# An Overview of Challenges and Opportunities for Innovation in Complex Generic Drug Product Development

**Xiaohui (Jeff) Jiang, PhD**
Deputy Director
Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA

**DIA Webinar on Complex Generic Drug Products**
**March 6, 2018**

# Outline

- Introduction to complex generic drug products
- FDA's considerations on demonstrating equivalence of complex generic drug products
- Case studies of GDUFA regulatory research on complex drug products
- Summary

The Generic Drug User Fee Act (GDUFA) is a law designed to speed access to safe and effective generic drugs to the public, and reduce costs to industry.

# Complex Products under GDUFA II

- Complex active ingredients
  - Complex mixtures of APIs, polymeric compounds, peptides
- Complex formulations
  - Liposomes, suspensions, emulsions, gels
- Complex routes of delivery
  - Locally acting such as ophthalmic, otic, dermatological and inhalational drugs
- Complex dosage forms
  - Long acting injectables and implantables, transdermals, MDIs
- Complex drug-device combinations

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

# Examples of Complex Products related to Today's Presentation

- Complex APIs

  Peptides, nucleotides, polymers, naturally-derived mixtures and other complex drug substances

- Long acting injectables (LAI)

  PLGA, suspensions and liposomal products

- Ophthalmic products

  Suspensions, emulsions, ointments and implants

# Promises about Generic Drugs

- FDA approved generic drugs are **Therapeutically Equivalent**
- They can be substituted for the RLD (brand product)
- Generics and their RLDs have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

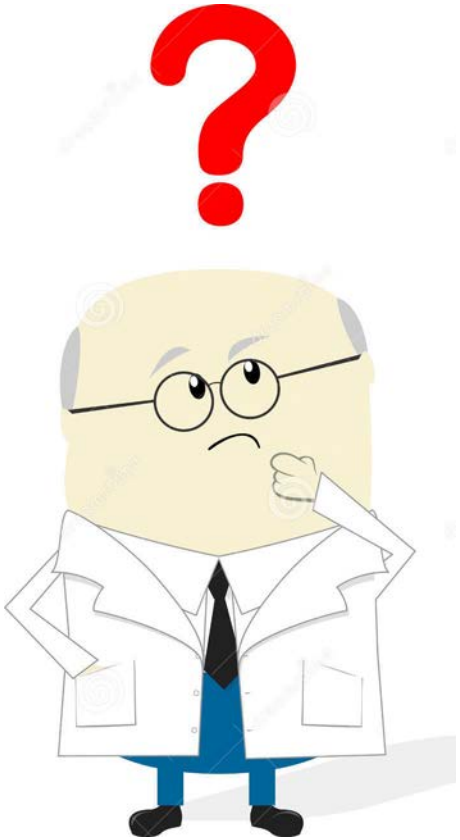
RLD: Reference Listed Drug

# Therapeutic Equivalents

- *Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

21 CFR 314.3

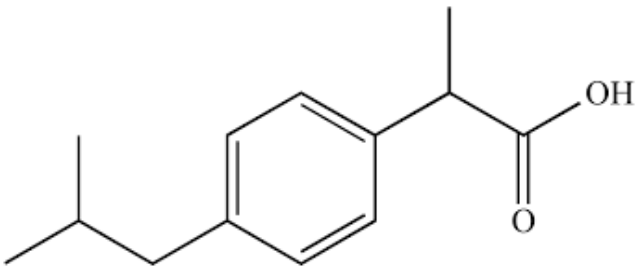
# Equivalence Determination
# “Simple” vs “Complex”



# Traditional Approach for Establishing Equivalence of an ANDA

- Active ingredient sameness — API characterizations
- Pharmaceutical equivalence — Same dosage forms …
- Bioequivalence — PK study …




# Pharmaceutical Equivalence

- *Pharmaceutical equivalents* are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, … …, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

21 CFR 314.3

# Challenges for Complex Generics

- Active ingredient sameness
  - Characterizing mixture of APIs
- Pharmaceutical equivalence
  - Comparing inactive ingredients if needed*
  - Comparing impurities if needed
- Bioequivalence
  - Locally acting …

➢ Same clinical effect and safety profile

How to demonstrate inactive ingredients, impurities and other allowed differences in a proposed drug product do not affect its safety or efficacy???

* If required under 21 CFR 314.94(a)(9) or recommended by a product specific guidance

# Bioequivalence

- *Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study … …

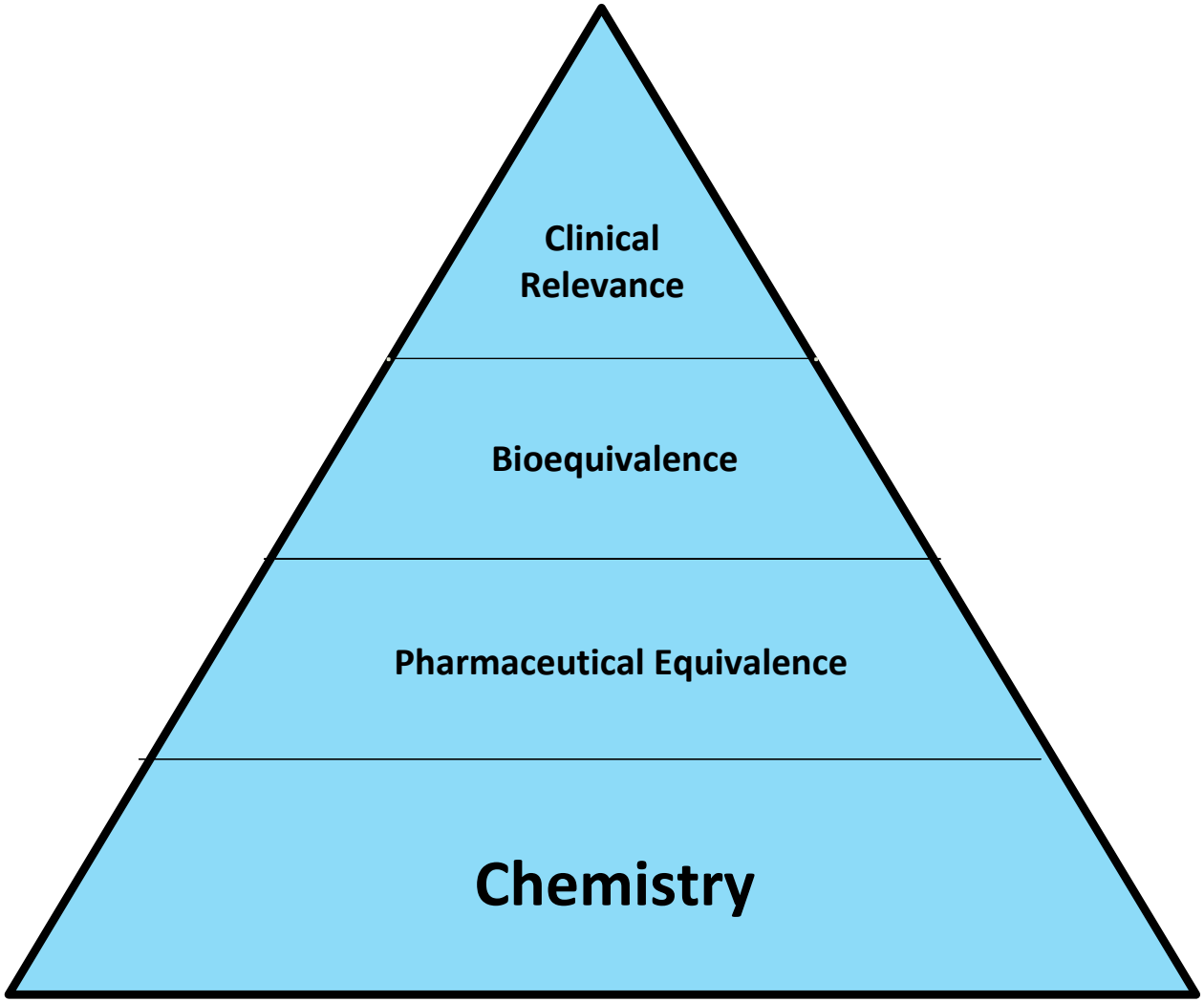
21 CFR 314.3

# Bioequivalence Approaches

- In vivo PK study or a correlated in vitro study
- In vivo urine study
- In vivo PD study
- In vivo clinical BE study
- In vitro test acceptable to FDA (usually dissolution rate test)
- Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence

21 CFR 320.24(b)

# Evaluations of Generic Drugs



# GDUFA Regulatory Science Priorities

Developing efficient and modern generic drug review tools in the following categories:

- Complex active ingredients, formulations, or dosage forms
- Complex routes of delivery
- Complex drug-device combinations
- Tools and methodologies for BE and substitutability evaluation

**Product-specific guidance (PSG) development**
**Pre-ANDA meeting, ANDA review and approval**

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

# Enhanced pre-ANDA Process in GDUFA II for Complex Drug Products

- Early stage
  - Regulatory science & PSG development
  - Pre-ANDA development meeting with goals
- Mid-stage
  - Publish PSG when available
  - Pre-ANDA development meeting for alternative approaches to PSG (different class)
  - Complex control correspondence for alternative method to PSG (same class)
- ANDA submission and review
  - Pre-ANDA submission meeting with goals
  - Mid-cycle review meeting

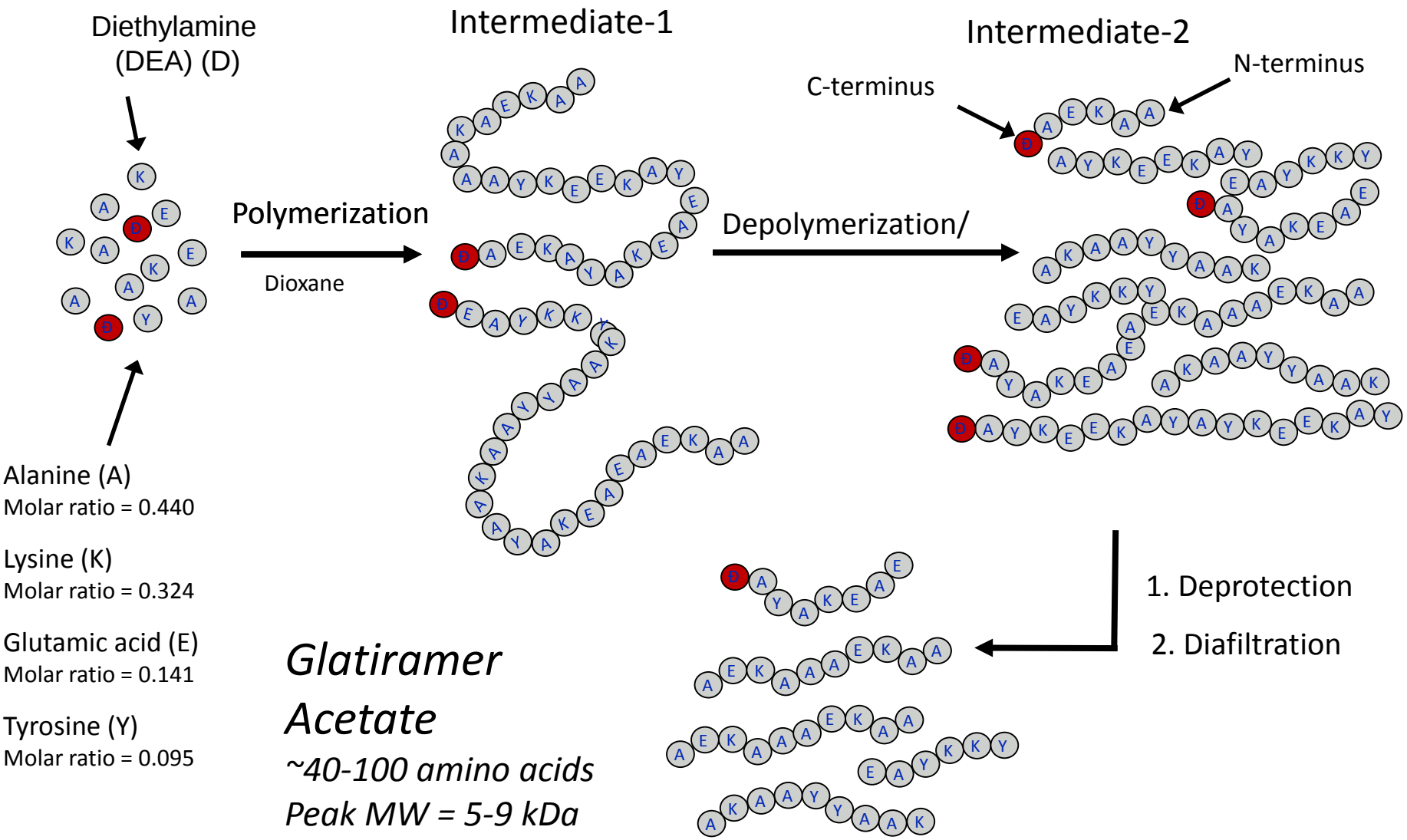
# Case Studies of GDUFA Regulatory Science Research

- Demonstrating Complex API Sameness
- Characterization of Complex Inactive Ingredients and Formulations
- Novel In Vitro Release Testing (IVRT) for Complex Formulations

# Copaxone (glatiramer acetate injection)

- Immunomodulator complex drug product for treatment of relapsing-remitting multiple sclerosis
- Mechanism of action is highly complex and not fully understood
- Synthetic amino acid copolymers
  - Mix of peptides formed from four amino acids at a defined molar ratio
  - With batch-to-batch variations
- NDA approved in 1996

# Glatiramer Acetate Synthesis

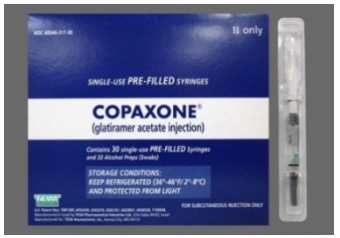



Konfino, E. et al. *Copolymer-1 improvements in compositions of copolymers* (1999), U.S.Pat. 5,981,589.

