Development of Generic Long Acting Injectables: Regulatory Challenges and Considerations

Yan Wang
Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs

2018 CRS Annual Meeting, NYC

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 Generic Drug User Fee Amendments (GDUFA) regulatory science program to support development of generic LAI drug products
- Conclusions

Long Acting Injectable Formulations

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

Drug	Brand name	Dosing freq.	Indication
Haloperidol decanoate	Haloperidol decanoate	4 weeks	Schizophrenia
Paliperidone palmitate	Invega Sustenna	4 weeks	Schizophrenia
Riperidone	Risperdal Consta	2 weeks	Schizophrenia
Octreotide	Sandostatin LAR depot	4 weeks	Acromegaly
Bupivacaine	Exparel	Single dose, 3 days	Pain Control

Challenges in LAIs 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
- …….

Challenges to Developing Generic LAIs

- Demonstration of qualitative (Q1) and quantitative (Q2) sameness of excipients prior to conduct of bioequivalence (BE) studies of 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.

PLGA-based LAIs (1 week ~ 6 months)

Poly(lactide-co-glycolide) (PLGA)

Lupron Depot®
leuprolide acetate for depot suspension
1-4 months MP 1989
7.5 mg/month

Zoladex 3-MONTH 10.8 mg DEPOT
GOSERELIN ACETATE IMPLANT
1, 3 months SI 1989
3.6 mg/month

Sandostatin LAR® Depot
(octreotide acetate for injectable suspension)
1 month MP 1998
20 mg/month

ATRIDOX®
(doxycycline hyclate) 10%
1 week, IS 1998
50 mg/week

Nutropin DEPOT®
(somatropin (rDNA origin) for injectable suspension)
1 month MP 1999
13.5 mg/month

TRELSTAR®
(triptorelin pamoate for injectable suspension)
1 month MP 2000
3.75 mg/month

Buserelin acetate
2, 3 months SI 2000
6.3 mg/2 months

Somatuline® Depot
(lanreotide) Injection
1 month MP 2000
60 mg/month

Arestin®
minocycline HCl 1mg
MICROSPHERES
2 weeks MP 2001
1 mg/2 weeks

Risperdal CONSTA®
risperidone Long-Acting Injection
2 weeks MP 2003
25 mg/2 weeks

Eligard®
(leuprolide acetate for injectable suspension)
1,3,4,6 months IS 2004
7.5 mg/month

Vivitrol®
(naltrexone for extended-release injectable suspension)
1 month MP 2006
380 mg/month

Ozurdex®
(dexamethasone intravitreal implant) 0.7 mg
3 months SI 2009
0.7 mg/3 months

TRELSTAR®
(triptorelin pamoate for injectable suspension)
6 months MP 2010
3.75 mg/month

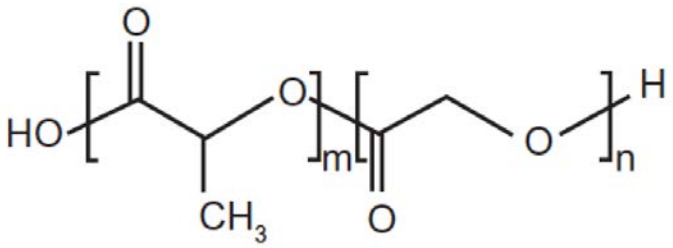
Once-weekly
BYDUREON®
exenatide extended-release for injectable suspension
His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2
1 week MP 2012
2 mg/week

Lupaneta Pack™
leuprolide acetate for depot suspension, 11.25 mg for intramuscular injection and norethindrone acetate tablets, 5 mg for oral administration
3 month, MP 2012
3.75 mg/month

Signifor® LAR
(pasireotide) for injectable suspension
1 month, MP 2014
20, 40, or 60 mg/month

Challenges for PLGA Based Products

- Complex inactive ingredients
  - **Poly(lactic-*co*-glycolic acid) (PLGA) copolymer**

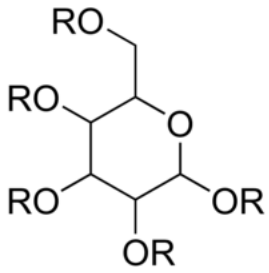


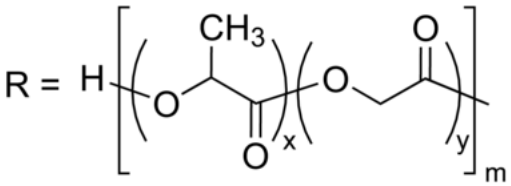
PLGA

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

- Ratio of lactic acid to glycolic acid
- Molecular weight ~5kDa -100kDa

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

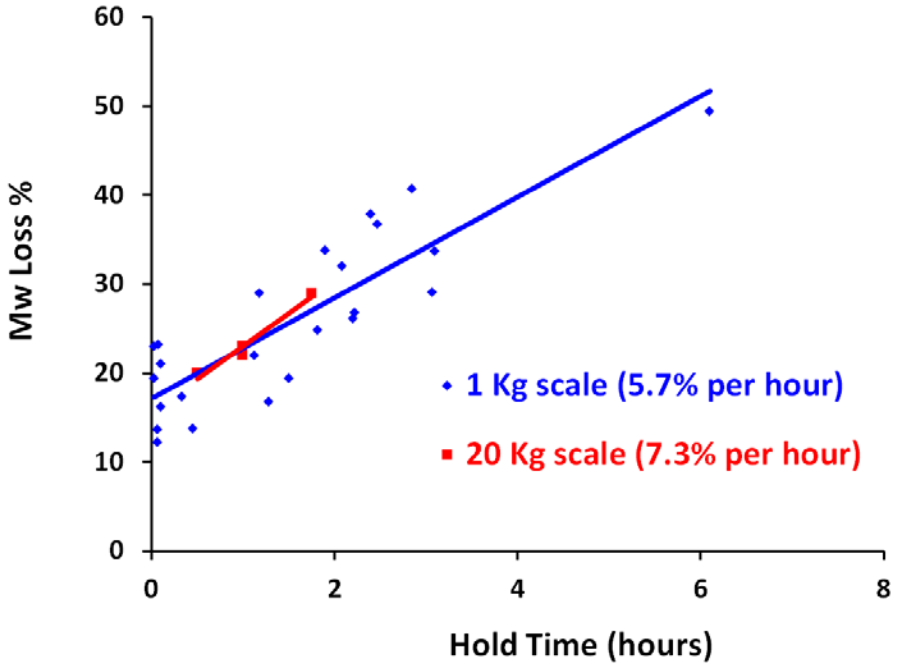




Sandostatin LAR depot
(octreotide acetate microsphere)

Challenges for PLGA Based Products (Cont.)

- Impact of manufacturing conditions on complex inactive ingredients (complex reverse engineering)

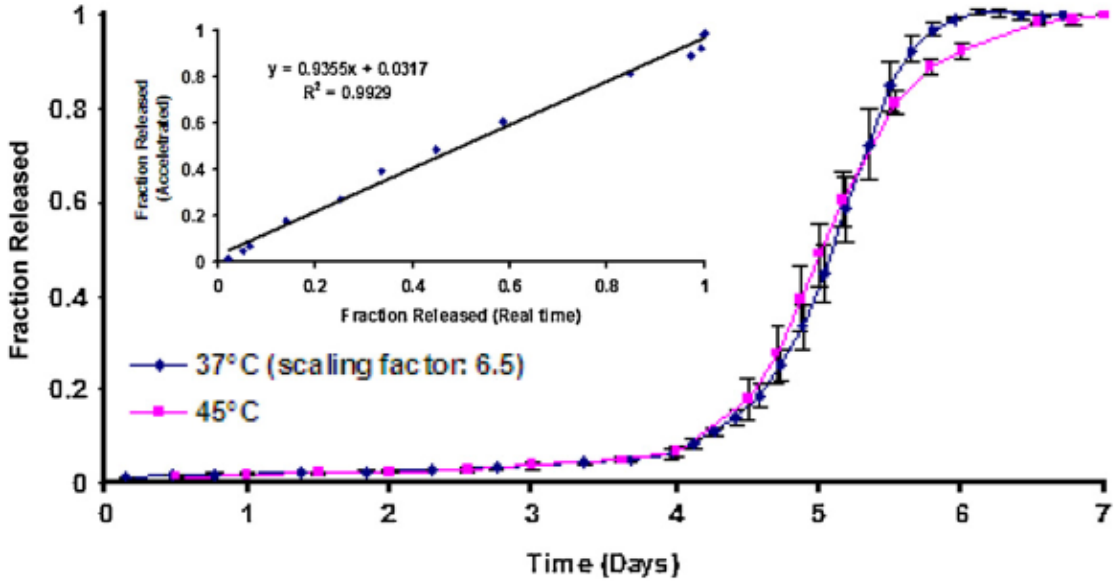


PLGA degradation during manufacturing of risperidone-PLGA microsphere

Alkermes, US 6,264,987 B1, 2001

Challenges for PLGA Based Products (Cont.)

