Novel *in vitro*, *ex vivo* and *in vivo* assessment of ophthalmic semi-solid drug products

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CONTROLLED RELEASE SOCIETY
CRS 2023 ANNUAL MEETING & EXPOSITION
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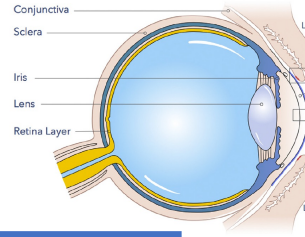
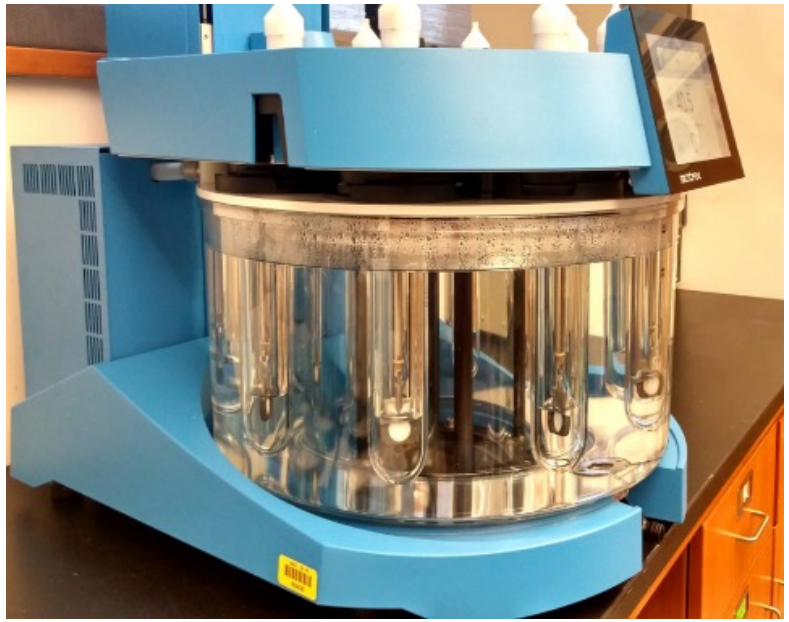
THE FUTURE OF DELIVERY SCIENCE

Challenges in Assessing Ophthalmic Ointments

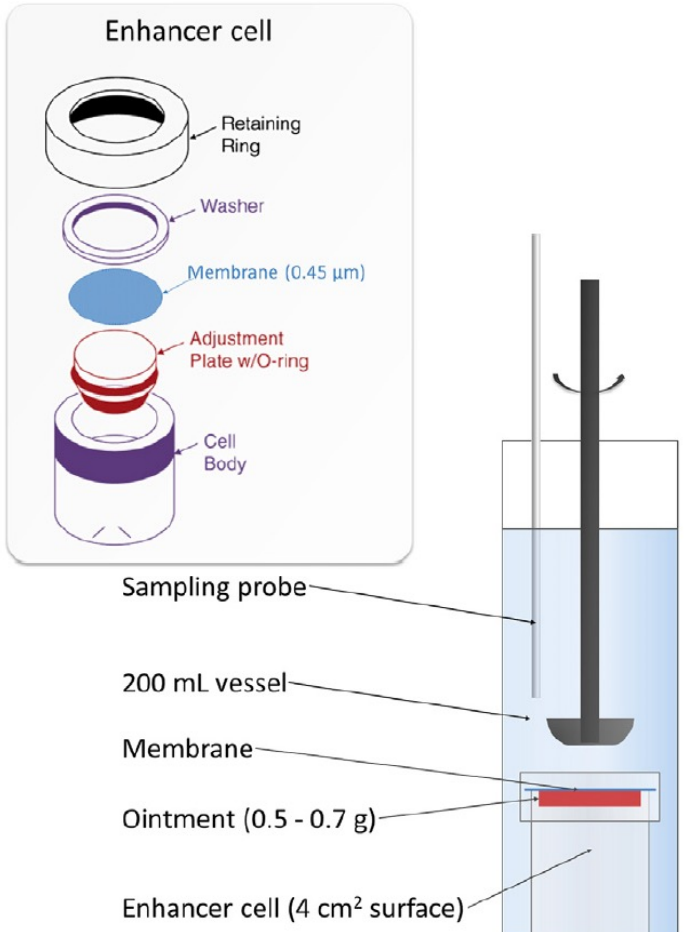


Challenges	Considerations
Low drug content requiring sensitive analytical approaches	LC/MS
Limited drug release, mainly from surface layer	Large surface area for in vitro release testing, membrane binding
Lack of compendial in vitro drug release testing methods	Apparatus setup, sample adaptors
Incomplete understanding on the impact of formulation properties on drug release profiles	Drug hydrophilicity, crystallinity, polymorphism, source, particle size
Lack of correlation between *in vitro* release, *ex vivo* test, and *in vivo* performance	Appropriate *in vitro* release, *ex vivo* studies, understand the correlation with *in vivo*

EVALUATION OF IN VITRO RELEASE APPARATUS SETUPS

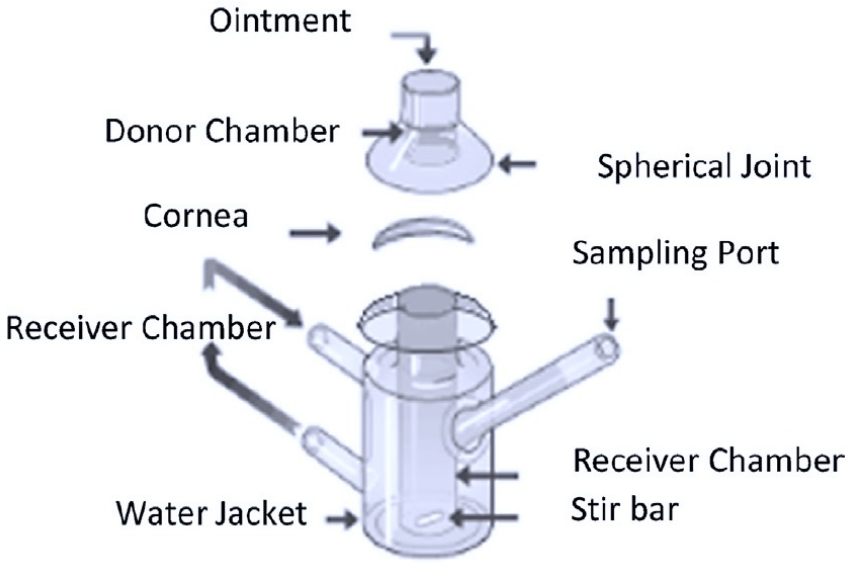


In vitro release testing (IVRT) for ophthalmic ointments



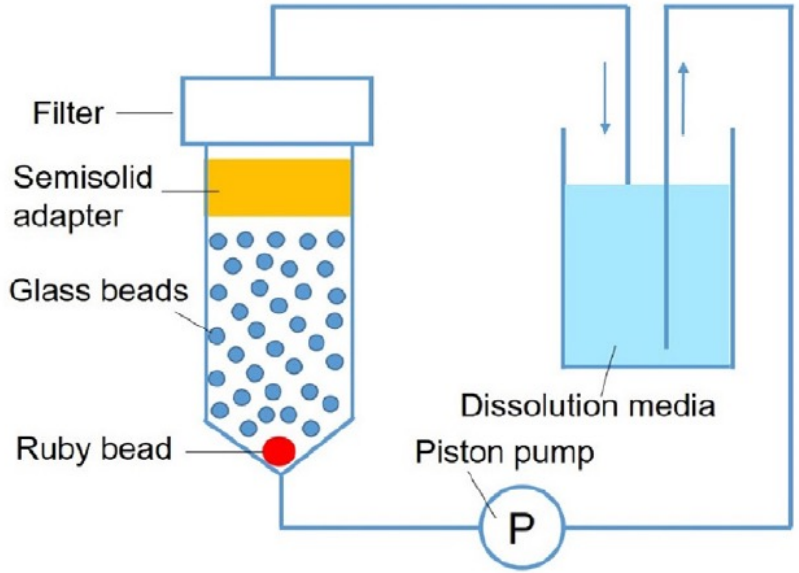
A: USP apparatus 2 with enhancer cells

Xi et al., 2015



B: Franz diffusion cells

Al-Ghabeish et al., 2015

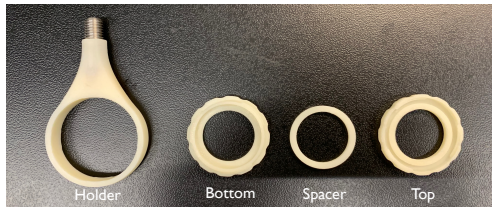


C: USP apparatus 4 with semisolid adapters

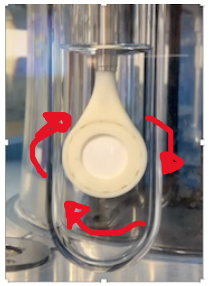
Bao et al., 2017

Dissolution Apparatus Optimization

Objective: To define optimal dissolution apparatus to study drug release from ophthalmic ointments and discriminate formulations.