# FDA Developed High Resolution Analytical Methods

## LC-MS Method:

- Digested GA and Copolymer-1 with Lys-C
- Separated using hydrophilic interaction (HILIC) column
- Monitored eluted peptides with high-resolution Orbitrap MS
- Compared resulting masses and chromatograms

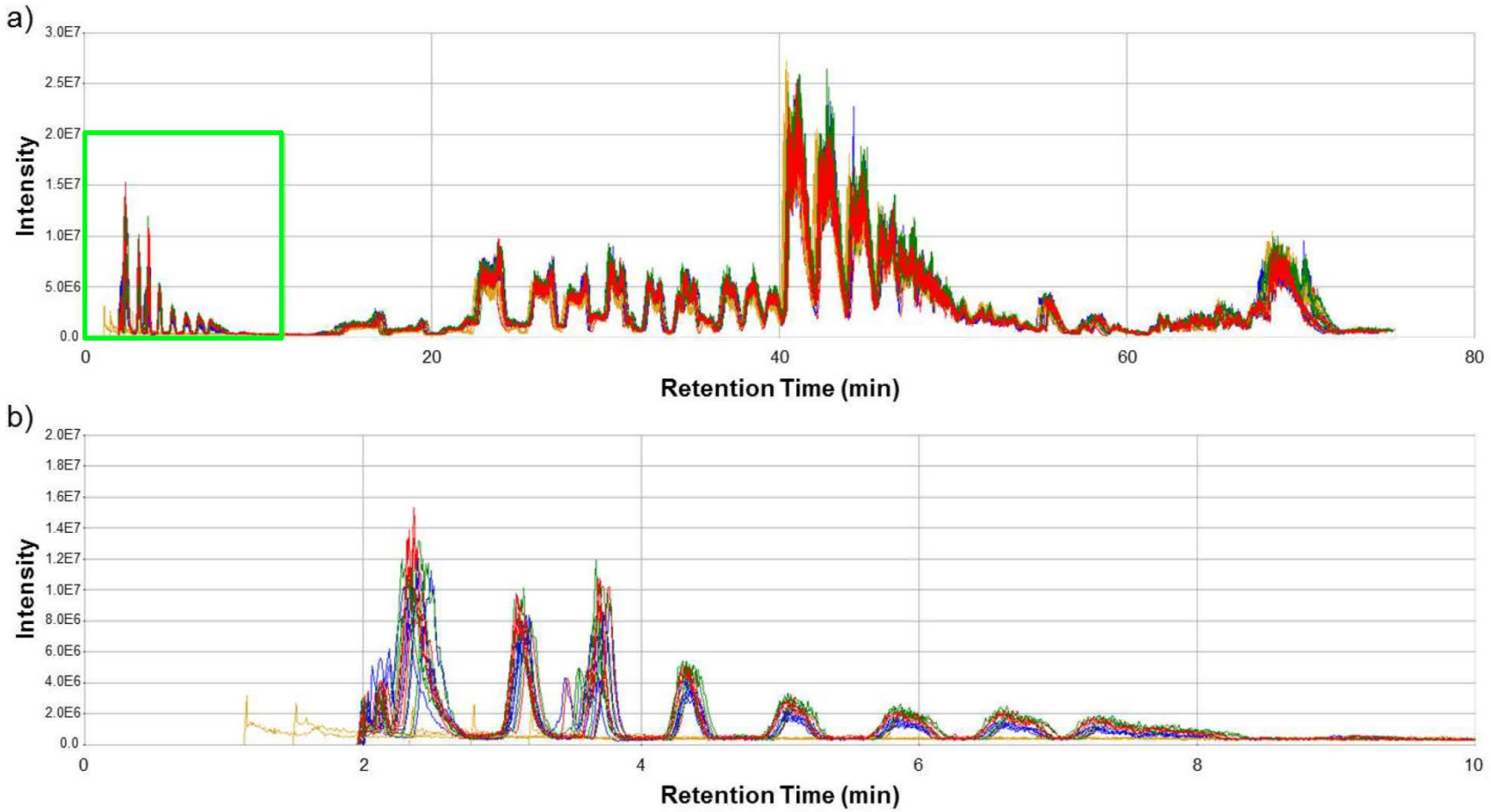



Glatiramer acetate (GA)


Copolymer-1

Rogstad, S.M., Pang, E., Sommers, C., Hu, M., Jiang, X., Keire, D.A., and Boyne, M.T. Modern analytics for synthetically derived complex drug substances: NMR, AFFF-MALLS and MS tests for glatiramer acetate. *Analytical and Bioanalytical Chemistry* (2015).

# LC-MS: Differential Analysis Chromatogram Overlay




Comparative analysis shows high overall similarity, with visible differences at early retention times. Alignment scores > 0.90.

# LC-MS: Sparse-PCA Statistical Analysis

**Table 7** Euclidean distances within three GA lots (P53462, P53506, and P53584). The one-way ANOVA was applied to the data of each column, showing no significant difference between the distances between different GA lots ($p>0.05$)

| Sample | P53462 | P53506 | P53584 |
|---|---|---|---|
| P53462 | 0.21±0.13 | 0.22±0.15 | 0.27±0.16 |
| P53506 | 0.23±0.12 | 0.27±0.16 | 0.21±0.11 |
| P53584 | 0.24±0.10 | 0.21±0.13 | 0.23±0.12 |

Within GA distance: 0.23±0.13
Between GA-Copolymer-1 distance: 0.36±0.06

Analysis of Euclidian distances showed that the distance between GA and Copolymer-1 was significantly greater (*p<0.01)* than the distance within the combined GA lots.

# FDA Published Product Specific Guidance on Glatiramer Acetate

Recommendations to demonstrate API sameness of a proposed generic product:

- Fundamental reaction scheme
- Physicochemical properties including composition
- Structural signatures for polymerization and depolymerization
- Results in biological assays

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495029.pdf

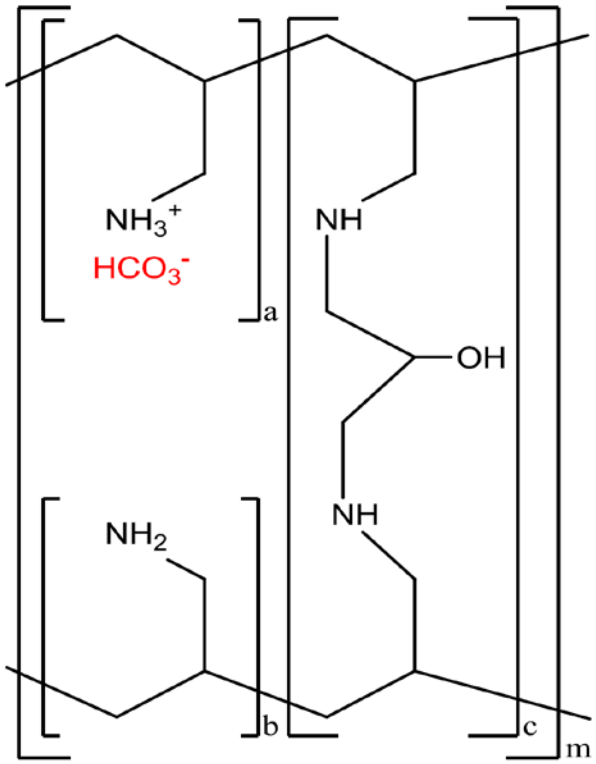
# Generic Glatiramer Acetate Approvals

- First generic (20 mg/mL) from Sandoz (Apr 2015)
- First generic (40 mg/mL) from Mylan (Oct 2017)
- Generic (20 mg/mL) from Mylan (Oct 2017)
- Generic (40 mg/mL) from Sandoz (Feb 2018)

# Renvela (sevelamer carbonate)

- Indications: a phosphate binder indicated for the control of serum phosphorus in patients with chronic kidney disease on dialysis
- Dosage forms: tablets and powder for oral suspension
- Mechanism of action: a non-absorbed crosslinked polymer containing multiple amines in a protonated form can bind phosphate in the GI tract.
- Initial U.S. approval: 2007

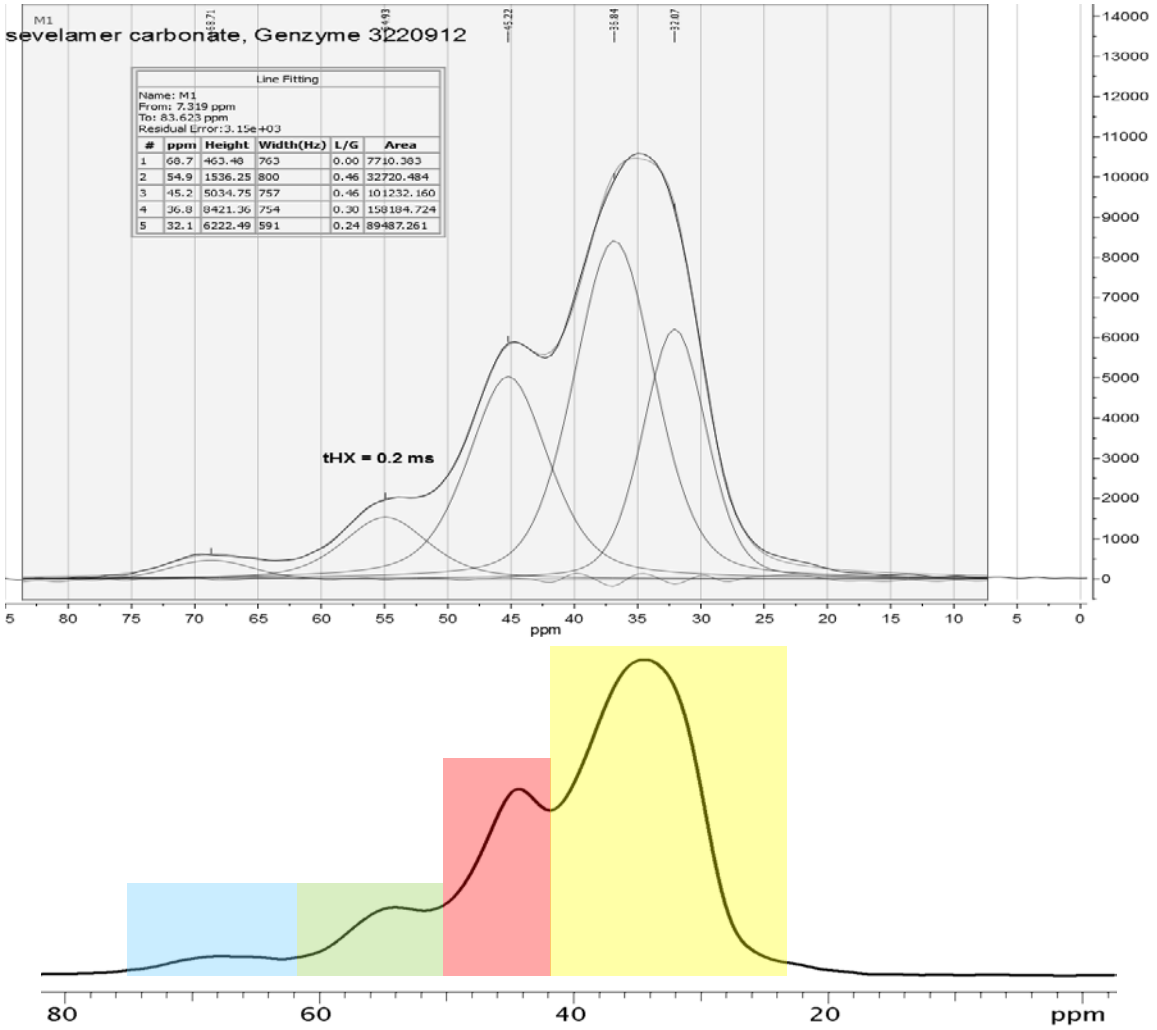
# Sevelamer: Complex API



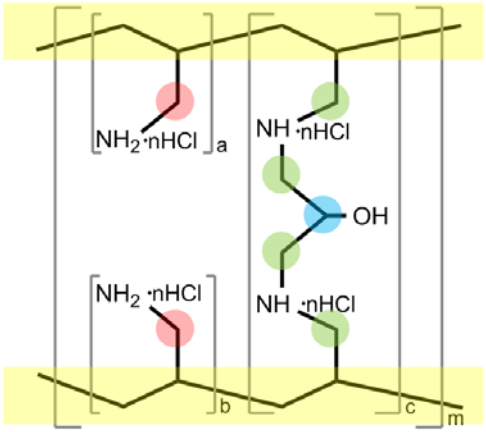

a, b = number of primary amine groups  a + b = 9
c = number of crosslinking groups  c = 1
m = large number to indicate extended polymer network

- Crosslinked polymers of polyallylamine cross-linked with epichlorohydrin
- Internal FDA study performed on API characterizations
- 1 ANDA approved for oral suspension and 5 ANDAs approved for tablets

# Solid-state $^{13}C$ NMR Analysis




- Individual peaks deconvoluted
- Peak areas calculated
- Relative peak areas are proportional to the number of carbon atoms in each electronic environment




J. Pharm. Sci. 101 (2012), 2681-2685.

# Product Specific Guidance Sevelamer Carbonate

- API sameness
  - Reaction scheme: same as on the RLD label
  - Characterizations
    - Degree of crosslinking ($^{13}C$ solid-state NMR)
    - Degree of protonation
    - Total titratable amine
    - Particle size
    - Elemental analysis
    - Additional characterizations: FTIR, Raman, XRD, DSC …

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089620.pdf

# Product Specific Guidance Sevelamer Carbonate (Cont'd)

- Bioequivalence
  - In vitro equilibrium binding study
  - In vitro kinetic binding study

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm089620.pdf

# Sevelamer Carbonate Timeline

- 2007: RLD approval
- 2008: Initial PSG (BE)
- 2009, 2010, 2011: PSG revisions (BE)
- 2012 – 2014: FDA internal studies
- 2015, 2016: PSG revision (API + BE)
- 2017: 1st sevelamer carbonate powder approval
- 2017: 1st sevelamer carbonate tablets approval

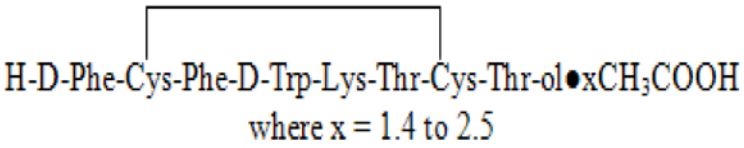
# Characterization of Complex Inactive Ingredients and Formulations

# Sandostatin LAR Depot
## (octreotide acetate for injectable suspension)

**11 DESCRIPTION**

Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxy-methyl) propyl]-, cyclic (2→7)-disulfide; [R-(R*,R*)].

The molecular weight of octreotide is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$) and its amino acid sequence is:




Sandostatin LAR Depot is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability.

Sandostatin LAR Depot is available as: sterile 6-mL vials in 3 strengths delivering 10 mg, 20 mg, or 30 mg octreotide-free peptide. Each vial of Sandostatin LAR Depot delivers:

| Name of Ingredient | 10 mg | 20 mg | 30 mg |
|---|---|---|---|
| octreotide acetate | 11.2 mg* | 22.4 mg* | 33.6 mg* |
| D,L-lactic and glycolic acids copolymer | 188.8 mg | 377.6 mg | 566.4 mg |
| mannitol | 41.0 mg | 81.9 mg | 122.9 mg |

*Equivalent to 10/20/30 mg octreotide base.

# Q1/Q2 Requirement for Generic Parenteral Products

- Demonstration of qualitative (Q1) and quantitative (Q2) sameness of inactive ingredients in parenteral drug products

21 CFR 314.94 (a)(9)(iii) – *Inactive ingredient changes permitted in drug products intended for parenteral use.*

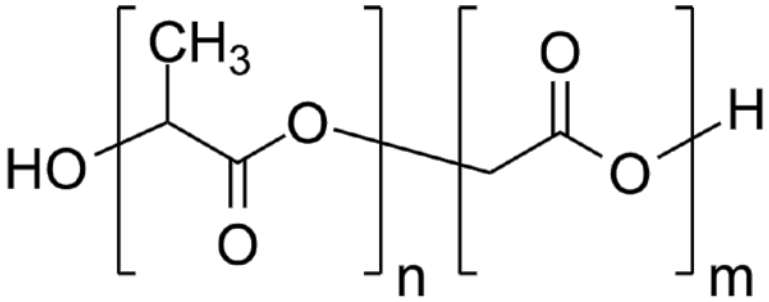
Generally, a drug product intended for parenteral use shall contain the same inactive ingredients (qualitatively the same – "Q1") and in the same concentration (quantitatively the same – "Q2") as the reference listed drug.

An applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

A formulation which contains an excipient not contained in the RLD and not considered to be an "exception excipient" cannot be submitted as an ANDA.

# Complex Inactive Ingredients

## Poly(lactide-co-glycolide) (PLGA)




**Lactide** **Glycolide**

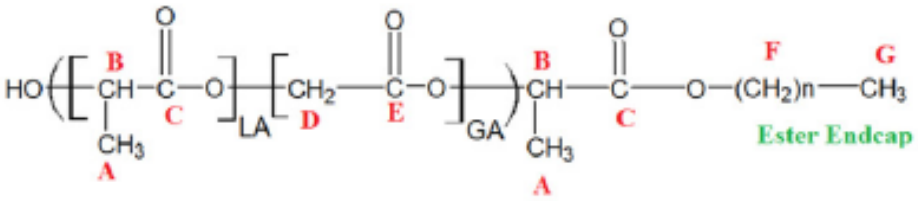
L:G Ratio

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| L | **100** | **90** | **80** | **70** | **60** | **50** | 40 | 30 | 20 | 10 | 0 | L |
| G | **0** | **10** | **20** | **30** | **40** | **50** | 60 | 70 | 80 | 90 | 100 | G |

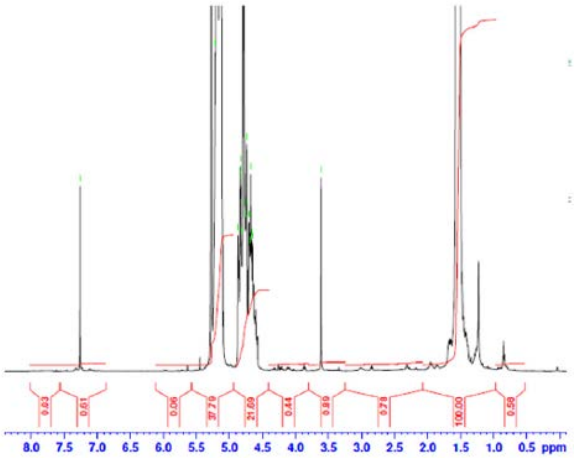
Solvent-dependent solubility

Insoluble in most solvents

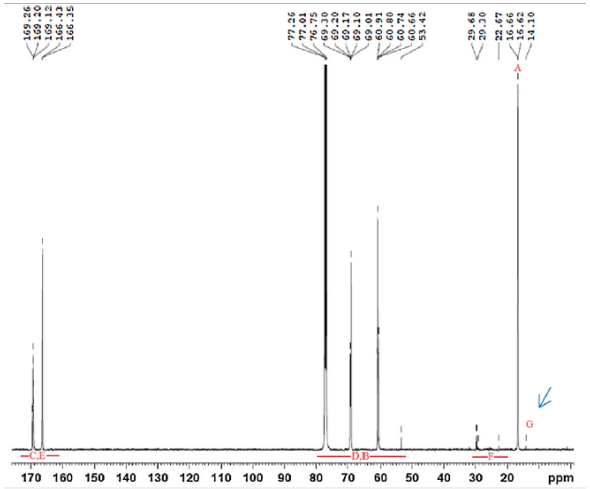
# Analysis Compositions of PLGA




L:G Ratio: $^{1}$H-NMR

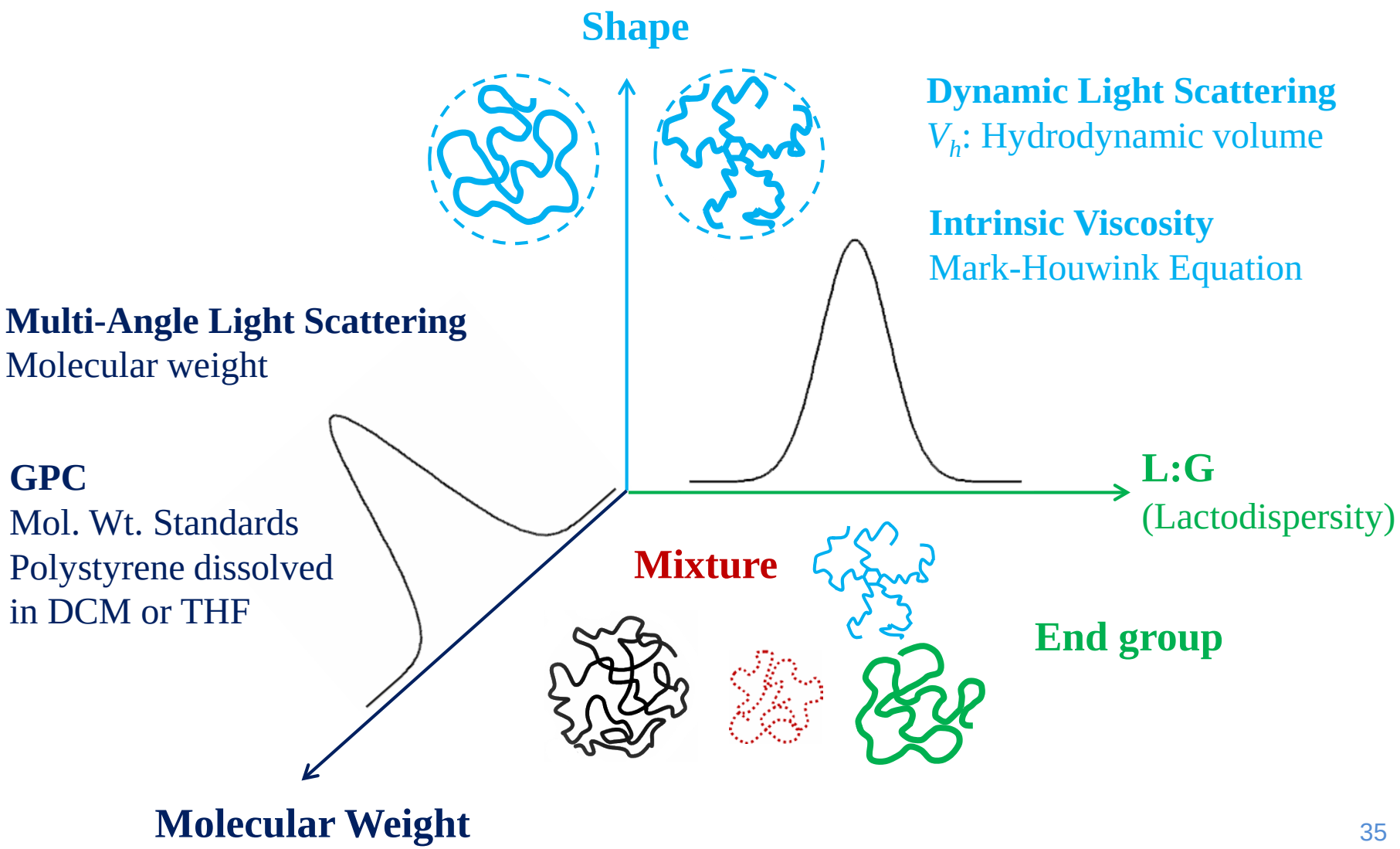



End Group: $^{13}$C-NMR

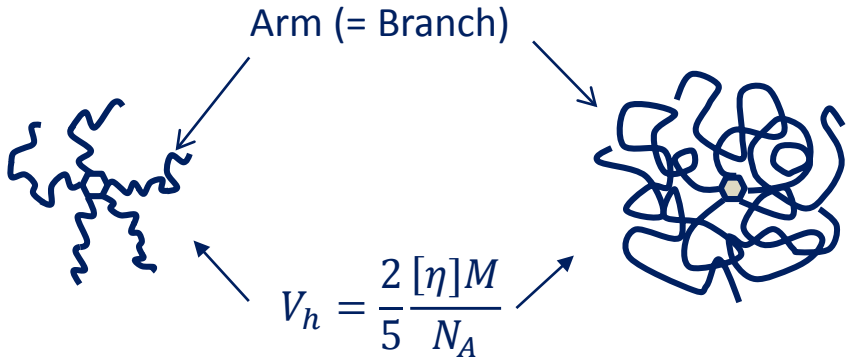



A protocol for assay of poly(lactide-co-glycolide) in clinical products.
J. Garner, S. Skidmore, H. Park, K. Park. S. Choi, & Y. Wang
International Journal of Pharmaceutics 495 (2015) 87–92

# Characterizations of PLGA

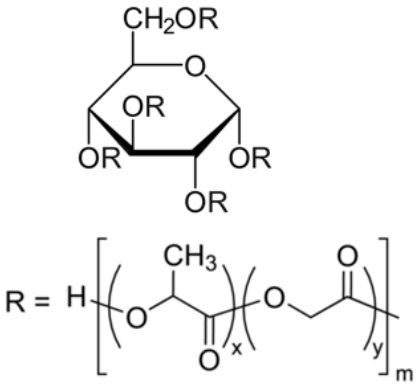


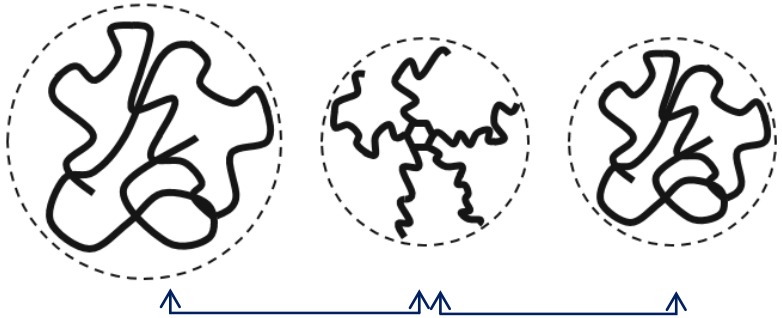
# Star-Shaped PLGA (Glucose-PLGA)




($V_h$: Hydrodynamic Volume)

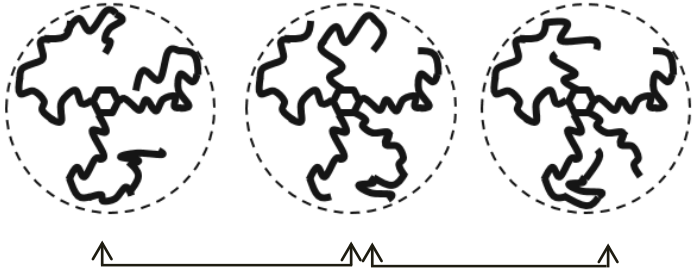
Low Molecular Weight High Molecular Weight



$M_{lin} = M_{star}$ $M_{star} > M_{lin}$

$V_{h,lin} > V_{h,star}$ $V_{h,star} = V_{h,lin}$



*f = 3* *f = 5* *f = 5*

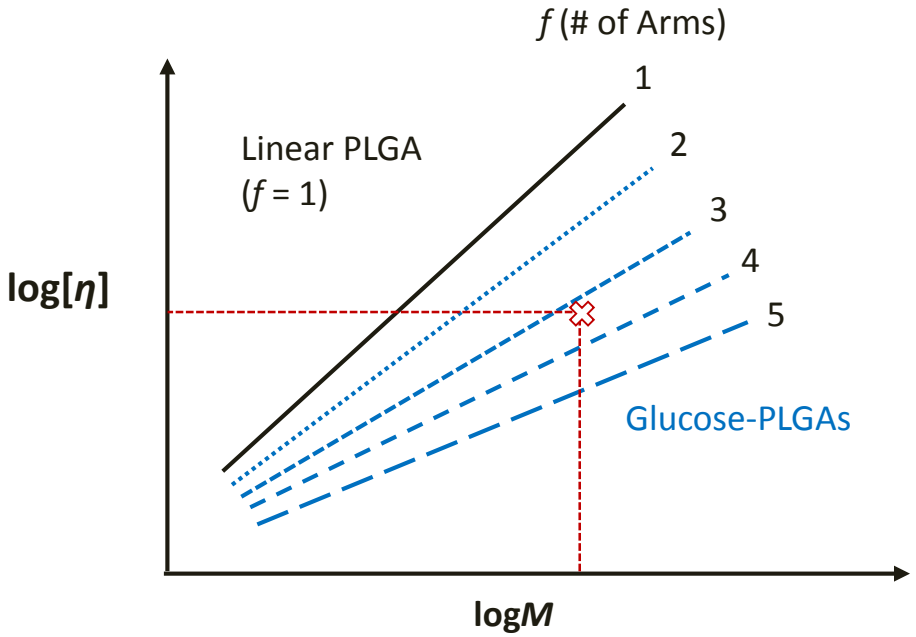
$PDI_{3arn} \approx PDI_{5arm}$ $PDI_{5arm} \leq PDI_{5arm}$

# GPC with Quadruple Detectors

| | |
|---|---|
| **1. Refractive index** | This establishes the exact concentration of the polymer. |
| **2. Multi-angle static light scattering (MASLS)** | The component measures the absolute weight average molecular weight ($M_w$) without any calibration using standard molecules, as well as the radius of gyration ($R_g$). The $R_g$ obtained from MASLS is not dependent on the shape. |
| **3. Dynamic light scattering** | This yields hydrodynamic volume ($V_h$), and thus hydrodynamic radius ($R_h$). $R_h$ describes the apparent size (i.e., radius) of the solvated, tumbling molecule. $R_h$ values are calculated assuming the molecule is spherical. |
| **4. Viscometer** | The viscometer provides intrinsic viscosity ($[\eta]$) values which provide Mark-Houwink coefficients and distributive properties of long chain branching and hydrodynamic volume $V_h$ of a polymer. |

