Innovative ophthalmic drug delivery: vancomycin and cefuroxime eye drops based on a self-emulsifying system (SEO)

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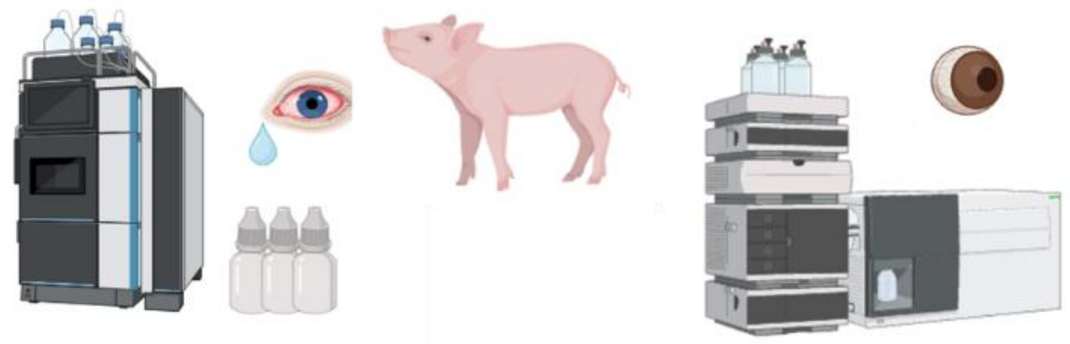
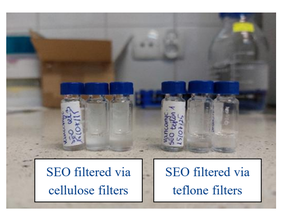
Introduction

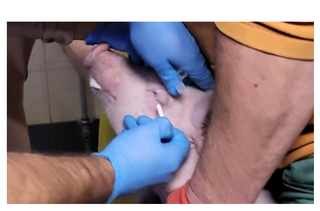
An innovative drug delivery technology using a self-emulsifying oil (SEO) converts into an emulsion upon contact with tear fluid, facilitating rapid dissolution of water-unstable antibiotics. Vancomycin hydrochloride (VAN) and cefuroxime sodium (CEF), selected for their clinical importance against resistant infections, were used as a model compounds. Preclinical safety, tolerance, and efficacy of SEO were confirmed in rabbits, accompanied by pharmacokinetic and tissue distribution studies for both antibiotics in SEO to overcame aqueous instability, and allowing potential clinical applicability [1-3].



Materials and Methods

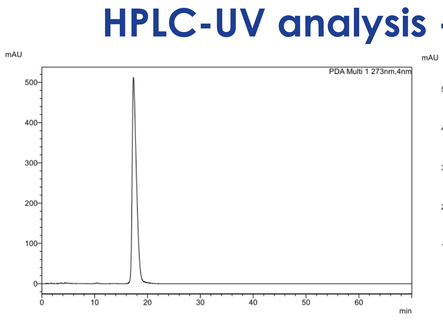
Analytical evaluation included instrumental methods such as HPLC-UV and LC-MS/MS for quantifying antibiotic content, impurities, and degradation products. Stability of VAN and CEF in SEO formulations were assessed immediately after preparation and during storage. *In vivo* studies on porcine models evaluated safety, tolerance, and antibiotic pharmacokinetics, using LC-MS/MS for eye tissue distribution studies.



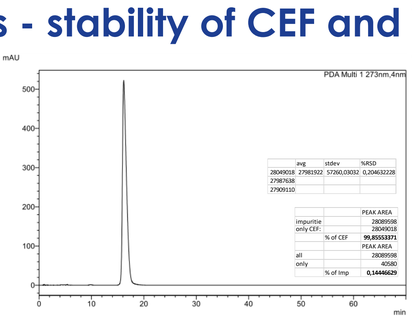


Results

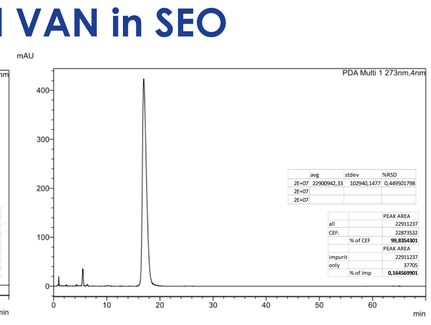
HPLC-UV analysis - stability of CEF and VAN in SEO

