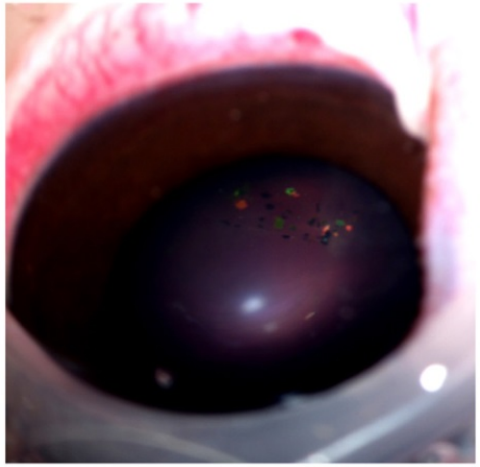
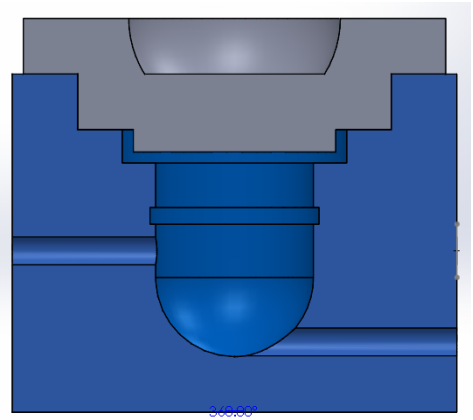
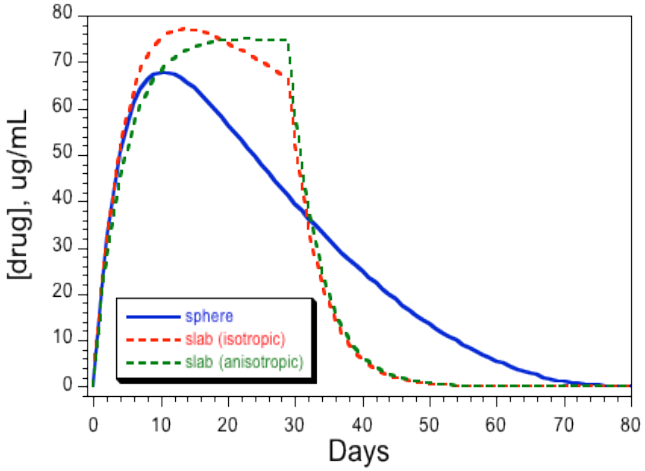
In vitro drug release testing of ophthalmic suspensions

Demonstrating Equivalence of Generic Complex Drug Substances and Formulations

FDA White Oak
6 October, 2017







FDA contract 1U01FD005173-01

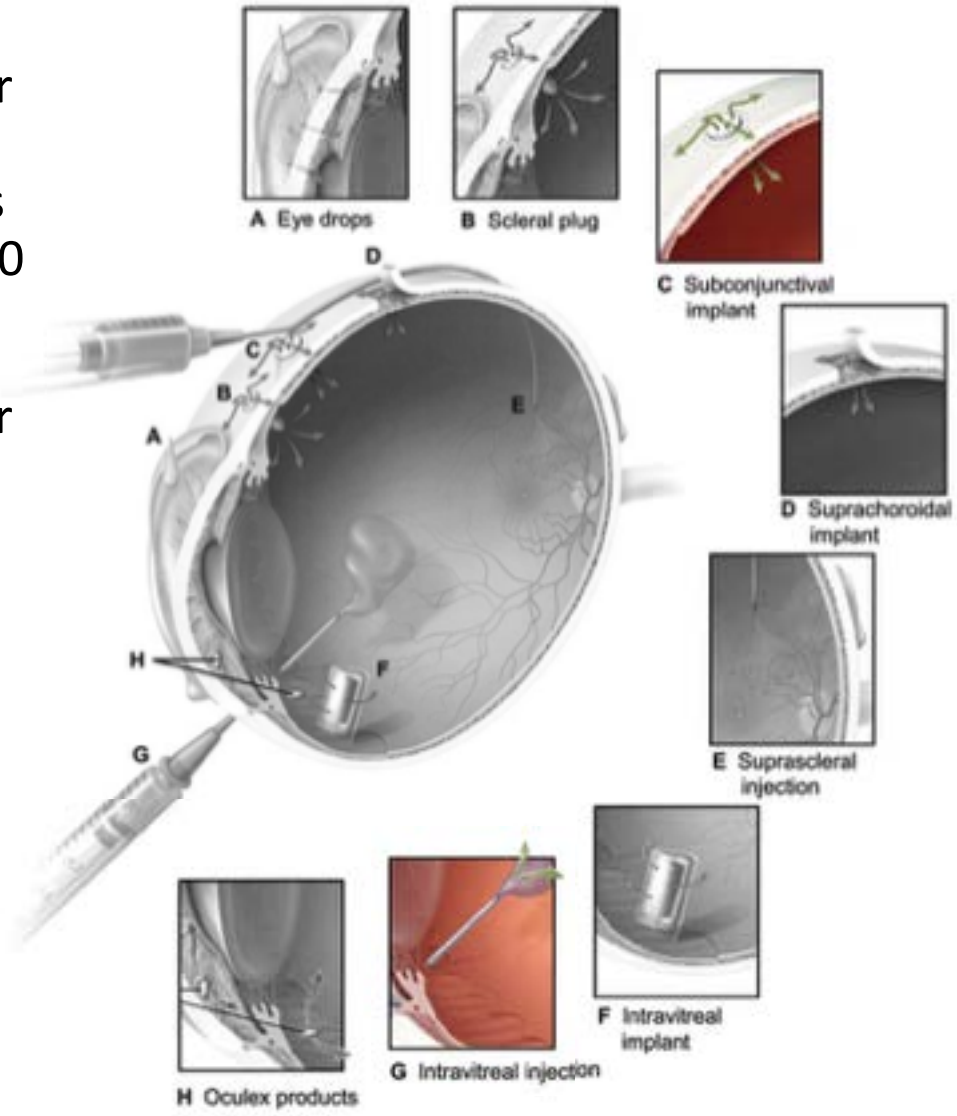
Long-acting intraocular drug delivery

- 9 million Americans over 40 suffer from Age-related Macular Degeneration (500,000 new cases of “wet” AMD per year, at $10,000 / case / year)*
- 4 million Americans over 40 suffer from Diabetic Retinopathy*
- Over $5 billion spent in 2003 on drugs to treat vision disorders**

Sources:

* Archives of Ophthalmology, vol. 122, Apr 2004

** National Eye Institute, 2003



http://www.visionproblemsus.org/index.html

Generic nanomaterials

U.S. Department of Health and Human Services

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Issues:

W. Jiang, R. Lionberger, L.X. Yu (FDA Office of Generic Drugs)
"In vitro and in vivo characterizations of PEGylated liposomal doxorubicin," Bioanalysis, 2011*, 3,* 333.