# Branching Frequency of PLGA

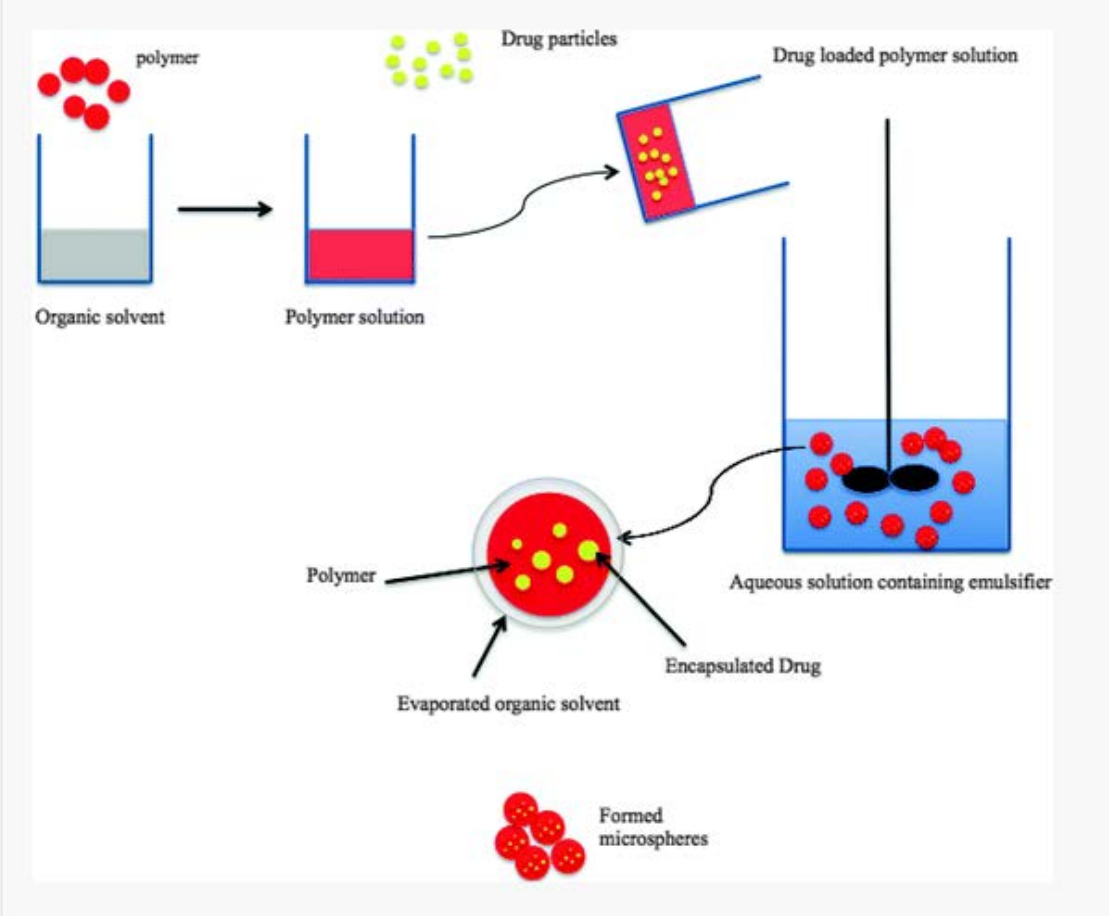
## Mark-Houwink Plots




$$[\eta] = \frac{5}{2} N_A \frac{V_h}{M} = \frac{5}{2} N_A \frac{4\pi}{3} \frac{<R_\eta^2>^{\frac{3}{2}}}{M} \left(\approx \frac{5}{2} N_A \frac{4\pi}{3} \frac{<R_h^2>^{\frac{3}{2}}}{M}\right) = \phi' \frac{<R_g^2>^{\frac{3}{2}}}{M} = KM^{\alpha}$$

# Preparation of Microspheres

Scheme of emulsion based solvent extraction/evaporation method




Y. Wang, D. J. Burgess, Microsphere Technologies, Long acting injections and implants, PP 167-194

# Impacts of Process Parameters on Properties of PLGA Product

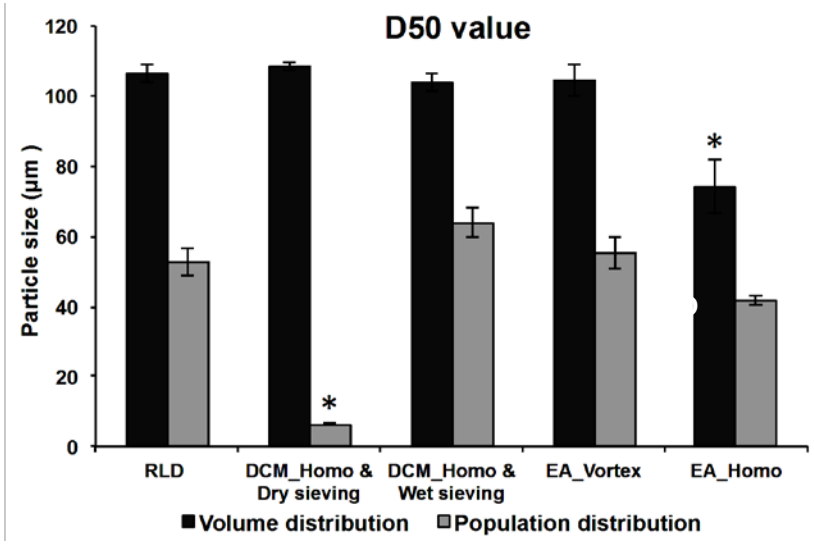
## Prepared compositional equivalent risperidone microspheres

| Sample | Solvent | Preparation Method | Drug Loading (%, w/w) |
|---|---|---|---|
| Risperdal® Consta® | - | - | 39.42±1.92 |
| Formulation_1 | DCM | Homogenization & dry sieving | 36.77±1.44 |
| Formulation_2 | DCM | Homogenization & wet sieving | 37.67±0.94 |
| Formulation_3 | EA | Vortex & wet sieving | 37.33±0.60 |
| Formulation_4 | EA | Homogenization & wet sieving | 36.45±1.23 |

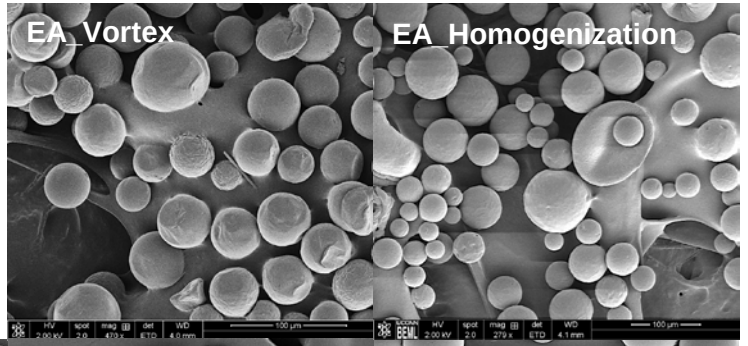
Shen J., Burgess D.J., *J. Control. Release, (2015)*

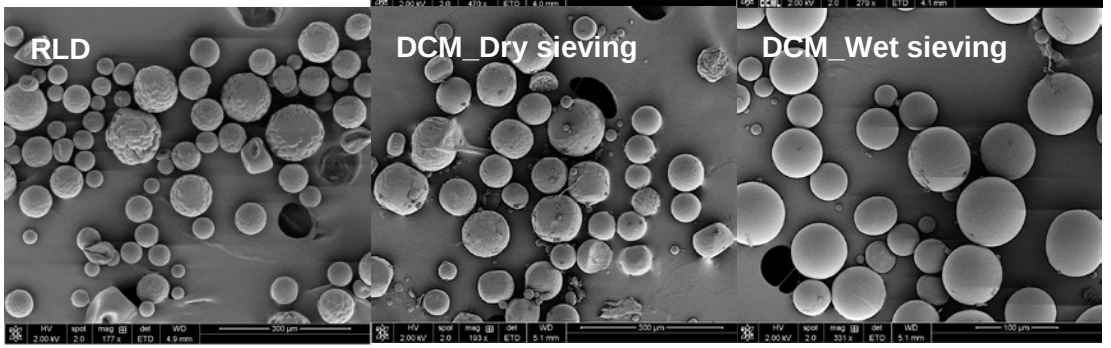
# Critical Physicochemical Properties of the Prepared Risperidone Microspheres

## Particle Size




**Porosity** **54.98%** **61.75%**

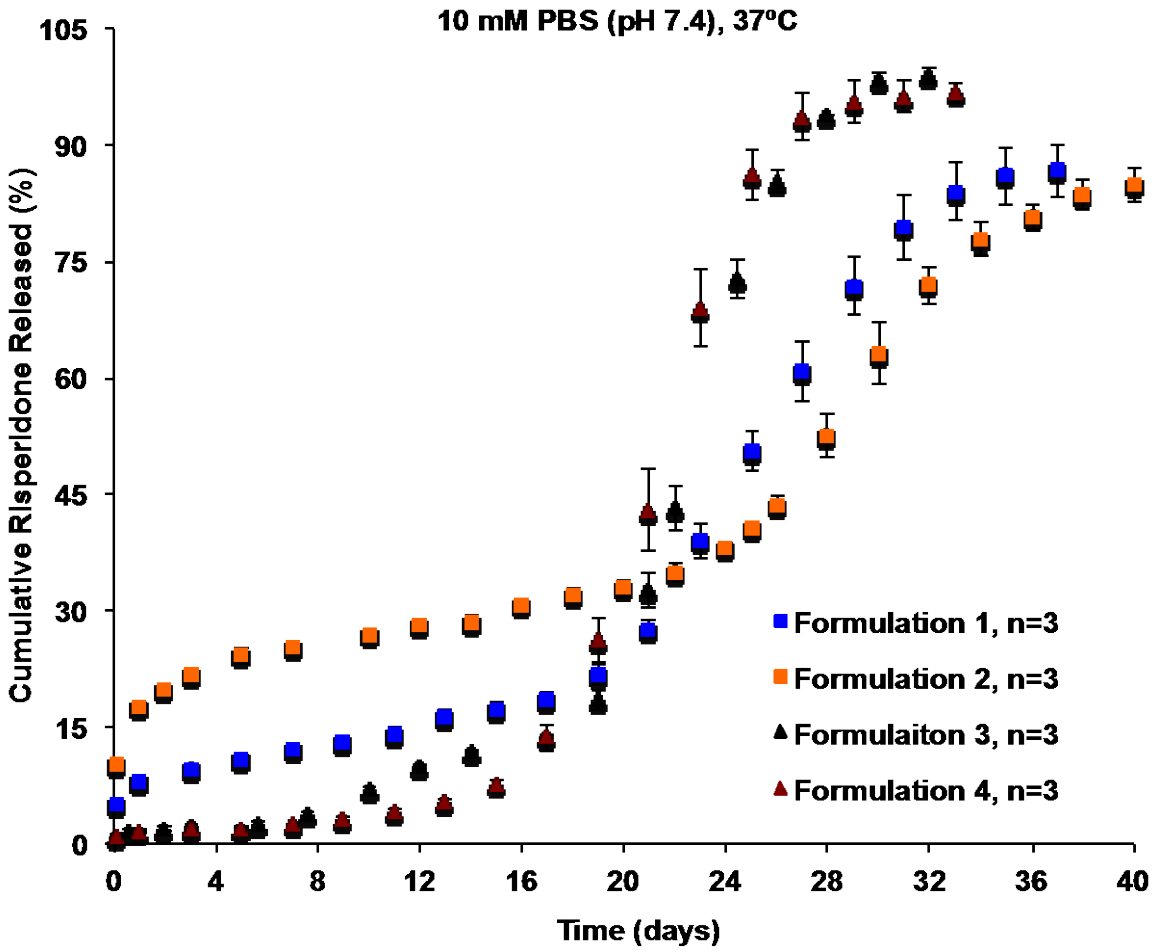



**Porosity** **43.97%** **43.19%** **46.04%**

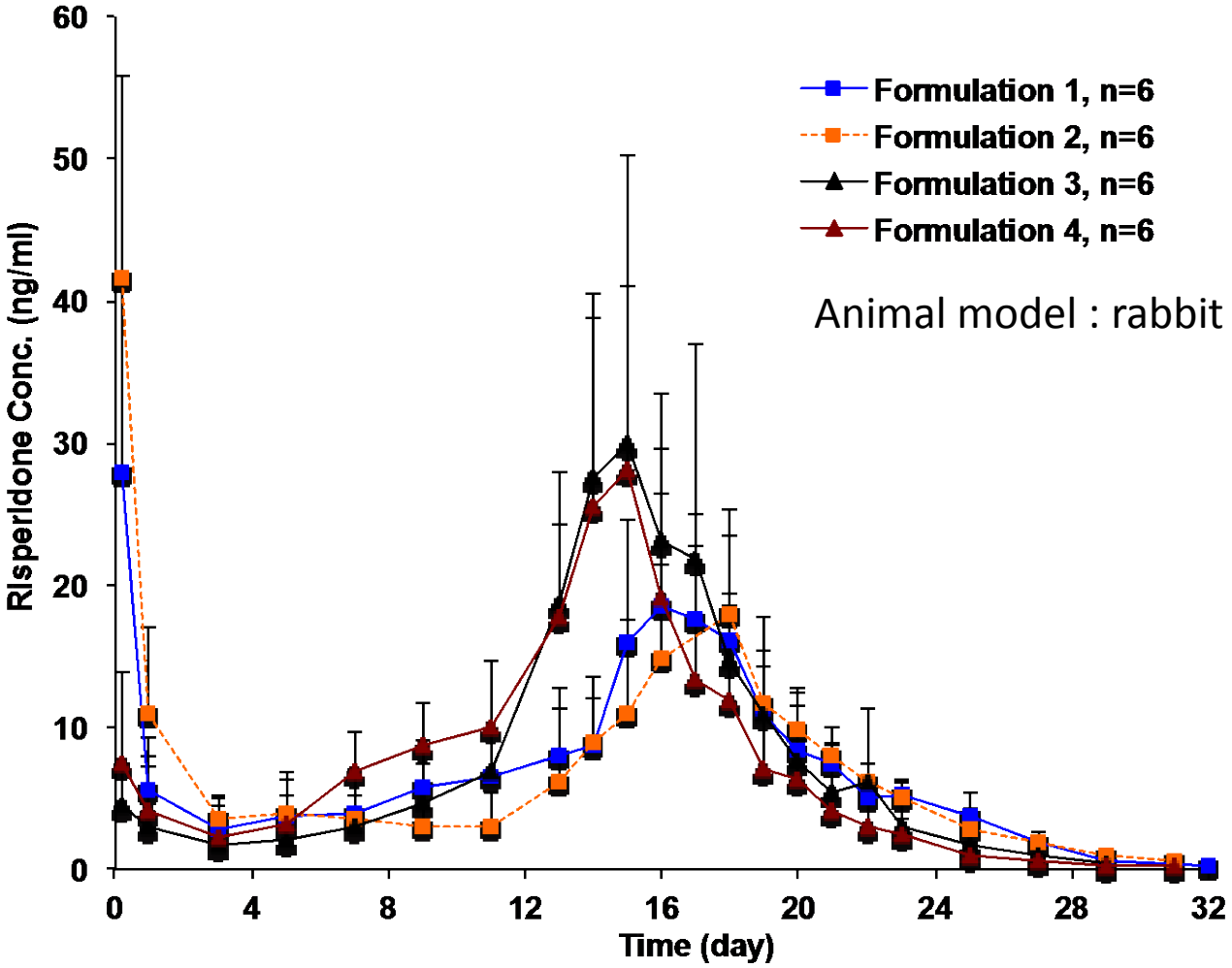
Shen J., Burgess D.J.,
*J. Control. Release, (2015)*