- Complicated multi-phasic in vitro drug release profiles and in vivo pharmacokinetics profiles

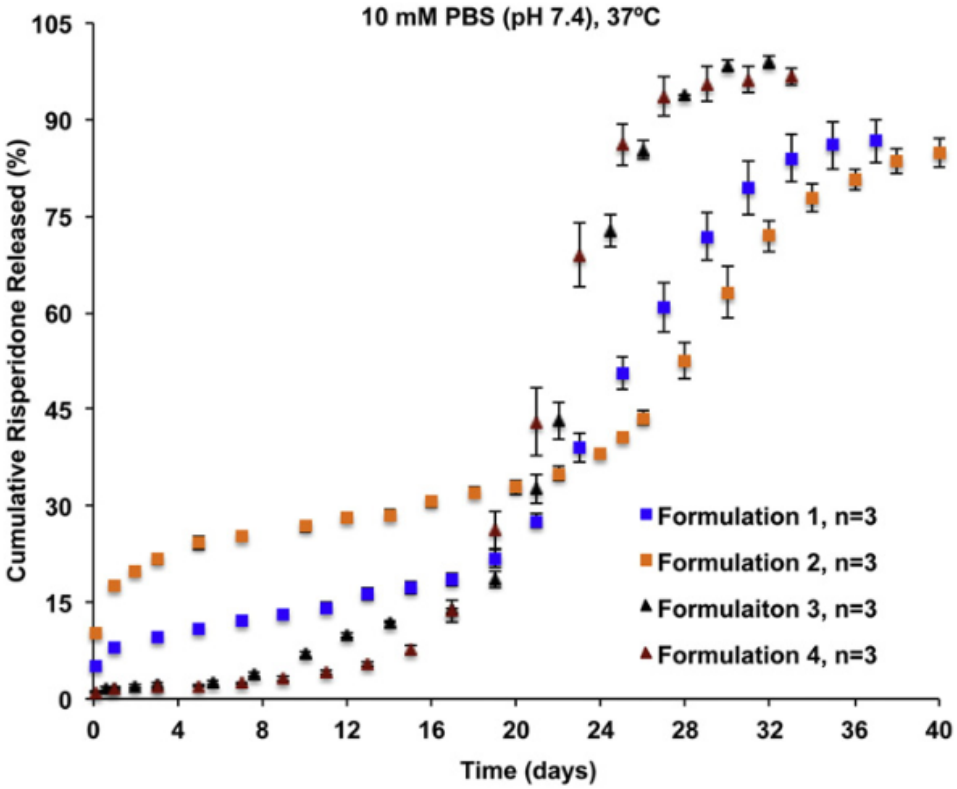


In vitro release profiles of Risperdal Consta 25 mg in 0.05 M PBS pH 7.4 at 37 °C and 45 °C

A. Rawat, U. Bhardwaj, D.J. Burgess. Comparison of in vitro–in vivo release of Risperdal® Consta® microspheres. (2012) Int J Pharm, 434(1-2), pp 115-121. http://dx.doi.org/10.1016/j.ijpharm.2012.05.006

Challenges for PLGA Based Products (Cont.)

- In vitro and in vivo drug release profiles are sensitive to manufacturing differences

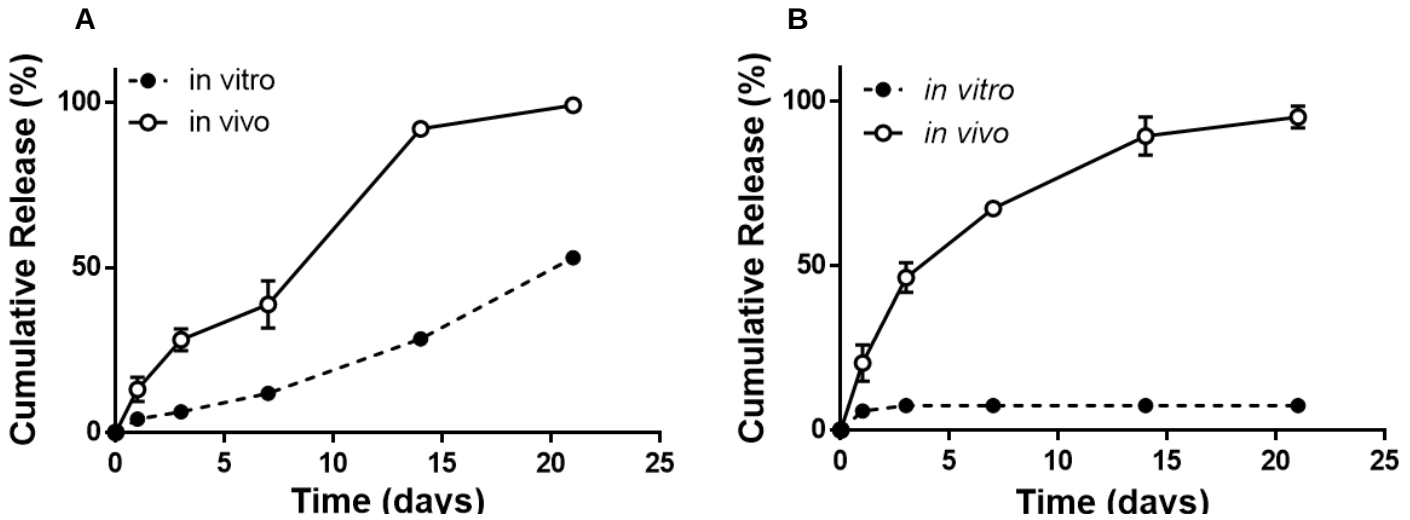


In vitro release profiles of the formulation composition equivalent risperidone microspheres with manufacturing differences obtained using USP apparatus 4 method at 37 °C in 10 mM PBS (pH 7.4)

J. Shen, S. Choi, W. Qu, Y. Wang, D.J. Burgess. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. (2015) Journal of Controlled Release. 218, pp. 2-12
http://dx.doi.org/10.1016/j.jconrel.2015.09.051

Challenges for PLGA Based Products (Cont.)

- Lack of compendial in vitro drug release testing methods, in vitro in vivo correlation, and complete understanding of drug release mechanisms



Contrasting in vitro and in vivo release from triamcinolone acetonide_1 (A) and triamcinolone acetonide_2 (B) microspheres.

Doty, A. C., Hirota, K., Olsen, K. F., Sakamoto, N., Wang, Y., Choi, S., Qu, W., Schwendeman, A. S. and Schwendeman, S. P., Validation of a cage implant for assessing in vivo performance of long-acting release microspheres, *Biomaterials*, 109, 88-96 (2016). http://ac.els-cdn.com/S0142961216303787/1-s2.0-S0142961216303787-main.pdf?_tid=9e506490-9caa-11e7-b96e-00000aab0f26&acdnat=1505764407_767d6cbf46bd78acfbbd0a00c9a8c685

Challenges for PLGA Based Products (Cont.)

- Complex BE study design, such as combination of in vitro and in vivo studies, or partial AUCs
  - Risperidone intramuscular injectable microspheres
    - In vitro drug release + In vivo, two period, crossover steady state in patients

- Duration of BE studies is much longer compared to conventional dosage forms, which results in potential high drop out rate
- Different strengths may require separate BE studies due to difference in formulation composition and release characteristics

GDUFA Research on LAIs

- GDUFA funded research on LAIs

1) To obtain a better understanding of the impact of properties of PLGA polymers on product performance;
2) To explore biorelevant in-vivo in-vitro corrections (IVIVCs) for biodegradable injectable PLGA microspheres;
3) To investigate dissolution methods for PLGA microsphere and implant drug products that can discriminate formulations with manufacturing differences;
4) To investigate potential peptide PLGA interactions during product manufacturing and use;
5) To develop modeling tools to facilitate development of generic LAI formulation development as well as bioequivalence guidances for LAI formulations;
6) To develop discriminatory and predictive real time and accelerated drug release methods for IUS;
7) To explore IVIVCs of long-acting periodontal drug products;
8) To investigate release mechanisms of multivesicular liposomes;
9) To explore IVIVCs of long-acting injectable suspensions

U.S. FOOD & DRUG ADMINISTRATION

Case I:

Characterization of PLGA Polymers

Establishment of Q1/Q2

The main challenge associated with establishment of Q1/Q2 sameness between the test and reference listed drug is the evaluation of Q1 sameness of PLA/PLGA.

PLA/PLGA are random copolymers with inherent heterogeneity and are available with various physicochemical properties which may vastly change product performance.

Establishment of Q1/Q2 (Cont.)

Some key physicochemical properties of PLA/PLGA include:

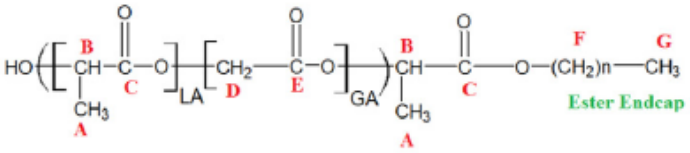
- Polymer composition (L to G ratio)
- Molecular weight and weight distribution
- Polymer architecture (linear vs star-shaped)
- Intrinsic viscosity
- Glass transition temperature
- Polymer end-cap
- Crystallinity

The key physicochemical properties of PLA/PLGA could be altered during manufacturing process.

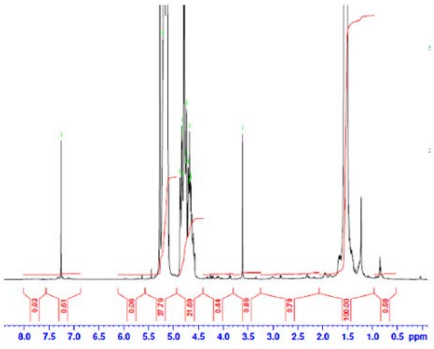
Methods of Characterizations

The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product for all strengths (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial). Please provide characterization data on poly(lactide-co-glycolide) (PLGA) for both the test and reference product including polymer composition (ratio between glycolic acid and lactic acid), molecular weight and weight distribution, and PLGA architecture (e.g., linear or star-branched PLGA). Additional data on PLGA characterization may be requested during the review of the ANDA.

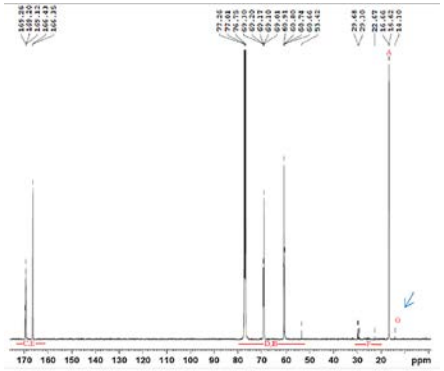
Molecular Weight: GPC



L:G Ratio: H-NMR



End Group: 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

Establishment of Q1/Q2 (Cont.)

Some key physicochemical properties of PLA/PLGA include:

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

The effect of each parameter on the product performance is product specific. Therefore, the key physicochemical properties that are necessary for evaluation of Q1 sameness is on a ***case-by-case basis***.

Establishment of Q1/Q2 (Cont.)

- The key physicochemical properties of PLA/PLGA could be altered during the manufacturing process. Therefore, in addition to the characteristics of the raw PLA/PLGA materials, it is critical to characterize PLA/PLGA using the finished product.

- The Q1/Q2 sameness of PLA/PLGA between the test and reference listed drug should be determined using the finished microspheres rather than the raw materials.