"One challenge in developing a nanoparticle drug-delivery system is understanding the critical physicochemical properties that may impact its in vivo performance and establishing analytical techniques that can adequately characterize in vitro and in vivo properties."

- *composition*
- *state of encapsulated drug*
- *internal environment*
- *size distribution*
- *surface chemistry*
- *electrical surface potential or charge*
- *in vitro leakage*
- *in vivo stability*
- *plasma pharmacokinetics*

Research, FDA. "For the past year, the FDA has been working to ensure that supplies of doxorubicin HCl liposome injection

Nanomaterials can be very sensitive to variations in manufacture

Brinker, C.J., et al, "Processing Pathway Dependence of Amorphous Silica Nanoparticle Toxicity: Colloidal vs Pyrolytic" *J. Am. Chem. Soc.* **2012,** *134*, 15790.

J|A|C|S JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

J. Am. Chem. Soc. **2012,** *134* (38), 15790-15804. Article

pubs.acs.org/JACS

Processing Pathway Dependence of Amorphous Silica Nanoparticle Toxicity: Colloidal vs Pyrolytic

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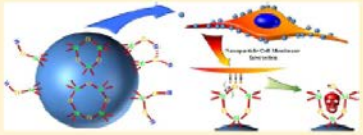
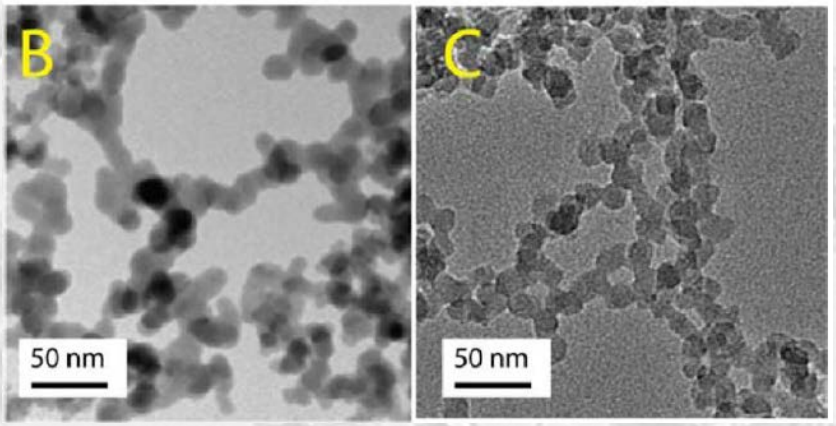
*"…we discovered for fumed silica an important toxicity relationship…whereas colloidal silicas were essentially nontoxic…**not all amorphous silicas are created equal**"*

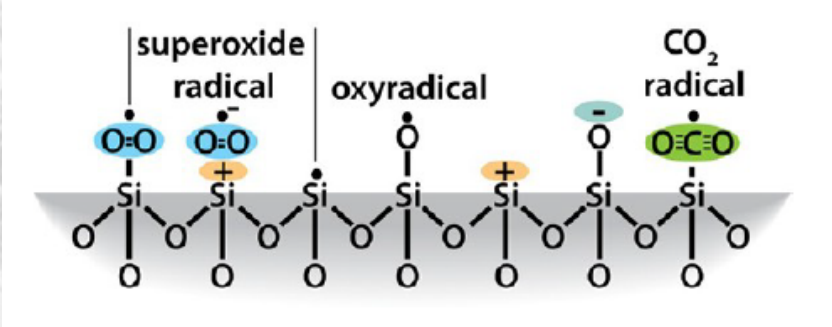
ABSTRACT: We have developed structure/toxicity relationships for amorphous silica nanoparticles (NPs) synthesized through low-temperature colloidal (e.g., Stöber silica) or high-temperature pyrolysis (e.g., fumed silica) routes. Through combined spectroscopic and physical analyses, we have determined the state of aggregation, hydroxyl concentration, relative proportion of strained and unstrained siloxane rings, and potential to generate hydroxyl radicals for Stöber and fumed silica NPs with comparable primary particle sizes (16 nm in diameter). On the basis of erythrocyte hemolytic assays and assessment of the viability and ATP levels in epithelial and macrophage cells, we discovered for fumed silica an important toxicity relationship to postsynthesis thermal annealing or environmental exposure, whereas colloidal silicas were essentially nontoxic under identical treatment conditions. Specifically, we find for fumed silica a positive correlation of toxicity with hydroxyl concentration and its potential to generate reactive oxygen species (ROS) and cause red blood cell hemolysis. We propose fumed silica toxicity stems from its intrinsic population of strained three-membered rings (3MRs) along with its chainlike aggregation and hydroxyl content. Hydrogen-bonding and electrostatic interactions of the silanol surfaces of fumed silica aggregates with the extracellular plasma membrane cause membrane perturbations sensed by the Nalp3 inflammasome, whose subsequent activation leads to secretion of the cytokine IL-1β. Hydroxyl radicals generated by the strained 3MRs in fumed silica, but largely absent in colloidal silicas, may contribute to the inflammasome activation. Formation of colloidal silica into aggregates mimicking those of fumed silica had no effect on cell viability or hemolysis. This study emphasizes that not all amorphous silicas are created equal and that the unusual toxicity of fumed silica compared to that of colloidal silica derives from its framework and surface chemistry along with its fused chainlike morphology established by high-temperature synthesis (>1300 °C) and rapid thermal quenching.