# In vitro Release Profile of the Prepared Risperidone Microspheres



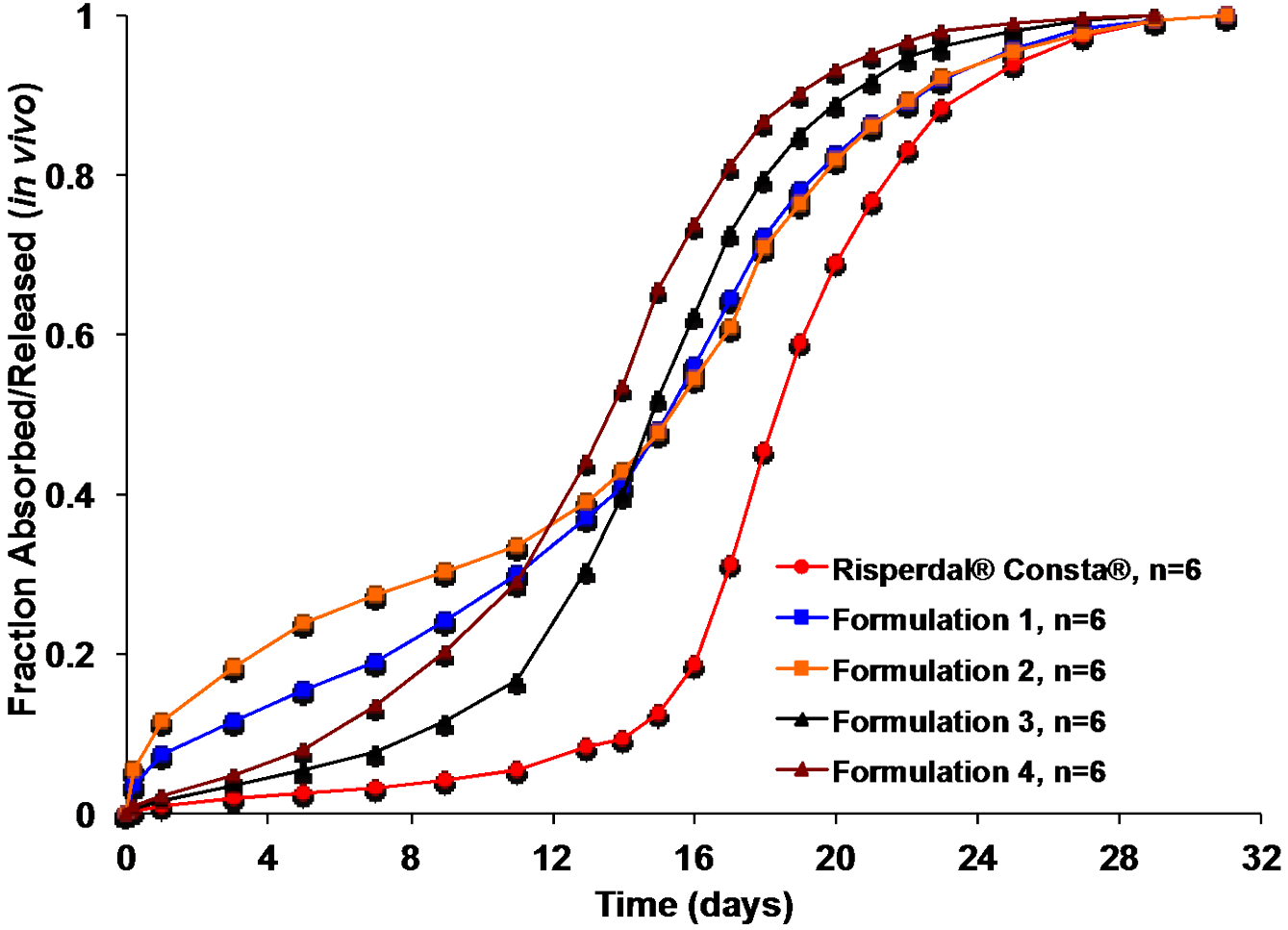

Shen J., Burgess D.J., *J. Control. Release, (2015)*

# In vivo Release Profile of the Prepared Risperidone Microspheres



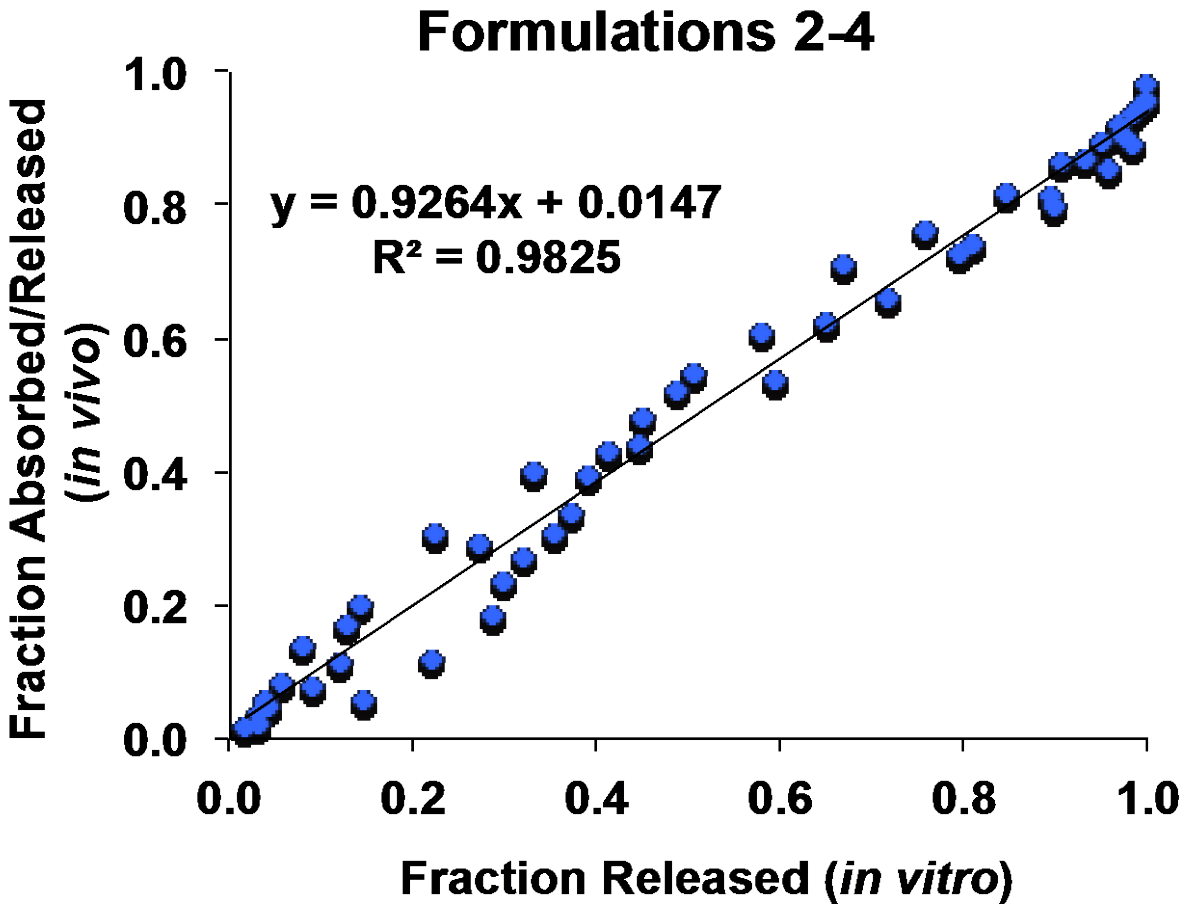

Shen J., Burgess D.J., *J. Control. Release, (2015)*

# Deconvoluted in vivo Release Profile of the Prepared Risperidone Microspheres



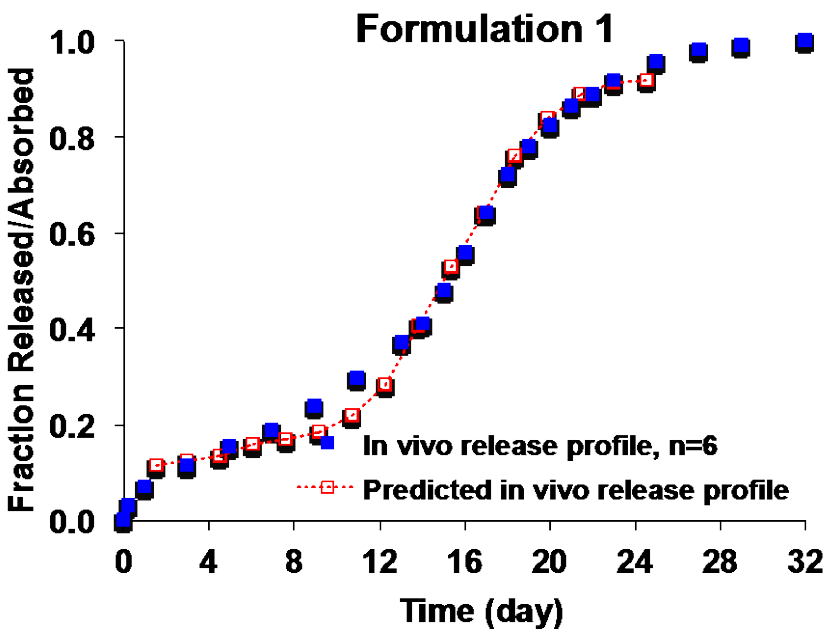

Shen J., Burgess D.J., *J. Control. Release, (2015)*

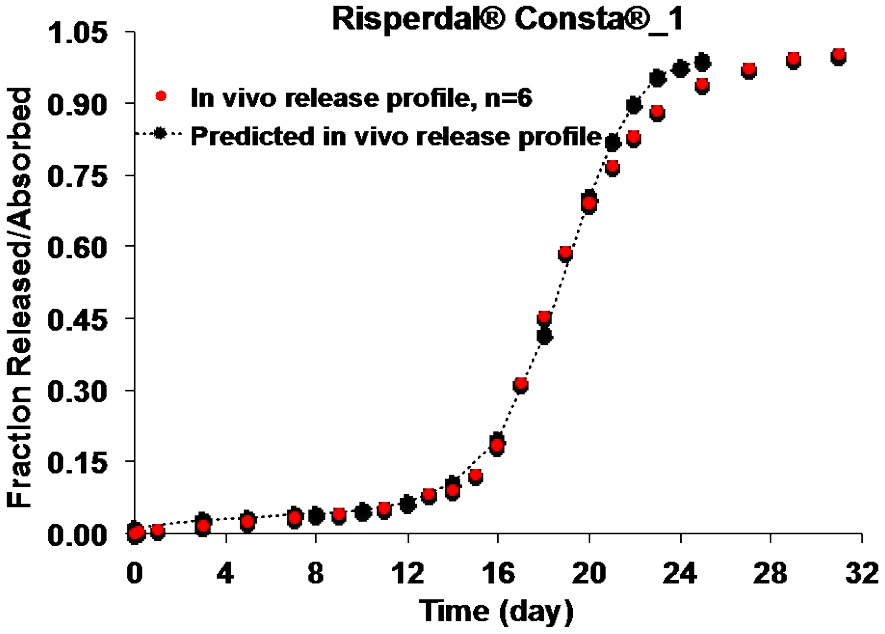
# Development of IVIVC Using Formulation 2, 3 and 4




Shen J., Burgess D.J., *J. Control. Release, (2015)*

# Predicated in vivo Release Profiles of Formulation 1 and the RLD



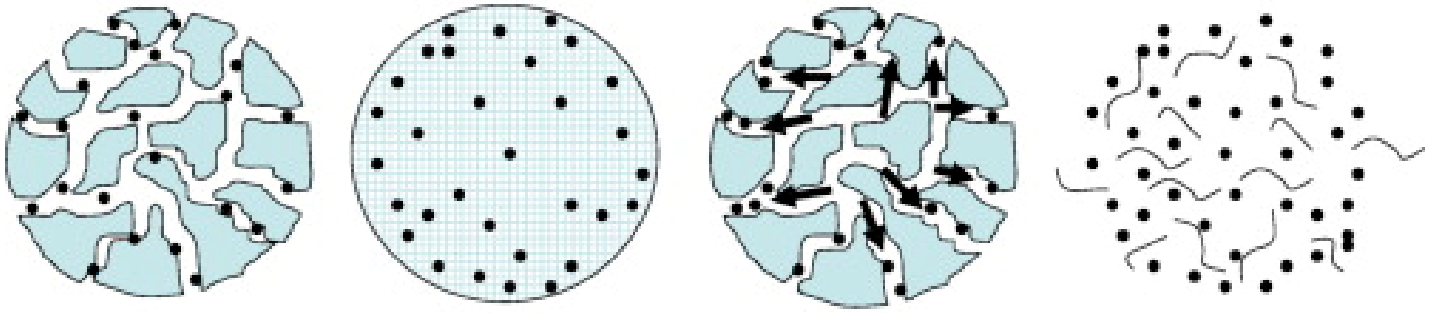

Shen J., Burgess D.J., *J. Control. Release, (2015)*

# Validation of the Developed IVIVC

| Internal validation | $C_{max}$ (µg/L) | | | AUC (µg/L*day) | | |
|---|---|---|---|---|---|---|
| | Pred. | Obs. | %PE | Pred. | Obs. | %PE |
| Formulation 2 | 19.64 | 41.62 | -52.81 | 188.26 | 200.41 | -6.06 |
| Formulation 3 | 40.49 | 29.98 | 35.06 | 219.14 | 229.07 | -4.34 |
| Formulation 4 | 35.58 | 28.68 | 24.08 | 201.12 | 220.95 | -8.97 |
| **Average absolute %PE** | | | 37.32 | | | 6.46 |
| **External validation** | | | | | | |
| Formulation 1 | 26.71 | 27.99 | -4.56 | 231.51 | 206.92 | 10.61 |
| **Prediction** | | | | | | |
| Risperdal® Consta® | 41.32 | 38.29 | 7.90 | 248.69 | 248.50 | 0.08 |

Shen J., Burgess D.J., *J. Control. Release, (2015)*

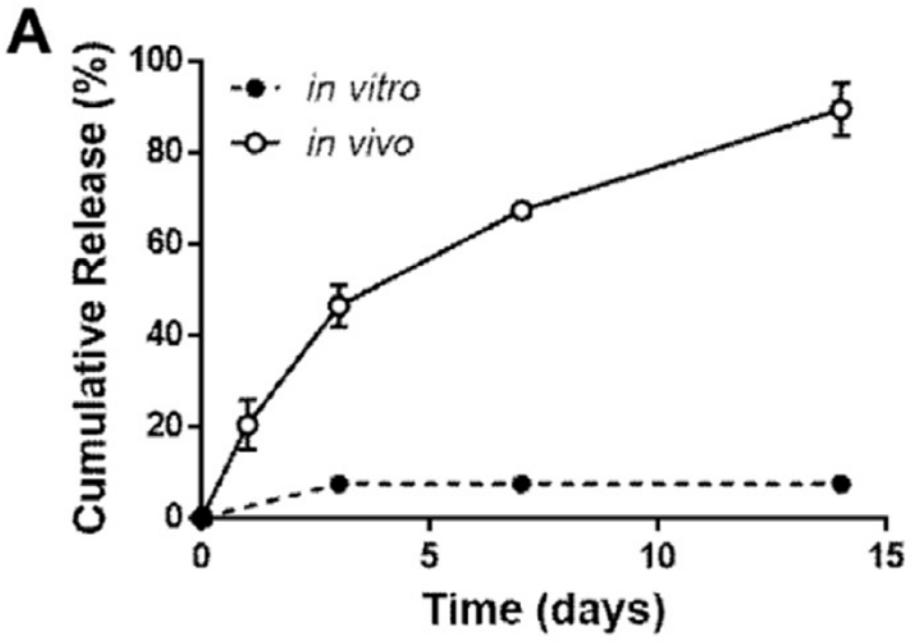
# Proposed Drug Release Mechanisms from PLGA Microspheres



