GDUFA RESEARCH AND REGULATORY INITIATIVES FOR COMPLEX OPHTHALMIC PRODUCTS

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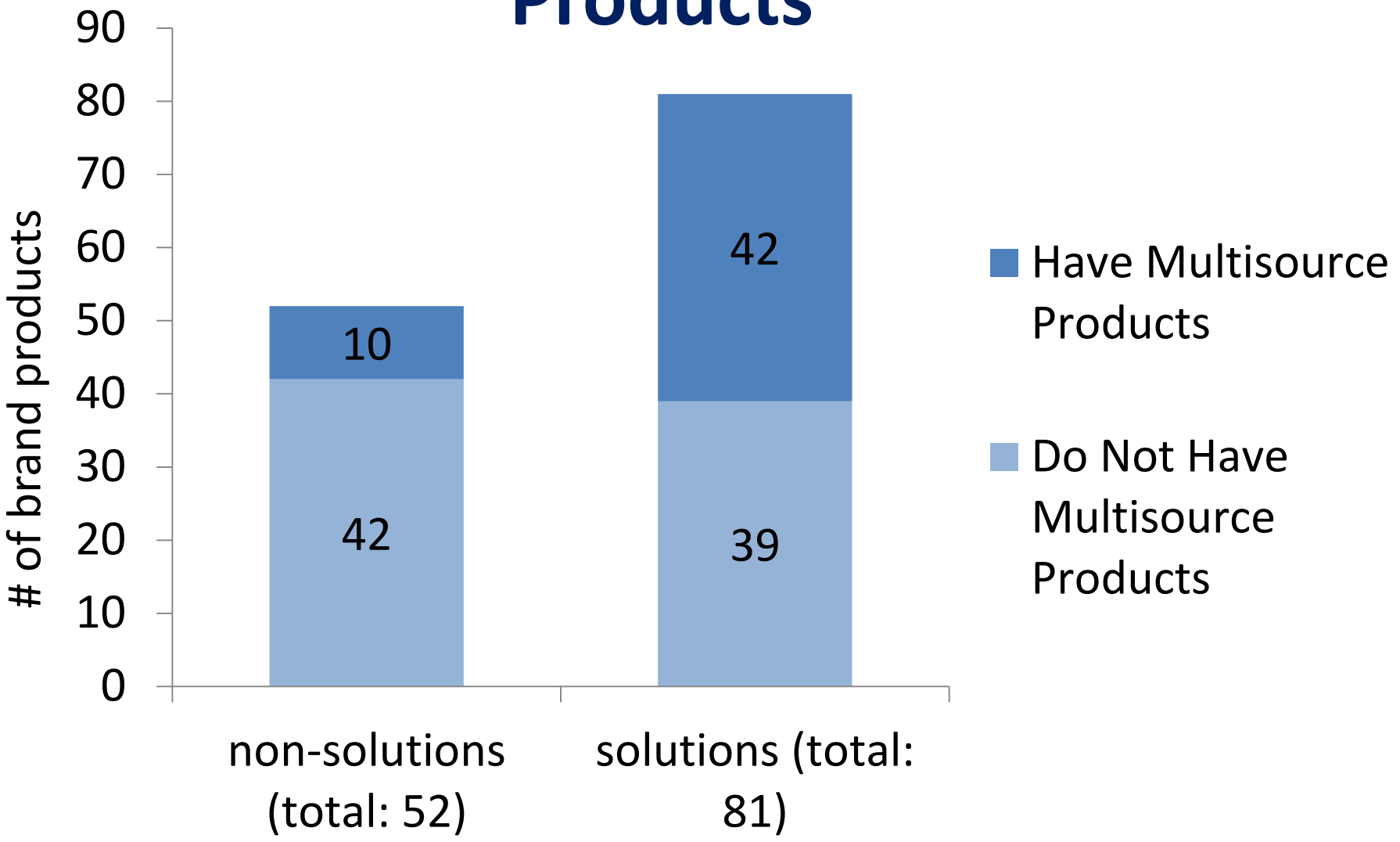
Approved Ophthalmic Brand Drug Products



*As of July 2017

Challenges in Generic Ophthalmic Drug Development and Approval

- Clinical studies require large numbers of subjects due to high intersubject variability
- For products with modest clinical efficacy, clinical studies may not be sensitive enough to detect differences when comparing a potential generic product to the branded product
- Alternative approaches to demonstrate equivalence (other than clinical studies) are warranted to provide a pathway for generic approval of ophthalmic products, such as in vitro studies

Generic Drug User Fee Amendments (GDUFA)

- Passed in July 2012 to speed access to safe and effective generic drugs to the public
- Requires user fees to supplement costs of reviewing generic drug applications and provide additional resources, including support for regulatory science research
- Agreement that user fees can directly support regulatory science research activities

Product-Specific Guidances with In vitro recommendations

- **Cyclosporine emulsion** (posted Jun 2013; revised Oct 2016)
- **Difluprednate emulsion** (posted Jan 2016)
- **Dexamethasone; Tobramycin suspension, 0.05%/0.3% and 0.1%/0.3%** (revised Jun 2016)
- **Bacitracin ointment** (revised Oct 2016)
- **Erythromycin ointment** (revised Oct 2016)
- **Nepafenac suspension, 0.1% and 0.3%** (revised Dec 2016)

Ophthalmic Research Program - Objectives

- Investigation of key physicochemical properties that affect drug release and ocular bioavailability
- Development of in vitro release testing methods which are predictive of in vivo release
- In vitro-In vivo correlations
- Physicochemical characterization methods
- Predictive modeling of ocular drug absorption