U.S. FOOD & DRUG ADMINISTRATION

Case II:

IVIVC of PLGA Microspheres

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

Compositionally Equivalent Risperidone Microspheres

- **Critical physicochemical properties of the prepared risperidone microspheres**

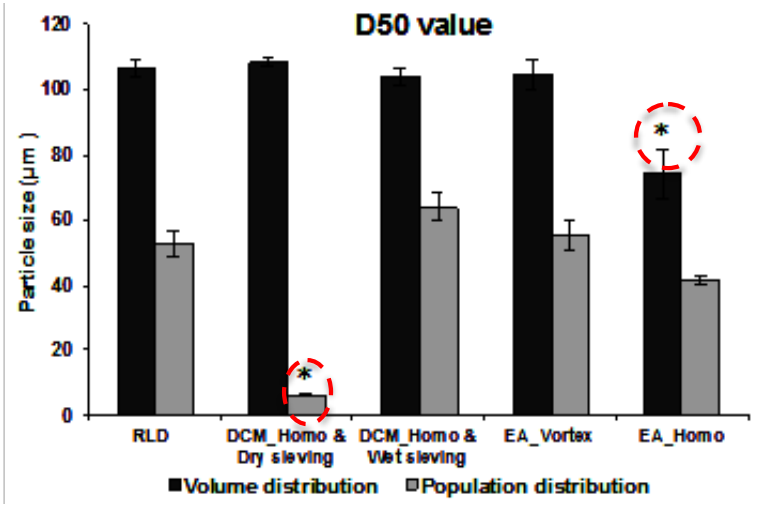
Table 1. Drug loading of the prepared risperidone microspheres.

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

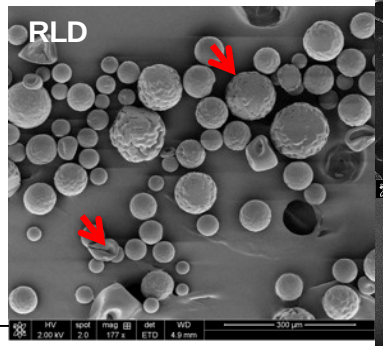
Shen J., Burgess D.J., *J. Control. Release, (2015)*

Case I: Compositionally Equivalent Risperidone Microspheres

- **Critical physicochemical properties of the prepared risperidone microspheres**



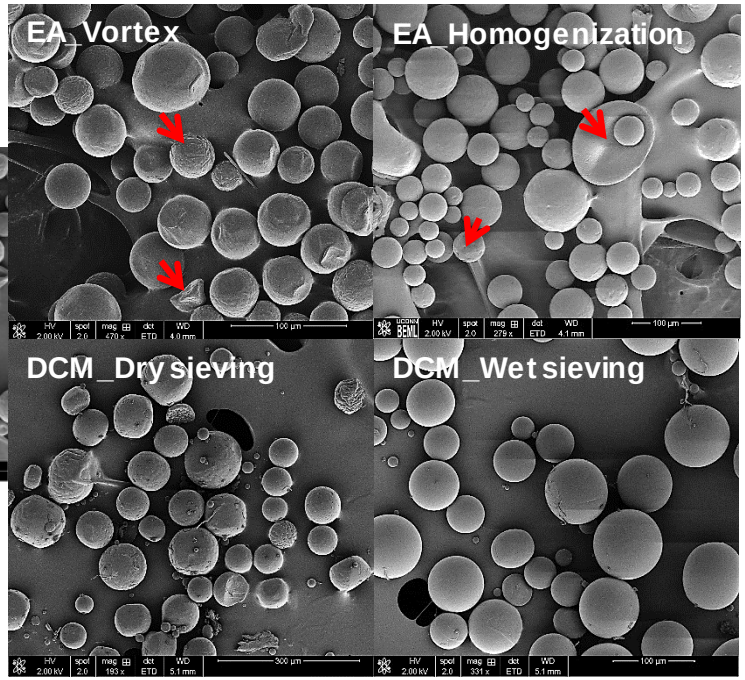
Sample	Solvent	Preparation Method
Risperdal® Consta®	-	-
Formulation_1	DCM	Homogenization & dry sieving
Formulation_2	DCM	Homogenization & wet sieving
Formulation_3	EA	Vortex & wet sieving
Formulation_4	EA	Homogenization & wet sieving



Porosity 43.97%

Porosity 54.98%

61.75%



Porosity 43.19%

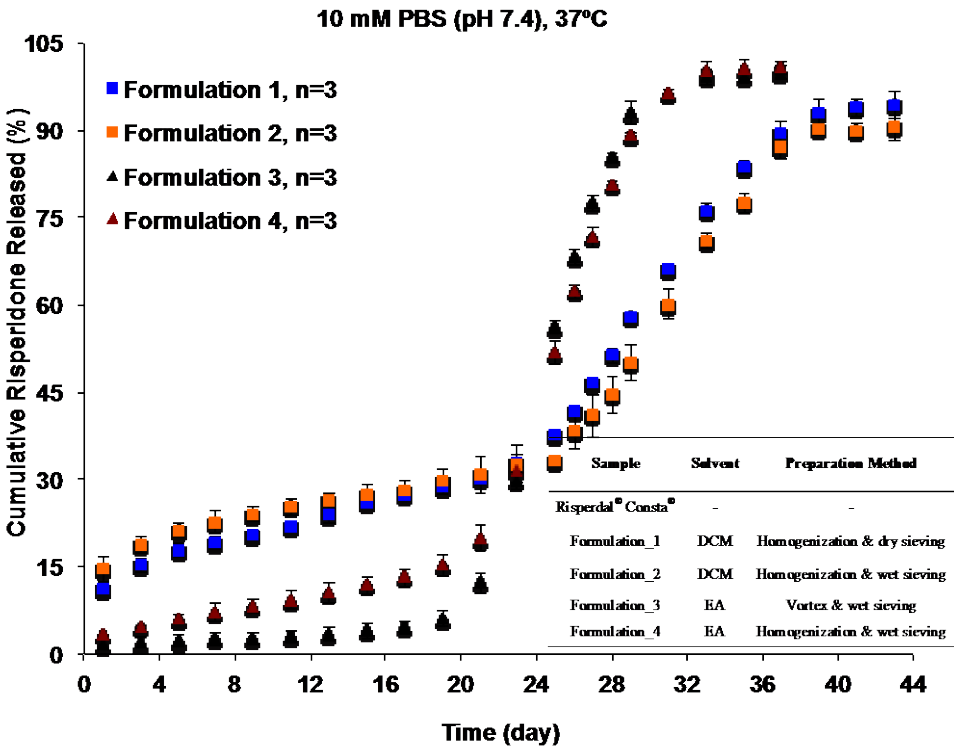
46.04%

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

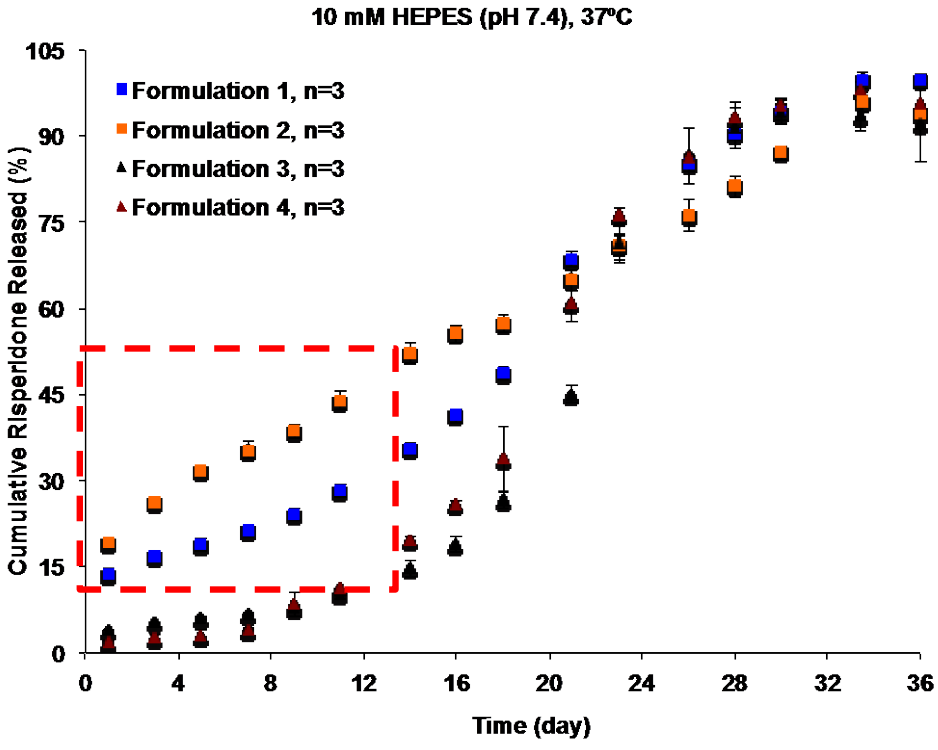
Case I: Compositionally Equivalent Risperidone Microspheres

- ***In vitro*** **release profiles of risperidone microspheres obtained using the sample-and-separate method**

Add surfactant (0.02% (v/v) Tween 20)



Sample	Solvent	Preparation Method
Risperdal® Consta®	-	-
Formulation_1	DCM	Homogenization & dry sieving
Formulation_2	DCM	Homogenization & wet sieving
Formulation_3	EA	Vortex & wet sieving
Formulation_4	EA	Homogenization & wet sieving