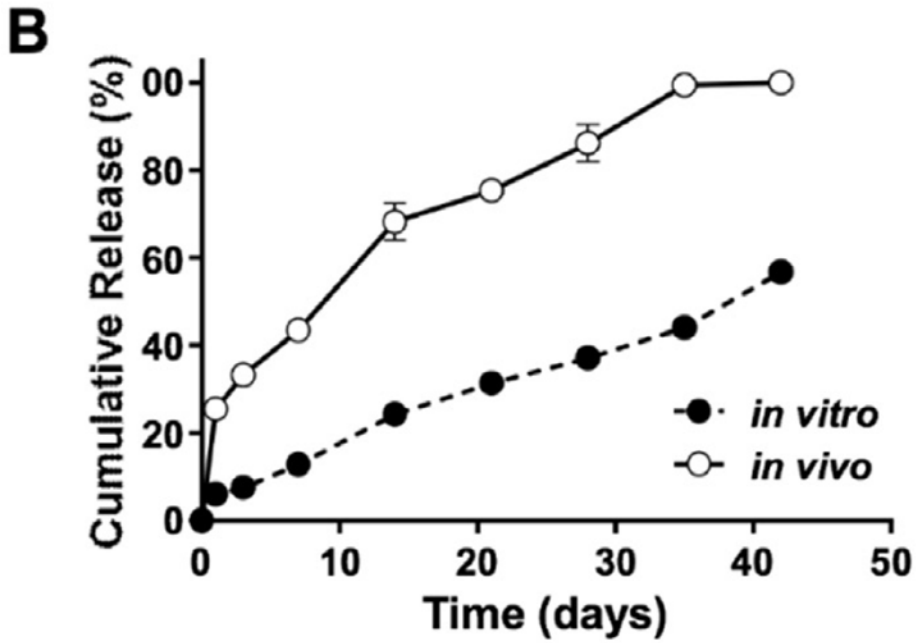

Fredenberg et al., *Int. J. Pharm.*, **415**, 34–52 (2011)

# Understanding Release Mechanisms of Drugs from PLGA Microspheres

Triamcinolone-loaded microspheres

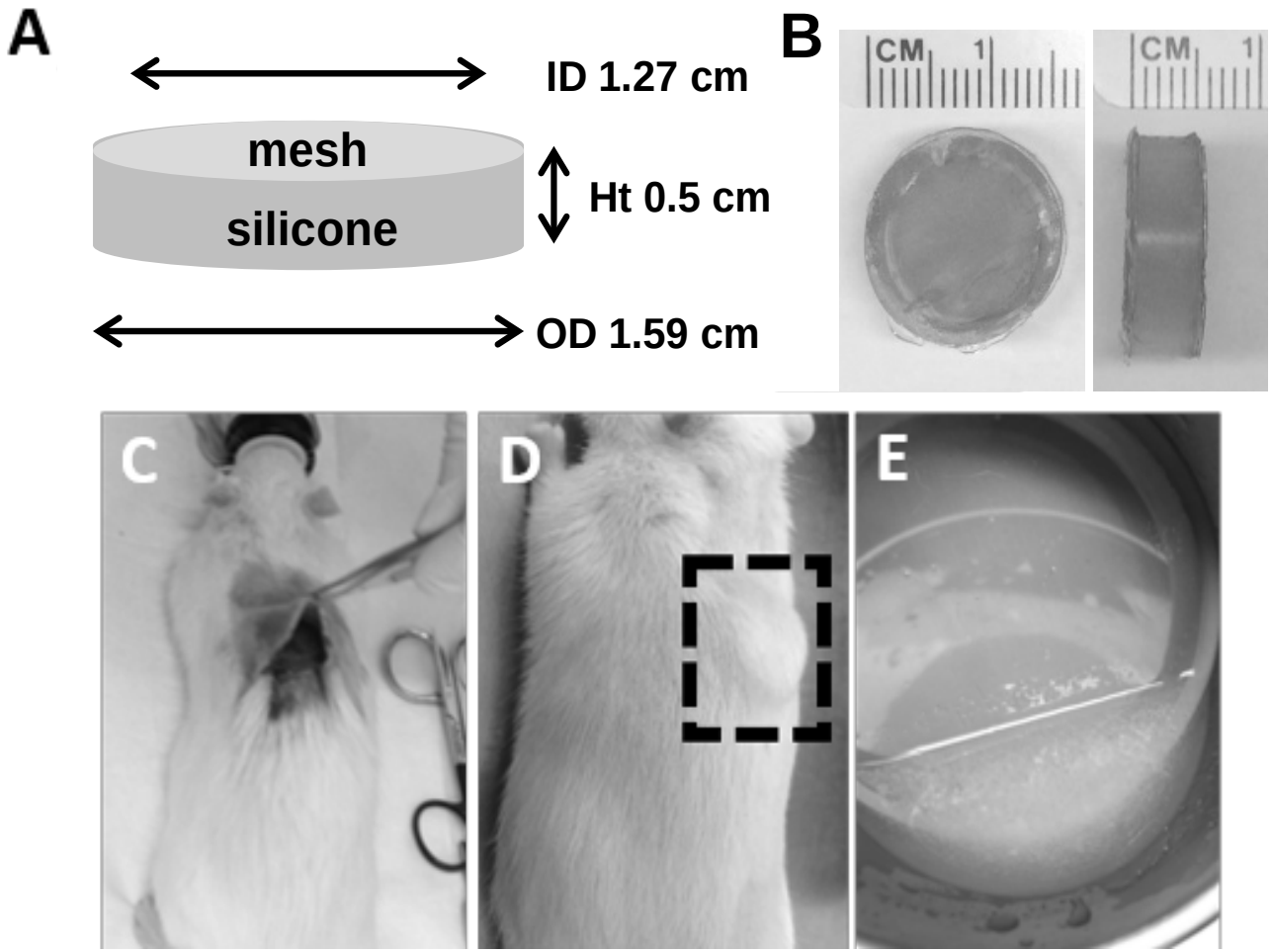



Leuprolide-loaded microspheres




Doty *et al. Biomaterials,* **109,** 88-96 (2016)

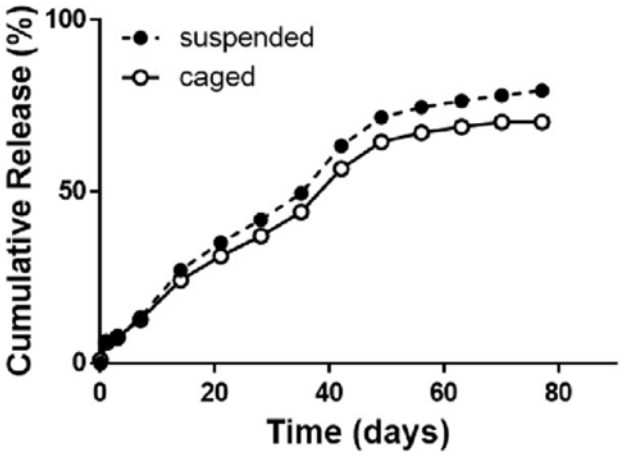
# Cage Model for Evaluation of Microsphere Performance in vivo

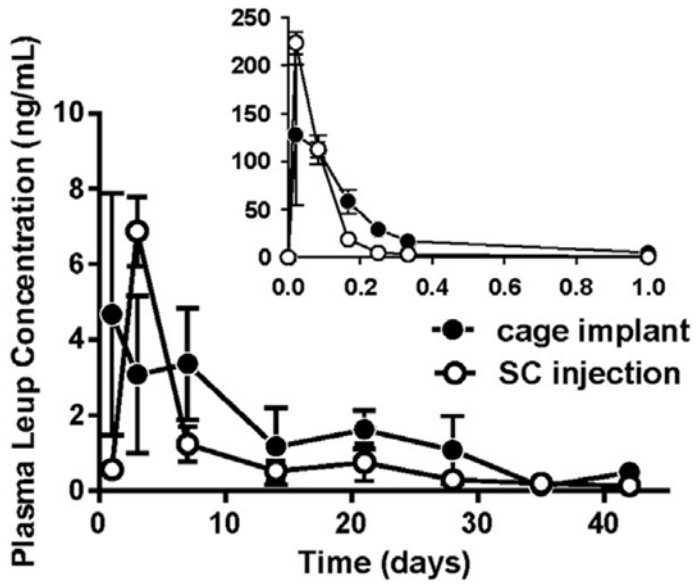


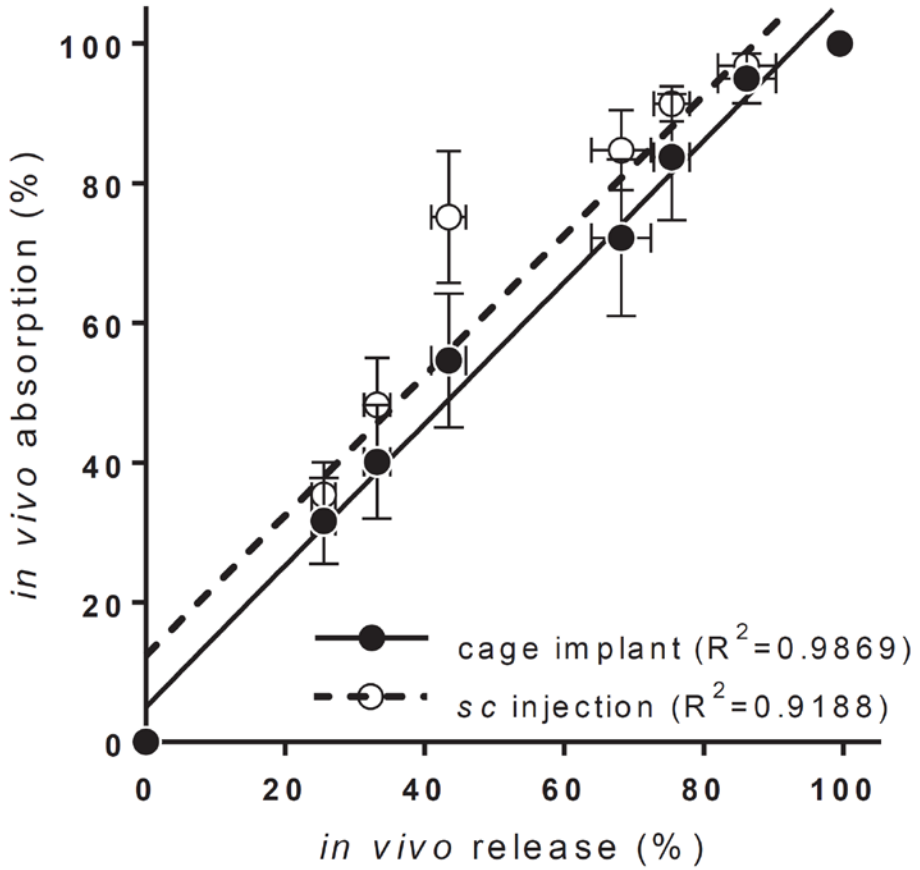

Doty *et al. Biomaterials,* **109,** 88-96 (2016)

# Validation of Cage Model

PK of the steroid triamcinolone acetonide (Tr-A)/PLGA 50/50 microspheres

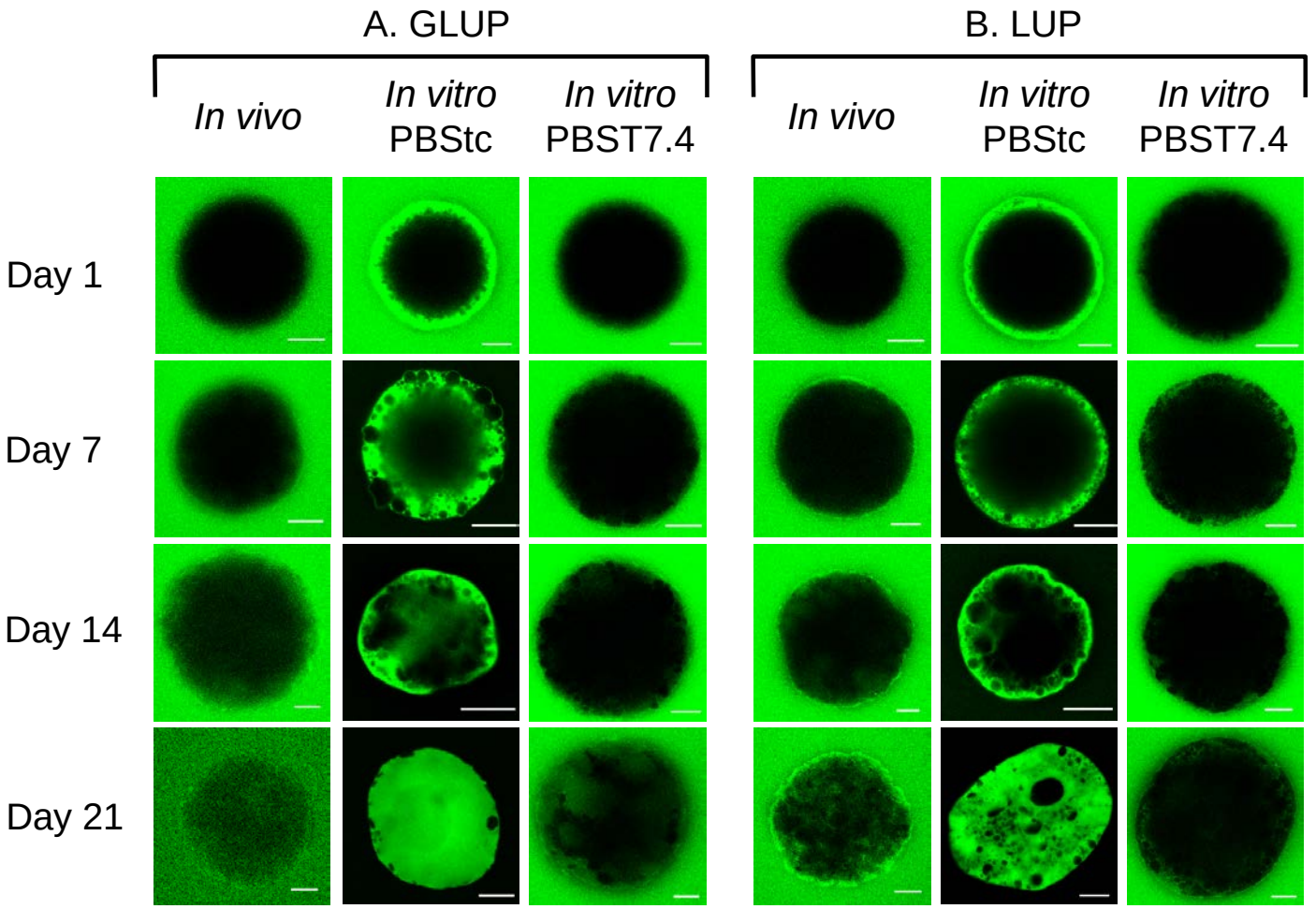



Doty *et al. Biomaterials,* **109,** 88-96 (2016)

