# Long Acting Injectable and Implantable Drug Product Development: Regulatory Challenges and Considerations

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# Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

# Outline

- Introduction
- Challenges in development and evaluation of long acting injectable/implantable (LAI) drug products
- FDA's GDUFA regulatory science program to support development of generic LAI drug products
- Summary

# Long acting injectable/implantable formulations

- Oil-based injectable solutions
- Injectable-drug suspensions
- Polymer and lipid based LAIs

# Oil-based injectable solutions

| Drug | Brand name | Admin route | Dosing freq. | Indication | Company | Vehicle |
|---|---|---|---|---|---|---|
| Haloperidol decanoate | Haloperidol decanoate | IM | Once a month | Schizophrenia | Ortho-McNeil Pharm | Sesame oil |
| Estradiol valerate | Delestrogen | IM | Every 4 weeks | Hormone therapy | Monarch Pharm | Sesame oil |
| Fluphenazine decanoate | Modecate | IM | Every 2-5 weeks | Schizophrenia | Sanofi-Aventis | Sesame oil |
| Zuclopenthixol decanoate | Clopixol Depot | IM | Every 2-4 weeks | Schizophrenia | Lundbeck | Sesame oil |
| Testosterone enanthate | Delatestryl | IM | Every 2-4 weeks | Hormone therapy | Endo Pharma | Sesame oil |

## Lipophilic drug dissolved in vegetable oil

# Long acting injectable suspensions

| Drug | Brand name | Admin route | Dosing freq. | Indication | Company | Vehicle |
|---|---|---|---|---|---|---|
| Paliperidone palmitate | Invega Sustenna | IM | Once a month | Schizophrenia | Janssen | WFI PS-20 PEG4000 |
| Olanzapine | Zyprexa Relprevv | IM | Every 2-4 weeks | Schizophrenia | Eli Lilly | WFI PS-80 |
| Medroxyprogesterone acetate | Depo provera | IM | Every 3 months | Hormone therapy | Pfizer | WFI PS-80, PEG3350 |

**Drugs with low solubility suspended in aqueous media**

# Polymer and lipid-based LAR products

| Drug | Brand name | Drug category | Admin route | Dosing freq. | Indication | Company |
|---|---|---|---|---|---|---|
| Resperidone | Risperdal Consta | Small molecule | IM | 2 weeks | Schizophrenia | Janssen Alkermes |
| Octreotide | Sandostatin LAR depot | Octapeptide | IM | 1 month | Acromegaly | Norvatis |
| Goserelin | Zoladex | Decapeptide | IM | 1, 3 months | Prostate cancer | AstraZeneca |
| Leuprolide | Lupron Depot | Nonapeptide | IM | 1, 3, 4, 6 months | Prostate cancer | Takeda/Abbott |
| Triptorelin | Decapeptyl/ Telstar/ Pamoerlin | Decapeptide | IM | 1, 3, 6 months | Prostate cancer | Ispen/Watson/Reddy/Debiopharm |
| Exenatide | Bydureon | 39-amino acid peptide | SC | 1 week | Type 2 diabetes | Amylin/BMS/ Alkermes |
| Cytarabine | DepoCyt | Small molecule | Intrathecal | 14 or 28 days | Lymphomatous meningitis | Pacira |
| Bupivacaine | Exparel | Small molecule | Direct to surgical site | Single dose, 3 days | Postsurgical analgesia | Pacira |

# Challenges in LAR product development

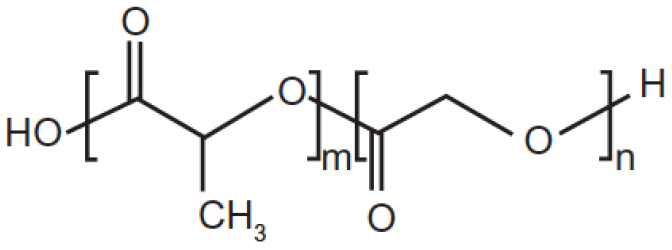
- Complex formulation and excipients
- Small process and raw material changes could result in significant product changes
- Complicated characterizations
- Release mechanisms (especially in vivo) are not fully understood
- No standard *in vitro* drug release assay
- Few models correlating *in vitro* drug release with *in vivo* pharmacokinetics
- Challenges in scale up
- …….

# PLA/PLGA based LAI drug products

| Drug Product (Active Ingredient) | Dosage Form | Route of Administration | Indication(s) |
|---|---|---|---|
| Ozurdex (Dexamethasone) | Implant | Intravitreal | macular edema, non-infectious uveitis, and diabetic macular edema |
| Zoladex (Goserelin acetate) | Implant | Subcutaneous | Prostate cancer |
| Atridox (Doxycycline hyclate) | In situ forming gel | Periodontal | periodontitis |
| Eligard (Leuprolide acetate) | In situ forming gel | Subcutaneous | advanced prostate cancer |
| Lupron (Leuprolide acetate) | Microsphere | Intramuscular | endometriosis |
| Lupron Depot (Leuprolide acetate) | Microsphere | Intramuscular | advanced prostatic cancer |
| Lupron Depot-PED (Leuprolide acetate) | Microsphere | Intramuscular | central precocious puberty |
| Trelstar (Triptorelin pamoate) | Microsphere | Intramuscular | advanced prostate cancer |
| Risperdal Consta (Risperidone) | Microsphere | Intramuscular | schizophrenia and bipolar I disorder |
| Signifor LAR (Pasireotide pamoate) | Microsphere | Intramuscular | acromegaly |
| Vivitrol (Naltrexone) | Microsphere | Intramuscular | alcohol dependence |
| Arestin (Minocycline HCl) | Microsphere | Periodontal | periodontitis |
| Bydureon (Exenatide) | Microsphere | Subcutaneous | type 2 diabetes |
| Sandostatin LAR (Octreotide) | Microsphere | Subcutaneous | acromegaly |
| Signifor (Pasireotide) | Microsphere | Subcutaneous | cushing's disease |

# Complex excipients

- **Poly(lactic-*co*-glycolic acid) (PLGA) copolymer**

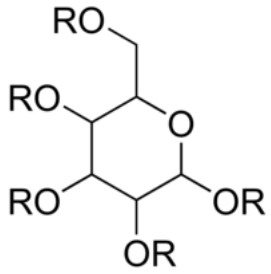


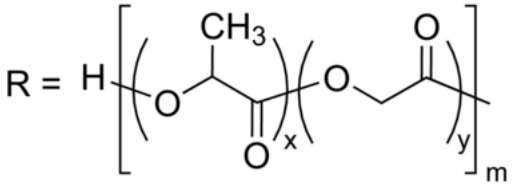

PLGA

m = number of units of lactic acid
n = number of units of glycolic acid

- Ratio of lactic acid to glycolic acid
- Molecular weight/weight distribution

- **Glucose star polymer, D,L-lactic and glycolic acids copolymer**




Sandostatin LAR depot
(octreotide acetate microsphere)



http://www.sigmaaldrich.com/catalog/product/aldrich/764876?lang=en&region=US

# Critical PLGA physicochemical properties

- Polymer composition (L to G ratio)
- Molecular weight and weight distribution
- Polymer architecture (linear vs star-shaped)
- Glass transition temperature
- Polymer end-cap
- Crystallinity

Generic parenteral PLGA microsphere drug products should be Q1/Q2 equivalent to Reference Listed Drug (RLD).

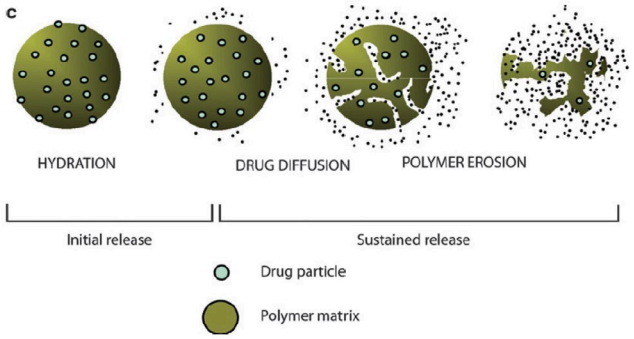
Q1: same excipient  Q2: same amount

# Complex drug release

- **Multiple factors impact drug release**

  Polymer composition; polymer molecular weight; API chemical property; manufacture process; matrix size and shape; drug loading; pH; releasing media……

- **Complex drug release mechanisms**
  - Multi-phasic release profiles




- **No compendial in vitro drug release testing method**
  - Unlike oral formulations, no standardized test procedures (e.g., USP methods) for parenteral microsphere products.
  - The process of establishing release method and acceptance criteria is complicated.
- **Challenging to correlate in vitro drug release with in vivo pharmacokinetics**



DeYoung MB et. al. Diabetes Technol Ther. 2011 Nov;13(11):1145-54 http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM399483.pdf