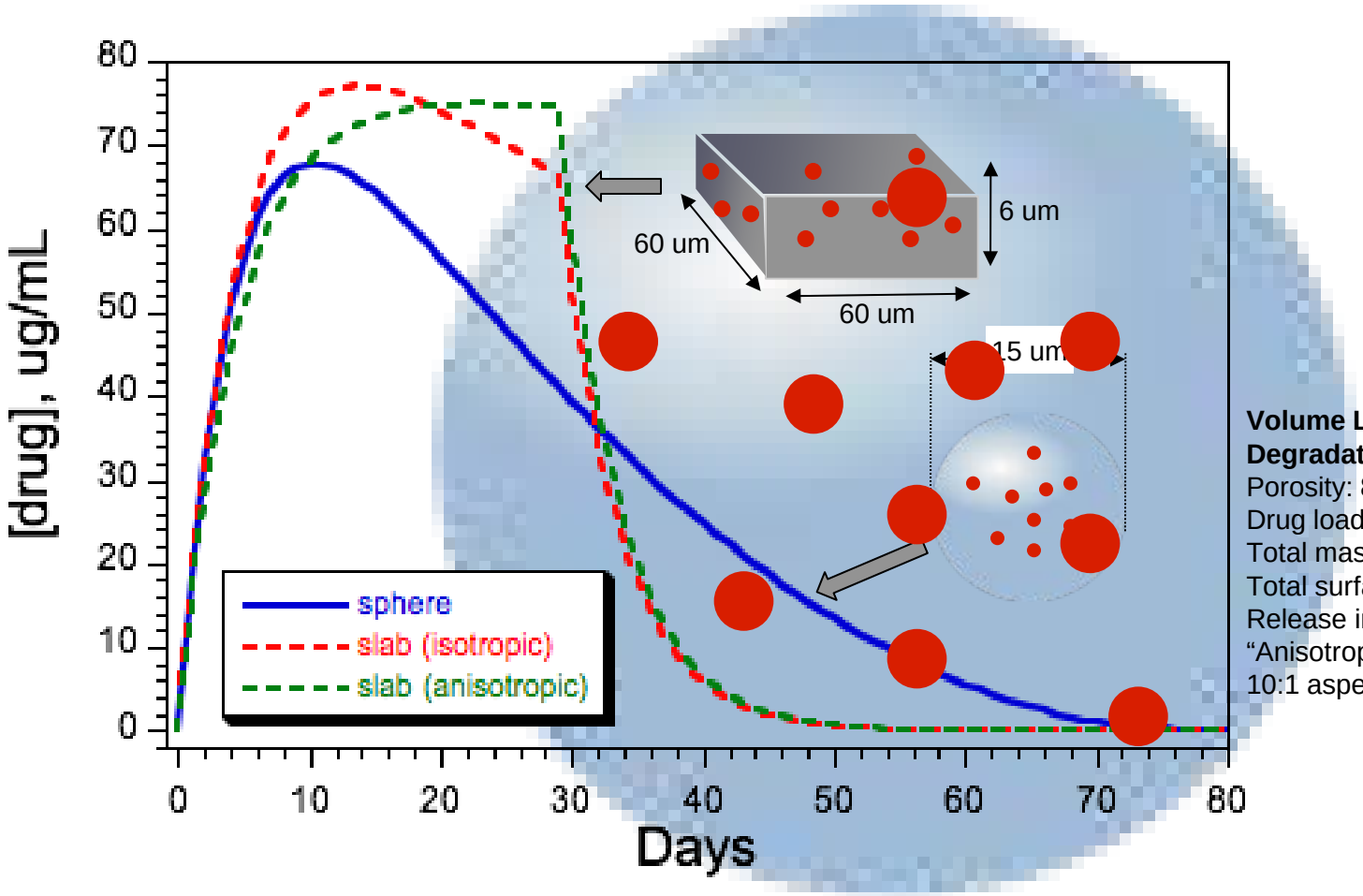
SiO_2



fumed silica *colloidal silica*



Particle shape determines release profile



Volume Loading, Degradation induced release
Porosity: 80%
Drug loading: 10 ug/mg
Total mass of particles: 200 mg
Total surface area: 800 cm^2
Release into 4.5 mL reservoir
"Anisotropic" dissolution trace is 10:1 aspect ratio

- Tabular particles dissolve more uniformly than spherical
- Anisotropic (1-d) dissolution flattens release profile

$$\text{rate of dissolution} = k \frac{S}{r} (C - C_{sat})$$

Drug delivery systems for the eye

Name	Type/Composition	Drug	Disease	Treatment period
Vitrasert	Implant, Polyvinyl alcohol, ethylene vinyl acetate	Ganciclovir	Virus (herpes, cytomegalovirus (CMV), etc)	5-8 months
Retisert	Implant, silicone, polyvinyl alcohol, cellulose	Fluocinolone Acetonide	Uveitis	2.5 years
Ozurdex	Implant (rod), PLGA	Dexamethasone	Macular degeneration and edema, uveitis, vein occlusion	3-6 months
Iluvien	Implant (rod), polyimide, polyvinyl alcohol	fluocinolone acetonide	Diabetic macular edema (DME)	3 years
Triesence	Microsphere suspension, Tween80	Triamcinolone Acetonide	ocular inflammation	3 months

Need for in vitro simulator

- Predict *in vivo* performance to optimize design of DDS
- Reduce number of animal experiments during development
- Differentiate between similar formulations for generic drug validation (FDA)

Goals

Design and validate a vitreous model for dissolution of particles and implants

- Flow cell design
- Test different media to mimic vitreous
- Conduct *in vitro* release studies

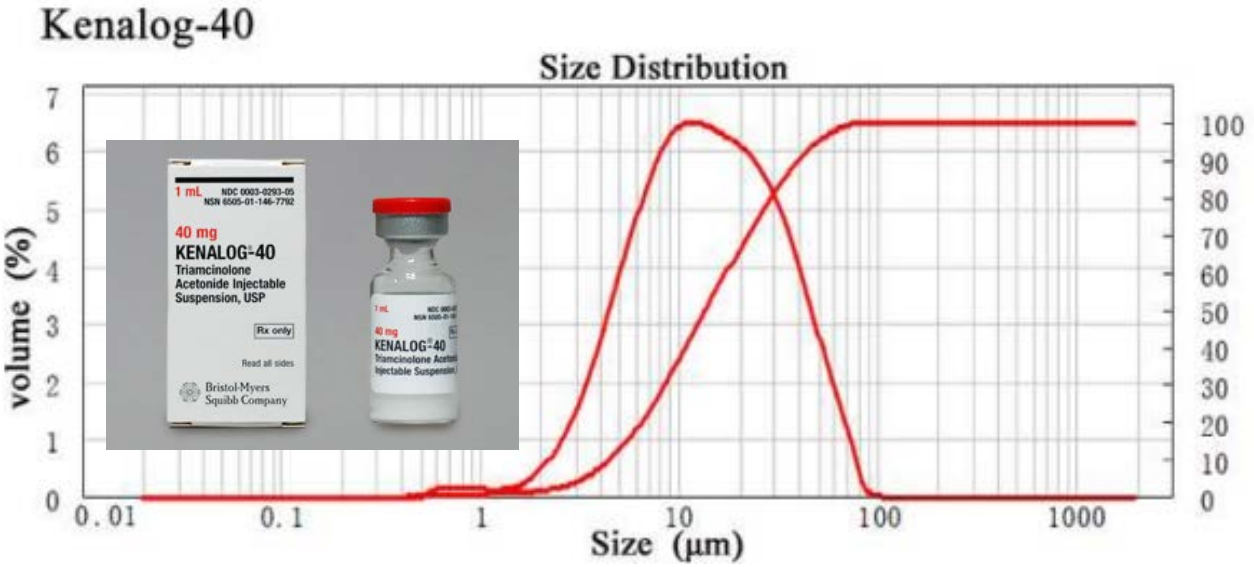
Benchmark results against literature and *in vivo* data