Extramural Research Projects

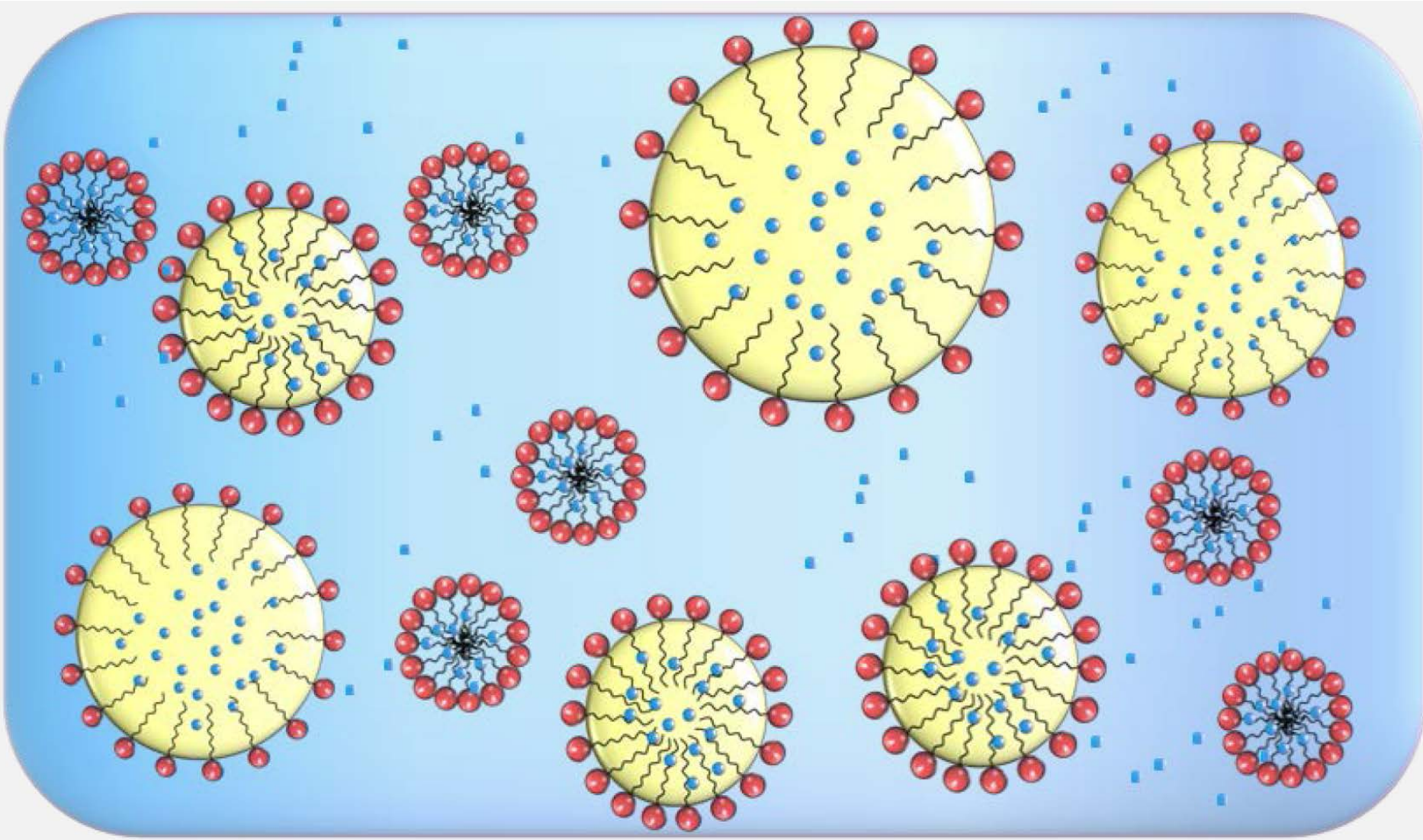
Grant/Contract #	Project Title	Award Institution	Award Year	Project Status
1U01FD004929	***In Vitro In Vivo Correlations of Ocular Implants***	University of Colorado-Denver	2013	Completed
1U01FD004927	***An IVIVC System to Facilitate the Development of a Generic Vitrasert***	Auritec Pharmaceuticals	2013	Completed
1U01FD005180	***Topical Ophthalmic Suspensions: New Methods for Bioequivalence Assessment***	University of Eastern Finland	2014	Completed
1U01FD005184	***Dissolution Methods for Topical Ocular Emulsions***	Texas A&M University	2014	Completed
1U01FD005173	***Modeling of the Vitreous for In Vitro Prediction of Drug Delivery of Porous Silicon Particles and Episcleral Plaques***	University of San Diego	2014	Completed

Grant/Contract #	Project Title	Award Institution	Award Year	Project Status
1U01FD005177	***Evaluation and Development of Dissolution Testing Methods for Semisolid Ocular Drug Products***	University of Connecticut	2014	Completed
1U01FD005174	***Dissolution Methods for Predicting Bioequivalence of Ocular Semisolid Formulations***	University of Connecticut	2014	Completed
1U01FD005219	***An Integrated Multiscale-Multiphysics Modeling and Simulation of Ocular Drug Delivery with Whole-Body Pharmacokinetic Response***	CFD Research Corporation	2014	Ongoing
1U01FD005211	***PBPK Modeling and Simulation for Ocular Dosage Forms***	Simulations Plus, Inc.	2014	Ongoing
HHSF223201610105C	***Pulsatile Microdialysis for In Vitro Release of Ophthalmic Emulsions***	Physical Pharmaceutica, LLC	2016	Ongoing

Intramural Research Projects

Project Title	Start Year	Status
Physicochemical Characterization of Ophthalmic Drug Products	2012	Ongoing
In Vitro Release and Drug Distribution in Different Phases of Ophthalmic Emulsion Products	2016	Ongoing
Tear Film Breakup Time and Bioavailability Modeling-Based Predictions of Cyclosporine Ophthalmic Emulsion	2016	Ongoing
Dexamethasone Distribution in Ocular Tissues and Plasma Following a Single Unilateral Topical Ocular Administration of the Tobramycin/Dexamethasone Suspension to Male New Zealand White Rabbits	2016	Ongoing

CYCLOSPORINE OPHTHALMIC EMULSION



Qu, H., et al. Determination of globule size distribution of cyclosporine ophthalmic emulsions using asymmetric flow field flow fractionation. 2017 CRS Annual Meeting

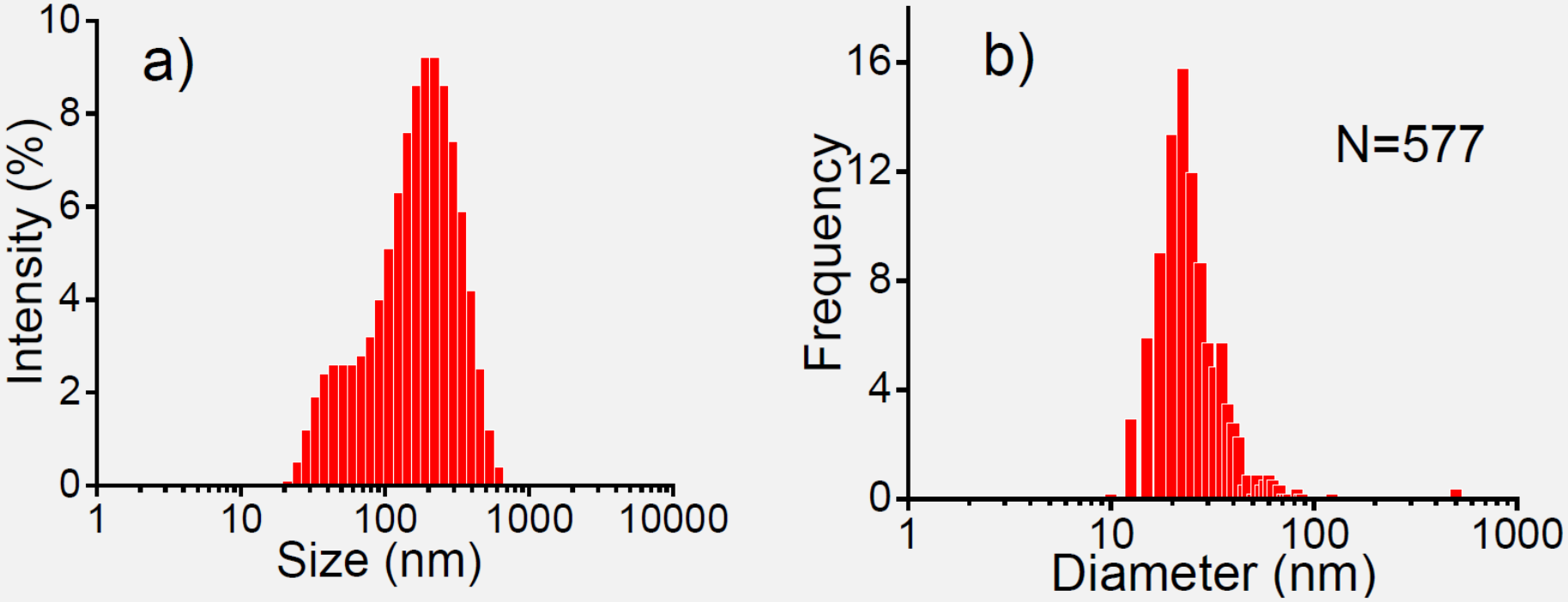
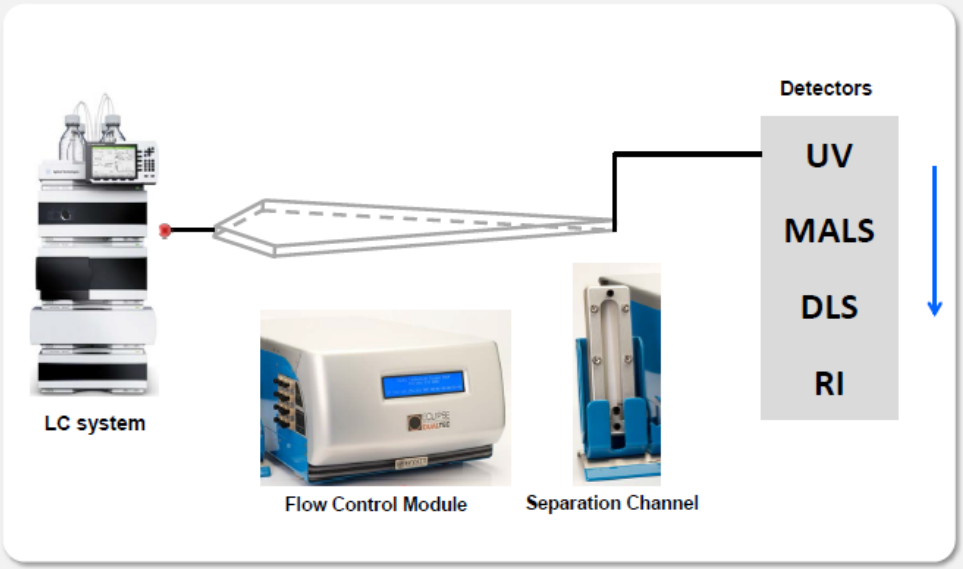