# GDUFA research

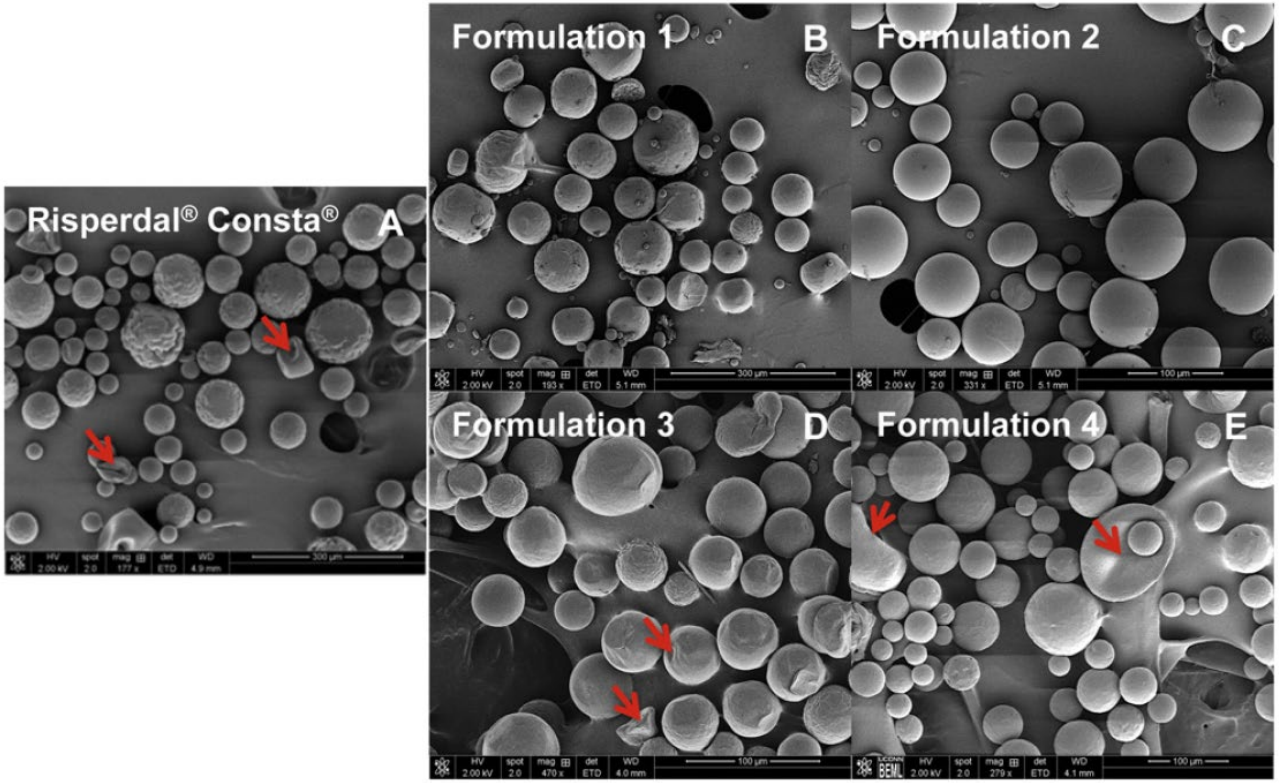
Since 2013, FDA/OGD has funded **9** grants/contracts for development and characterization of PLA/PLGA-based generic drug products:

- Characterizations of PLGA polymers and PLGA based microspheres and implants
- IVIVC
- Modeling and simulation

# IVIVC of risperidone microspheres

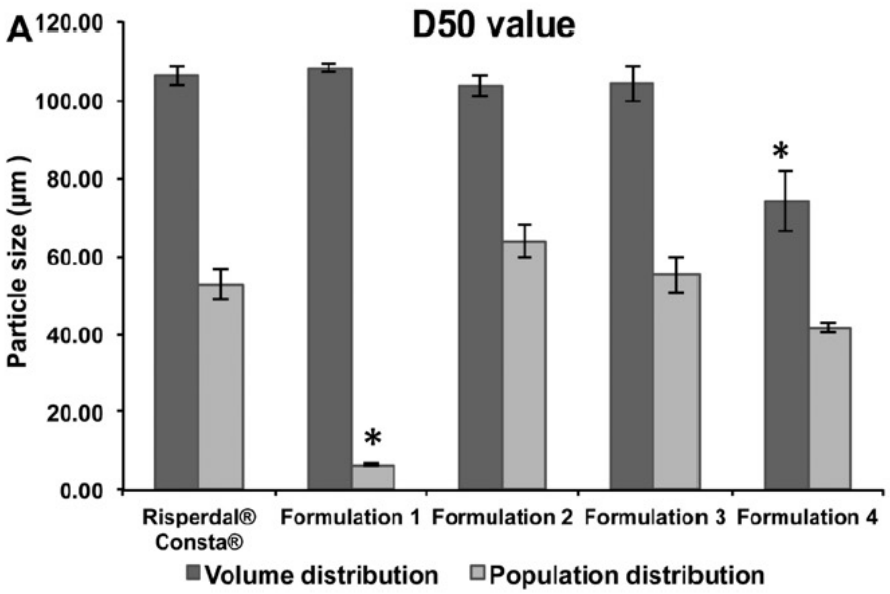
- Q1/Q2 formulations:
  - Similar PLGA as that used in Risperdal® Consta®
  - Different manufacturing processes (homogenization, vortex mixing, solvents) resulted in different physicochemical properties (porosity, particle size)
- Two release methods investigated:
  - USP Apparatus II (Sample-and separate)
  - USP Apparatus IV
- Level A IVIVCs established in rabbits based on USP Apparatus IV data

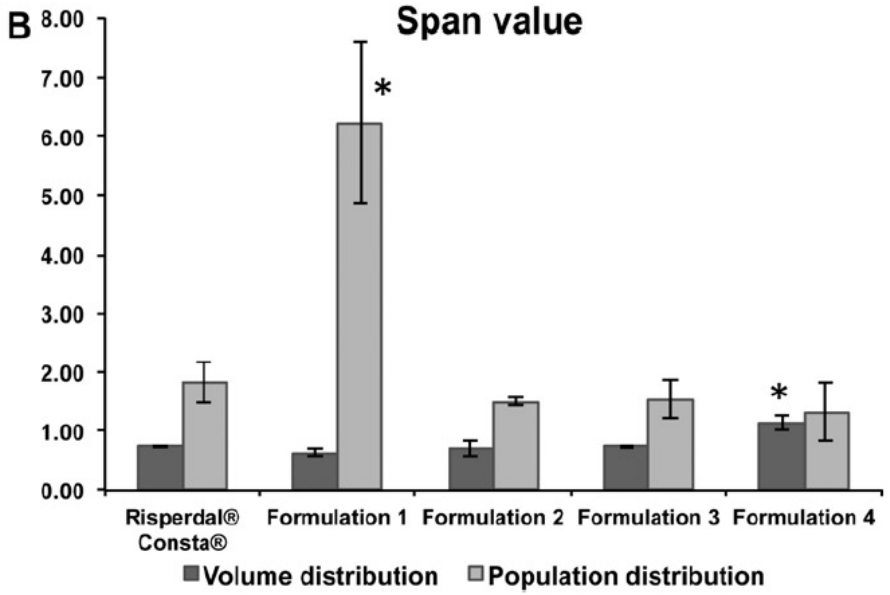
Shen J, et al. J Control Release. 2015 Nov 28;218:2-12
Shen J, et al. Int J Pharm. 2016 Feb 10;498(1-2):274-82




| Sample | Solvent | Preparation method | Porosity (%) |
|---|---|---|---|
| Risperdal Consta | -- | -- | 43.97 ± 4.60 |
| F1 | DCM | Homogenization & dry sieving | 43.19 ± 4.60 |
| F2 | DCM | Homogenization & wet sieving | 46.04 ± 42.90 |
| F3 | EA | Vortex & wet sieving | 54.98 ± 1.25 |
| F4 | EA | Homogenization & wet sieving | 61.75 ± 1.08 |