- Perform in vivo release studies
- Develop models and recommendations to correlate in vitro and in vivo drug release profiles

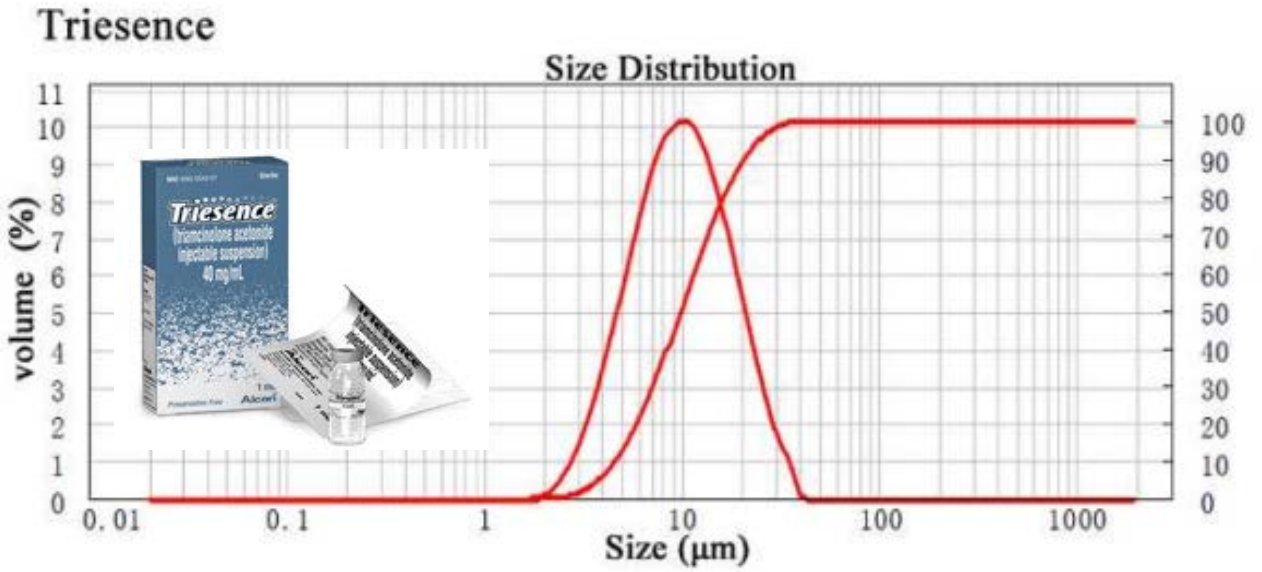
Kenalog40 *vs* Triesence

treat uveitis by intraocular injection

- API: Triamcinolone
- Crystalline
- Broad size distribution
- Benzyl alcohol preservative
- Salts, surfactants
- For intra-articular and intramuscular use
- Half-life in the eye (4mg, rabbit): 23d
- Used off-label for uveitis



- API: Triamcinolone
- Crystalline
- Narrow size distribution
- No preservative
- Salts, surfactants
- Half-life in the eye (4mg, rabbit): 24d
- FDA approved for uveitis



Invest. Ophthalmol. Vis. Sci. **54**, 2178-2185 (2013), Retin.-J. Retin. Vitr. Dis. **33**, 522-531 (2013), Retin.-J.

Kenalog40 *vs* Triesence

treat uveitis by intraocular injection

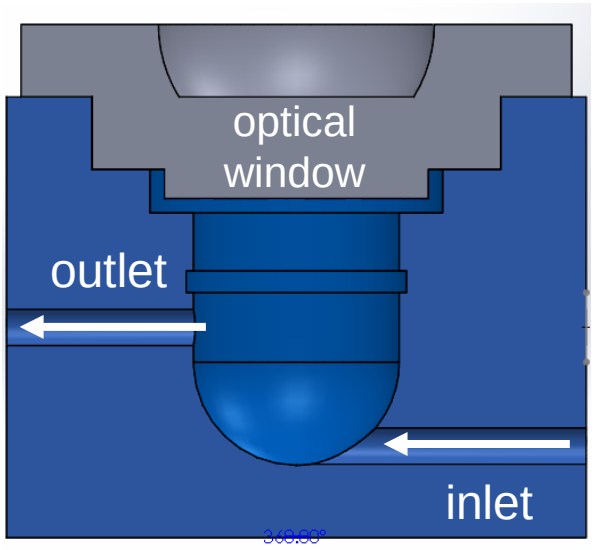
	Kenalog40	**Triesence**
Triamcinolone Acetonide (Active Ingredient)	40 mg/mL	40 mg/mL
Sodium Chloride	0.65%	Possibly Reduced (concentration not available)
Benzyl Alcohol	0.99% (w/v)	Not Included
Carboxymethylcellulose Sodium	0.75%	0.5%
polysorbate 80	0.04%	0.015%
pH (adjusted with NaOH or HCl)	5.0 – 7.5	6 – 7.5
Additional Inactive Ingredients	Water	Calcium chloride (dihydrate), magnesium chloride (hexahydrate), potassium chloride, sodium acetate (trihydrate), sodium citrate, and water

Static *vs* Flow system

	Static	Flow
Plumbing	Single vial per sample	Requires separate pumps, tubing for each sample
Sampling	Discrete	Continuous
Analytics	Simple	Difficult (dilute analyte)
Control of dissolution rate	Based on sample interval Not representative of physiology	Readily adjusted