Figure 3. Globule size distribution analysis of Restasis® by a) DLS and b) cryo-TEM

Qu, H., et al. Determination of globule size distribution of cyclosporine ophthalmic emulsions using asymmetric flow field flow fractionation. 2017 CRS Annual Meeting

Asymmetric flow field flow fractionation (AF4)

Agilent 1260 liquid chromatography and Wyatt Eclipse DualTec AF4 system coupled with UV, MALS, DLS and RI detectors.



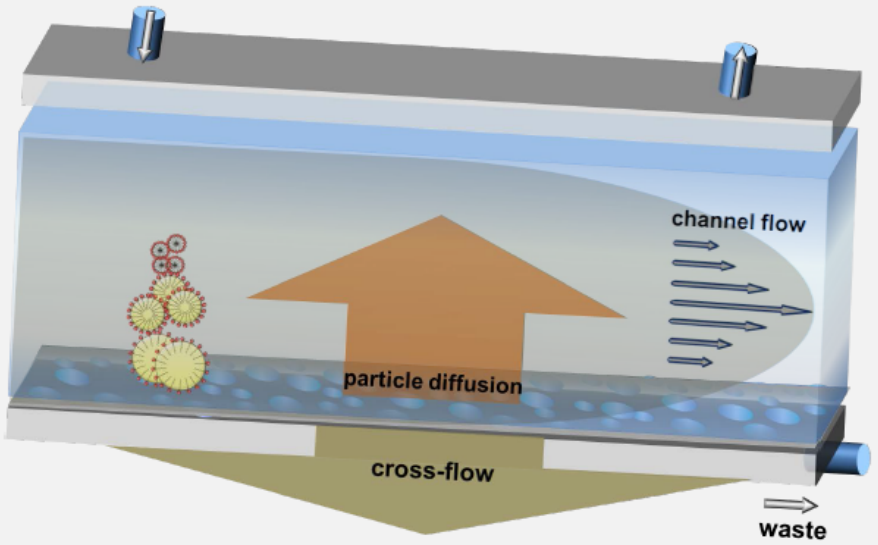
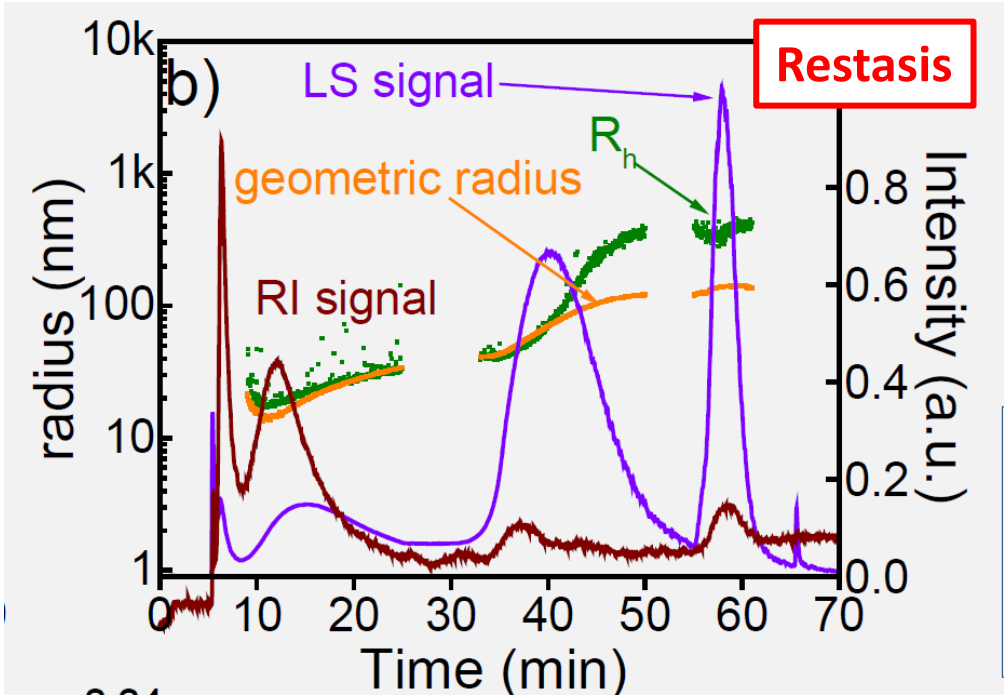


Figure 2. AF4 system components (left); and separation principles inside the channel (right).

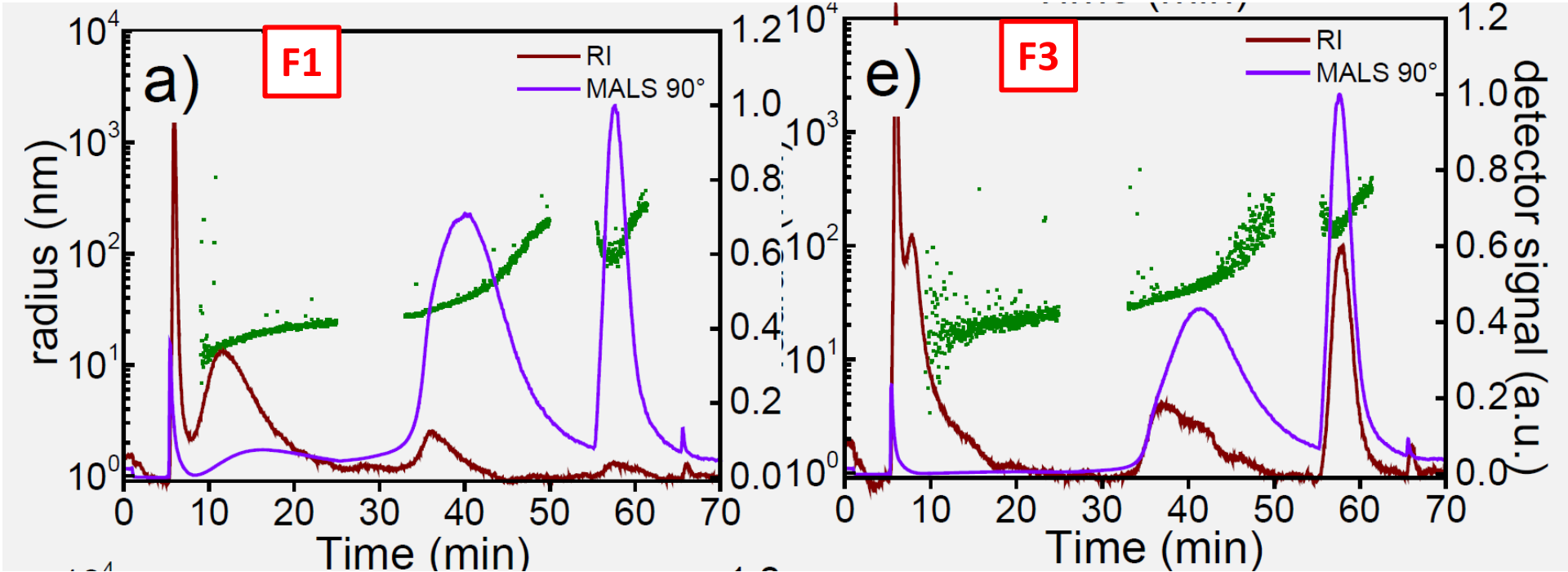
Qu, H., et al. Determination of globule size distribution of cyclosporine ophthalmic emulsions using asymmetric flow field flow fractionation. 2017 CRS Annual Meeting