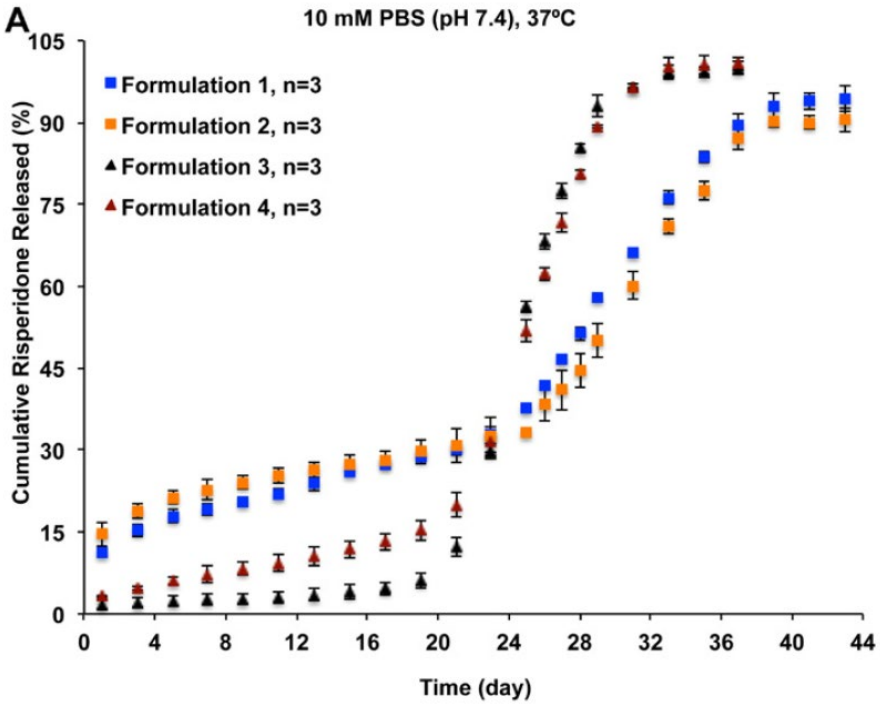
# Particle size distribution



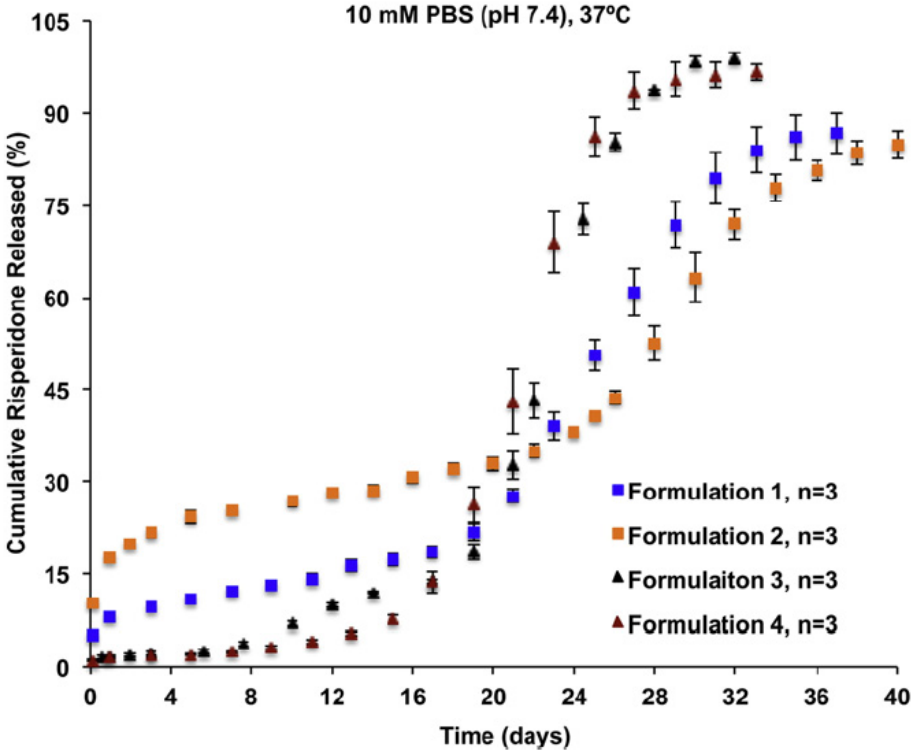



# In vitro release profiles

USP Apparatus II Sample and separate

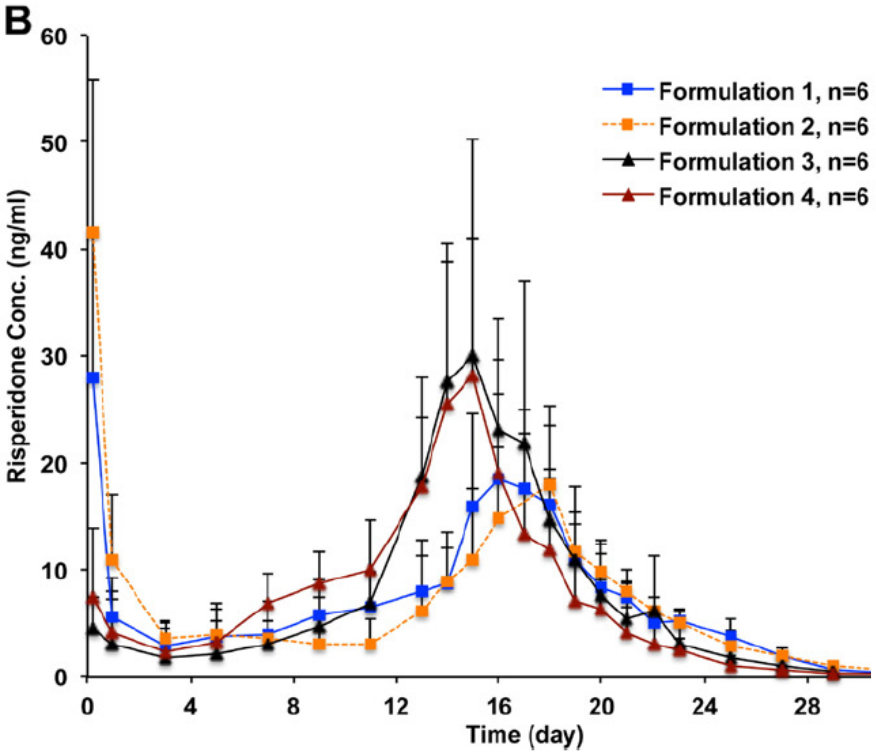



USP Apparatus IV Flow through cell

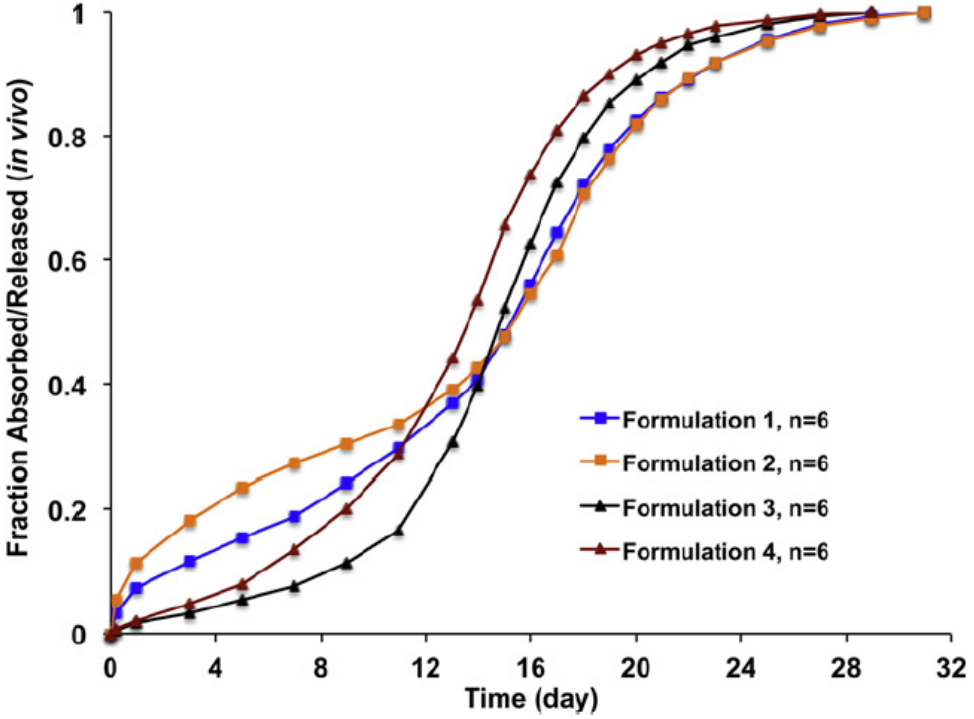


# In vivo release profiles

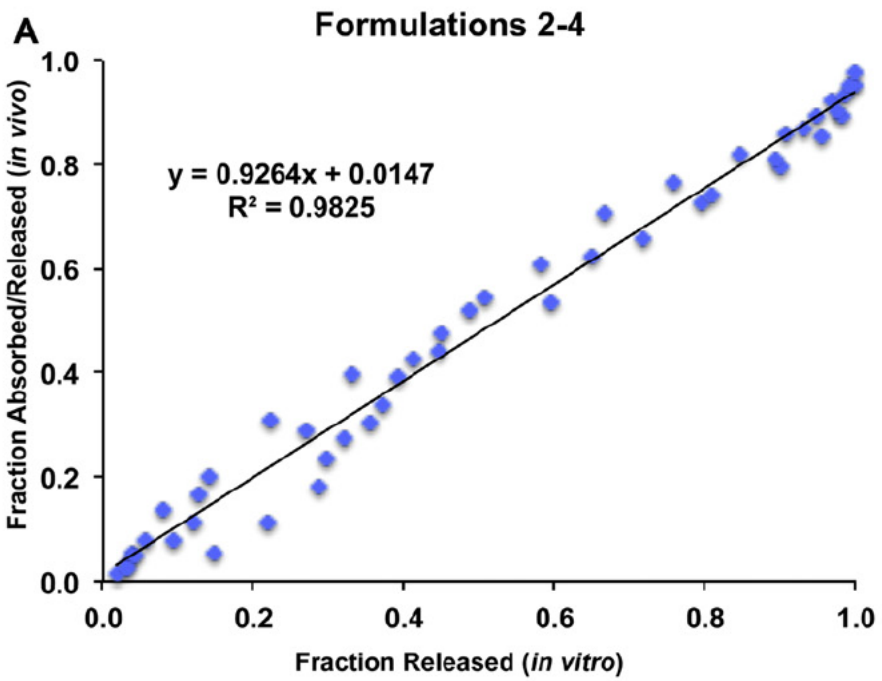
## In vivo PK profile

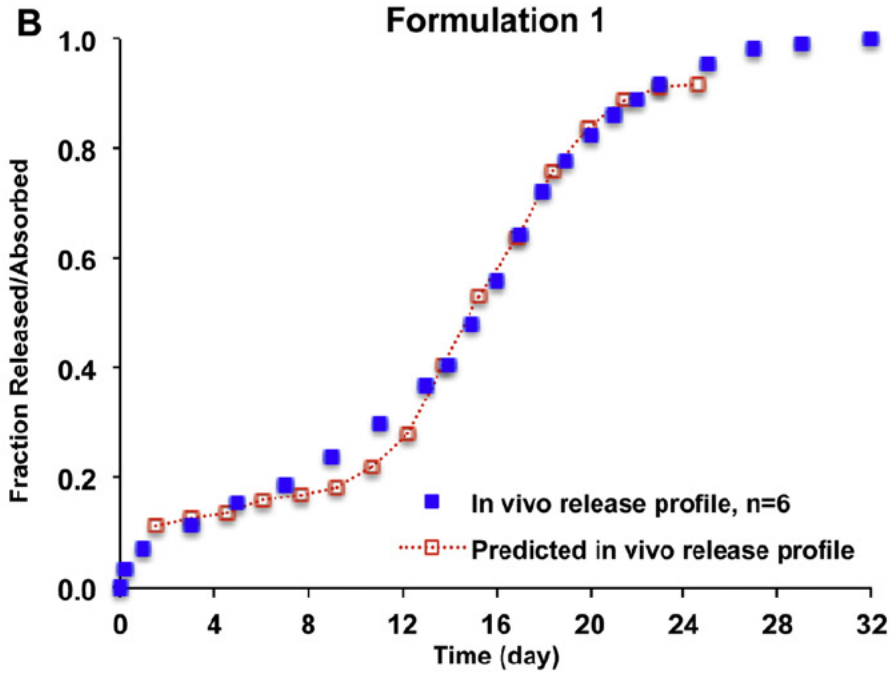