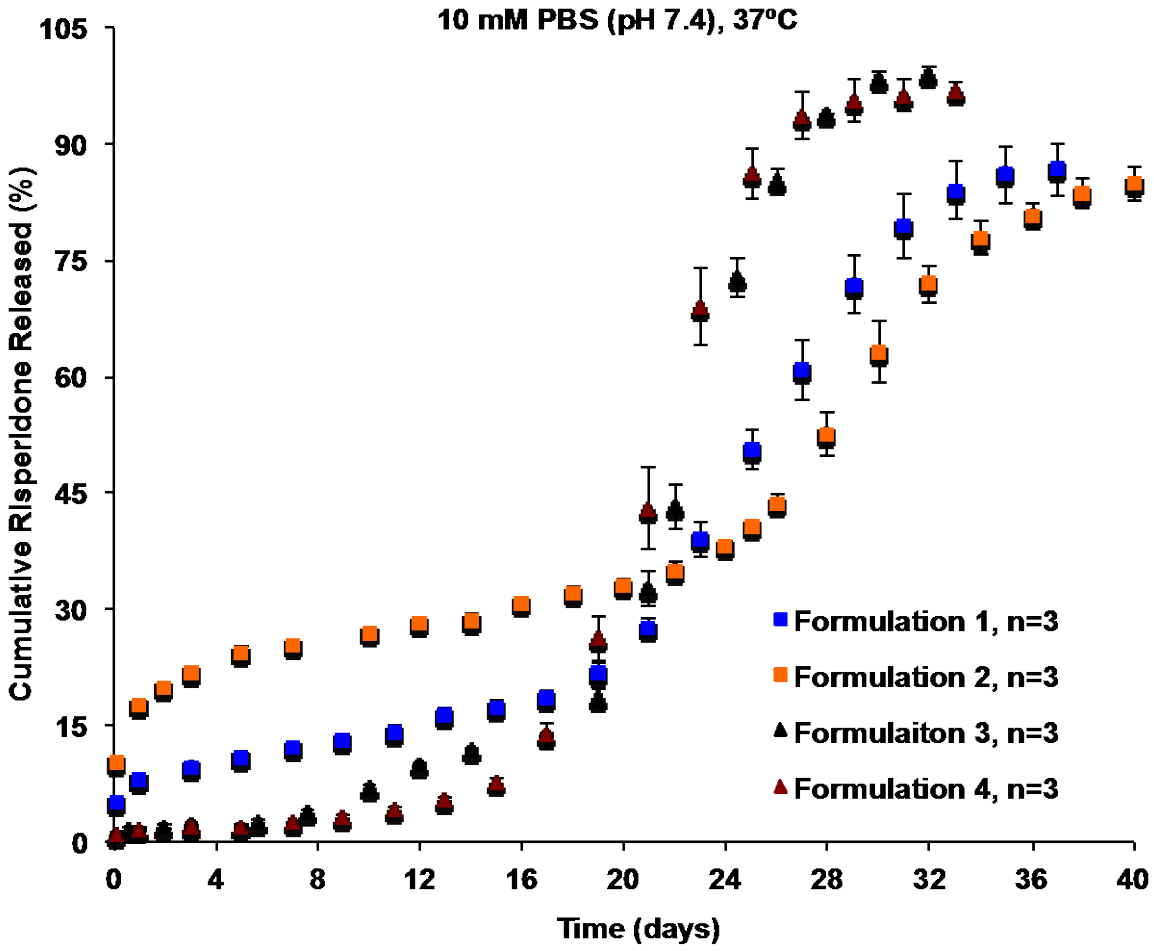


Microsphere aggregation was observed.

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

Case I: Compositionally Equivalent Risperidone Microspheres

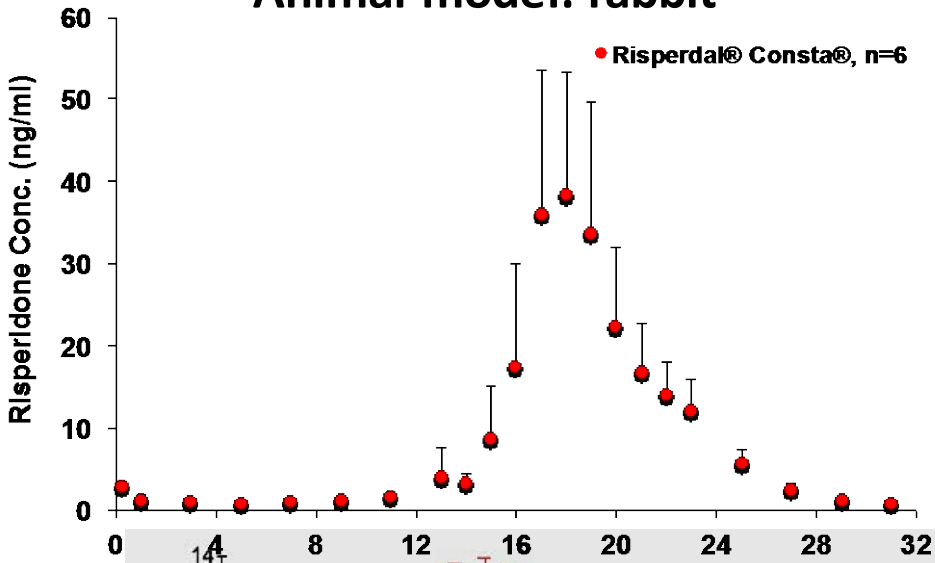
- ***In vitro*** **release profiles of risperidone microspheres obtained using the developed USP apparatus 4 method**

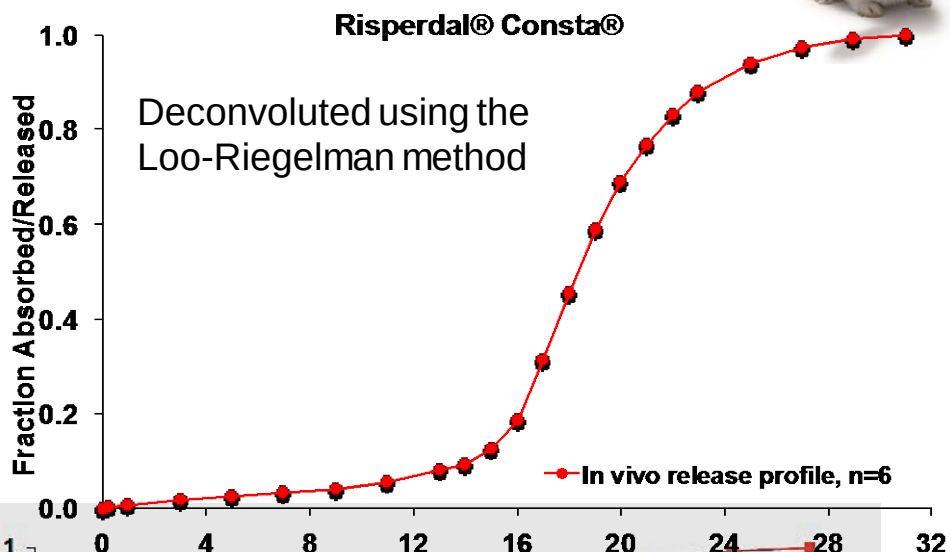


Shen J., Burgess D.J., *J. Control. Release, (2015)*

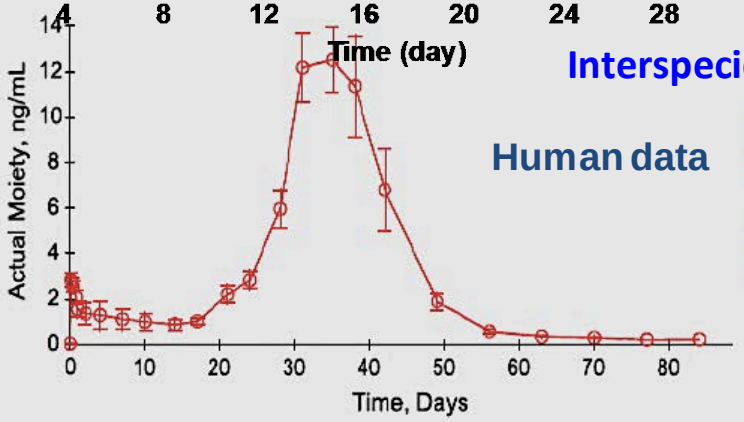
Case I: Compositionally Equivalent Risperidone Microspheres

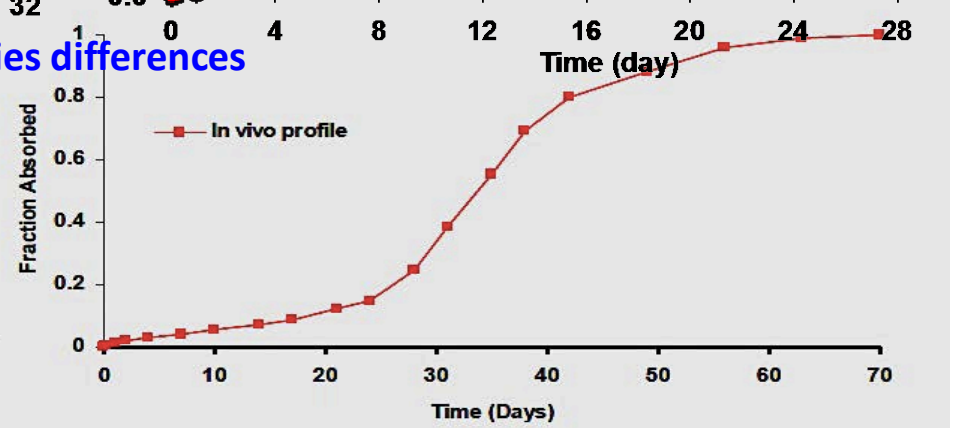
- ***In vivo* release testing**
  - **Animal model: rabbit**