In vitro flow cell design

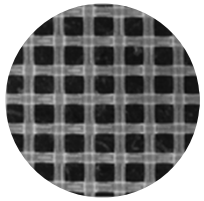
Teflon flow cell



Lid with quartz window

Fittings and mesh filters

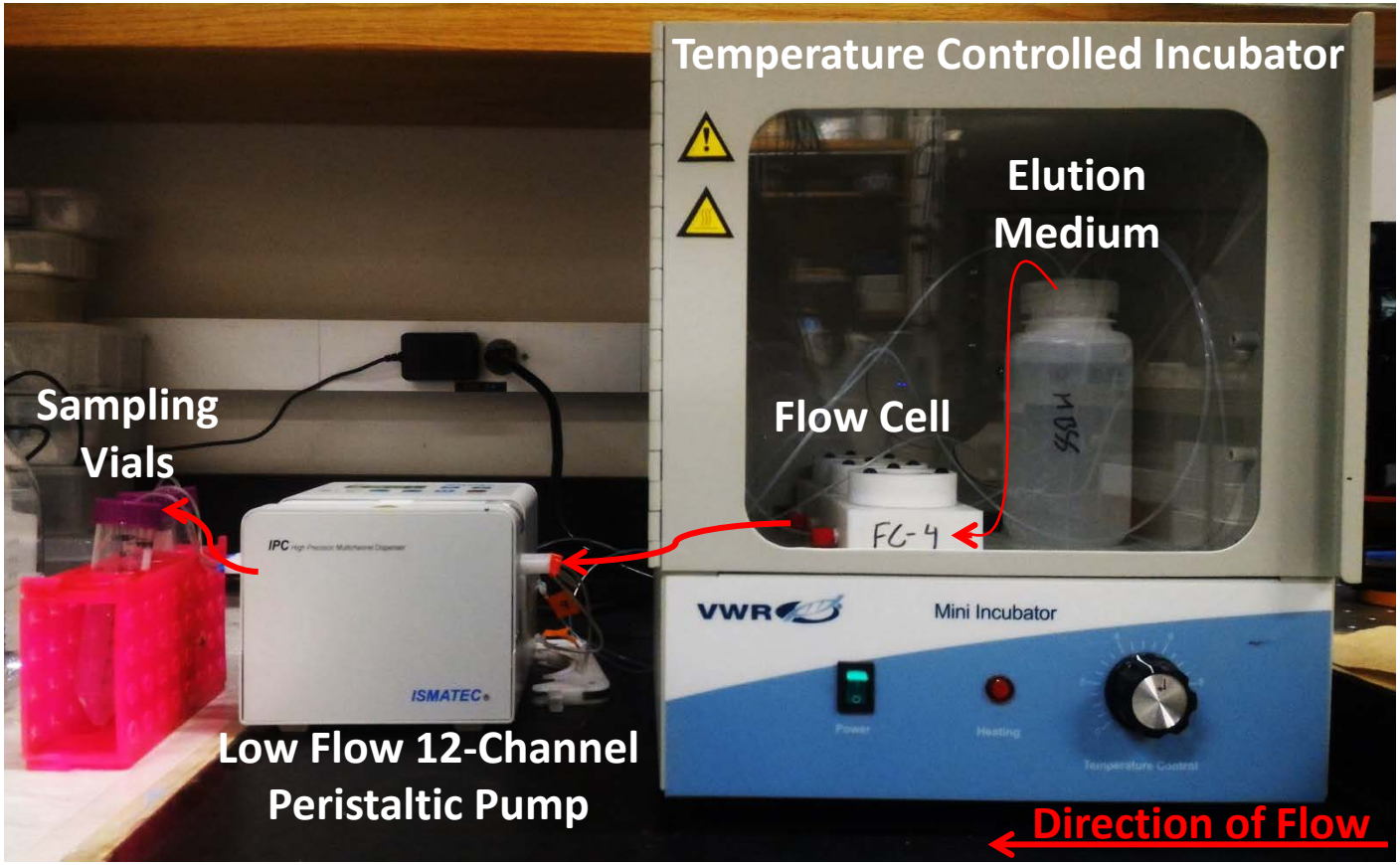
10um pores



+

In vitro system

- Sample daily
- Flow rate
  - 1.5 mL/day
  - 7.5 mL/day
  - 15 mL/day
- Analysis
  - HPLC – UV-Vis
  - Extract ½ life

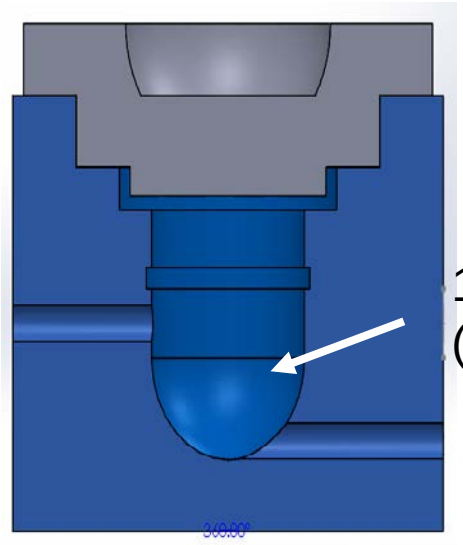


The elution matrix

simulating vitreous fluid

- Volume
- Viscosity
- Chemical composition:
  - HBSS
  - Hyaluronic acid
  - Collagen

Concentration of Hyaluronic Acid (mg/mL)	Viscosity (cP)
0 (Hank's Balanced Salt Solution, HBSS)	1.0
0.05	$1.1 \pm 9x10^{-3}$
0.1	$1.3 \pm 5x10^{-3}$
0.5	3.0 ± 0.01
1.0	4.7 ± 0.6



1.5 mL
(rabbit vitreous volume)