## Deconvoluted in vivo profiles



# Level A IVIVC

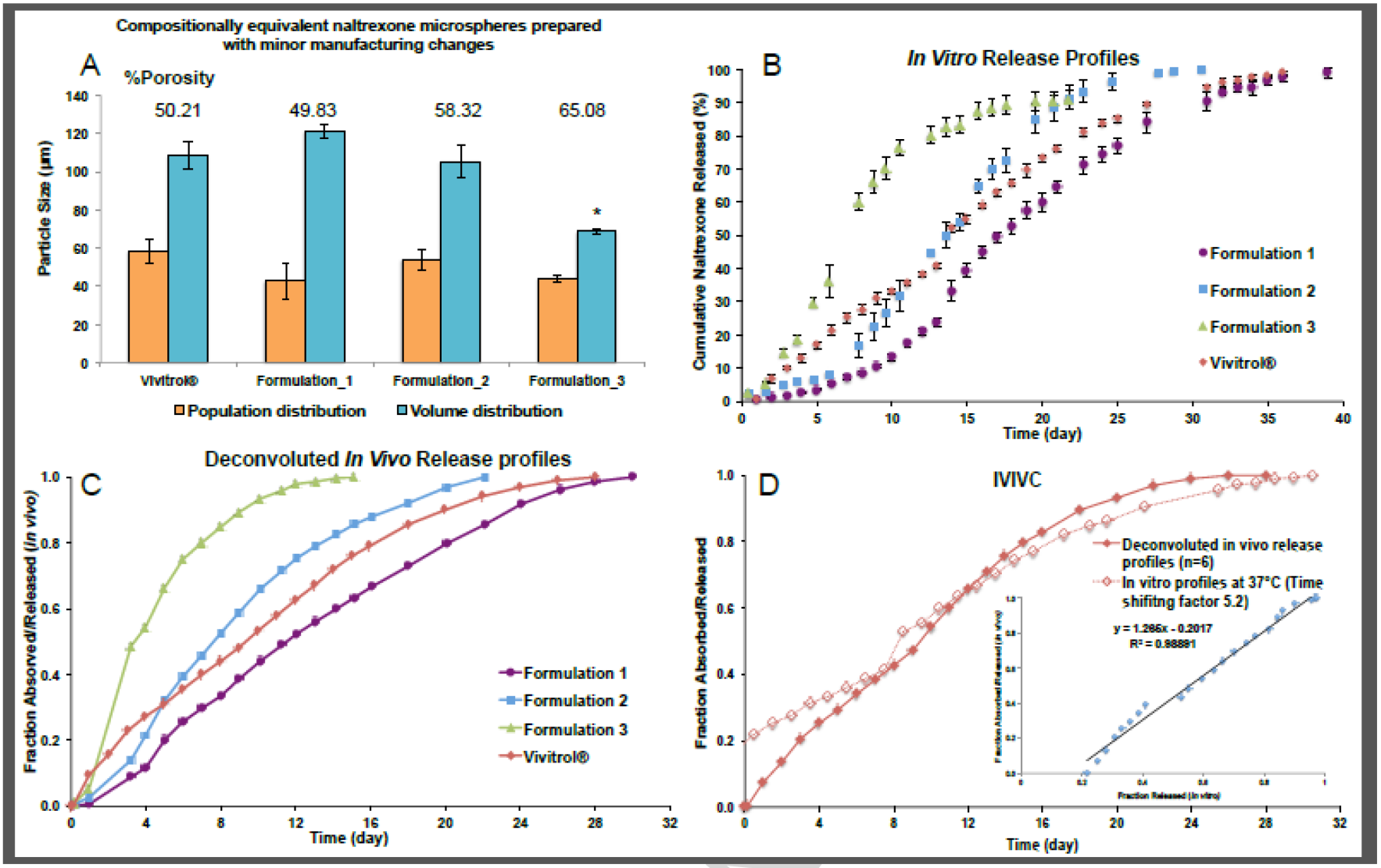


# Validation and prediction of IVIVC

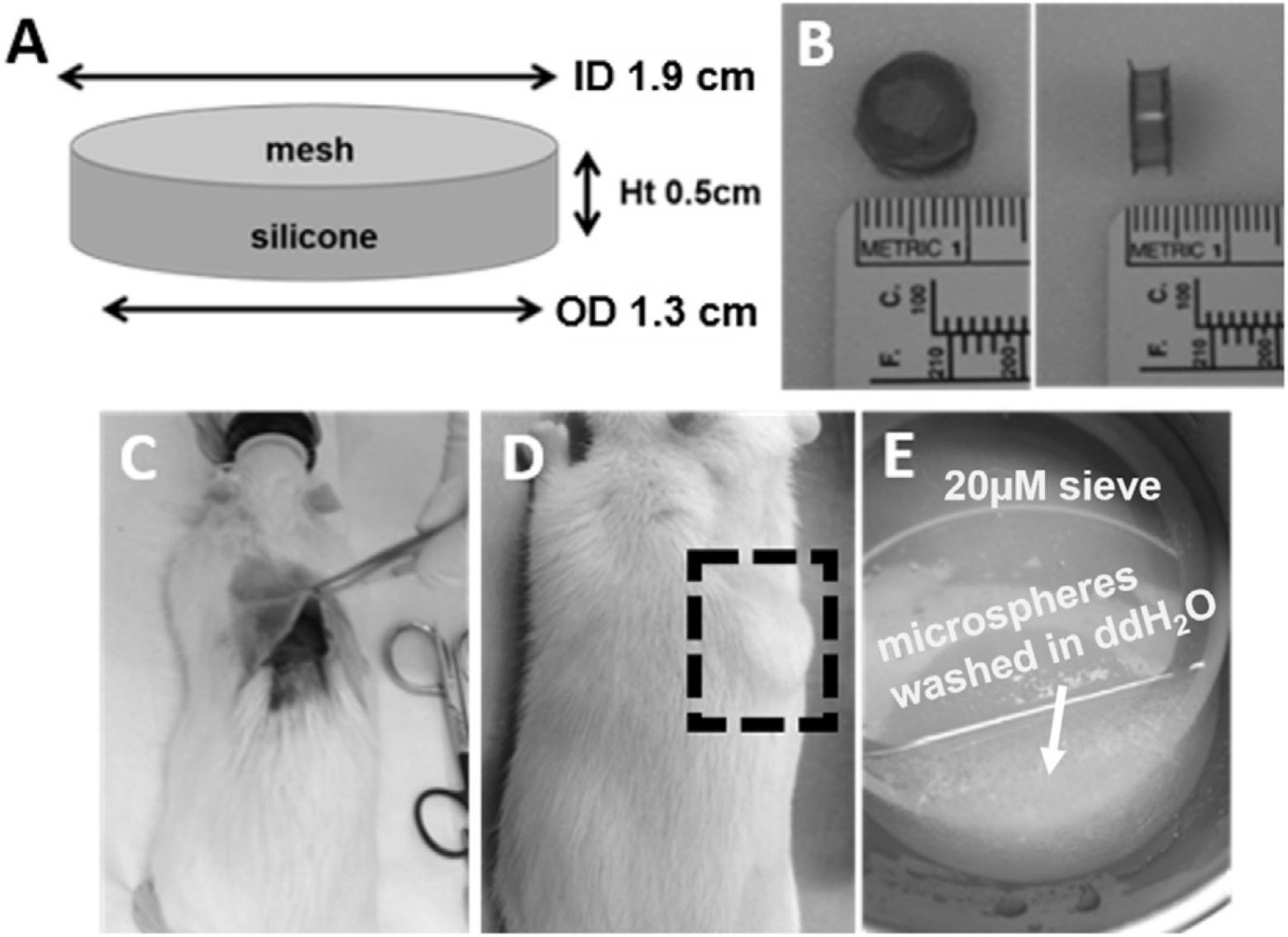
| | $C_{max}$ (μg/L) | | | AUC (μg/L * day) | | |
|---|---|---|---|---|---|---|
| | Pred. | Obs. | %PE | Pred. | Obs. | %PE |
| *Internal validation* | | | | | | |
| Formulation 2 | 19.64 | 41.62 | −52.81 | 188.26 | 200.41 | −6.06 |
| Formulation 3 | 40.49 | 29.98 | 35.06 | 219.14 | 229.07 | −4.34 |
| 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 |