Interspecies differences

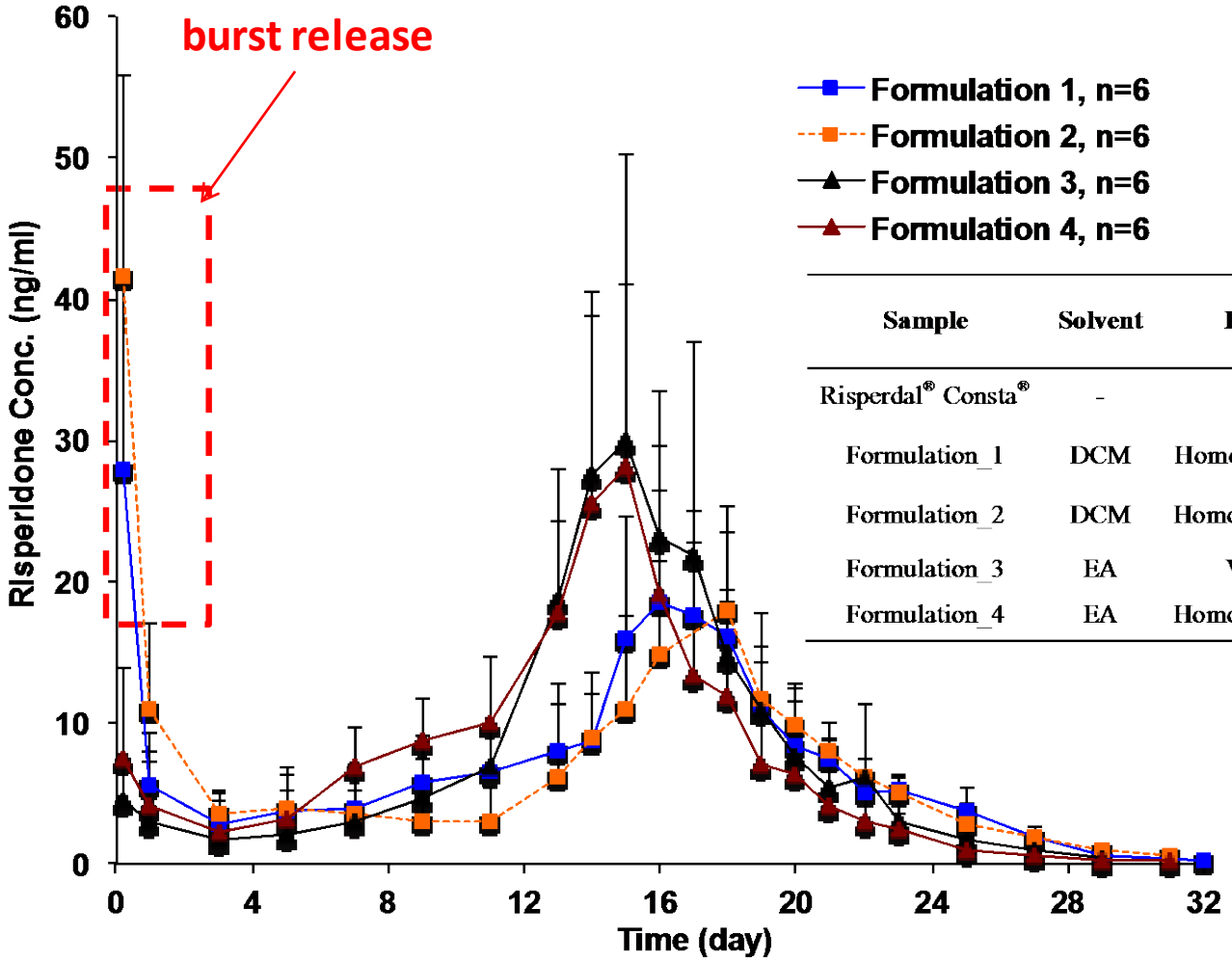




Rawat A., Burgess, D.J., *Int. J. Pharm., 2012*; Shen J., Burgess D.J., *J. Control. Release, (2015)*

Case I: Compositionally Equivalent Risperidone Microspheres

- **In vivo release testing**

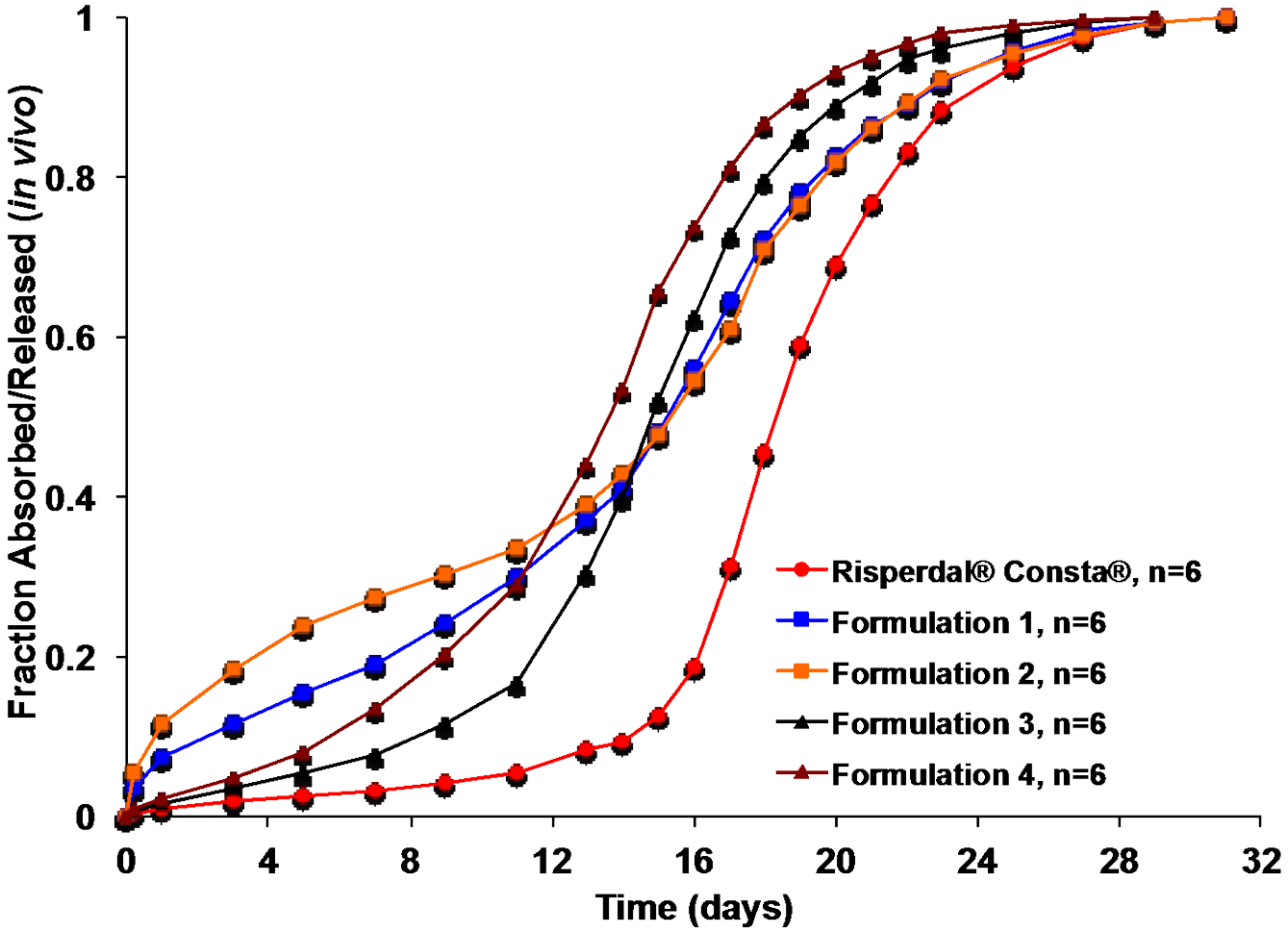


Sample	Solvent	Preparation Method
Risperdal® Consta®	-	-
Formulation_1	DCM	Homogenization & dry sieving
Formulation_2	DCM	Homogenization & wet sieving
Formulation_3	EA	Vortex & wet sieving
Formulation_4	EA	Homogenization & wet sieving

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

Case I: Compositionally Equivalent Risperidone Microspheres

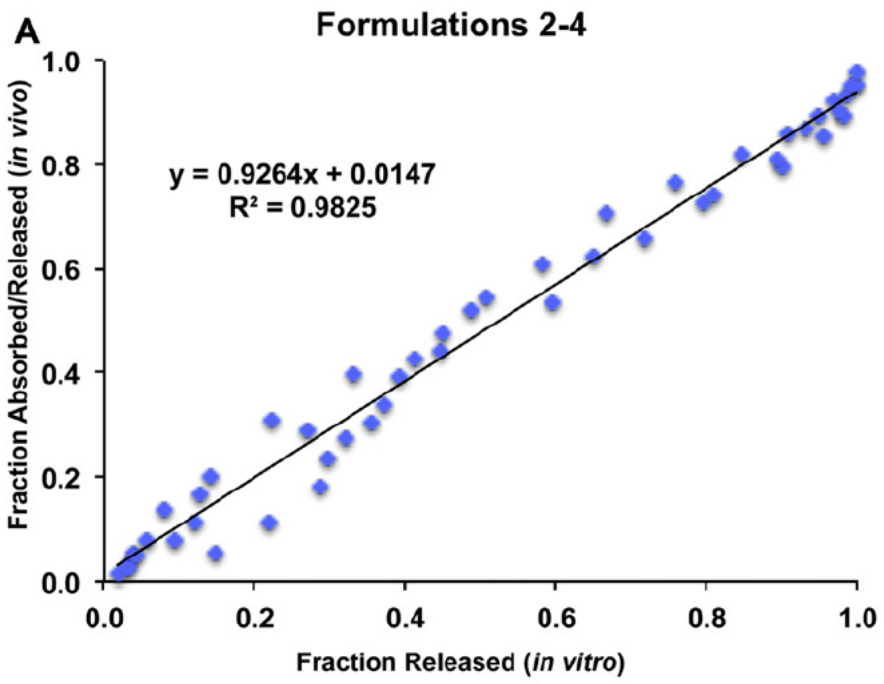
- **Deconvoluted *in vivo* release profiles**