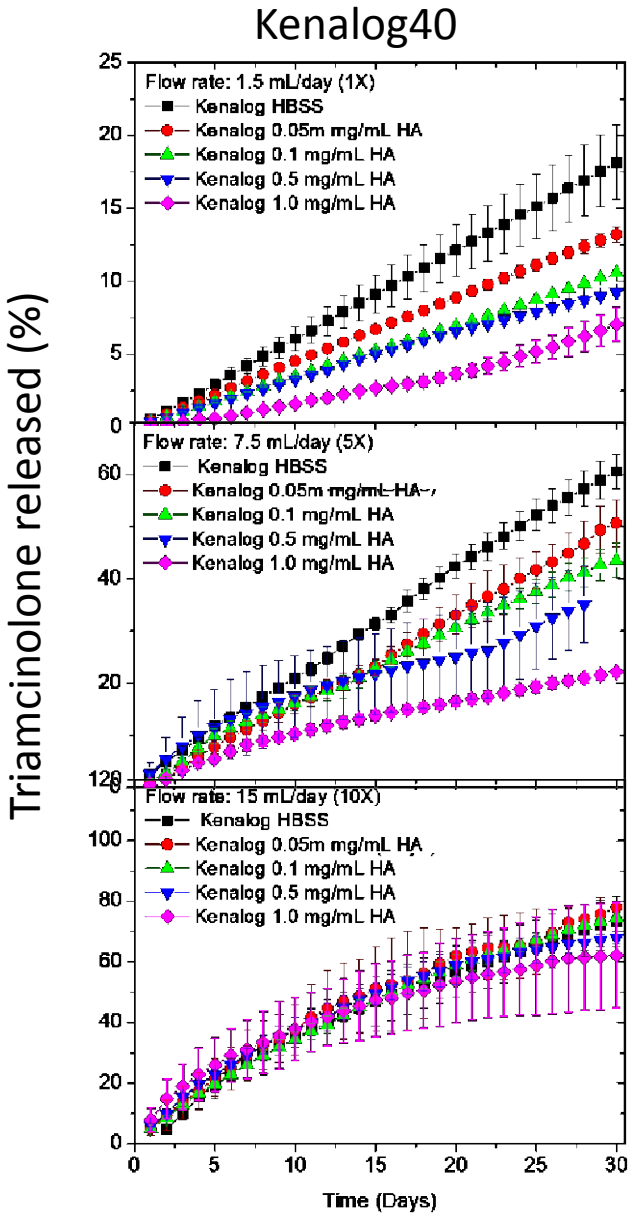
Conditions tested

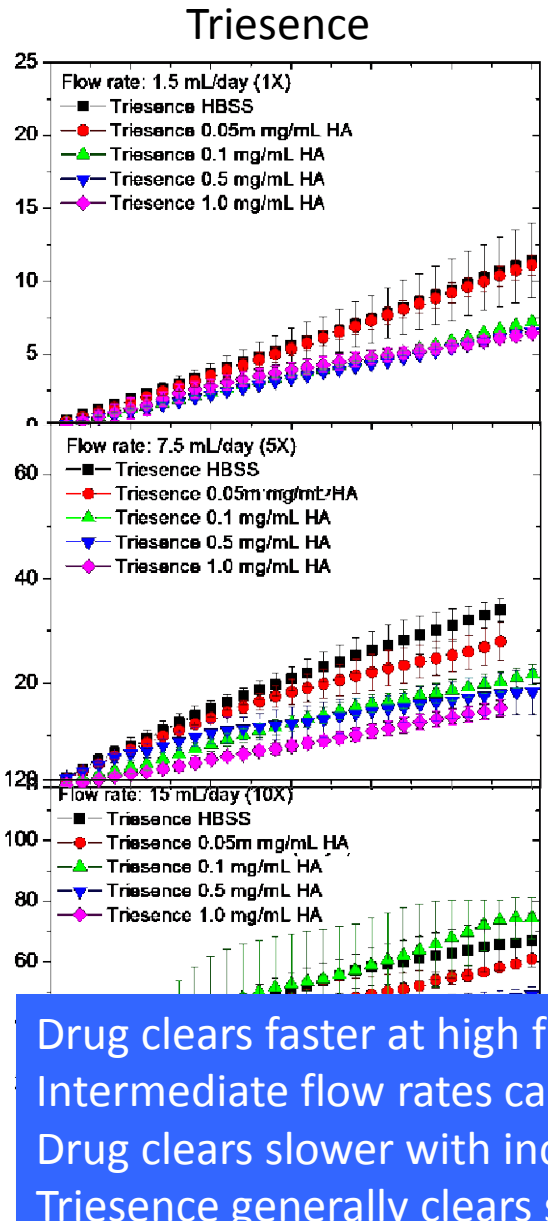
for Kenalog40 and Triesence formulations

Flow rate	Concentration of hyaluronic acid (ug/mL) Increasing viscosity -->				
	0	50	100	500	1000
static					
1 uL/min					
5 uL/min			Closest match to in vivo		
10 uL/min					