# Level A IVIVC of naltrexone microspheres



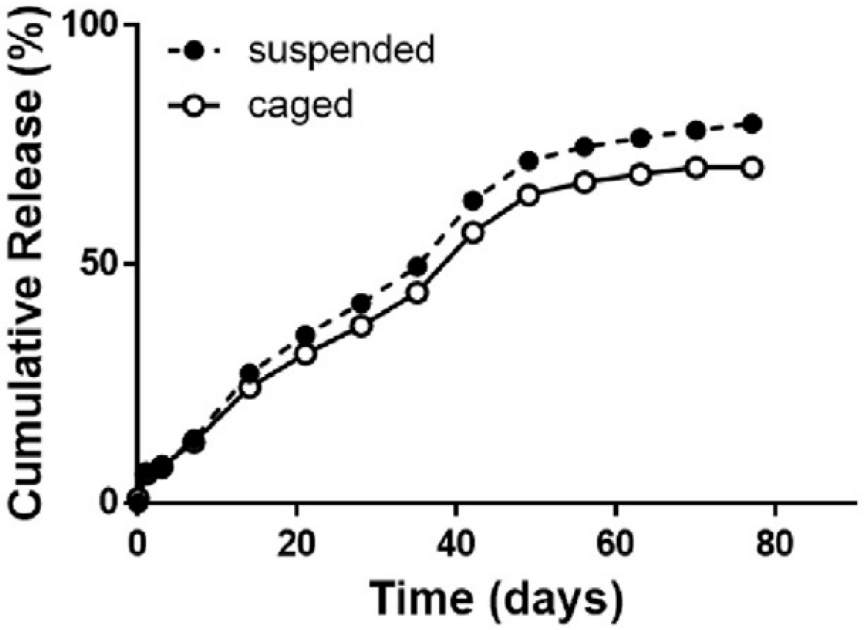

Andhariya J, et al. J Control Release. 2017 June 10;255:27-35

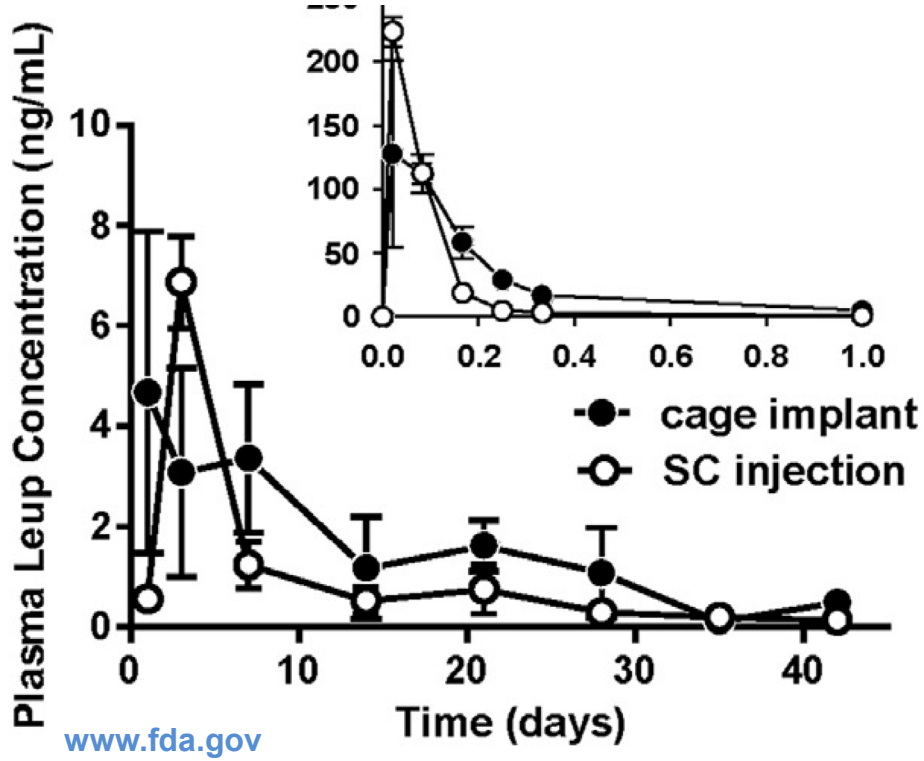
# Cage model to assess in vivo release

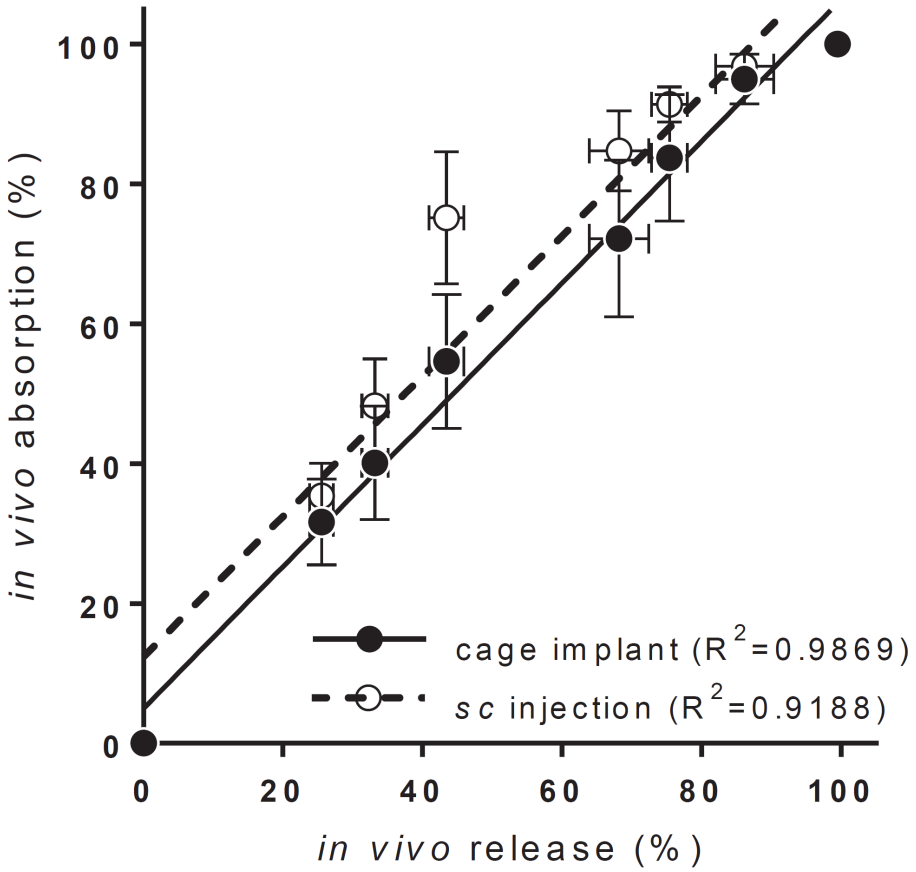





Doty AC, et al. Biomaterials. 2016 Dec;109:88-96

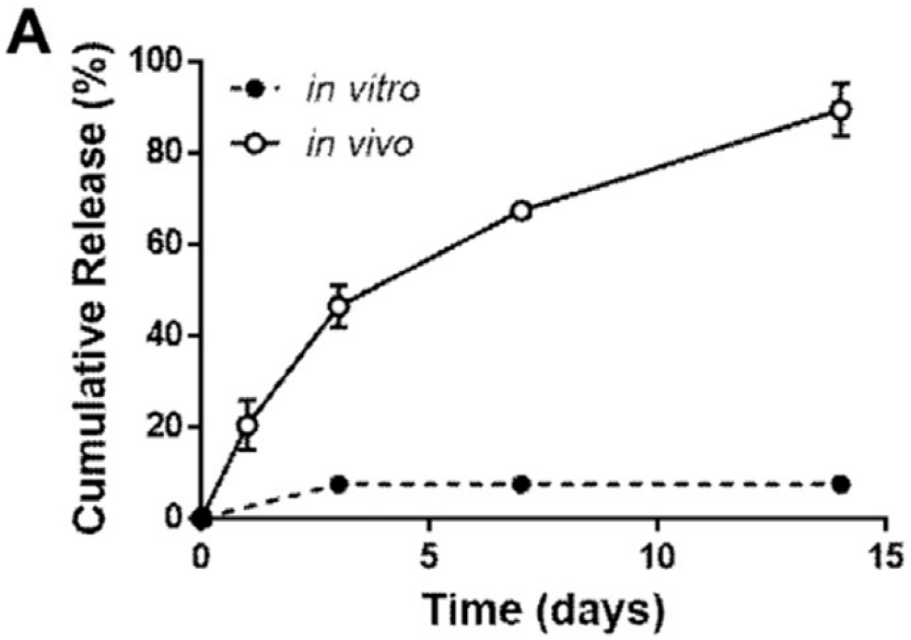

Cumulative Release (%)
100
50
0
suspended
caged
0
20
40
60
80
Time (days)


Plasma Leup Concentration (ng/mL)
10
8
6
4
2
0
200
150
100
50
0
0.0
0.2
0.4
0.6
0.8
1.0
cage implant
SC injection
0
10
20
30
40
Time (days)

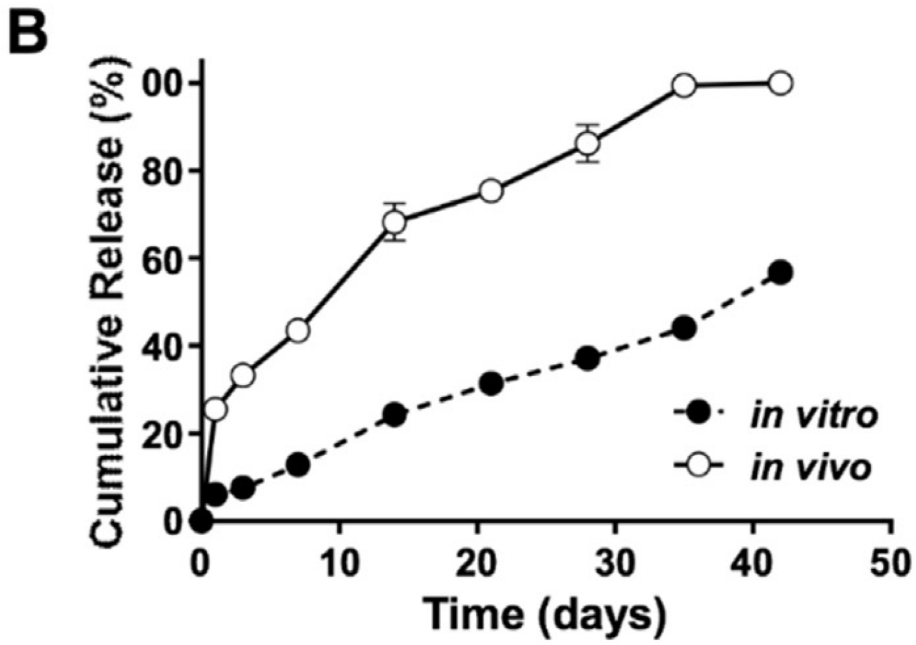

in vivo absorption (%)
100
80
60
40
20
0
cage implant (R2=0.9869)
sc injection (R2=0.9188)
0
20
40
60
80
100
in vivo release (%)