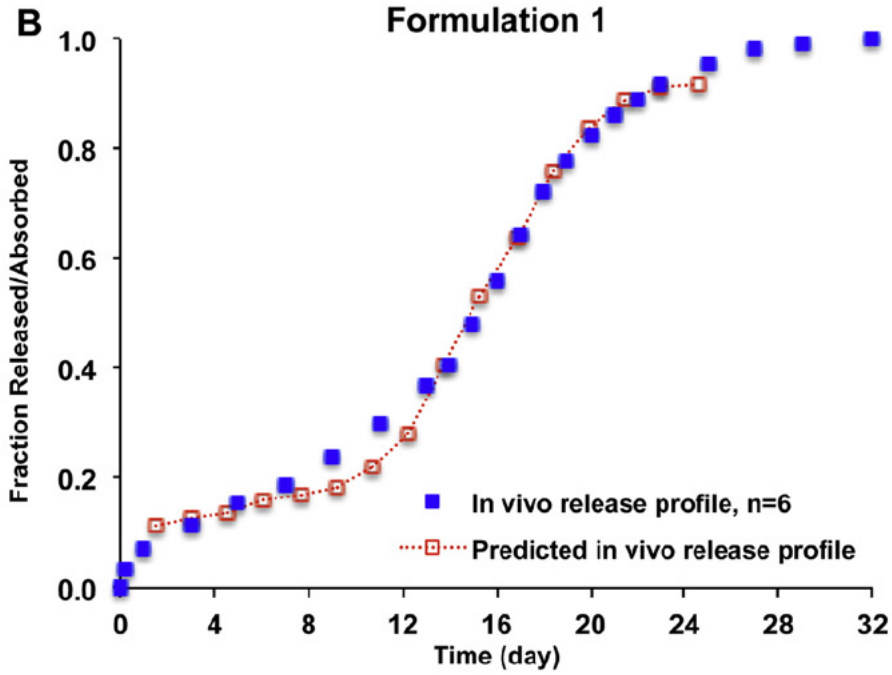


Shen J., Burgess D.J., *J. Control. Release, (2015)*

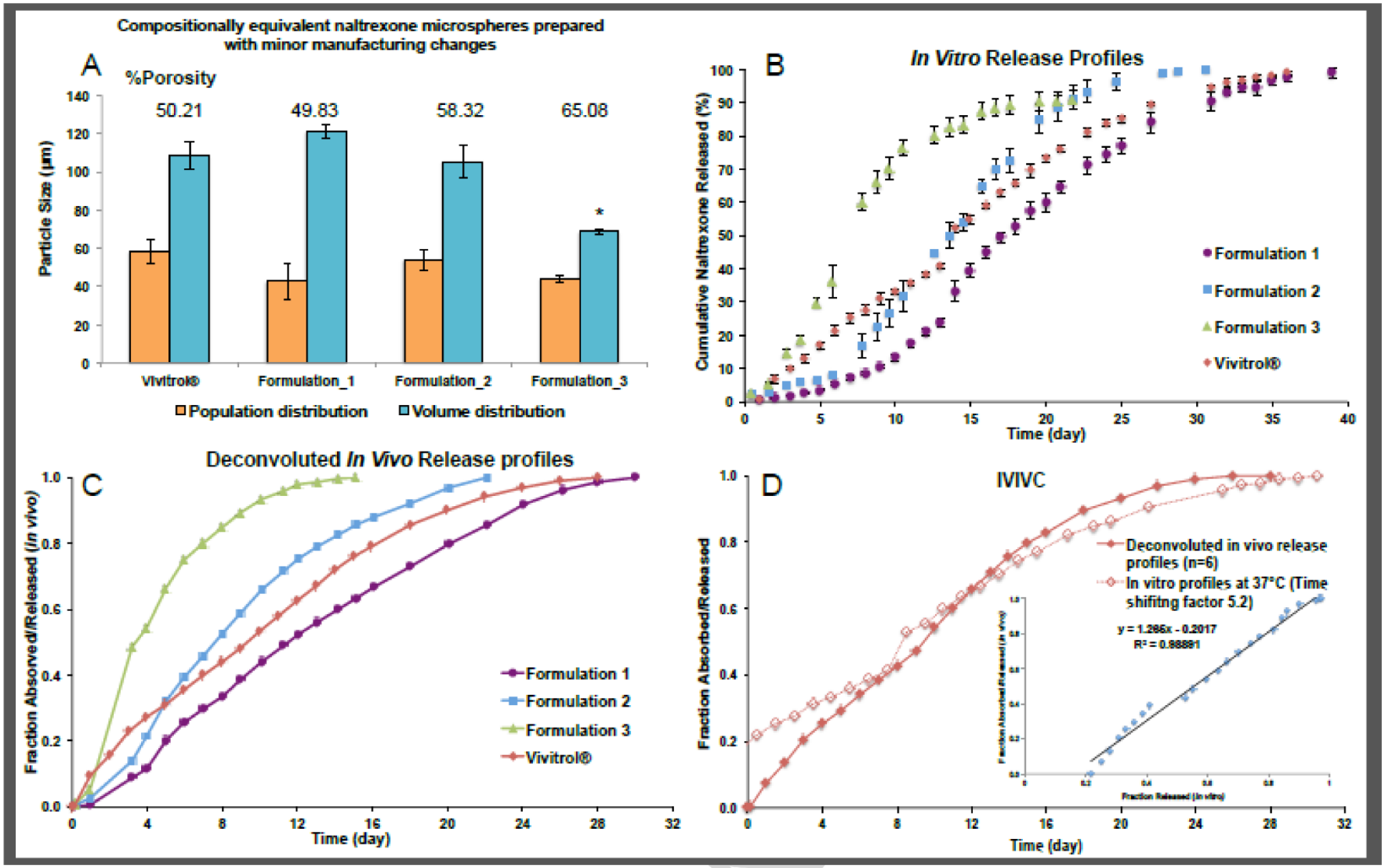
29

Level A IVIVC





Level A IVIVC of naltrexone microspheres



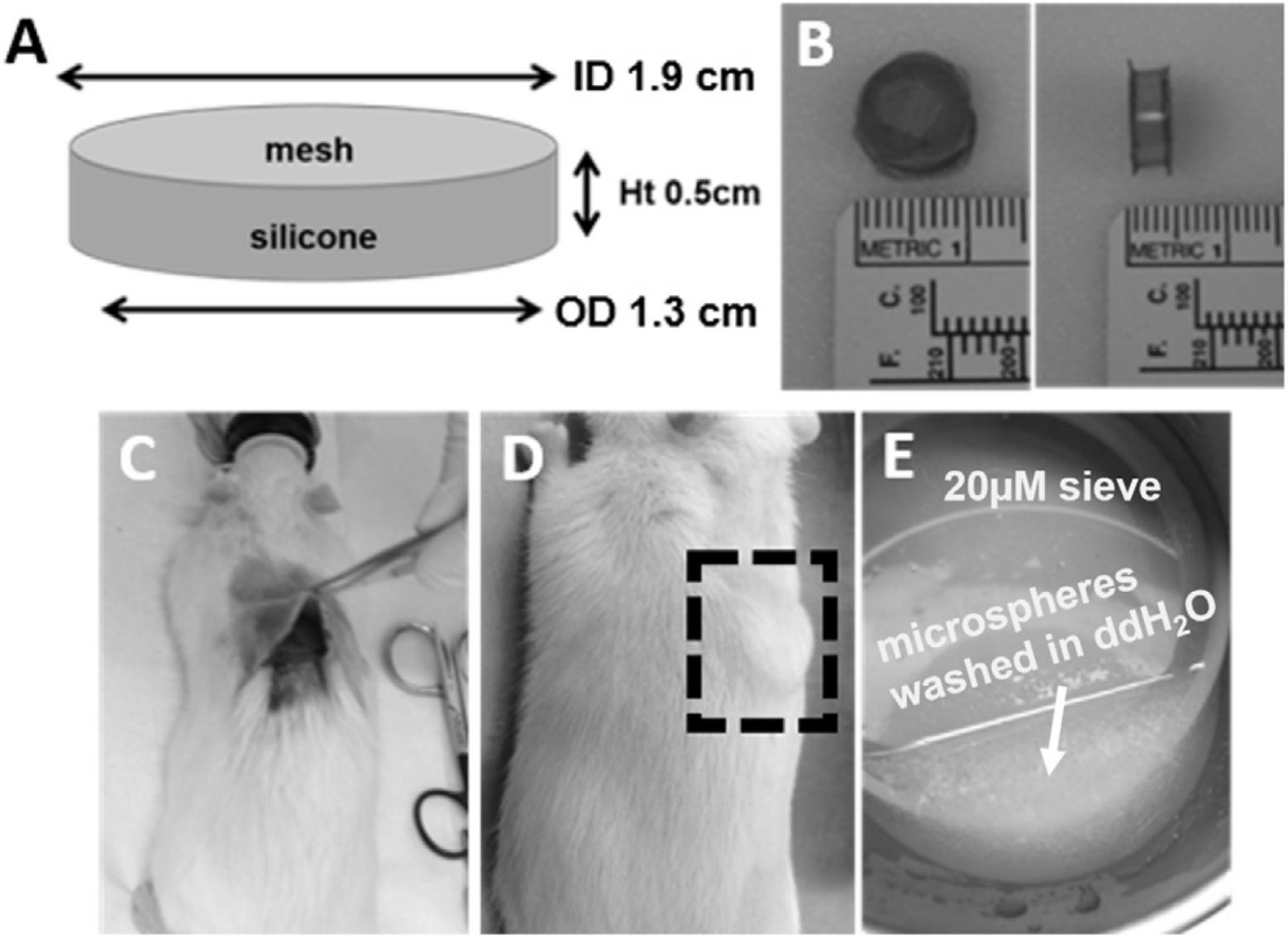
Andhariya J, et al. J Control Release. 2017 June 10;255:27-35

U.S. FOOD & DRUG ADMINISTRATION

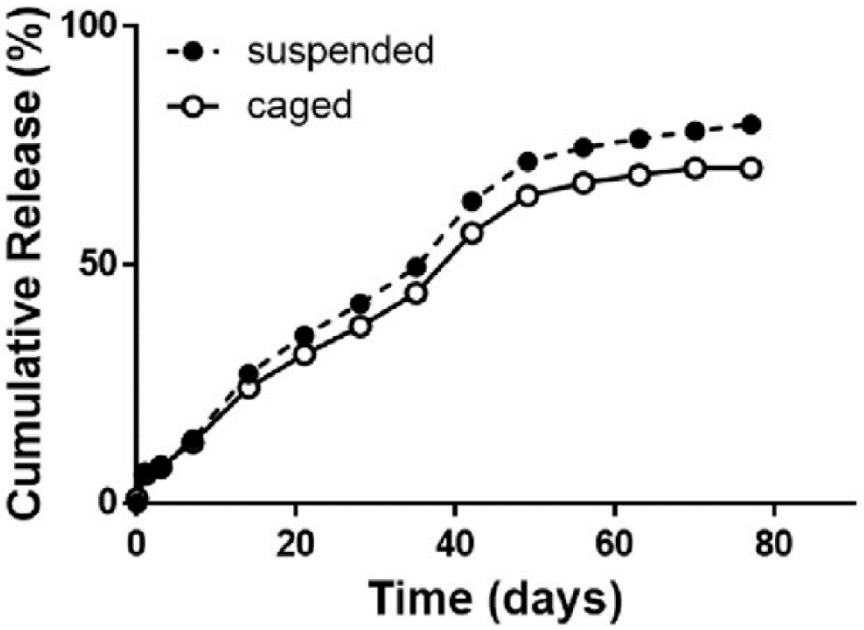
Case III:

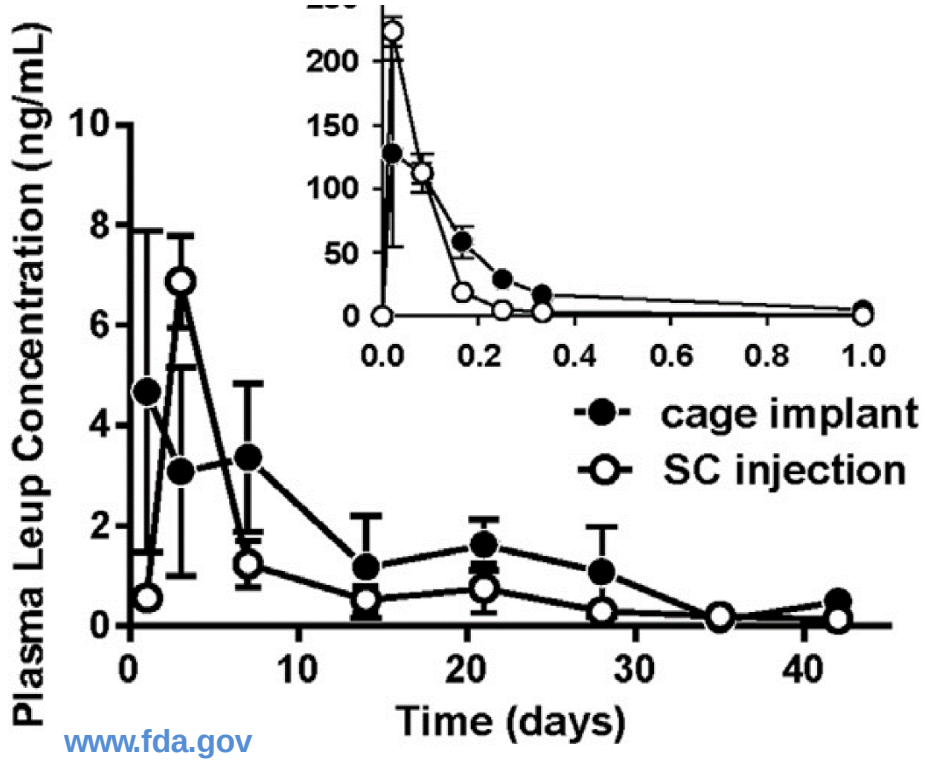
A Cage Model for Investigating In Vivo Release Mechanisms

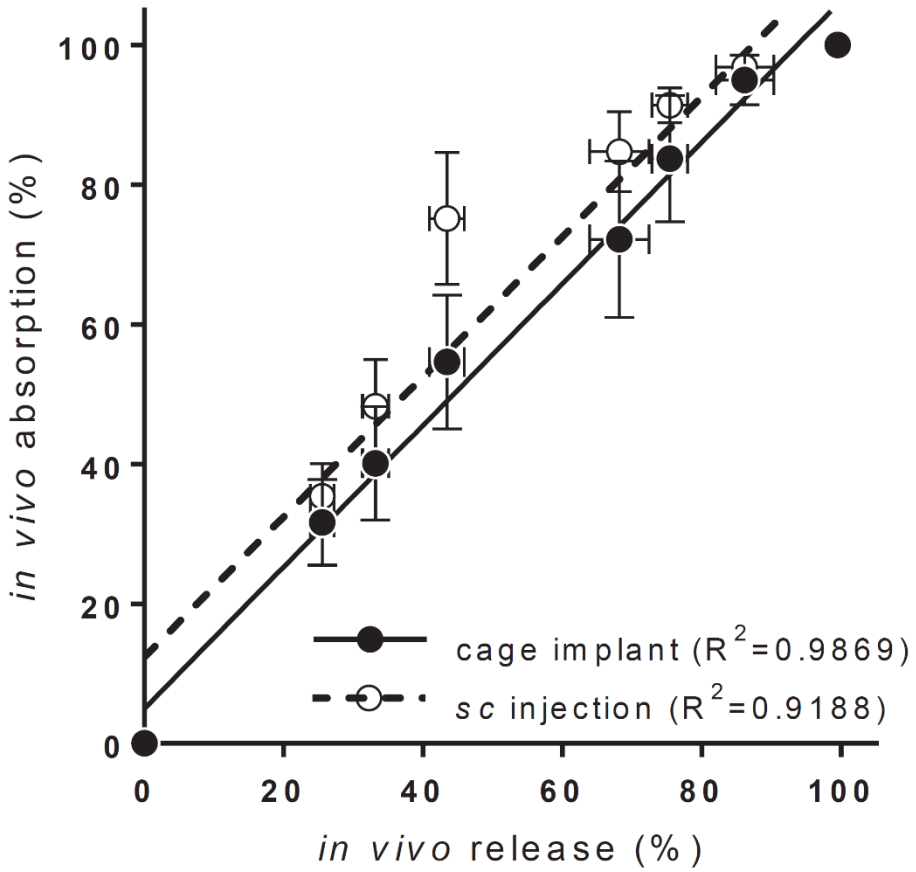
Cage Model to Assess In Vivo Release



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

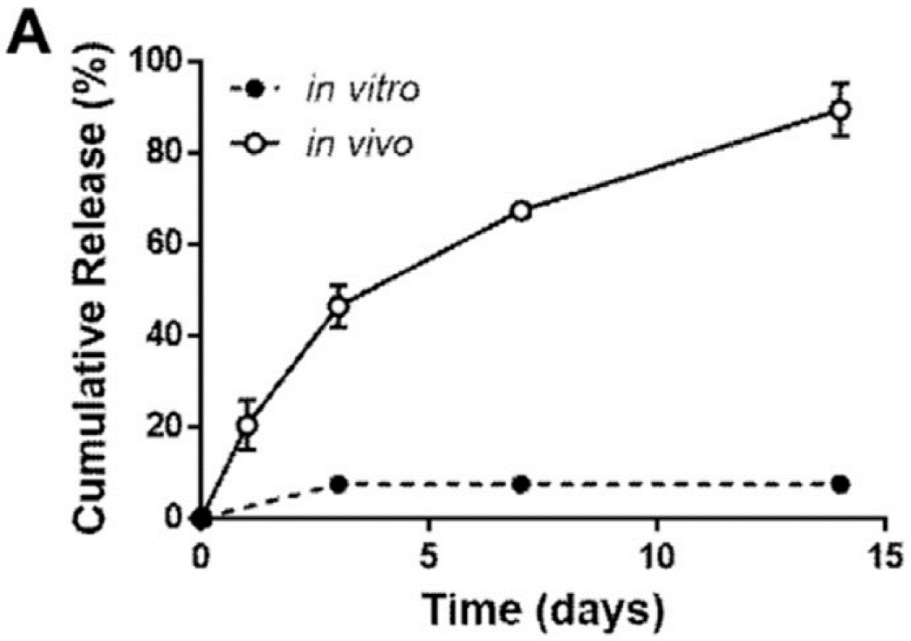

Cumulative Release (%)
100
50
0
suspended
caged
0
20
40
60
80
Time (days)


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)

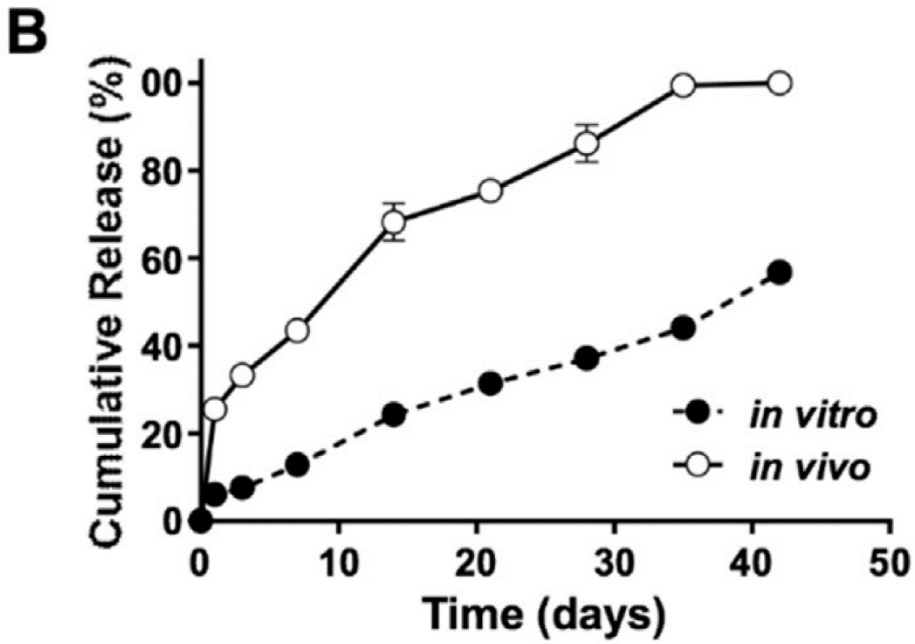

in vivo absorption (%)
100
80
60
40
20
0
cage implant (R2=0.9869)
sc injection (R2=0.9188)
0
20
40
60
80
100
in vivo release (%)