Processing condition for in-house formulation		
Formulation	**Temperature (°C)**	**Microfluidization Pressure, Cycles**
F1	70	20 Kpsi, 6 cycles
F2	70	20 Kpsi, 2 cycles
F3	70	10 Kpsi, 6 cycles

Qu, H., et al. Determination of globule size distribution of cyclosporine ophthalmic emulsions using asymmetric flow field flow fractionation. 2017 CRS Annual Meeting



Qu, H., et al. 2017 CRS Annual Meeting



Pulsatile Microdialysis (PMD)

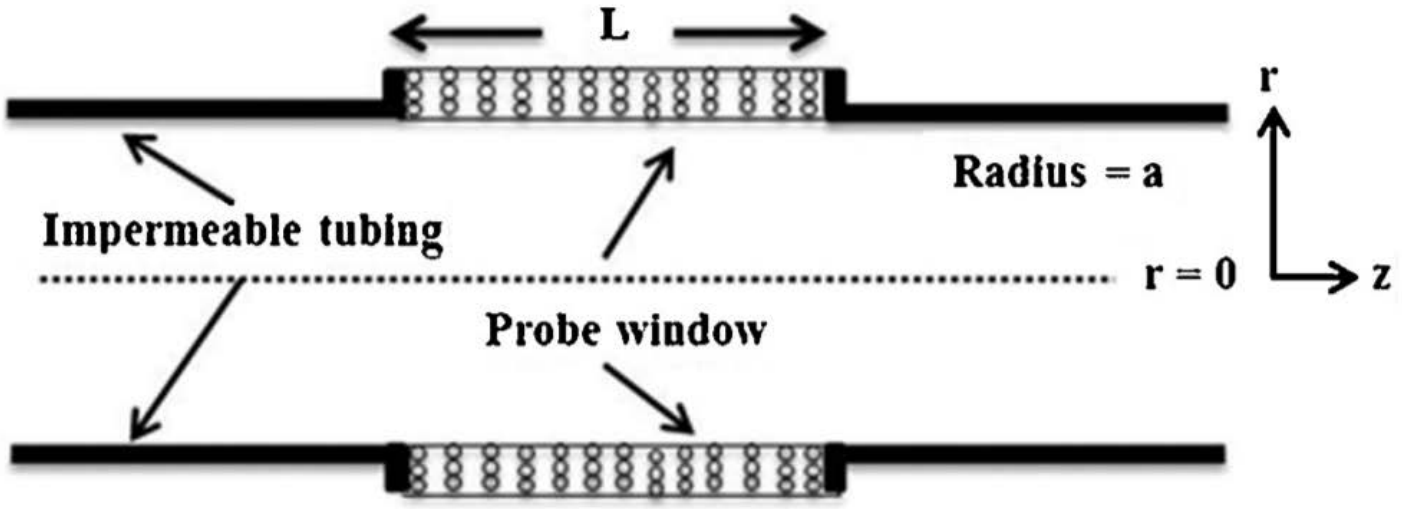
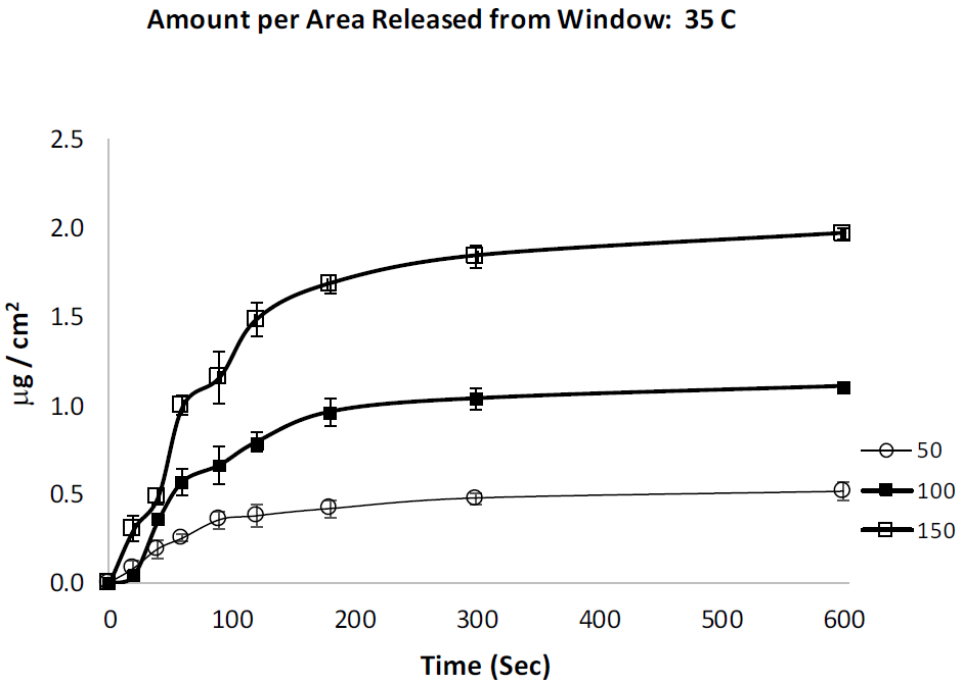
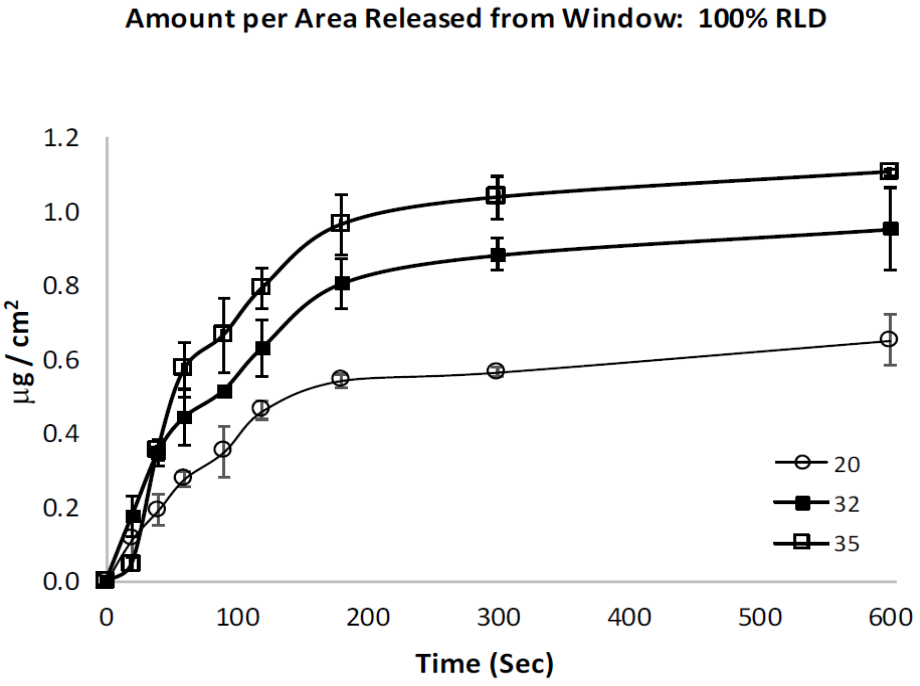


Fig. 1. A schematic diagram of a microdialysis probe.