# Understanding release mechanisms of drug from PLGA microspheres

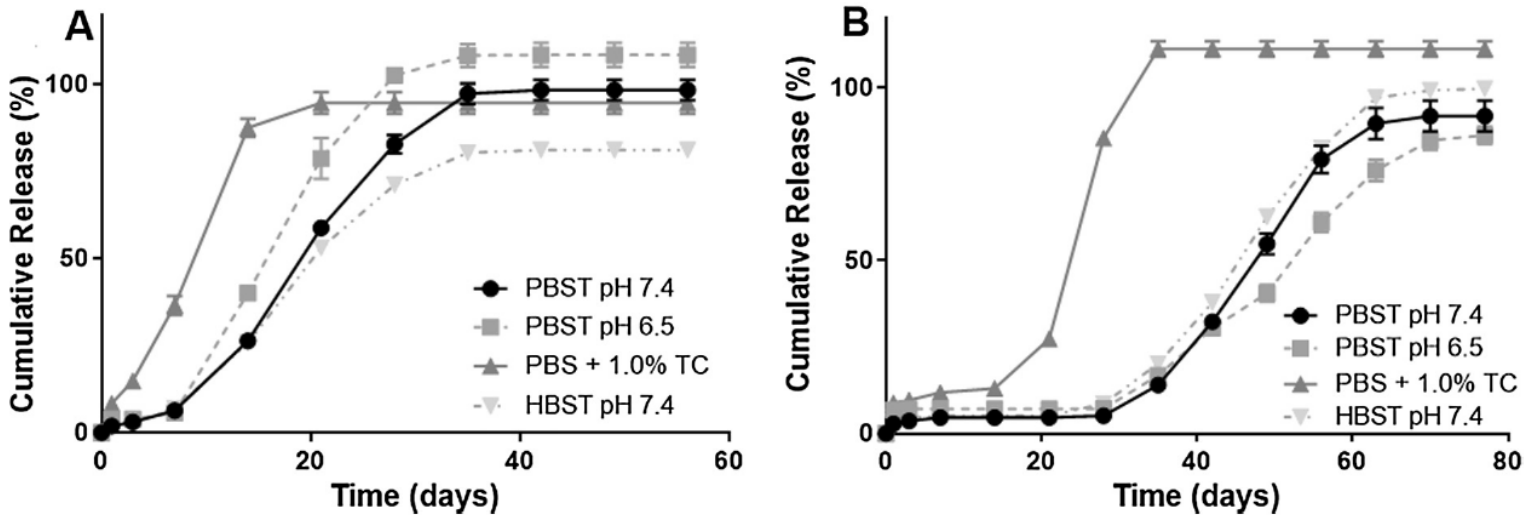
Triamcinolone-loaded microspheres




Leuprolide-loaded microspheres



# Understanding release mechanisms of Tr-A from PLGA microspheres

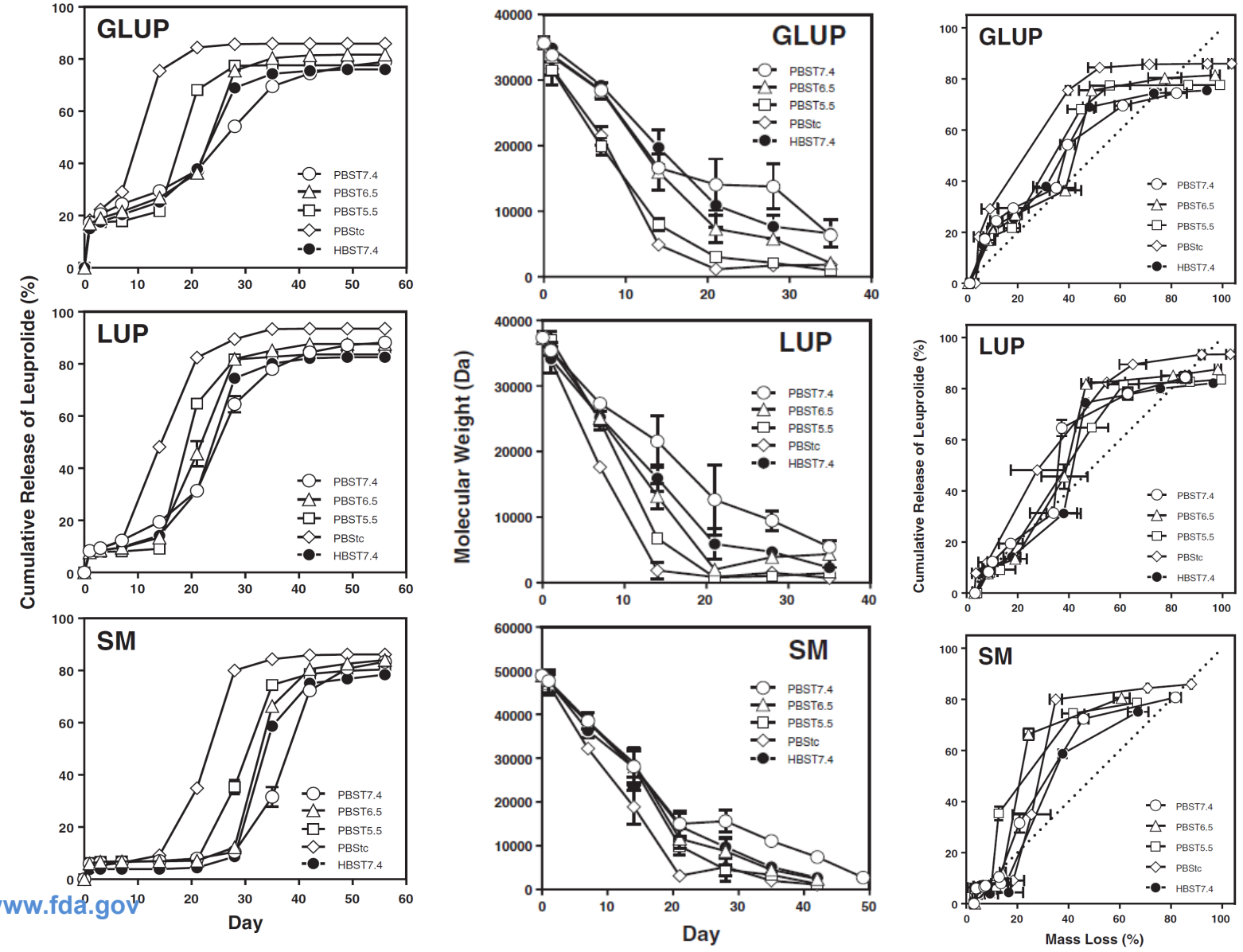



Characteristic times (in days) of release and erosion from Tr-A_1 and Tr-A_2 microspheres. Values represent mean ± SEM, n = 3.$T_{50}$ ratios were calculated from mean values of $t_{50}$release and $t_{50}$mass loss in each media.

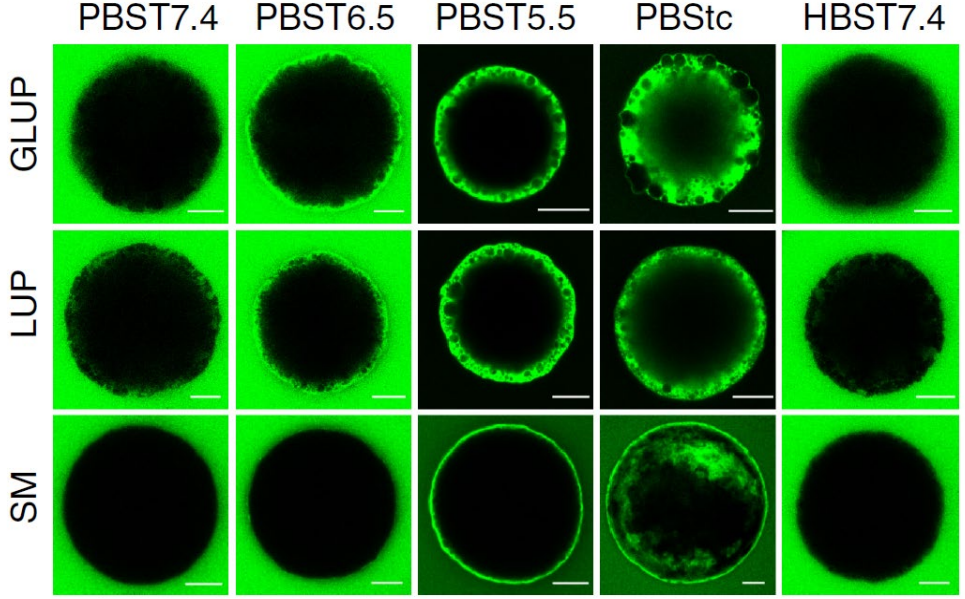
| | | PBST pH 7.4 | PBST pH 6.5 | PBS + 1.0% TC | HBST pH 7.4 |