Injected dose: 4 mg • Volume of vitreous: 1.5 mL • static = 1 turnover/day

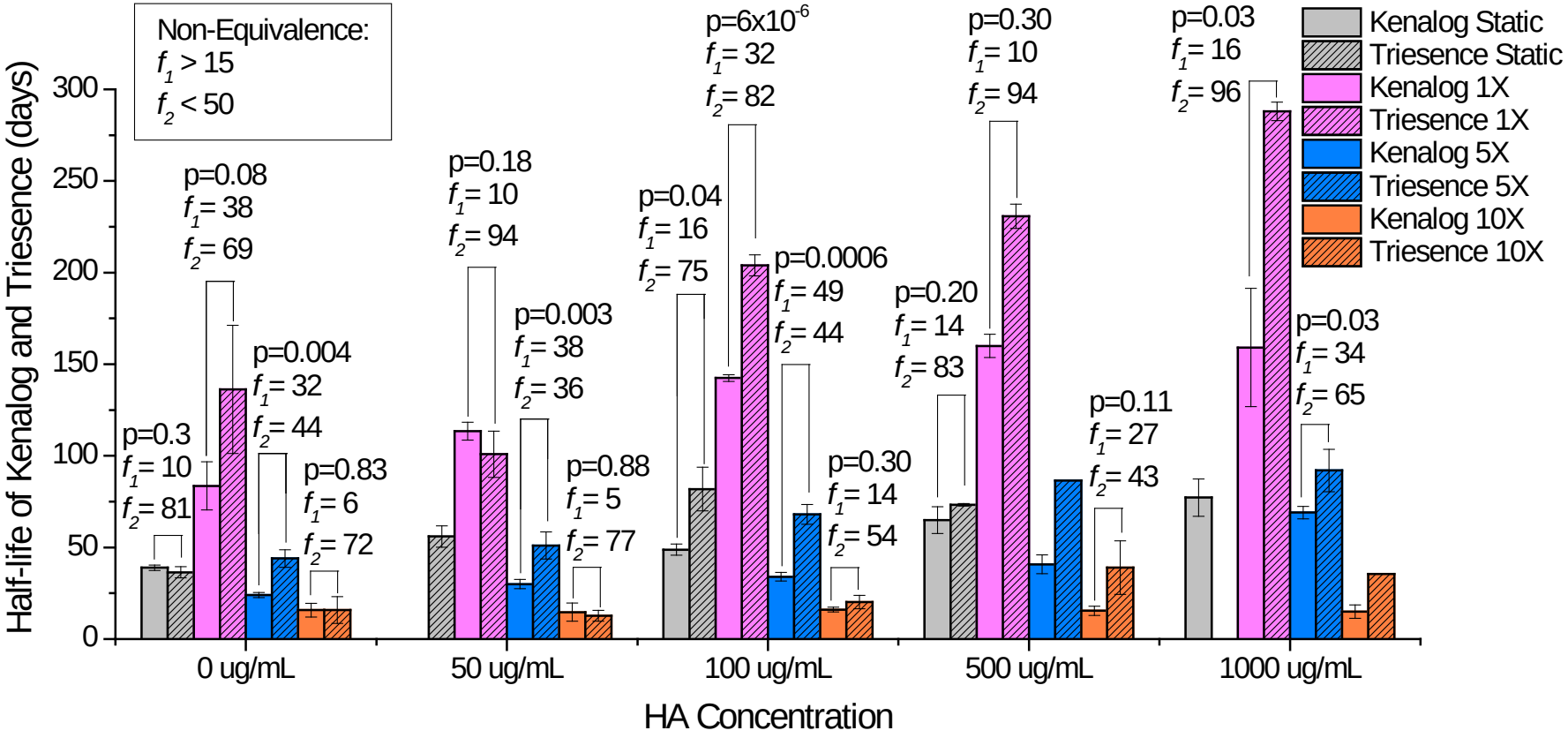
In Vitro Results



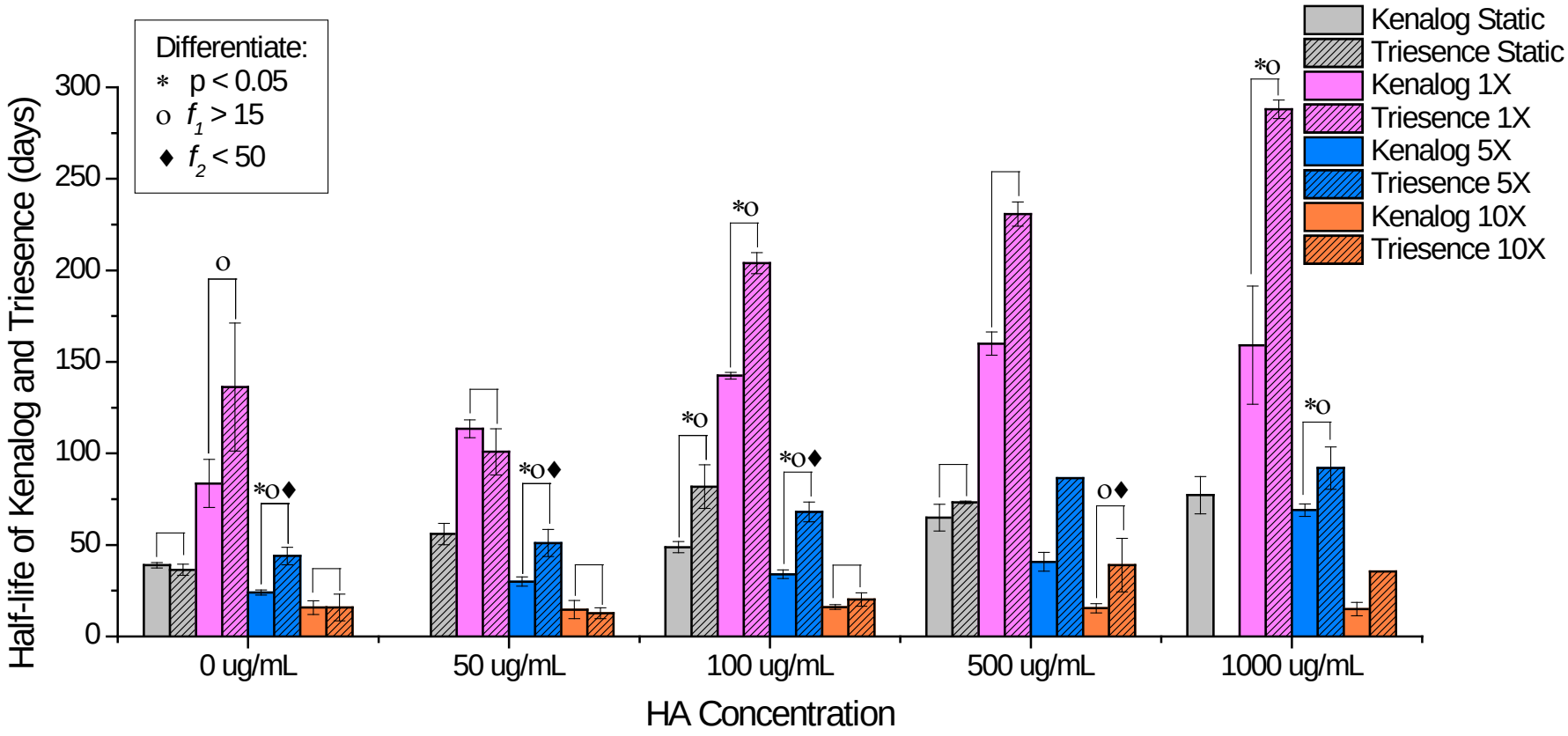


Drug clears faster at high flow
Intermediate flow rates can give best discrimination
Drug clears slower with increasing [HA]
Triesence generally clears slower than Kenalog

In Vitro Results



In Vitro Results



Conditions that discriminate

Kenalog40 and Triesence formulations

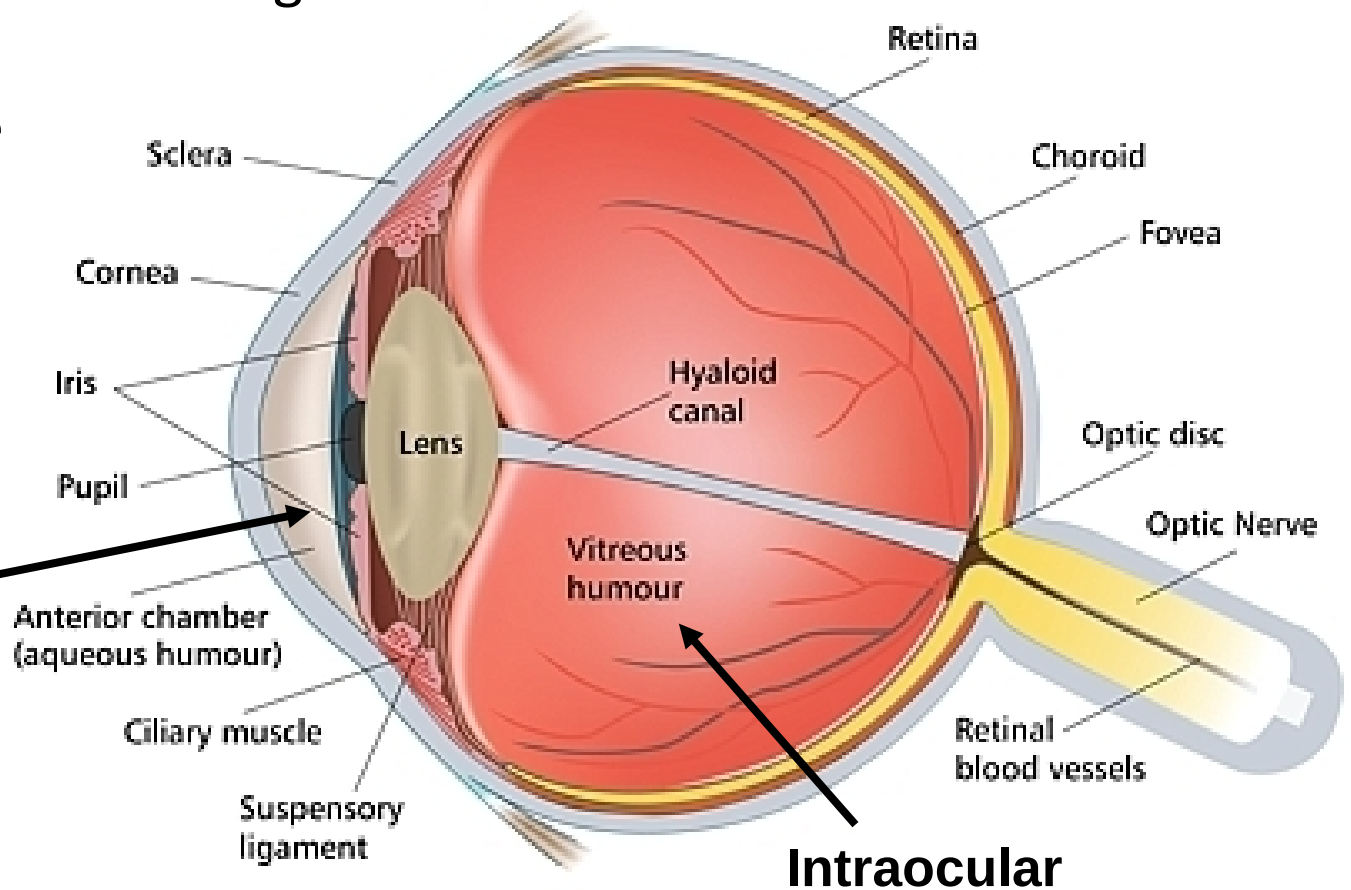
Flow rate	Concentration of hyaluronic acid (ug/mL) Increasing viscosity -->				
	0	50	100	500	1000
static	no	no	no	no	no
1 uL/min	no	no	no	no	no
5 uL/min	yes	yes	Closest match to in vivo	no	no
10 uL/min	no	no	no	yes	no