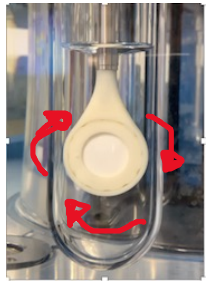


Compartments of two-side semisolid adapter
surface area = 3.15 cm^2 /each side



USP 1
2- side adapter
Surface area = 6.30 cm^2

VS

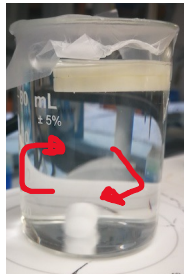


USP 1
2- side adapter using
plastic block one side
Surface area = 3.15 cm^2

VS

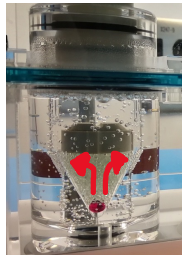
USP II
1- side adapter
Surface area = 1.77 cm^2

VS



2- side adapter: MB facing to media using magnetic stirrer
Surface area = 3.15 cm^2

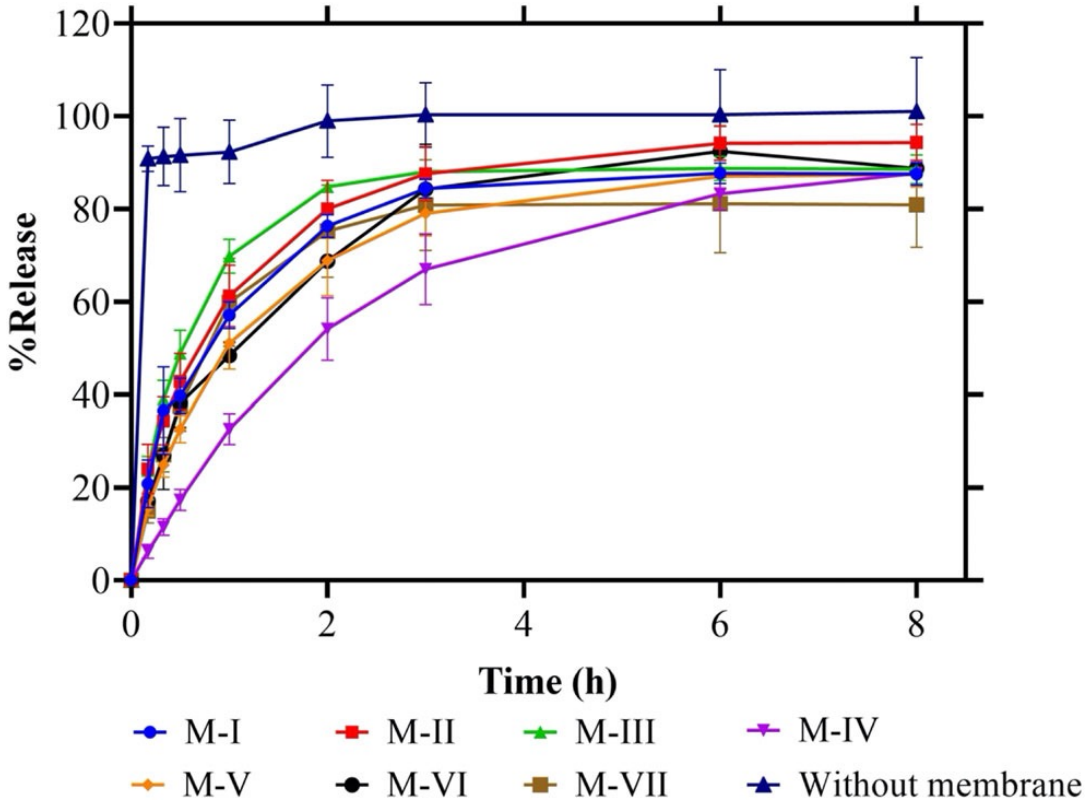
VS

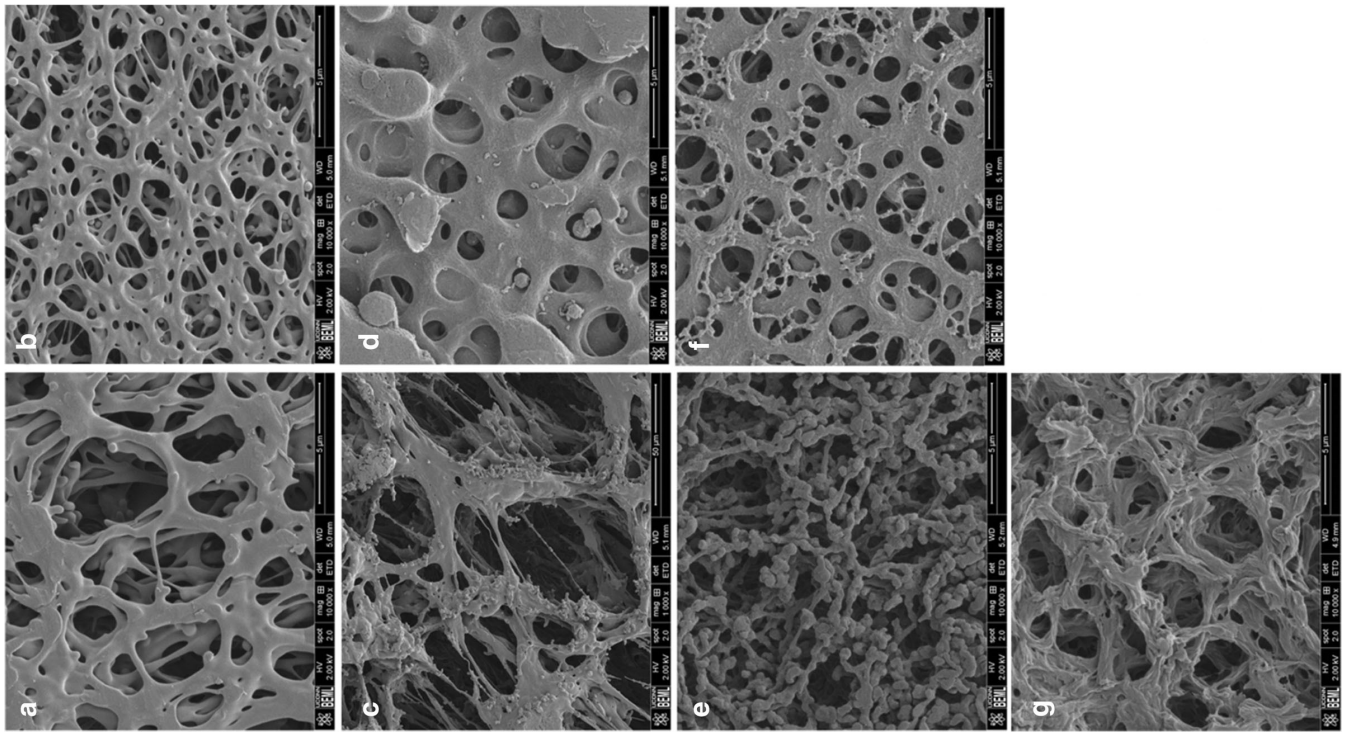


USP IV
1- side adapter
Surface area = 1.77 cm^2

Factors:
1) Surface area
2) Flow direction, agitation

Membrane Impact on Drug release

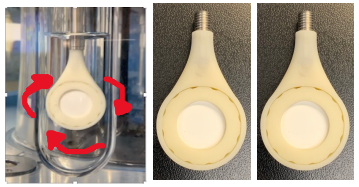


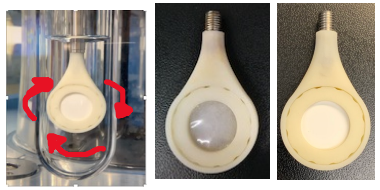


1.2 µm PES member was selected due to low drug binding and high differentiating ability