|---|---|---|---|---|---|
| Tr-A_1 | $t_{50,release}$ | 19.0 ± 0.4 | 16.6 ± 0.4 | 8.0 ± 0.4* | 17.6 ± 0.2 |
| | $t_{50,erosion}$ | 25 ± 8 | 18.6 ± 0.8 | 15 ± 1 | 18 ± 2 |
| | $t_{50,release}/t_{50,erosion}$ | **0.77** | **0.89** | **0.52** | **0.96** |
| Tr-A_2 | $t_{50,release}$ | 46.8 ± 0.6 | 50.1 ± 0.8 | 25.0 ± 0.3* | 46.1 ± 0.3 |
| | $t_{50,erosion}$ | 46 ± 3 | 39 ± 2 | 18 ± 2*† | 43 ± 2 |
| | $t_{50,release}/t_{50,erosion}$ | **1.02** | **1.28** | **1.43** | **1.06** |

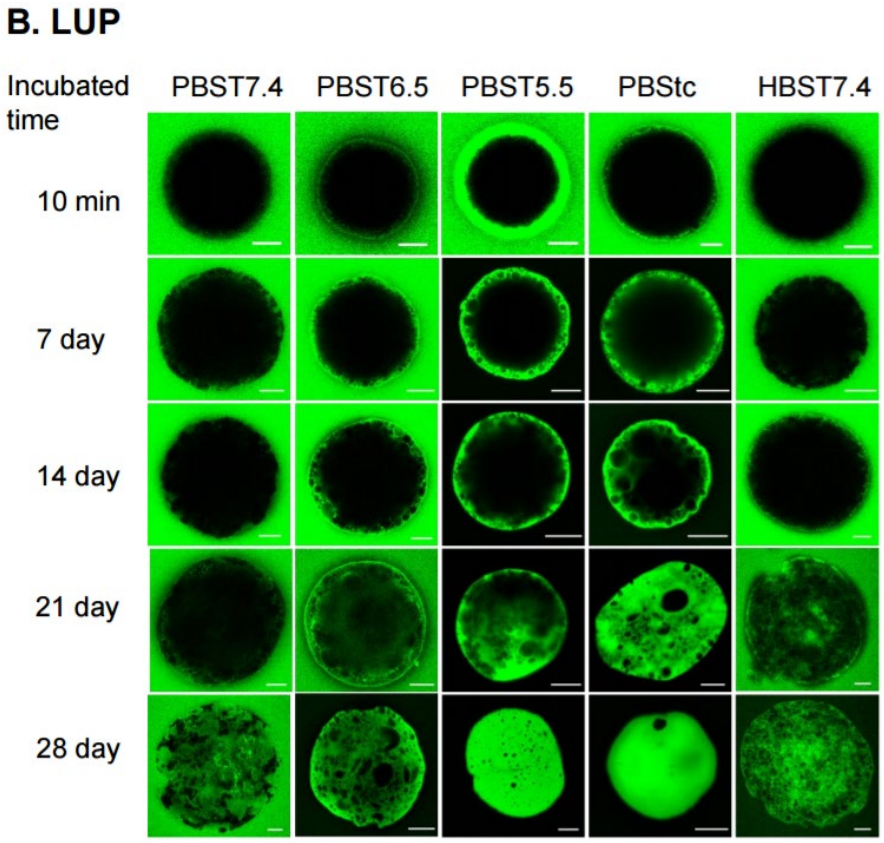
* $p < 0.05$ compared to PBST pH 7.4.
† linear regression was used.

