more effective in preventing and treating ocular infection in a corneal scratch model than commercial Vigamox® at the same concentration with reduced frequency of application
- Reduction of dosing frequency can increase adherence, and thus, effective prevention and treatment of infection, improving patient care

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