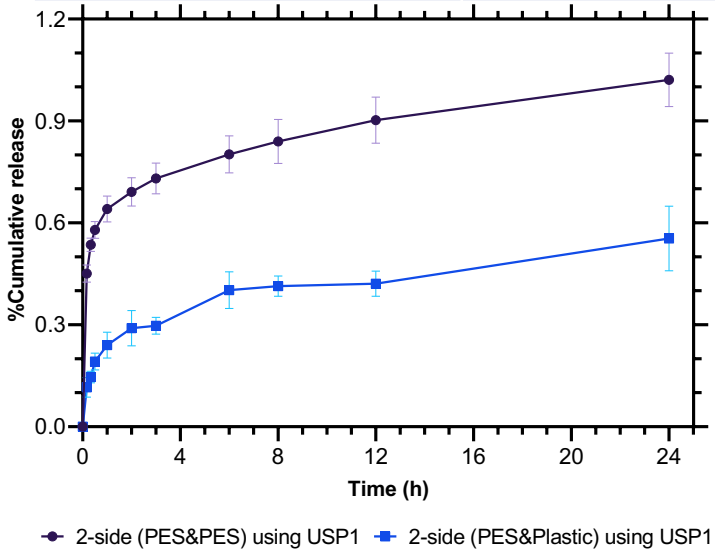
Mekjaruskula C, Beringhs AO, Luo W, Xu Q, Halquist M, Qin B, Wang Y, Lu X. Impact of Membranes on In Vitro Release Assessment: a Case Study Using Dexamethasone. AAPS PharmSci Tech. 2021 Jan 10;22(1):42.

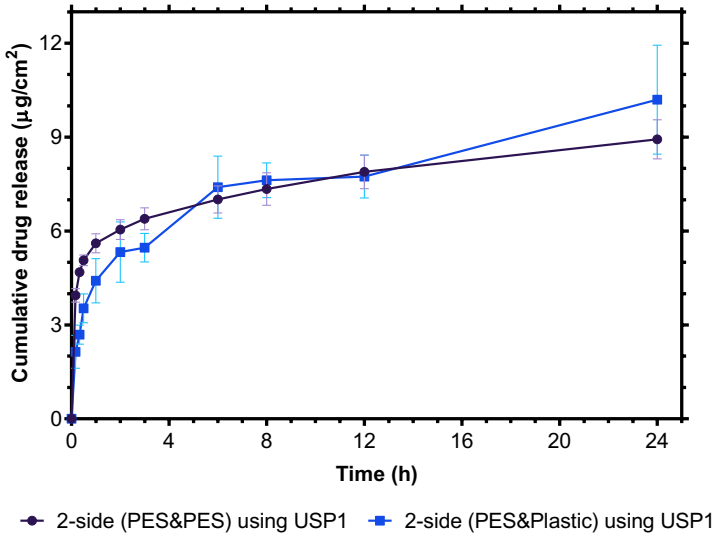
FACTORS: 1) SURFACE AREA

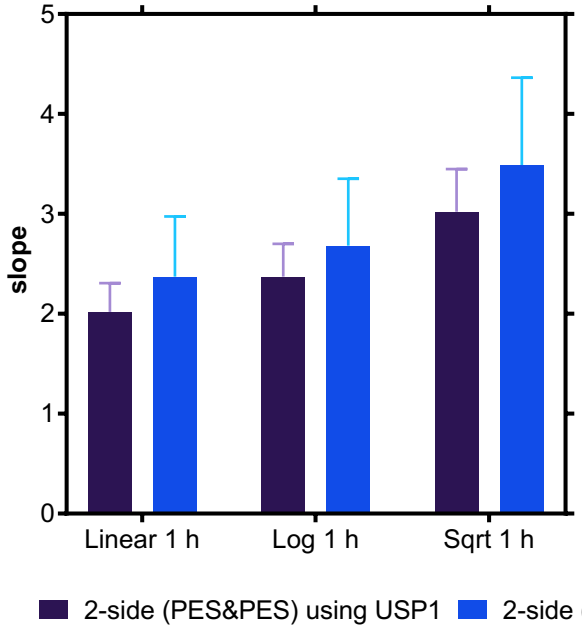




Parameter	USP Apparatus I	USP Apparatus I
Membrane	1.2 µm PES + 1.2 µm PES	1.2 µm PES + Plastic
Surface area	6.30 cm^2	3.15 cm^2
Release medium	STS with 0.1% Tween® 80, 37°C	
Ointments	1% DEX in IGI® 386	

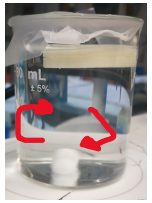




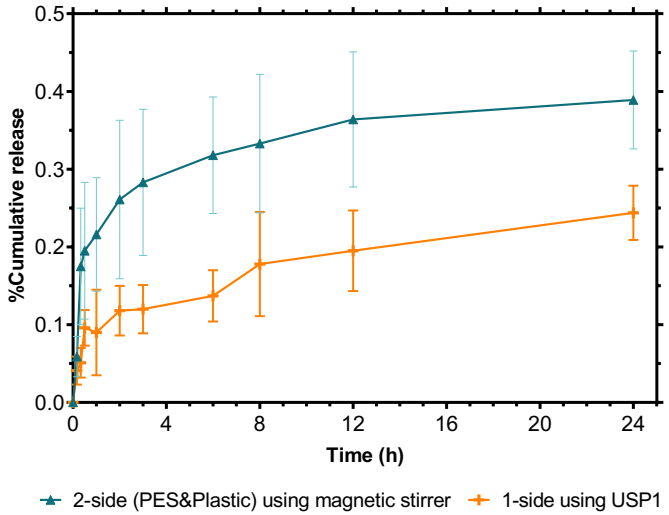


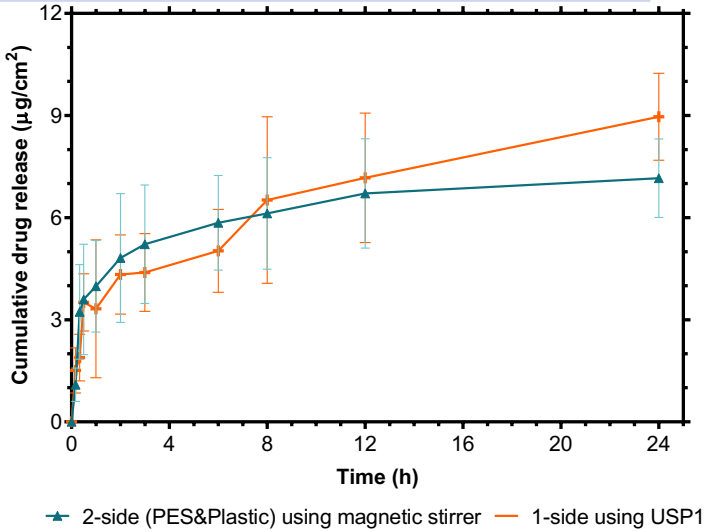
There was **no significant difference** between 2 models.