Shah, KB et al., Int J Pharm 468 (2014) 64-74.

Pulsatile Microdialysis (PMD)





Q1/Q2 cyclosporine ophthalmic emulsions containing 50%, 100%, 150% drug load relative to the RLD (left), or 100% drug load relative to the RLD (right). The x-axis corresponds to resting time, and the y-axis is the amount of cyclosporine released from the PMD probe window per area. The receiver medium was either (A) kept at 35 °C or (B) varied between 20 °C, 32 °C, and 35 °C. Data points represent the average from three replicates ± standard deviation. Courtesy of Robert Bellantone, Physical Pharmaceutica, LLC.

OPHTHALMIC OINTMENTS

Table 1
The drug content uniformity of the loteprednol etabonate ointment formulations.

Formulations	Average Drug Loading ± SD (%, w/w)	RSD (%)
SRTOWP19	0.48 ± 0.01	2.87
SRTNWP19	0.49 ± 0.01	1.60
SRTVWP19	0.54 ± 0.02	3.00
SRTPWP19	0.49 ± 0.02	3.47
HMICOWP19	0.49 ± 0.01	1.22
HMICNWP19	0.47 ± 0.00	0.91
HMICVWP19	0.52 ± 0.01	1.94
HMICPWP19	0.51 ± 0.01	2.62
HMRTOWP19	0.51 ± 0.02	3.27
HMRTNWP19	0.48 ± 0.01	1.05
HMRTVWP19	0.50 ± 0.01	2.43
HMRTPWP19	0.50 ± 0.01	1.16

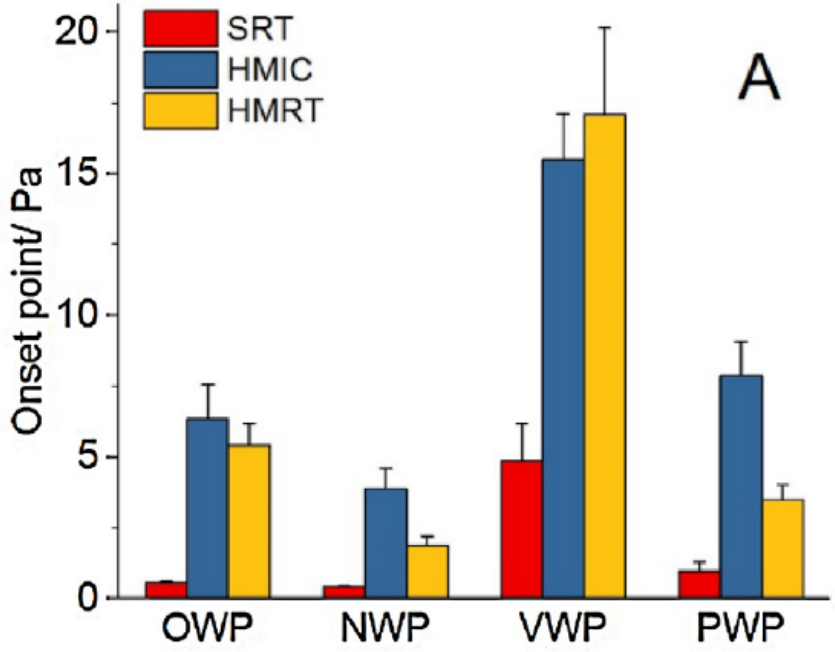
Simple mixing at RT (SRT)

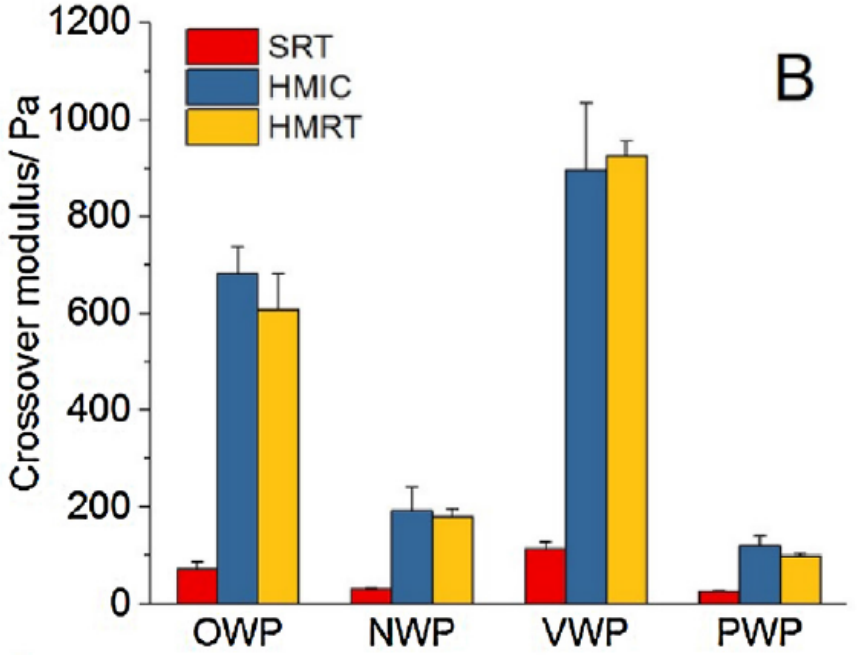
Hot melting and mixing with cooling (HMIC)

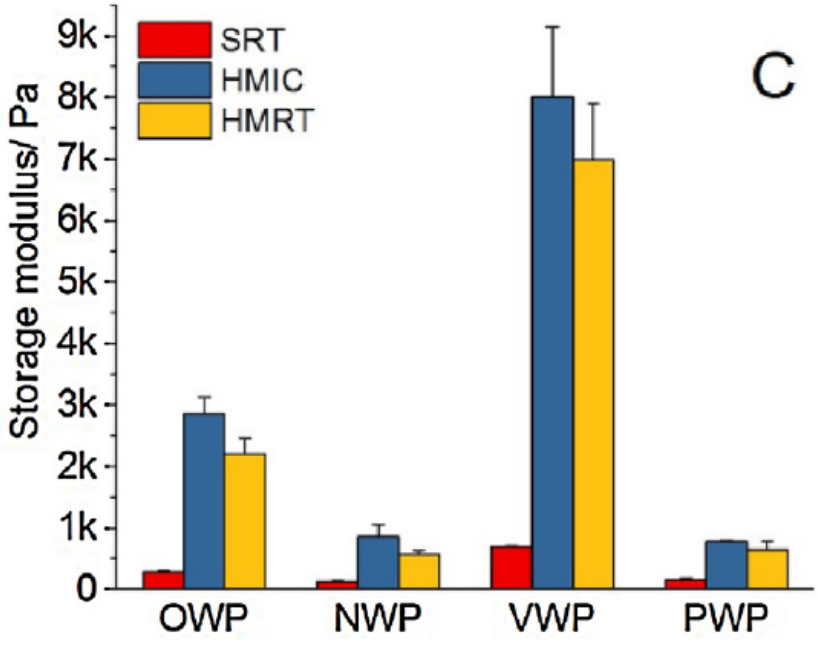
Hot melting and mixing at RT (HMRT)