Injected dose: 4 mg • Volume of vitreous: 1.5 mL • static = 1 turnover/day

"Yes" indicates $p < 0.05$, $f_1 > 15$, $f_2 < 50$

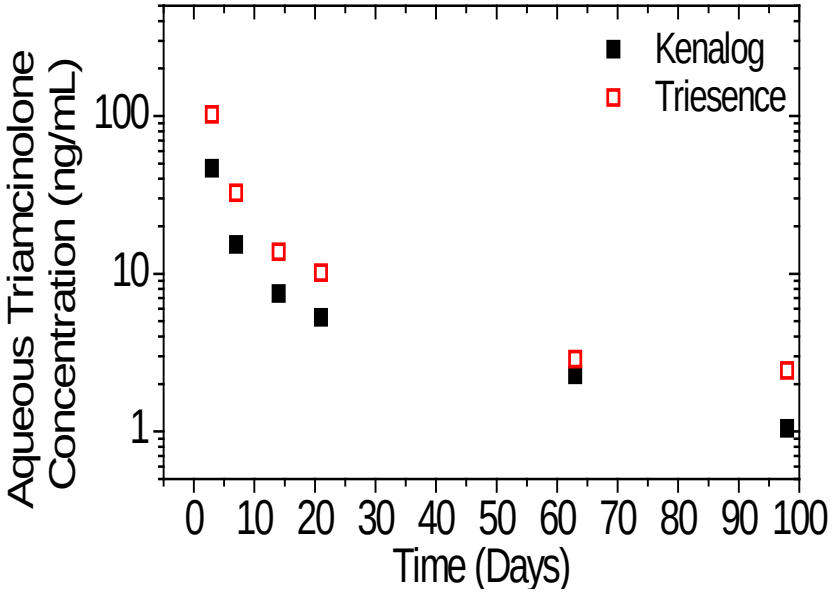
In Vivo Results

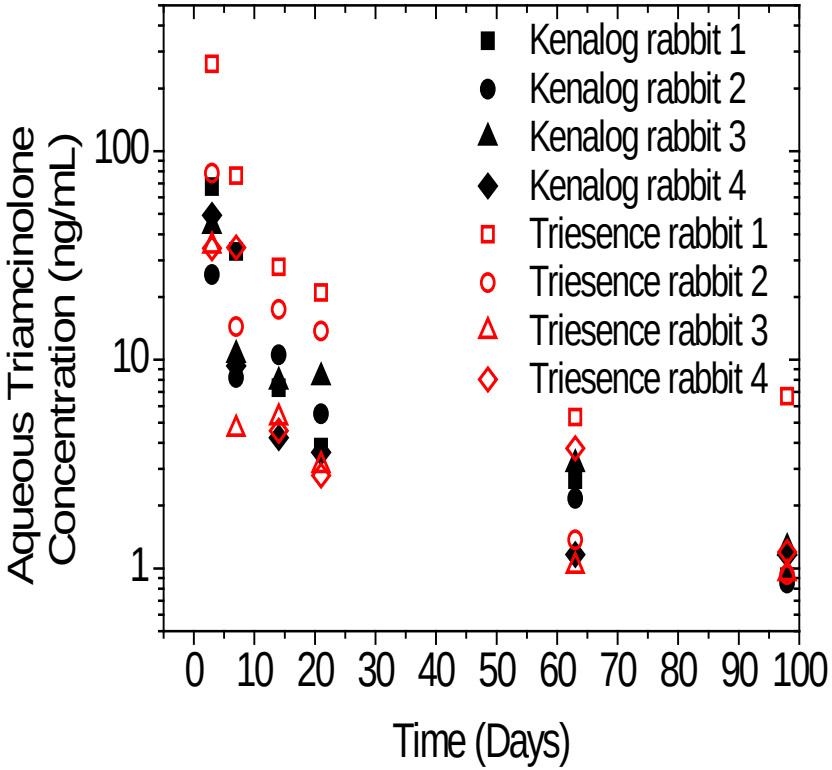
- Tap aqueous
  - Prevent removal of drug depot
  - Less invasive
  - 50 uL



In Vivo Results

- Tap aqueous
  - Prevent removal of drug depot
  - Less invasive
  - 50 uL
- HPLC-MS analysis
- Toxicity: 1 TE rabbit
- Cannot differentiate
  - High variation between rabbits





Summary and Recommendations

1. **Continuous flow system is convenient in evaluating the pharmacokinetics (esp. particulate based systems) in vitro.**
2. **When comparing two similar formulations, specific flow rate and dissolution viscosity conditions can be adjusted to differentiate closely similar ophthalmic formulations: Kenalog40 vs Triesence.**
3. **Flow system can be adjusted to match *in vivo* performance.**
4. **Studies on the effect of inactive ingredients on pharmacokinetics are needed.**

Thanks

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Yan Wang (FDA)

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