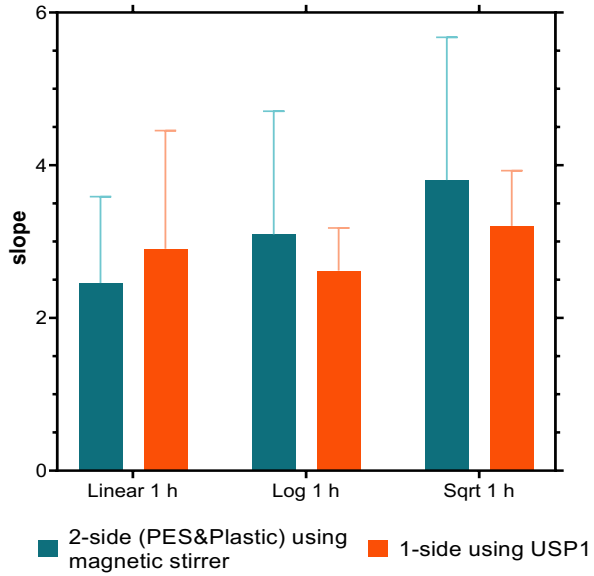
FACTORS: 1) SURFACE AREA



Parameter	USP Apparatus II	Magnetic stirrer
Adapter	1-side	2-side
Membrane	1.2 µm PES	1.2 µm PES + Plastic
Surface area	1.77 cm^2	3.15 cm^2
Release medium	Simulated tear solution (STS) with 0.1% Tween® 80, 37˚C	
Ointments	1% DEX in IGI® 386	

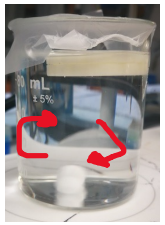




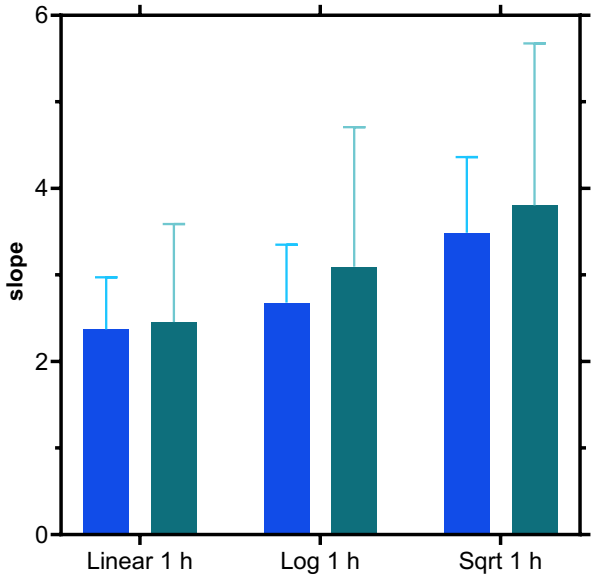


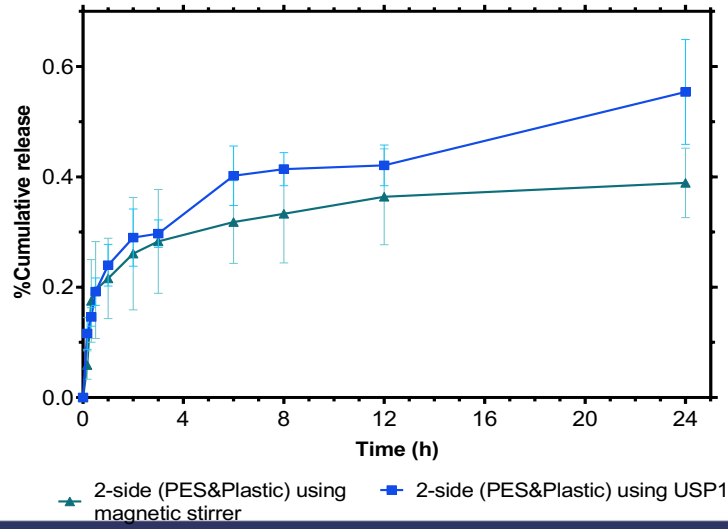
There was **no significant difference** between 2 models.

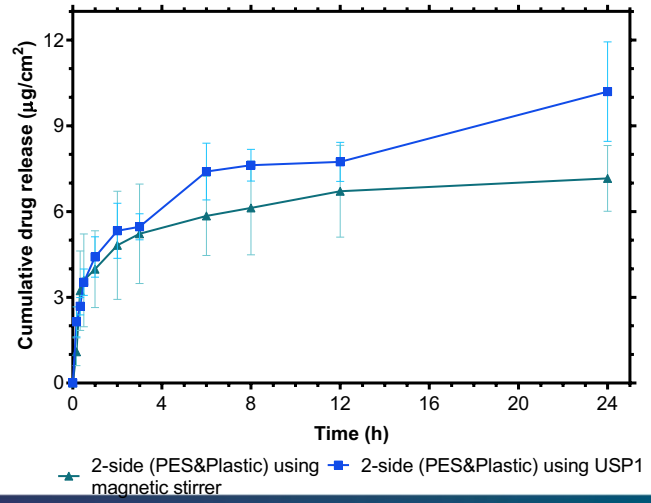
FACTORS: 2) FLOW DIRECTION



Parameter	USP Apparatus I	Magnetic stirrer
Membrane	1.2 µm PES + Plastic	1.2 µm PES + Plastic
Surface area	3.15 cm^2	3.15 cm^2
Release medium	STS with 0.1% Tween® 80, 37°C	
Ointments	1% DEX in IGI® 386	







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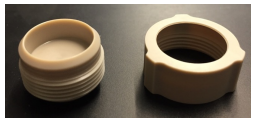
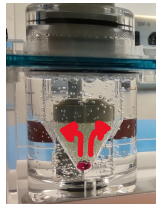
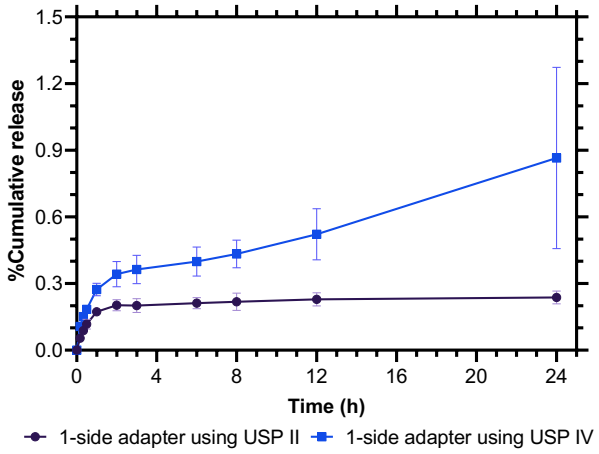
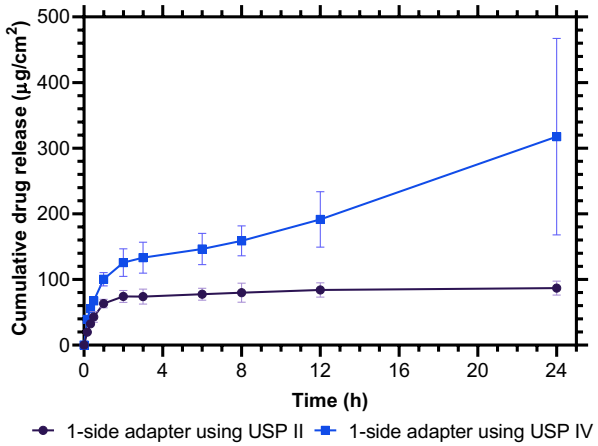
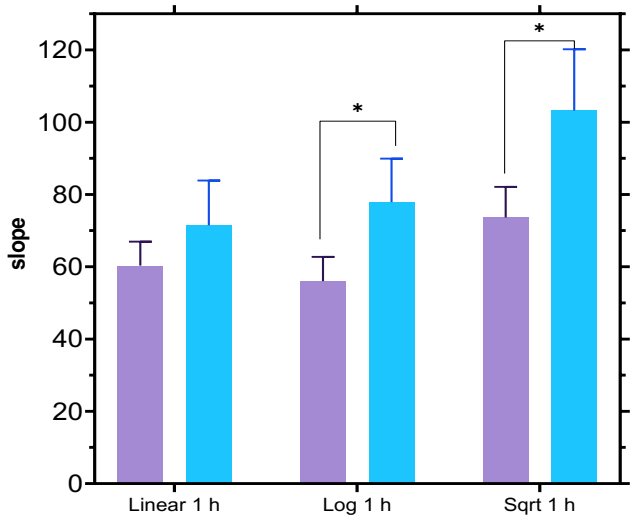