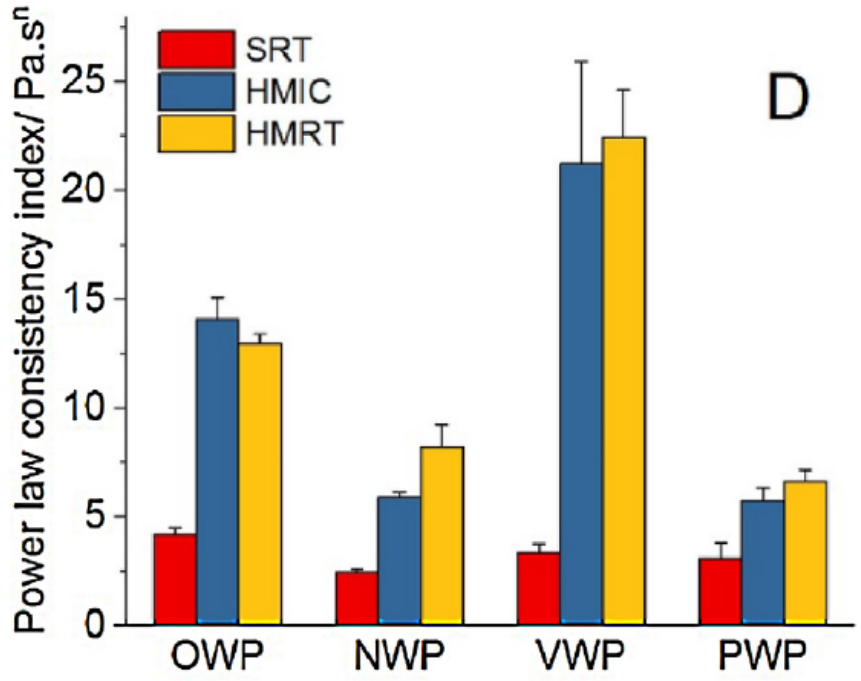
White petrolatum:
OWP - lab grade
NWP, VWP, PWP - USP grade

Bao, Q., et al. In vitro release testing method development for ophthalmic ointments. Int J Pharm. 526 (2017) 145-156.









Bao, Q., et al. Int J Pharm. 526 (2017) 145-156.

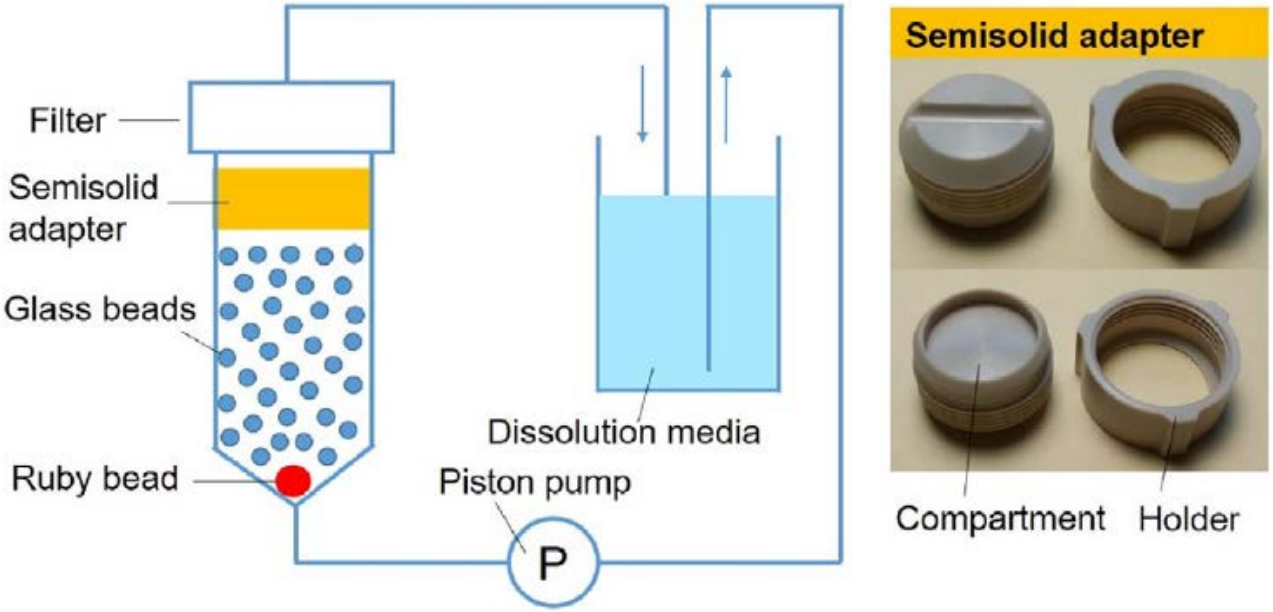


Fig. 1. Graphic demonstration of USP apparatus 4 with semisolid adapters.