# Microstructural Changes during in vitro and in vivo Release of Leuprolide from R503H

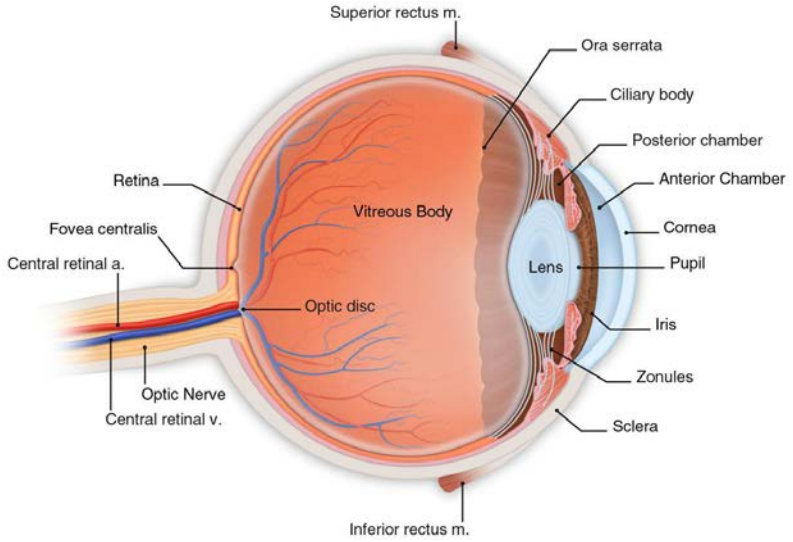



GLUP = + gelatin with leuprolide  LUP = – gelatin with leuprolide

K. Hirota *et al*, *J. Controlled Release*, 244, 302-313 (2016)

# Novel In Vitro Release Testing (IVRT) for Complex Formulations

# Ophthalmic Drug Products




| Dosage Form (2016 sales) | Number of marketed Reference products | % products that have a generic |
|---|---|---|
| Solutions ($3.9B) | ~79 | 60% |
| Suspension ($1.2B) | ~20 | 10% |
| Emulsion ($2.0B) | 2 | 0 |
| Ointment ($400M) | 21 | 24% |

# Demonstrating Bioequivalence of Locally Acting Ophthalmic Products

## In vivo studies

Locally acting ophthalmic products present challenging bioequivalence measures

**Clinical endpoint:**

- Endpoint can be semi-qualitative and confounded by patient disease state
- Poor discriminator between similar products

**Local PK: Aqueous humor**

- Sparse sampling with high variability
- Large sample population required

# Role of IVRT

- In general, IVRT for bioequivalence determination is one component of a totality of evidence approach
  - IVRT can be recommended as part of in vitro testing to demonstrate sameness between two products with highly similar formulations
  - IVRT can be recommended in conjunction with in vivo tests to demonstrate equivalence between formulations with known differences
- Once validated, IVRT can also be used as a specification to control product quality and/or acceptability of post-approval manufacturing changes

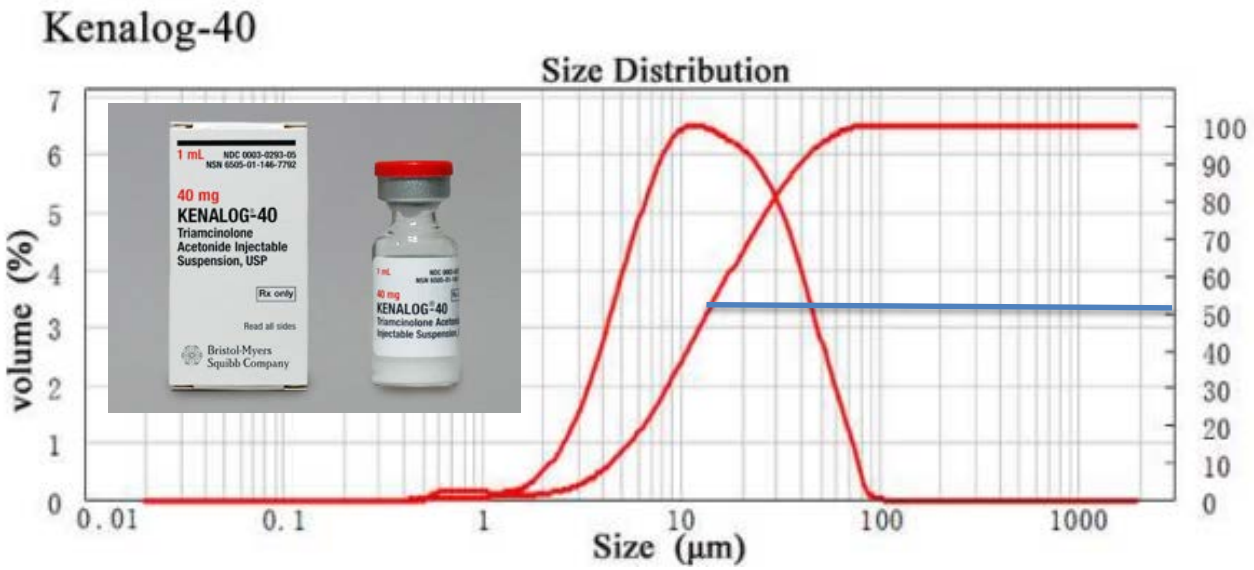
# Expectations of IVRT

- An IVRT method should be capable of discriminating the effect of process variability in the production of the test formulation

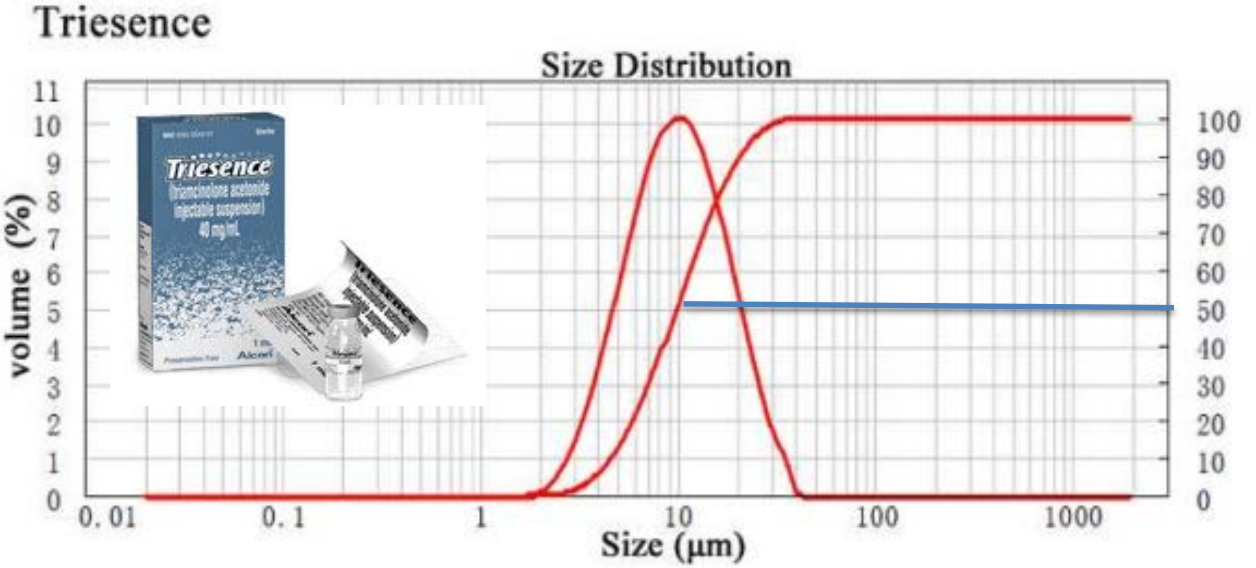
- IVRT should be conducted with drug products manufactured under target conditions and compared to drug products that are intentionally manufactured with meaningful variations in formulation and manufacturing parameters:
  - particle size, drug loading, types and/or amounts of excipients

# Kenalog40 vs Triesence

- 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

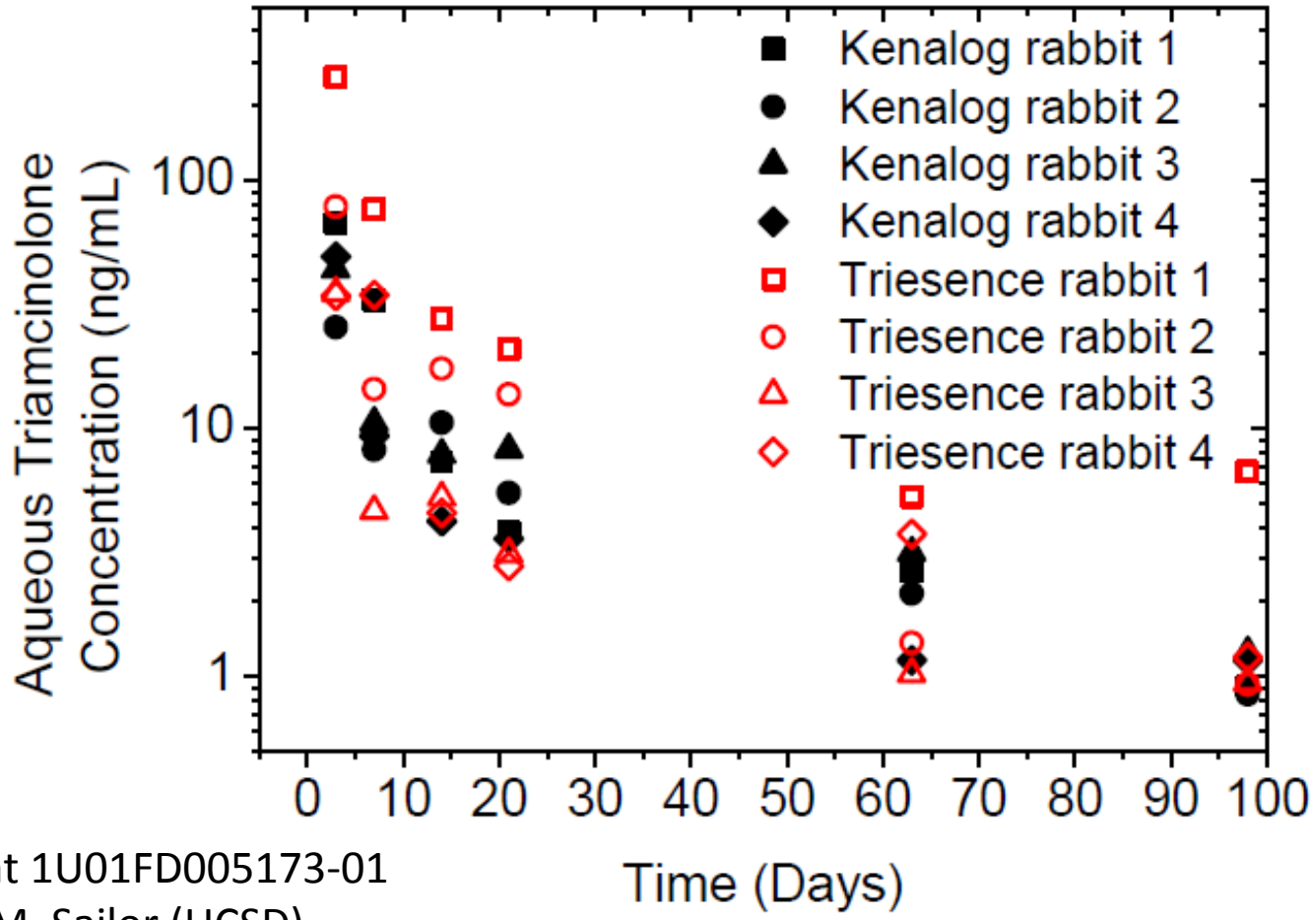



- API: Triamcinolone
- Crystalline
- Narrow size distribution
- No preservative
- Salts, surfactants
- Half-life in the eye (4mg, rabbit): 24d
- FDA approved for uveitis



# In vivo Aqueous Humor PK in Rabbit

In vivo PK indicated that there is a minimal measured difference between the two drug formulations

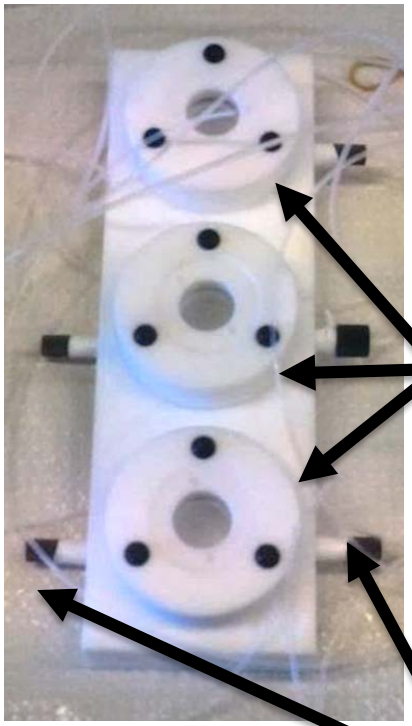



FDA grant 1U01FD005173-01
PI: Prof. M. Sailor (UCSD)

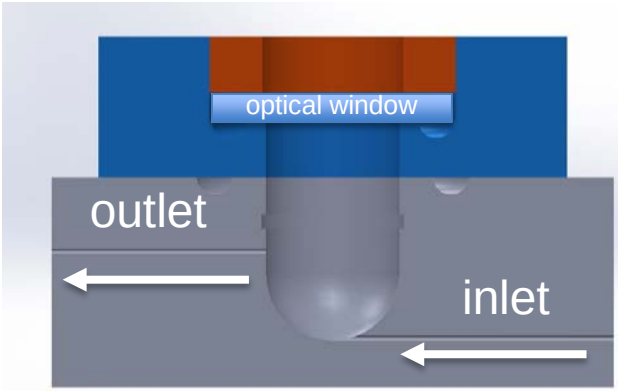
# Developed IVRT Flow Cell

## Tested Conditions

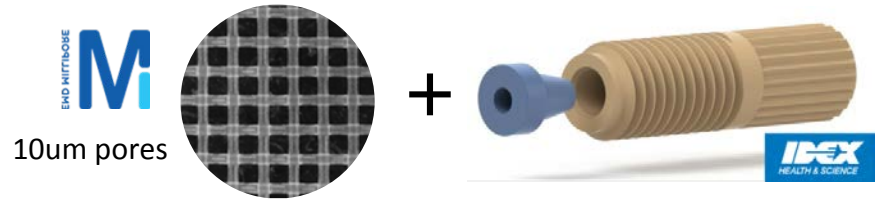
- Flow rate
  - 1.5 mL/day (1X)
  - 7.5 mL/day (5X)
  - 15 mL/day (10X)
- Simulating Vitreous Fluid; Hank's Balanced Salt Solution, HBSS with Hyaluronic Acid:
  - 0, 0.05, 0.1, 0.5, & 1 (mg/mL)