Parameter	USP Apparatus II	USP Apparatus IV
Adapter	1-side	1-side
Membrane	1.2 µm PES	1.2 µm PES
Surface area	1.77 cm^2	1.77 cm^2
Release medium	STS with 0.1% Tween® 80, 37°C	
Ointments	10% DEX in IGI® 386	

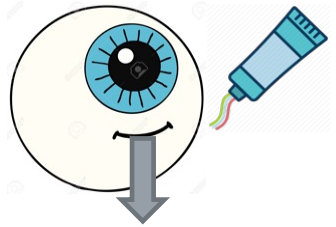


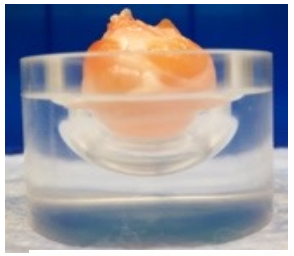


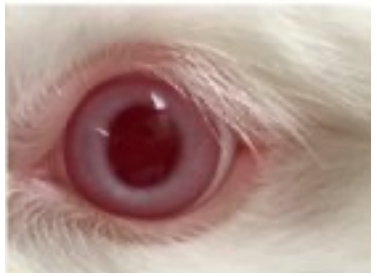


- Larger surface area, higher percent cumulative drug release
- Release amount and rate per surface area were consistent
- Agitated flow of USP IV **enhanced** hydrophobic drug (dexamethasone) release from the ointments and increased its release rates when compared to the immersion cells.

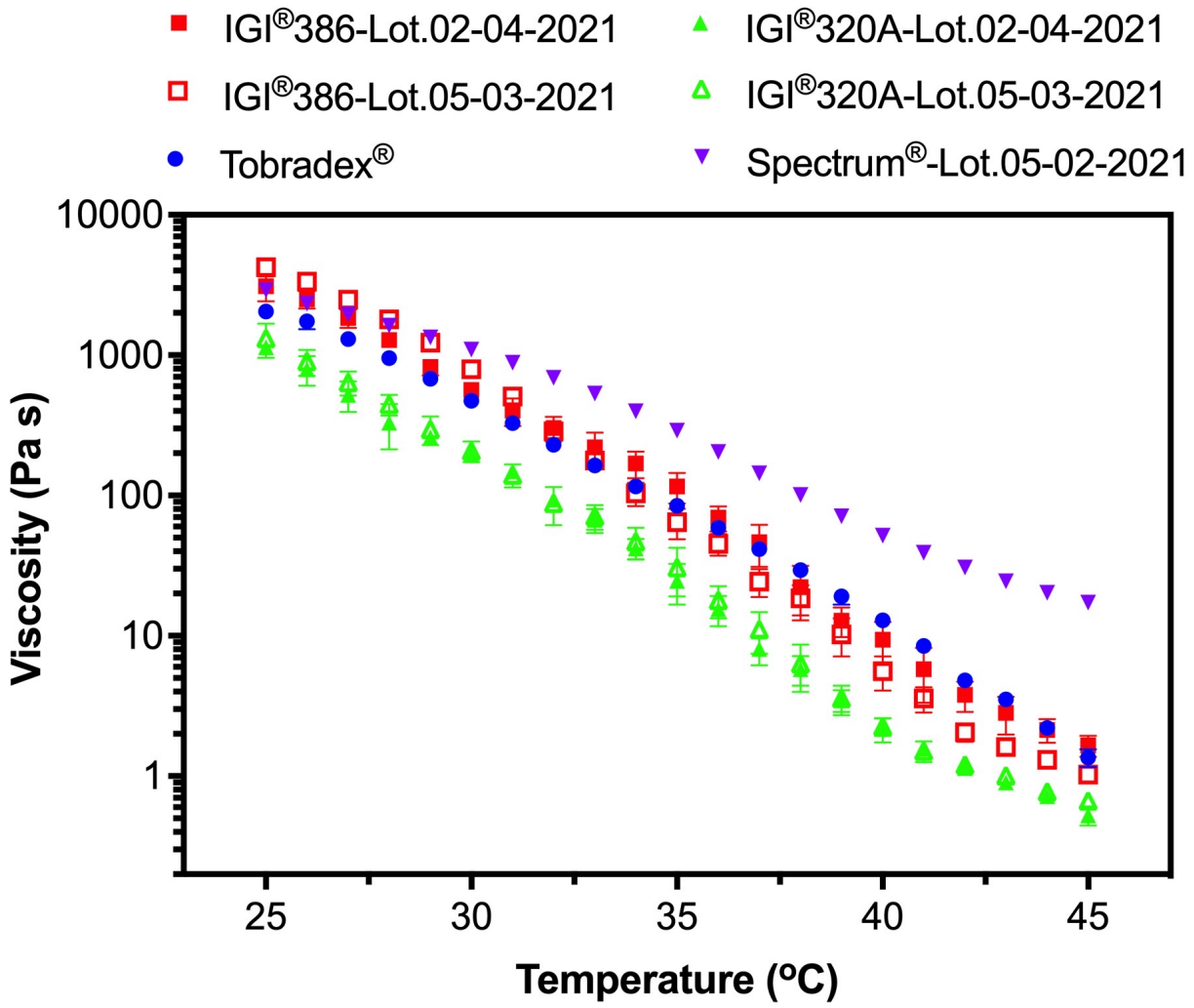
VITRO, EX-VIVO AND *IN VIVO* ASSESSMENT COMPARISON







RHEOLOGICAL PROPERTIES-TEMPERATURE SWEEP



IN VITRO RELEASE TESTING

Dissolution Parameters	USP Apparatus I
Samples	1) Tobradex® ointments 0.3% TOB/0.1% DEX 2) 0.3% TOB/0.1% DEX in IGI® 386 3) 0.3% TOB/0.1% DEX in IGI® 320A 4) 0.3% TOB/0.1% DEX in Spectrum®
Weight of sample	0.58 g/adapter
Release medium	80 mL of STS
Temperature	40°C
pH	7.4
Stirring Speed	200 rpm
Membrane	1.2 µm PES from Sterlitech®
Dissolution apparatus	3D-Printed Two-side Adapter in USP apparatus I
Aliquot removed	1 mL (replaced with 1 mL fresh medium after withdrawn)
Sampling times	5, 10, 15, 30, 45 min, 1, 2, 4, 7 h

3D-Printed Two-side Adapter in USP apparatus I

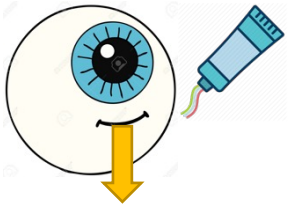
0.3% TOB/0.1% DEX ointments

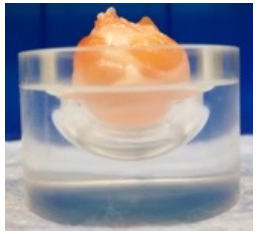
Rx

TOB	0.3%
DEX	0.1%
Mineral oil	5%
Chlorobutanol	0.5%
Petrolatum qs to	100%

Ex vivo release study

Eyes	Frozen rabbit eyes, thaw & incubate in STS 1 h (n=3)
Ointments	1) Tobradex® ointments 0.3% TOB/0.1% DEX 2) 0.3% TOB/0.1% DEX in IGI® 386 3) 0.3% TOB/0.1% DEX in IGI® 320A 4) 0.3% TOB/0.1% DEX in Spectrum® Apply 30 mg on the eye
Media	STS 650 µL
Temperature	34°C
Timepoints	5, 10, 15, 30, 45 min, 1, 2, 4 h





- Release media
- Aqueous humor
- Cornea

[Tissue collection and extraction were performed following VCU method.]