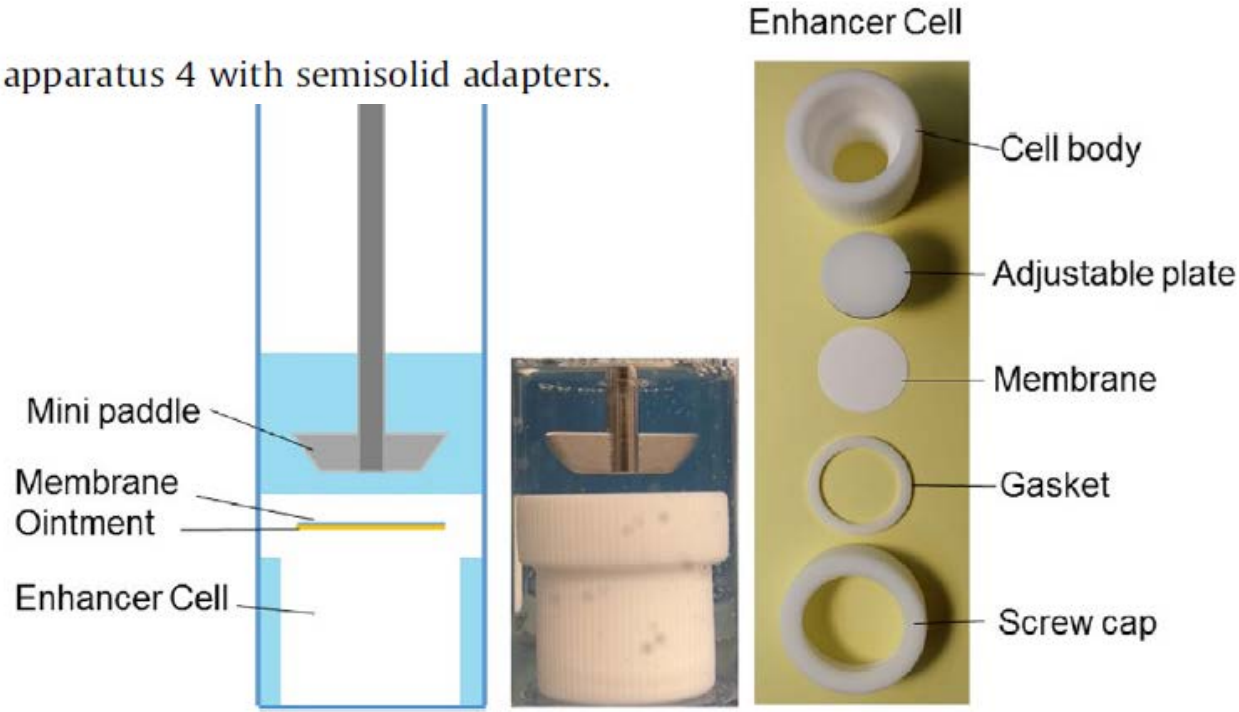
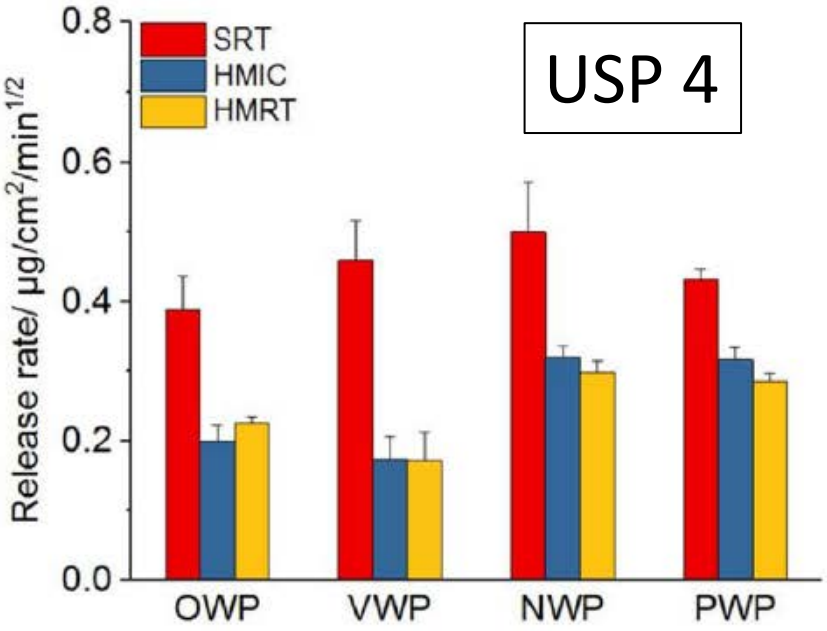
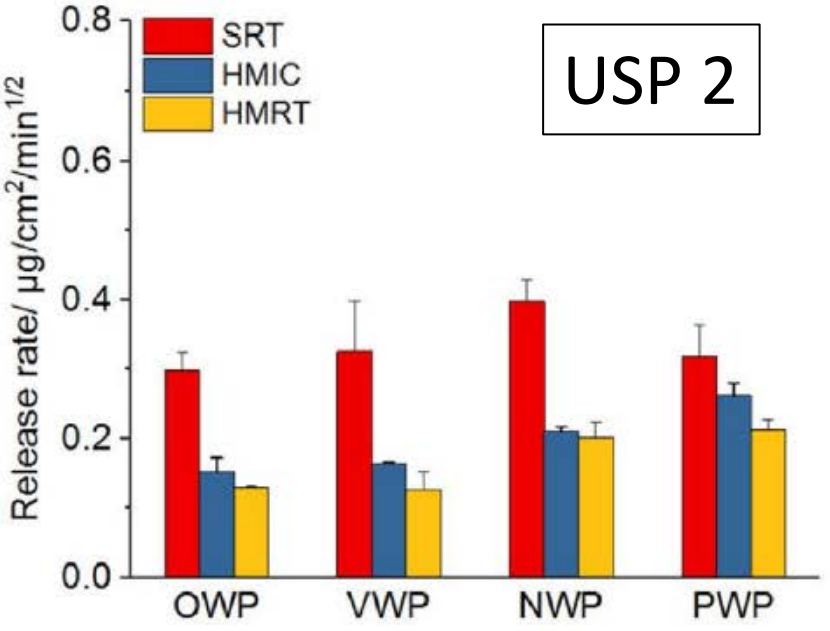
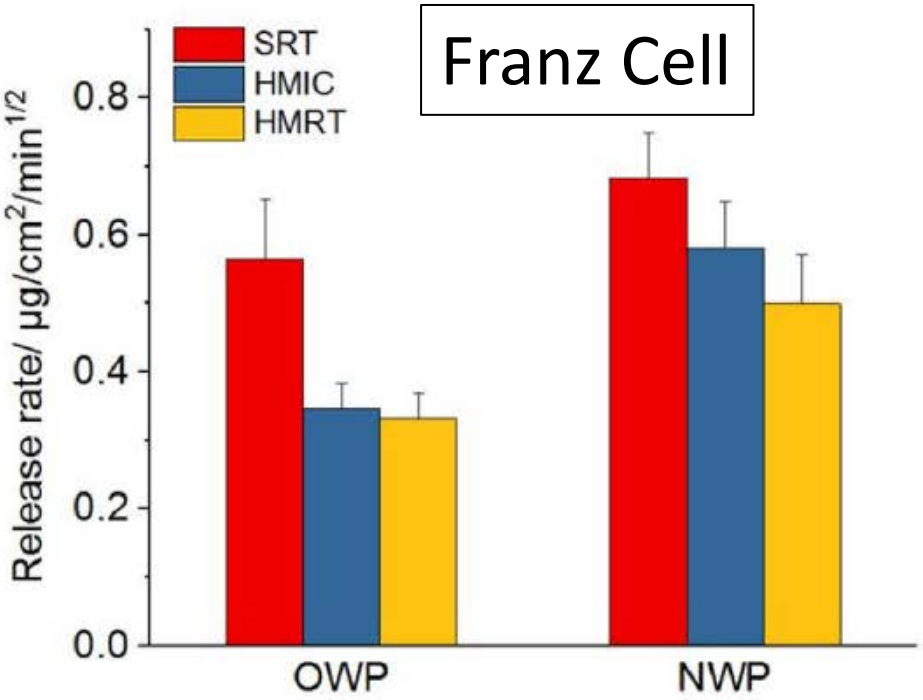


Fig. 2. Graphic demonstration of USP apparatus 2 with enhancer cells.

Bao, Q., et al. Int J Pharm. 526 (2017) 145-156.