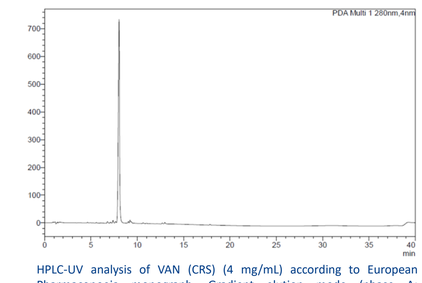


HPLC-UV analysis of CEF (CRS) (1 mg/mL) according to European Pharmacopoeia monograph. Isocratic elution mode (acetonitrile:acetic acid buffer pH 3.4 (1:99, v/v), Column: SphereClone (125 × 4.6 mm; 5 µm, Phenomenex. Oven temperature: 20°C (ambient); flow: 1.5 mL/min; injection: 20 µL; UV detection: 273 nm; analysis time: 70 min.

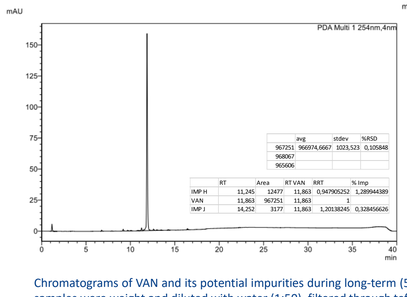


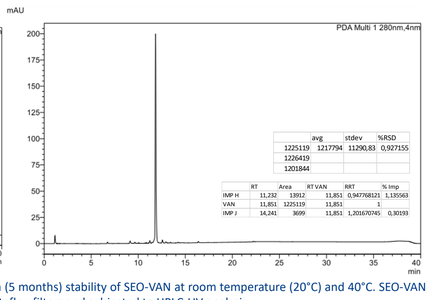
Chromatograms of CEF and its potential impurities (mainly Impurity A) during short-term (1 month) and long-term (5 months) stability of SEO-CEF at room temperature. SEO-CEF samples were weight and diluted with water (1:50), filtered through teflon filters and subjected to HPLC-UV analysis.





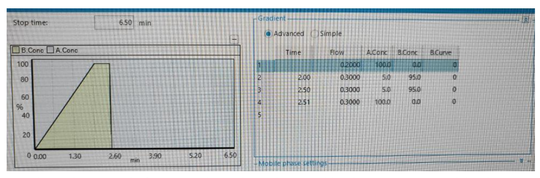
HPLC-UV analysis of VAN (CRS) (4 mg/mL) according to European Pharmacopoeia monograph. Gradient elution mode (phase A: acetonitrile:methanol:buffer A (3:4:93, v/v/v); phase B: acetonitrile:methanol:buffer A (10:40:50, v/v/v); column: Water Acquity SCH C18 (1,7 µm, 2,1×150 mm). Oven temperature: 40°C; flow: 0.27 mL/min; injection: 2 µL; UV detection: 280 nm; analysis time: 35 min.



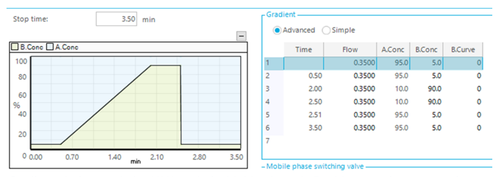


Chromatograms of VAN and its potential impurities during long-term (5 months) stability of SEO-VAN at room temperature (20°C) and 40°C. SEO-VAN samples were weight and diluted with water (1:50), filtered through teflon filters and subjected to HPLC-UV analysis.

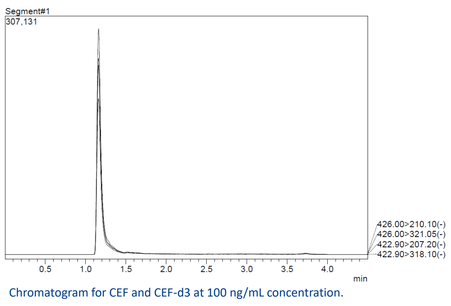
LC-MS/MS conditions for CEF and VAN analysis



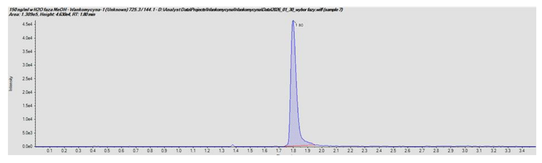
Gradient elution mode for CEF and CEF-d3 analysis. Moble phase A: water; mobile phase B: acetonitrile. Column: Ascentis Express F5 50x2.1mm, 2.7 µm. Oven temperature: 30°C. MS/MS System: Shimadzu 8060. Analysis were performed in negative ionization mode.