Pharmacokinetics studies in rabbits

Ocular tissue collection method set up and optimization ex vivo

Ocular tissue collection method set up in vivo

In Vivo PK of branded Tobradex ointment

Artificial Tear/Aqueous Humor/Tear/ Cornea/Plasma

Detectability

Recovery

Selectivity

Validation

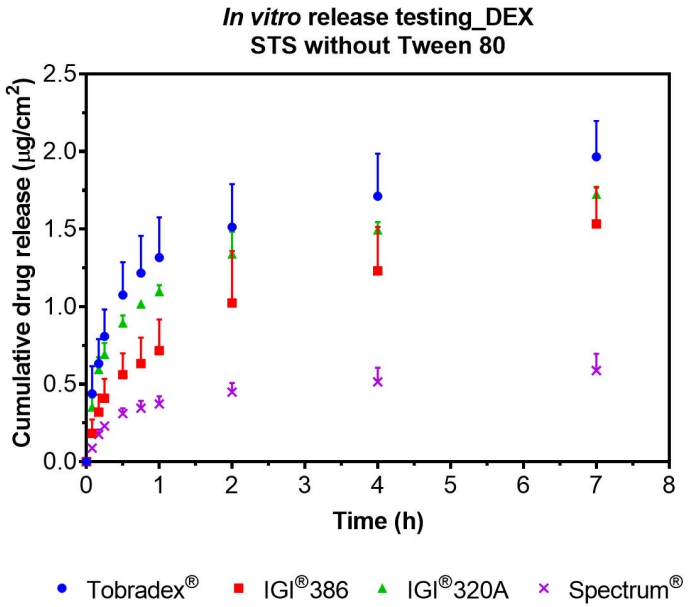
Partial Validation(s)

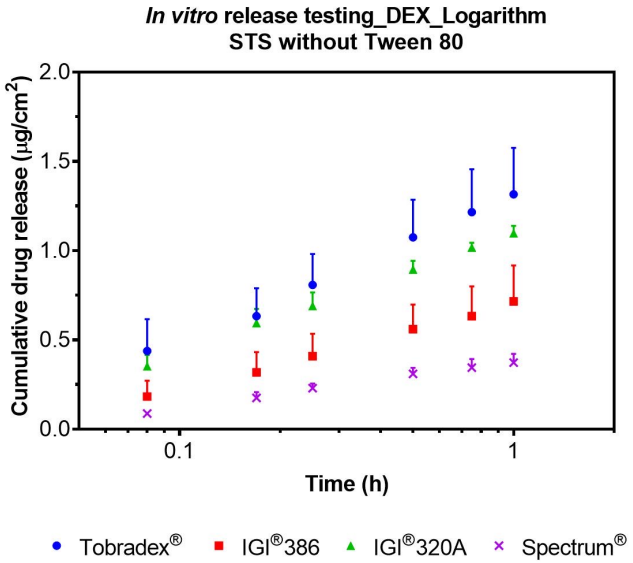
In Vivo PK for generic ointments

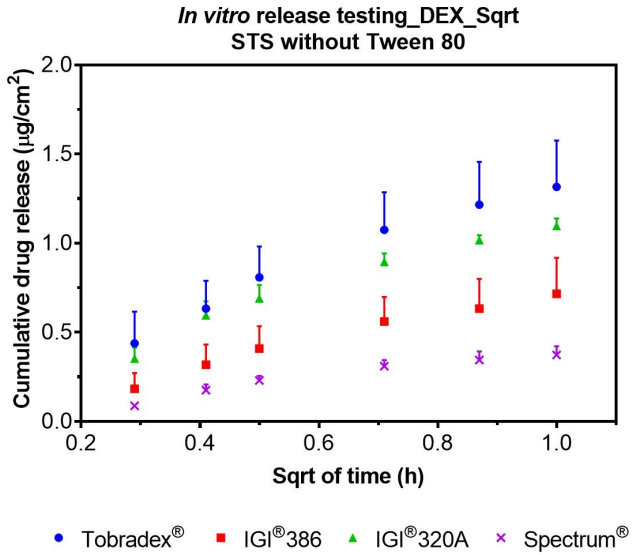
PK Data Analysis

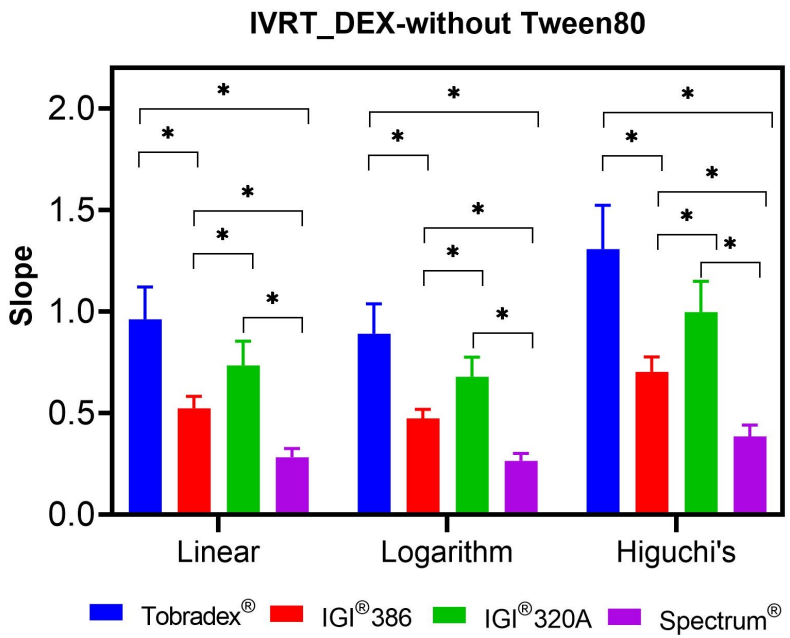
Meng T, Kosmider L, Chai G, Moothedathu Raynold AA, Pearcy AC, Qin B, Wang Y, Lu X, Halquist MS, Xu Q. LC-MS/MS method for simultaneous quantification of dexamethasone and tobramycin in rabbit ocular biofluids. J Chromatogr B. Analyt Technol Biomed Life Sci. 2021 Apr 30;1170:122610. Epub 2021 Mar 1.