## Teflon flow cells

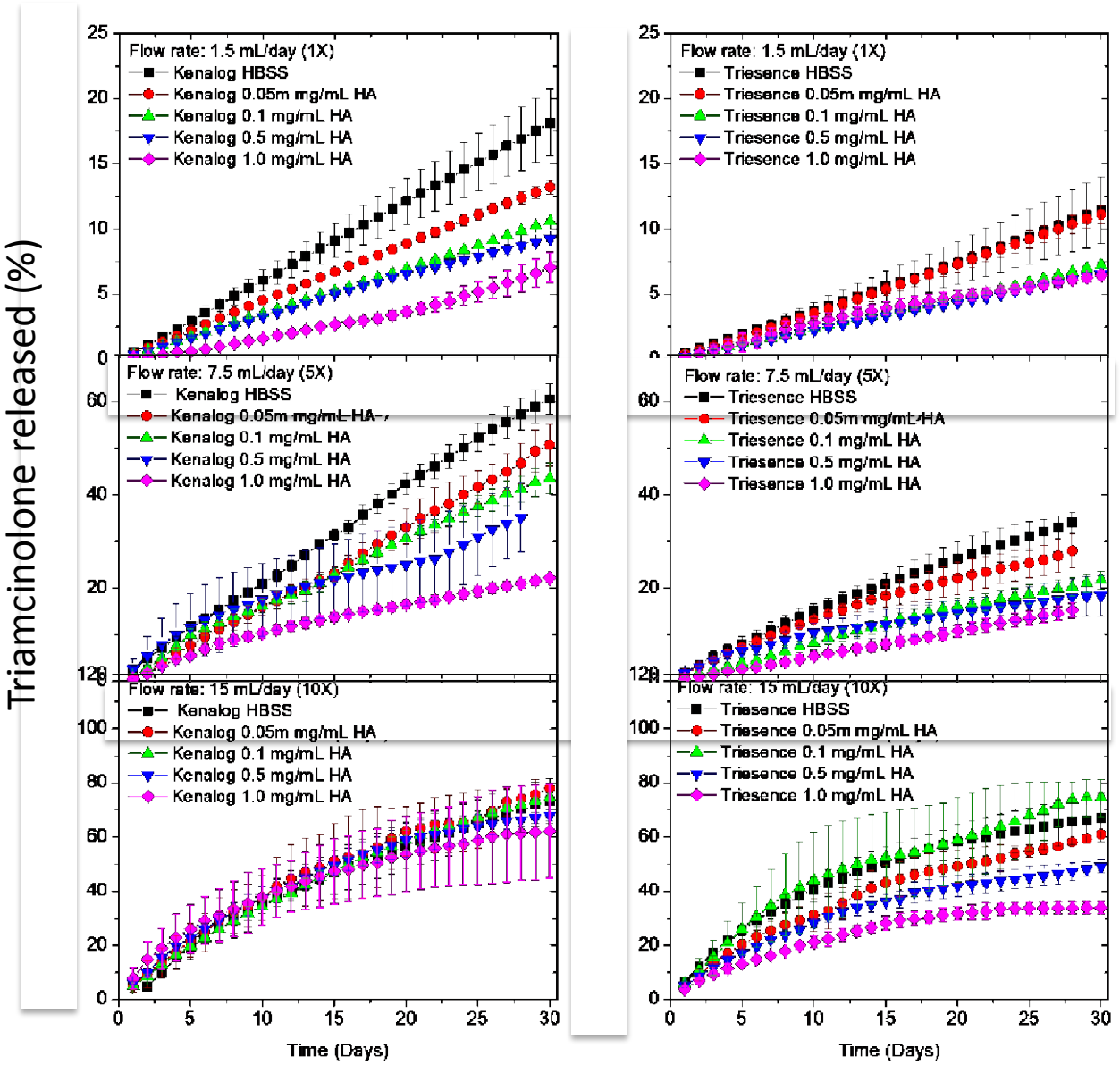



## Fittings and mesh filters

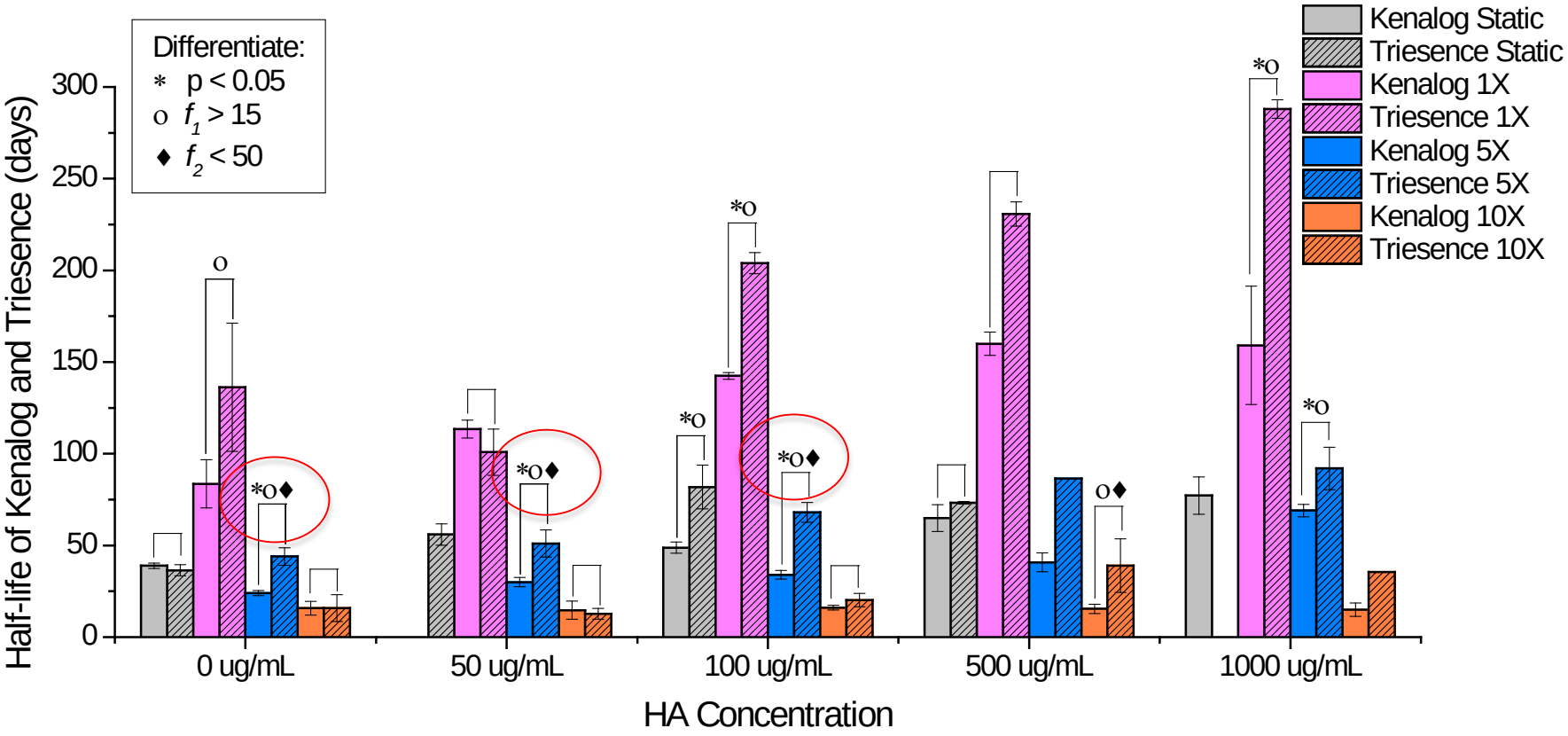



FDA grant 1U01FD005173-01
PI: Prof. M. Sailor (UCSD)

# Kenalog40 vs Triesence IVRT Results



# Discriminating Conditions Identified




solid bar: Kenalog 40
shaded bars: Triesence

FDA grant 1U01FD005173-01
PI: Prof. M. Sailor (UCSD)

# Optimized IVRT conditions

| Flow rate | Concentration of hyaluronic acid (mg/mL) Increasing viscosity --> | | | | |
|---|---|---|---|---|---|
| | 0 | 0.05 | 0.10 | 0.50 | 1.00 |
| static | | | | | |
| 1.5 mL/day (1X) | | | | | |
| 7.5 mL/day (5X) | | | | | |
| 15 mL/day (10X) | | | | | |

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

# Ophthalmic Emulsions

Ophthalmic emulsions (cyclosporine 0.05% and difluprednate 0.05%)

- Complex materials
  - Drug is distributed in several phases
  - Dissolution may not be required for release
- Short residence time in the eye
- When administered, form thin films on the ocular surface, and formulation temperature goes to ~35°C (ocular surface temp) in about 1 second

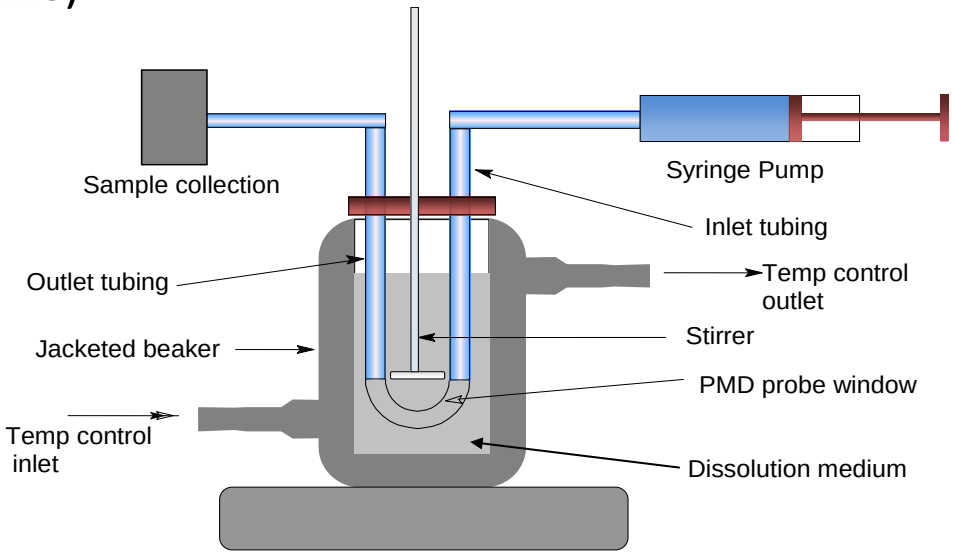
# Pulsatile Microdialysis (PMD)

- PMD is a sampling method used to determine drug release or changes in free drug concentrations
- Based on dialysis principle but with data as a function of time
  - Characterize processes and kinetics
  - Release, dissolution, binding, precipitation, etc.
- Unique features:
  - Rapid sampling (as often as every 15 seconds for solutions)
  - Small geometry (100 micron radius, very large surface area per volume)
- PMD is particularly useful when
  - System is changing quickly (e.g., dissolved concentration)
  - System is microscopically or macroscopically multiphasic
  - Characterizing unstirred media
- Theory of PMD is well understood, allows for meaningful data analysis

FDA Contract HHSF223201610105C PI: R. Bellantone (Physical Pharmaceutica LLC)

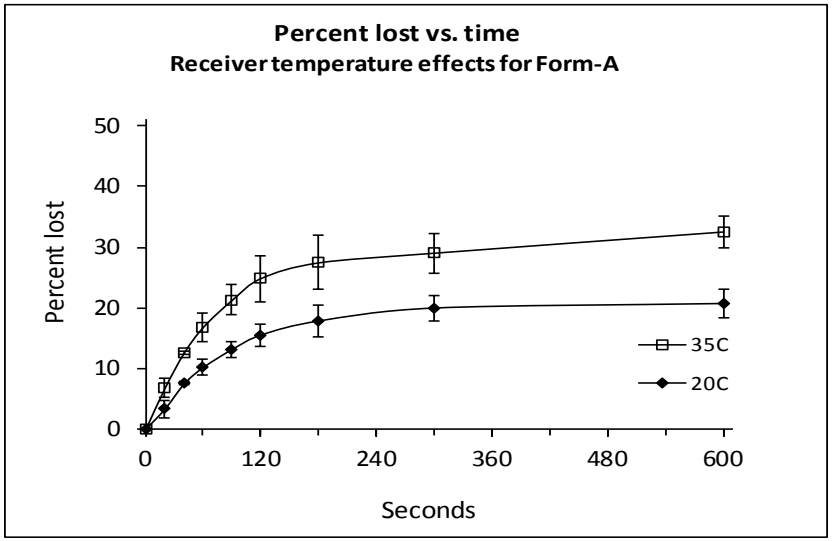
# Prototype PMD Setup

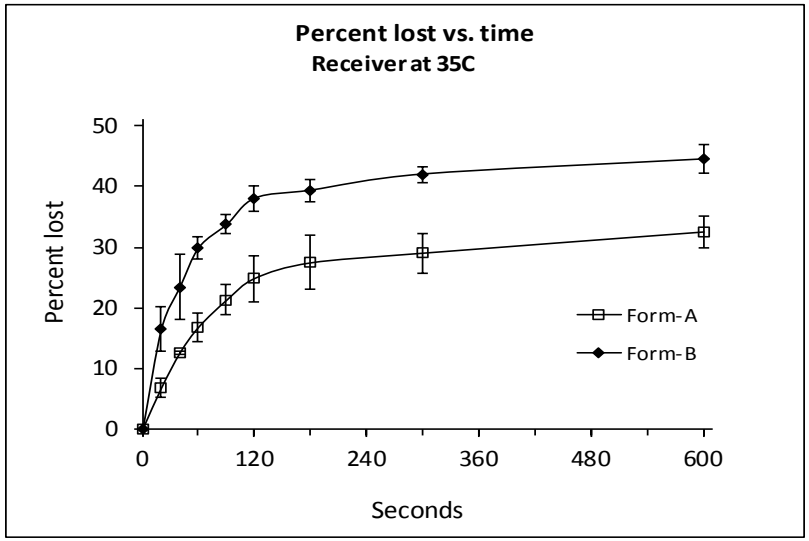
- A PMD probe is immersed in an external medium
- A liquid medium (dialysate) is
  - Pumped into the probe at a high flow rate (0-100 μL/min)
  - Stopped and allowed to remain for a specified resting time (typically 30-600 seconds)
  - Pumped out at the same flow rate and collected for assay
- Essentially an automated set of “diffusion cells”
  - Drug diffuses across window membrane
  - Each flushing sets up a new diffusion setup running for a given time (resting time)



# PMD Release of Cyclosporine Emulsions

- Two Q1/Q2 formulations (Form-A and Form-B) produced by different processes
- Overserved effects of temperature, and processing method
- Biphasic release patterns:
  - Drug in aqueous phase is immediately available to ocular tissues
  - Drug in globules takes longer to partition into ocular tissues



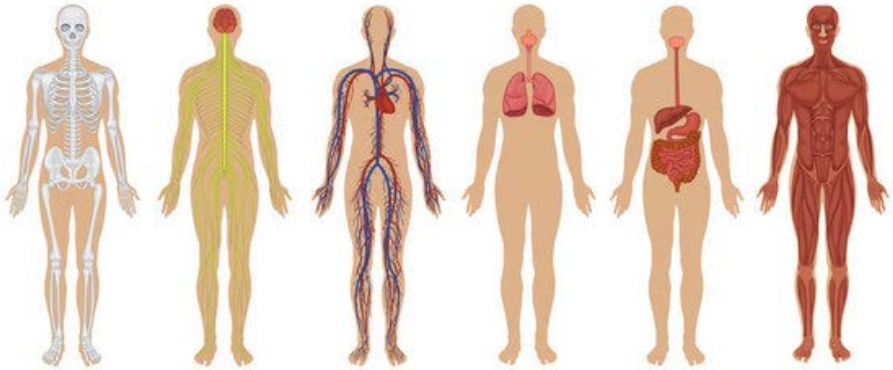

FDA Contract HHSF223201610105C PI: R. Bellantone (Physical Pharmaceutica LLC)

# GDUFA I Research Outcomes

- Issued 100+ research grants and contracts
- Published 788 PSGs (495 new and 293 revisions)
- Supported 65+ pre-ANDA meetings
- Outcomes from GDUFA research projects contributed to the approvals of 5 complex first generic ANDAs

GDUFA I: FY 2012 - 2017

# Bridging in vitro and in vivo studies



**In vivo performance**

**In vitro testing**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