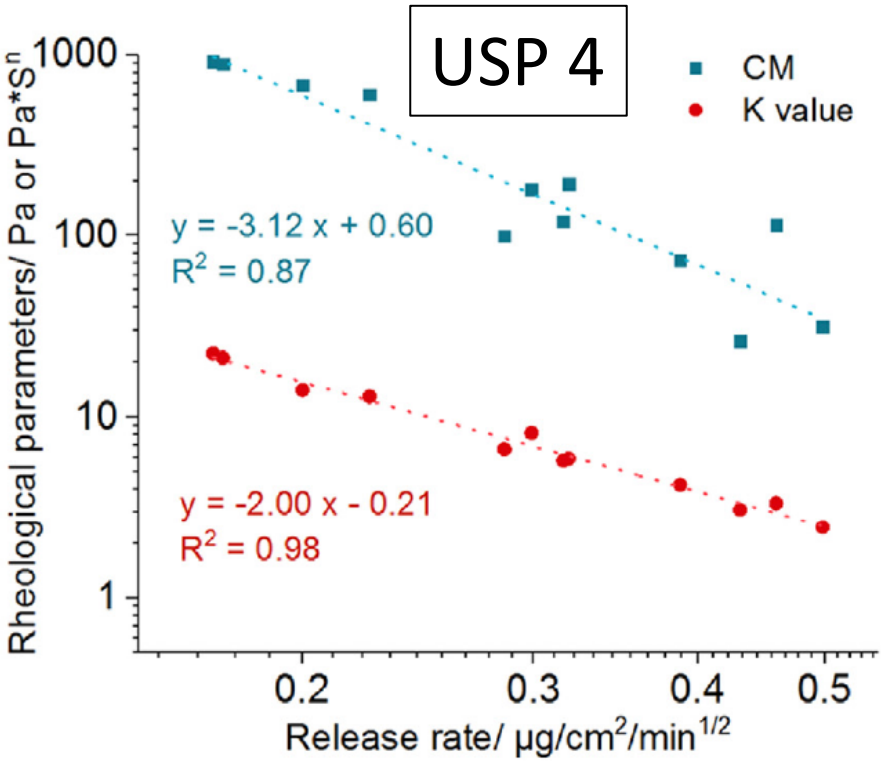


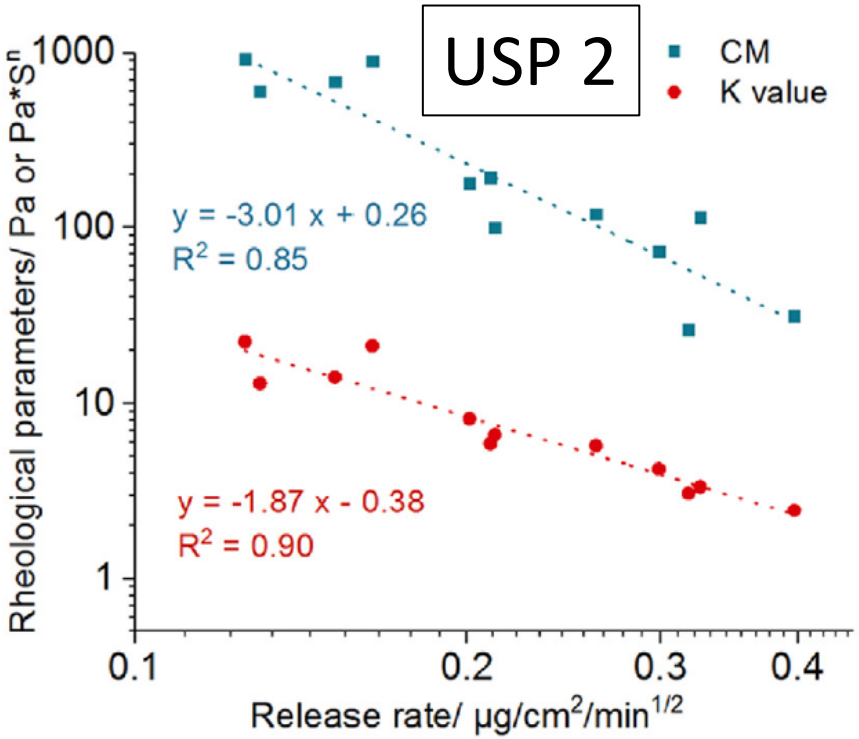




Bao, Q., et al. Int J Pharm. 526 (2017) 145-156.

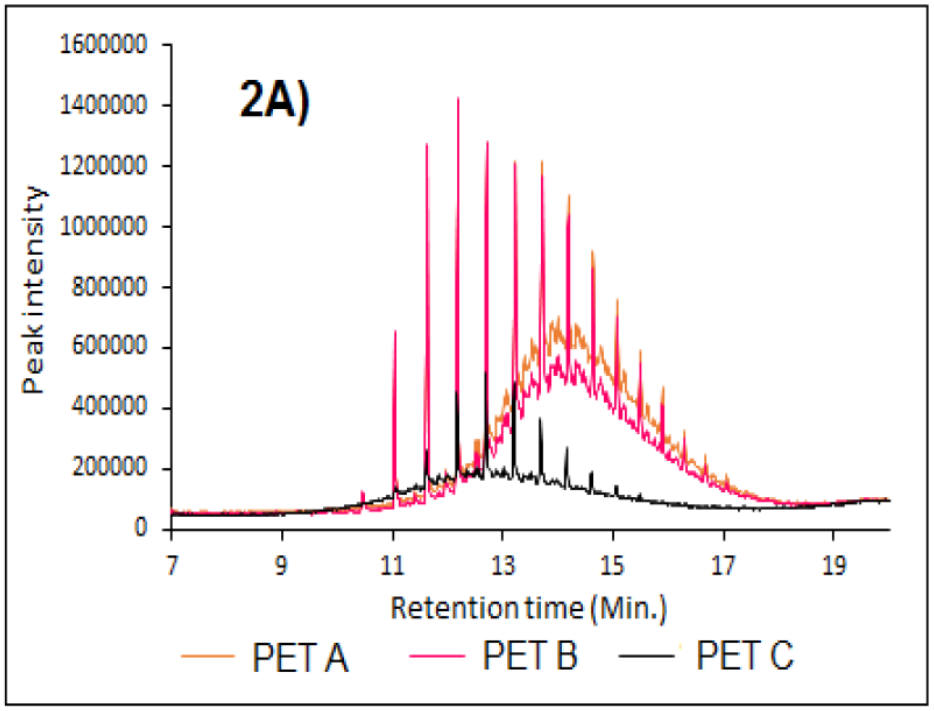
Log-log linear correlation of in vitro release rate and rheological parameters

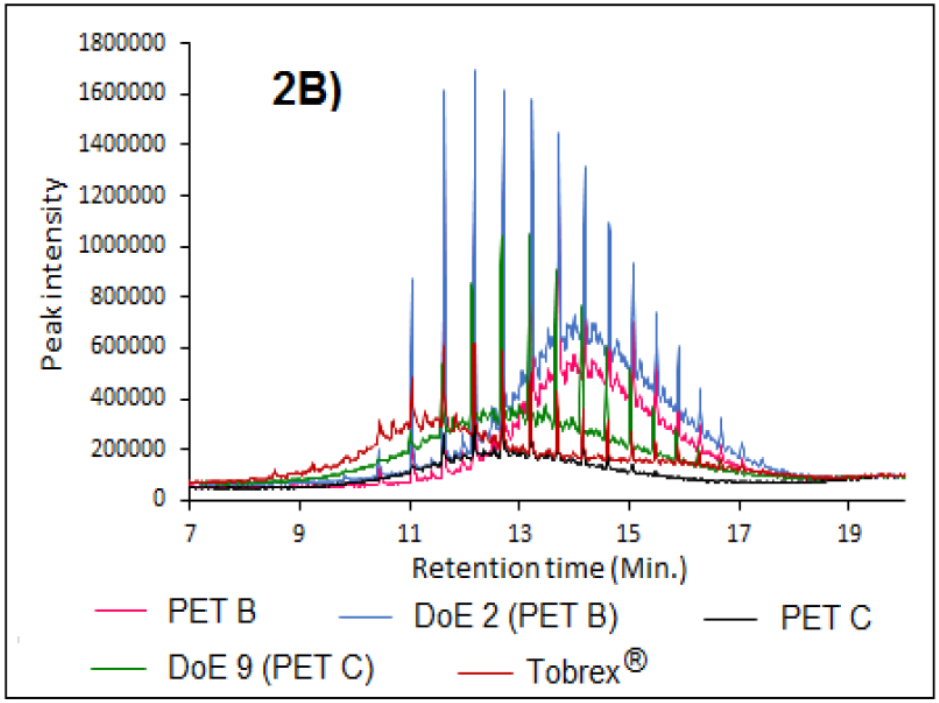




Bao, Q., et al. Int J Pharm. 526 (2017) 145-156.

GC-MS of Petrolatum





Patere, S., et al. Impact of Process and Quality Control on the Physicochemical Properties of Tobramycin Ophthalmic Ointments. 2017 CRS Annual Meeting.

Summary

- Scientific research is needed to support development of new approaches for bioequivalence of ophthalmic products
- A high resolution method based on AF4 was developed to characterize globule size distribution of cyclosporine ophthalmic emulsions
- In vitro release studies using PMD show rapid release of drug from ophthalmic emulsions within the first several minutes
- Both manufacturing process and excipient source influence physicochemical properties and in vitro drug release rates of ophthalmic ointments
- A strong correlation between rheological parameters and in vitro drug release rates was demonstrated

Annual Generic Drug Regulatory Science Research Report

- OGD publishes a public report of regulatory science research activities conducted under GDUFA annually
- A comprehensive report on research conducted during GDUFA I (FY13-FY17) will be published soon:
  - Project titles and collaborators
  - Publications and presentations
  - Outcomes
- Previous reports:
  - FY15: http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm500571.htm
  - FY16: https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm548872.htm

Questions?

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GDUFA Regulatory Science Website:

www.fda.gov/GDUFARegScience