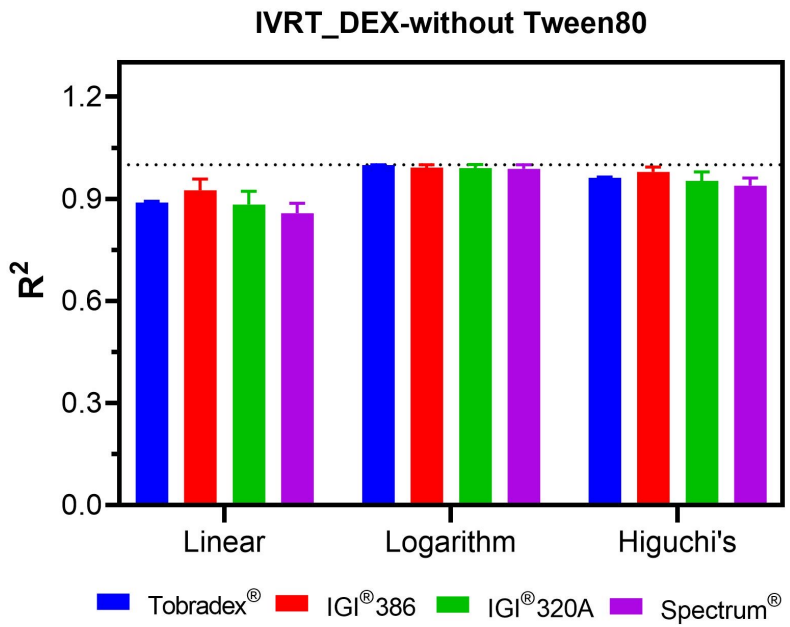
IN VITRO RELEASE TESTING



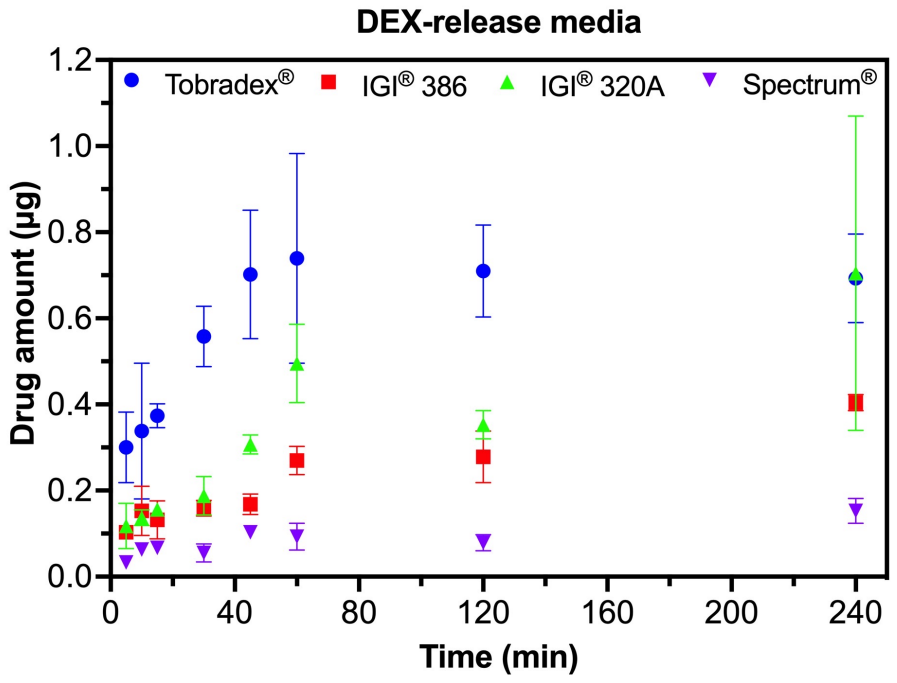


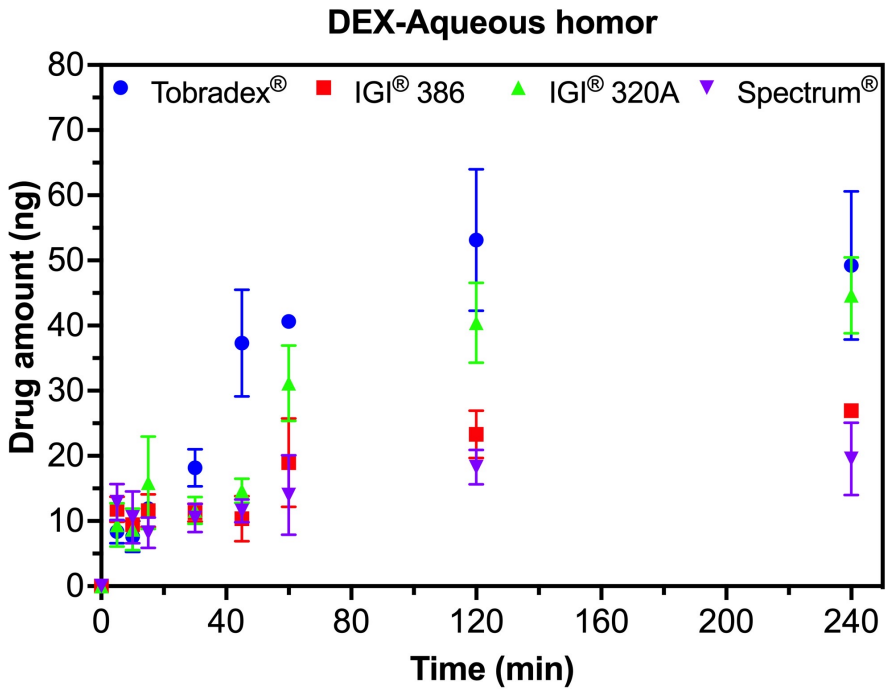






EX VIVO RELEASE : DEXAMETHASONE

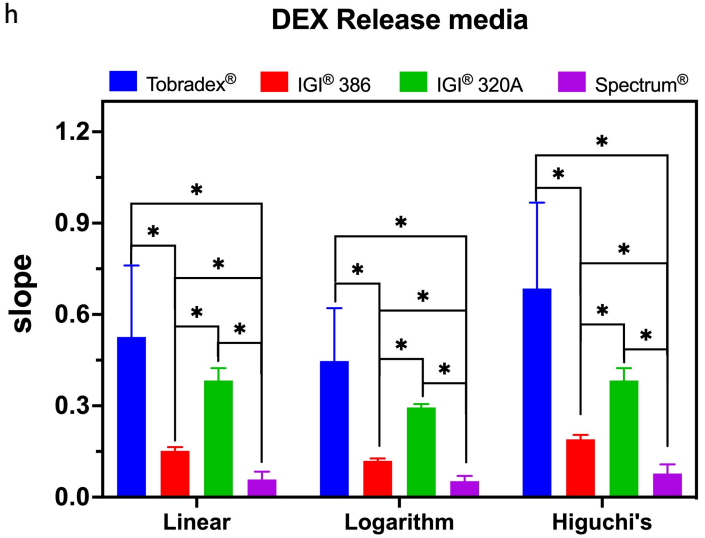




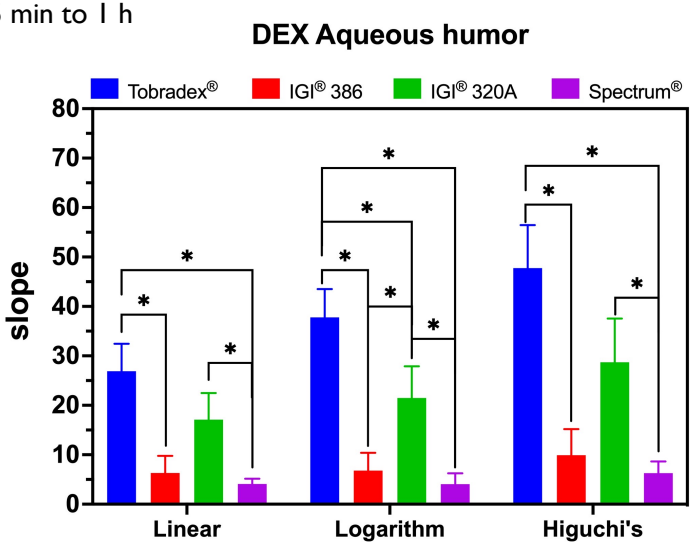
- Release media and aqueous humor : Tobradex > IGI 320A > IGI 386 > Spectrum
- Cornea: Tobradex > IGI 320A = IGI 386 > Spectrum