Gradient elution mode for VAN analysis. Moble phase A: 5 mM ammonium acetate in water with 0.05% formic acid; mobile phase B: 0.05% formic acid in methnol. Column: : Kinetex 1.7 µm EVO C18 100 Å. Oven temperature: 30°C. MS/MS System: AB Sciex QTRAP Citrine . Analysis were performed in negative ionization mode.

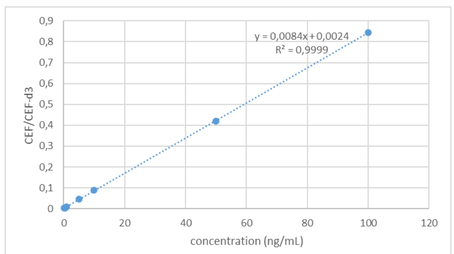


Chromatogram for CEF and CEF-d3 at 100 ng/mL concentration.

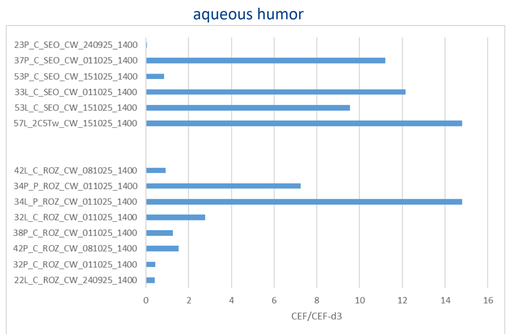


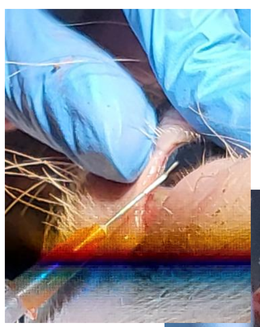
Chromatogram for VAN at 100 ng/mL concentration.
Monitored ions:
725,036 → 144,100 (DP – 76 V, CE – 21 V, CXP – 10 V)
725,036 → 100,100 (DP – 76 V, CE – 81 V, CXP – 12 V)
725,036 → 74,000 (DP – 76 V, CE – 95 V, CXP – 10 V)

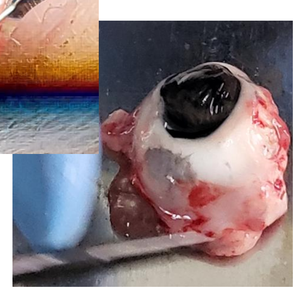
Analysis of CEF in aqueous humor and conjunctiva

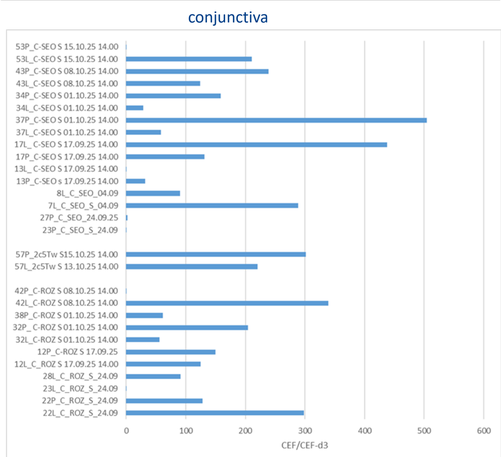


Instrumental calibration curve, and analysis of real aqueous humor and conjunctiva samples collected from eyes of pigs receiving 5% CEF in solution (ROZ) and 5% CEF in SEO.

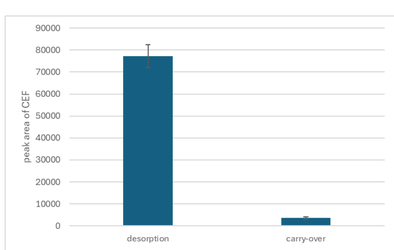








Analysis of Schirmer test strips with CEF/VAN from tears



Optimization of sample preparation for HPLC-UV analysis of CEF and VAN in tears collected with Schrimer test strips. Desorption was performed in 1mL of mobile phase for 30 in at 650 rpm.

Conclusions

- ✓ SEO-based suspension technology offers a breakthrough in delivery and stabilization of labile ophthalmic antibiotics
- ✓ preclinical data demonstrate safety, efficacy, and substantial stability improvements crucial for clinical translation
- ✓ promising enhanced therapeutic solutions for challenging ocular infections

ACKNOWLEDGEMENTS

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KRAJOWY PLAN ODBUDOWY
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