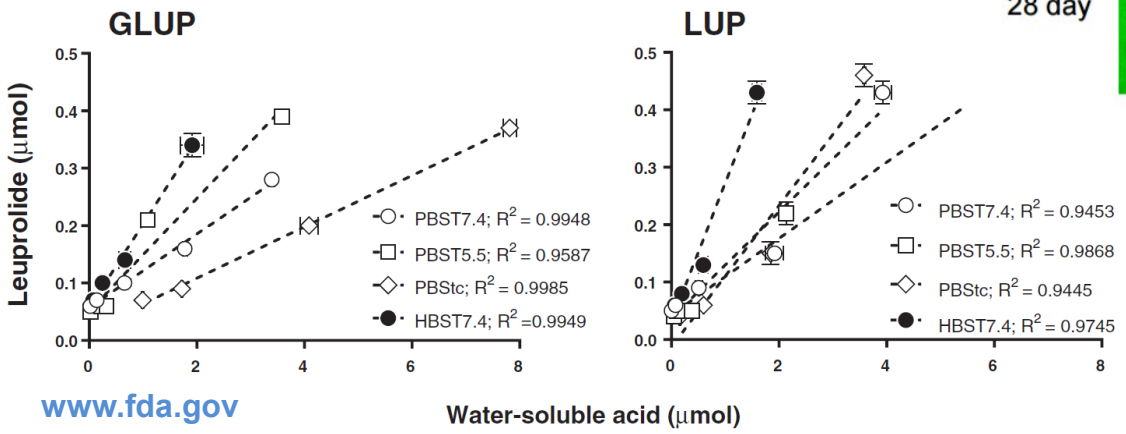
# Understanding release mechanisms of Leuprolide from PLGA microspheres



# Understanding release mechanisms of Leuprolide from PLGA microspheres



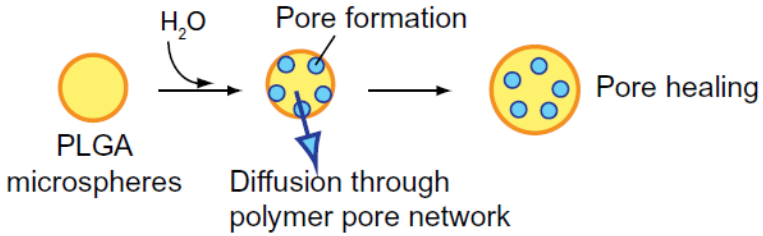




Hirota K, et al.
J Control Release. 2016 Aug 24.
pii: S0168-3659(16)30550-8

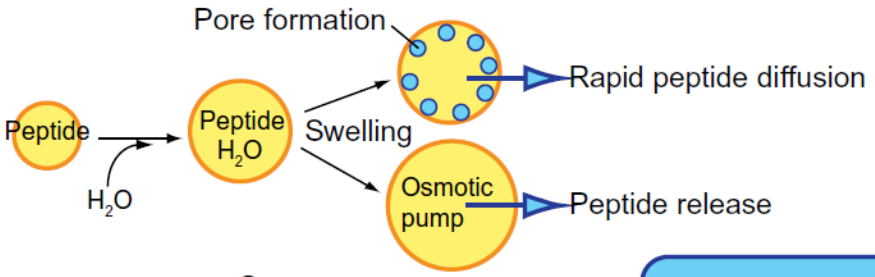
## Release mechanisms

1. Erosion (mass loss)

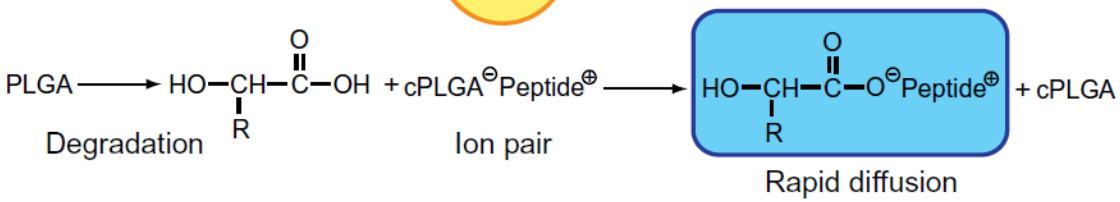

2. Diffusion/pore healing (early phase)




3. Water-mediated

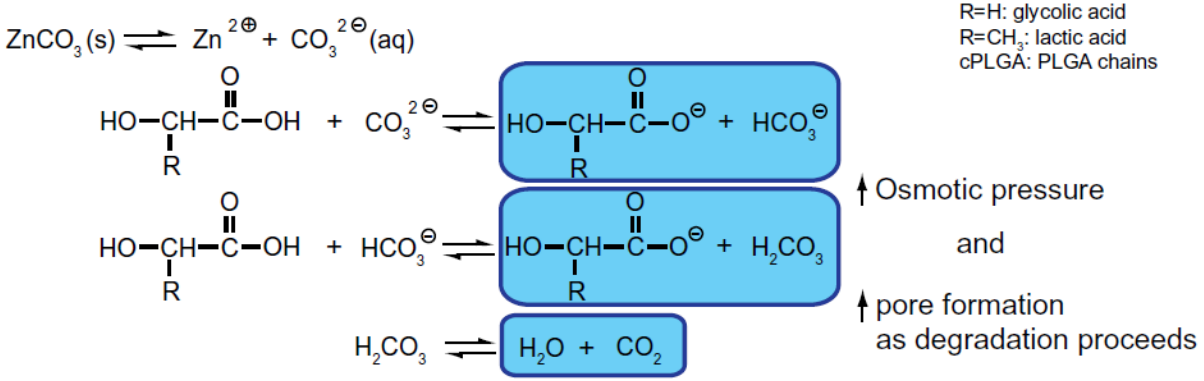



4. Desorption



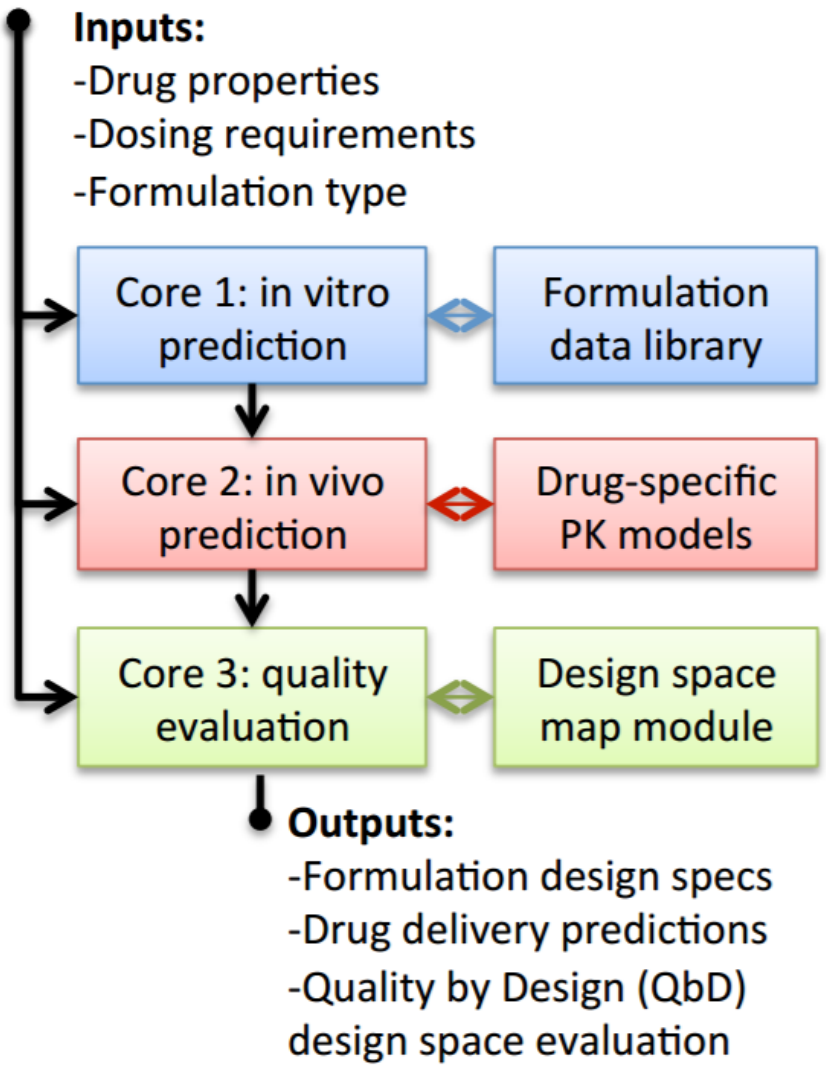

R=H: glycolic acid
R=$CH_3$: lactic acid
cPLGA: PLGA chains

5. Poorly soluble basee-induced pore formation (specific for SM)



# QronoMetrics

- Predictive software for design and development of biodegradable polymer drug products
- To develop a predictive mathematical model linking dissolution and PK profiles directly to critical quality attributes



# Conclusions

- Understanding of PLGA properties is key for successful development of PLGA based LAI products
- Level A IVIVCs have been successfully developed for Q1/Q2 risperidone PLGA microspheres and Q1/Q2 naltrexone PLGA microspheres in an animal model
- A cage model has been validated to assess in vivo performance of microspheres
- Two model drugs have been tested in in vitro studies for further understanding of the mechanisms of drug release from PLGA microspheres
- Study results can be used to inform recommendations for product-specific guidances, pre-ANDA meeting requests, and Controlled Correspondences

# Acknowledgements

**FDA:**

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Xiaohui Jiang

Markham Luke

Robert Lionberger

**University of Connecticut:** Diane Burgess

**University of Michigan:** Steven Schwendeman

**Akina Inc.:** Kinam Park

**Qrono Inc.:** Sam Rothstein

# Questions?

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