Ex vivo release : Dexamethasone

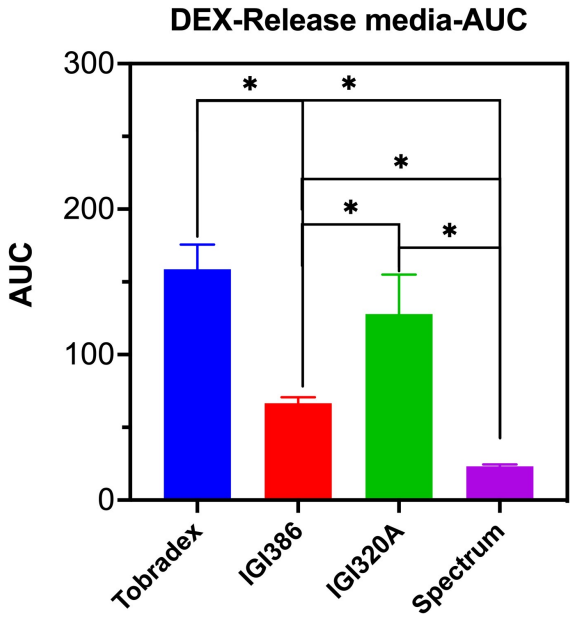
Slope from 5 min to 2 h

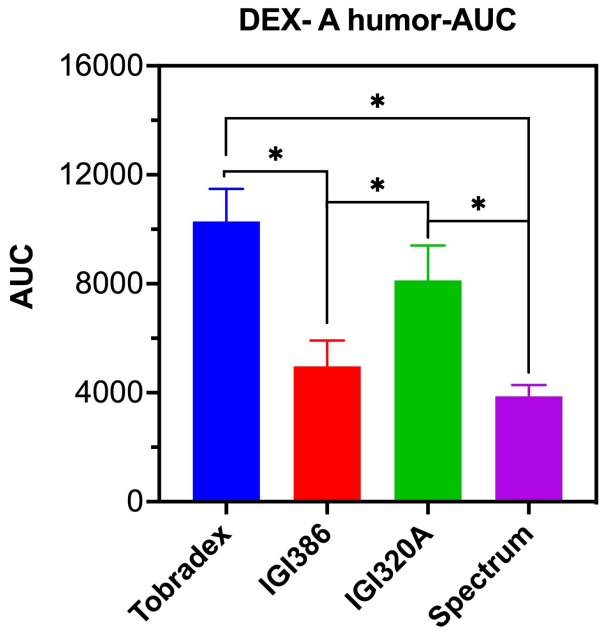


Slope from 5 min to 1 h

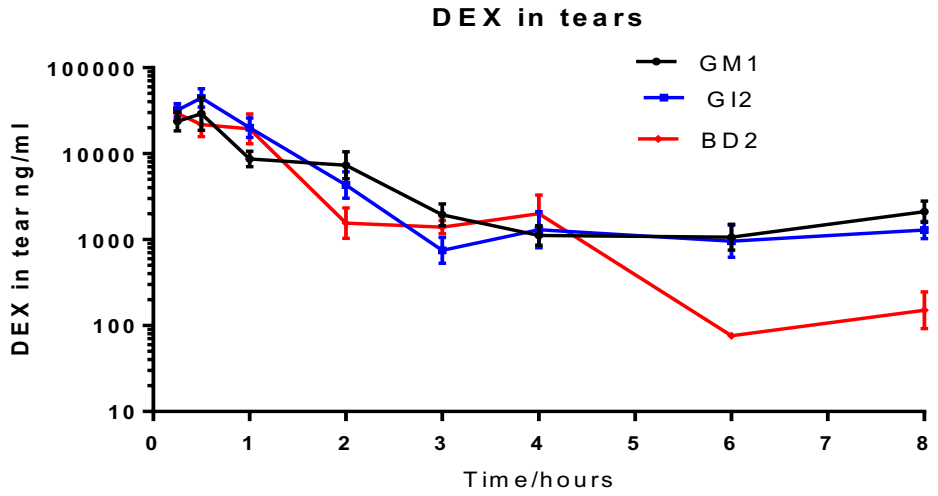


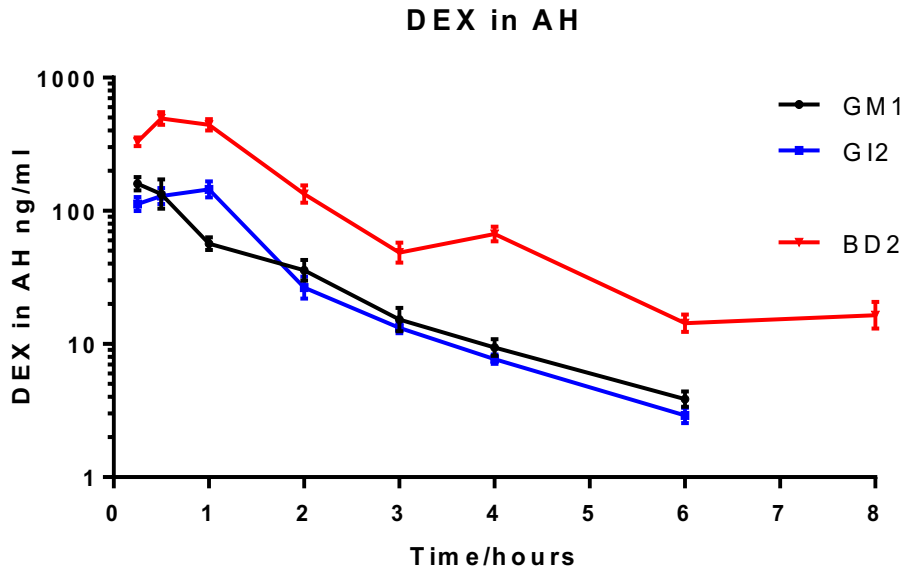
*AUC from 0 to 2h



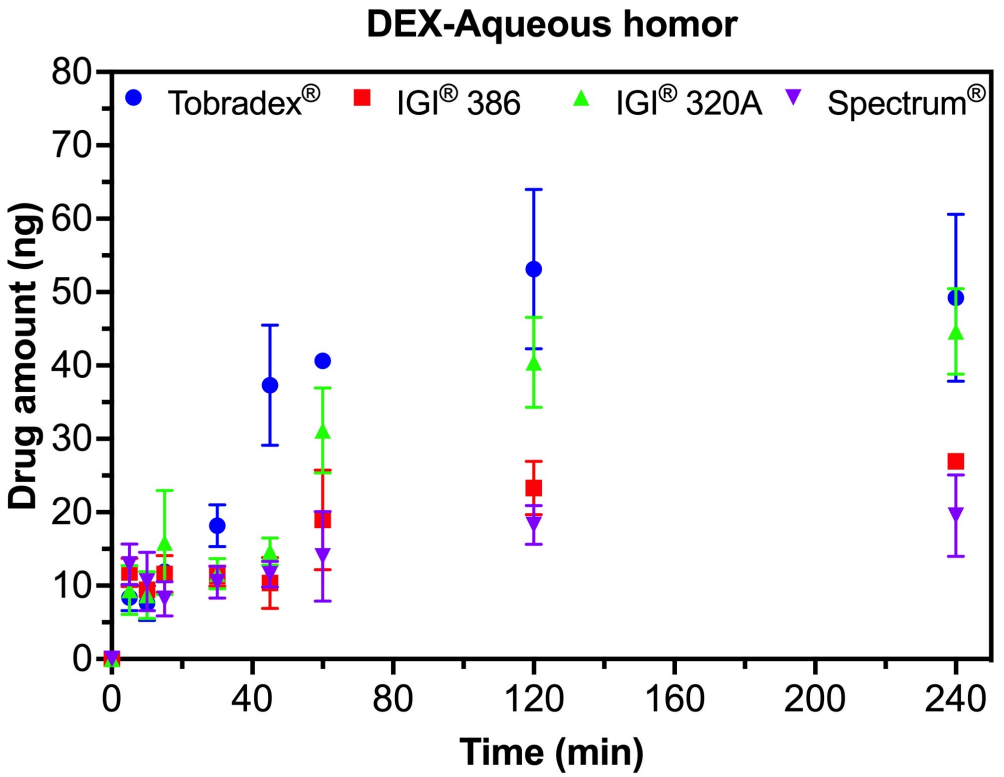


In vivo (rabbits) results





Ex-vivo



GM1: 1st generic formulation, Spectrum

GI2: 2nd generic formulation, IGI386 **BD: brand name**

SUMMARY ON THE ASSESSMENT METHODS

Method	Dexamethasone	Sensitivity for Differentiation
IVRT using STS without Tween80	Tobradex® > IGI® 386, Tobradex® > Spectrum® at $p<0.05$	Very sensitive
Ex vivo study	▪ Release media and aqueous humor : Tobradex > IGI 320A > IGI 386 > Spectrum	Sensitive and closer to *in vivo* results and also can cover the variations *in vivo*
In vivo study in rabbits	▪ No difference between generics ▪ Aqueous humor: Tobradex > generics	Can be variable

THANK YOU!

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