Understanding Release Mechanisms

Triamcinolone-loaded microspheres

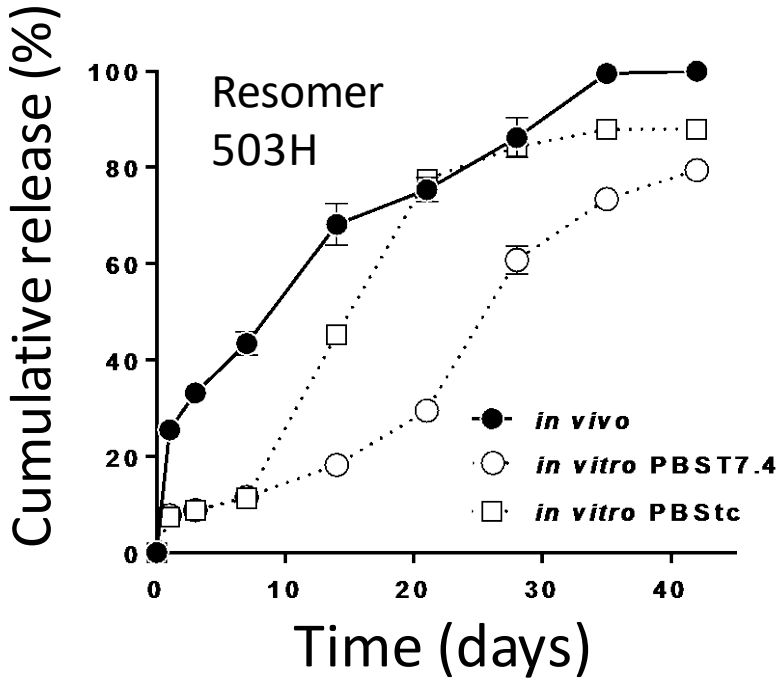


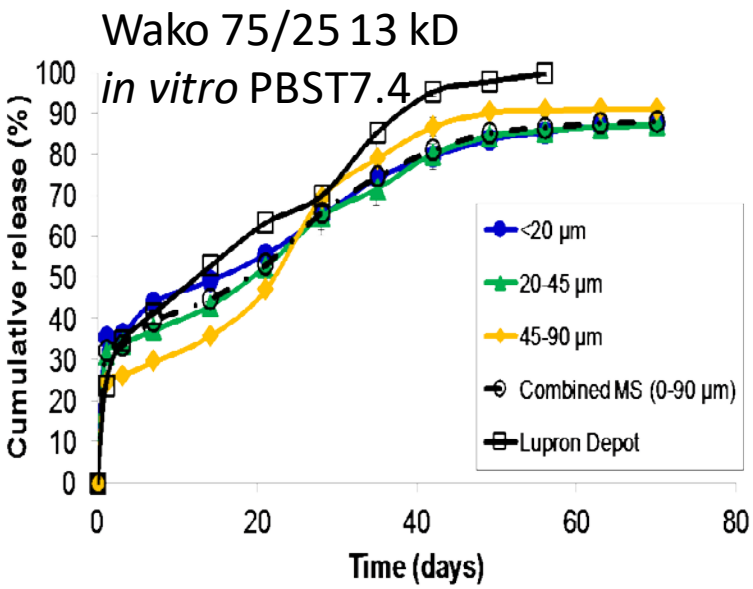
Leuprolide-loaded microspheres



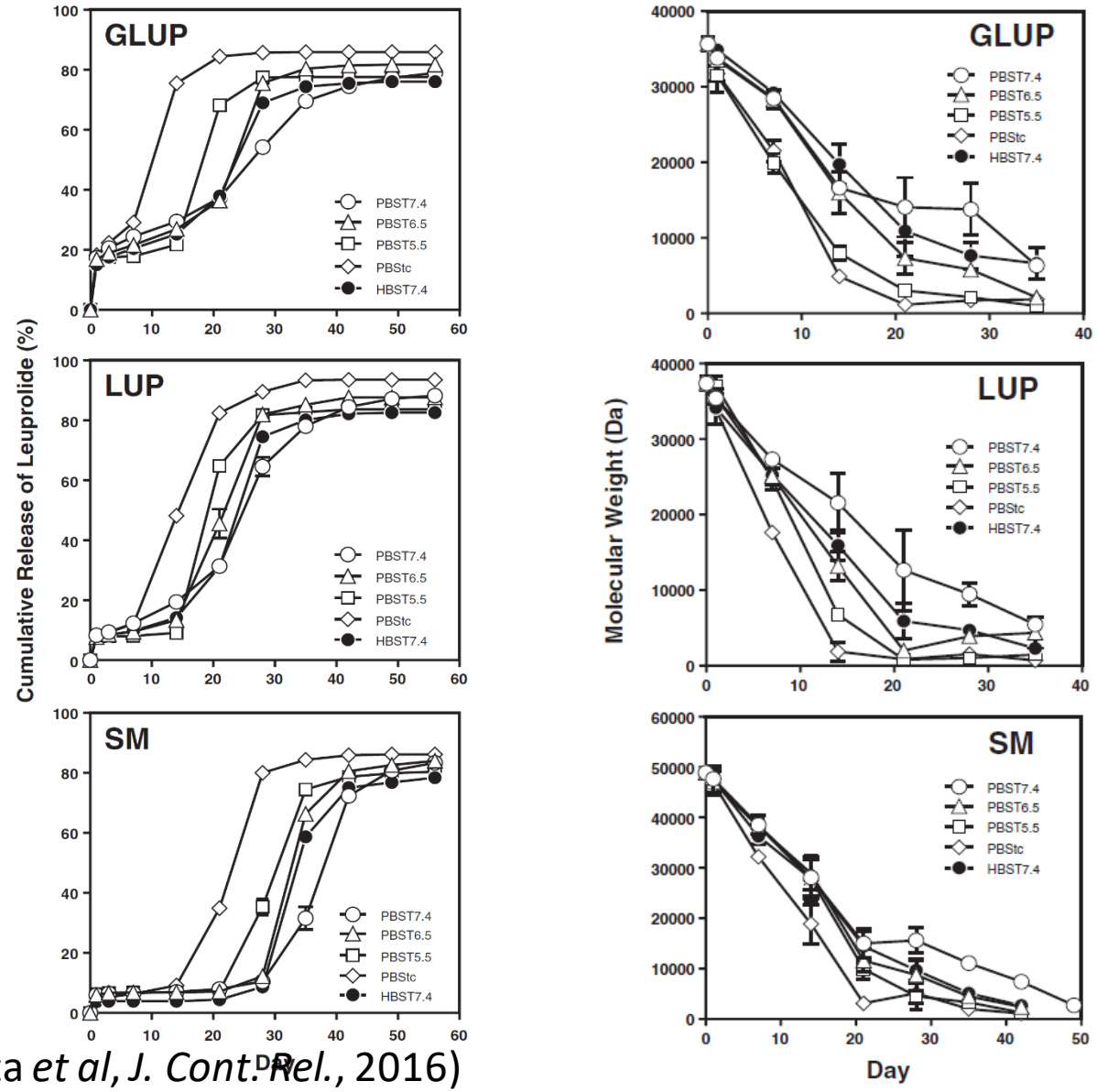
Continuous release of leuprolide from PLGA microspheres

(use low molecular weight PLGA)



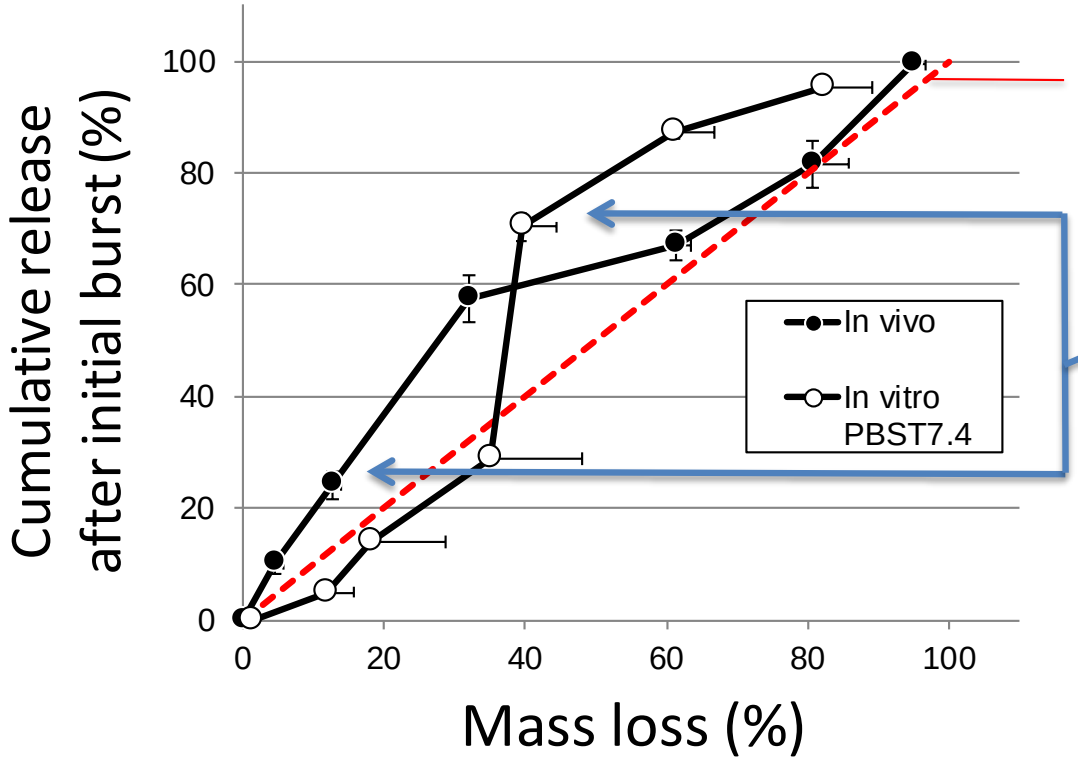


Understanding Release Mechanisms of Leuprolide



(Hirota *et al*, *J. Cont. Rel.*, 2016)

Comparing Mechanistic Signatures *In Vitro* and *In Vivo* for Leuprolide from R503H



release = mass loss line

Likely alternative operative mechanisms to mass loss

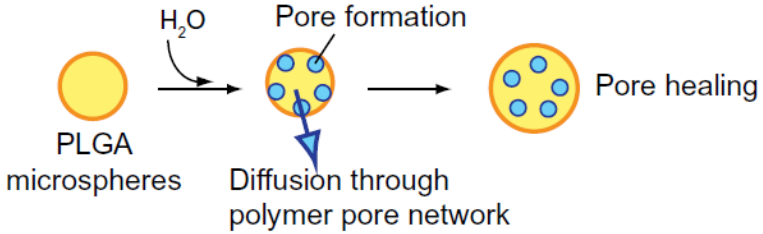
- *In vitro*: release = mass loss at *late times*
- *In vivo*: release = mass loss at *early times (from cage model)*

(Hirota *et al*, *J. Cont. Rel.*, 2016)

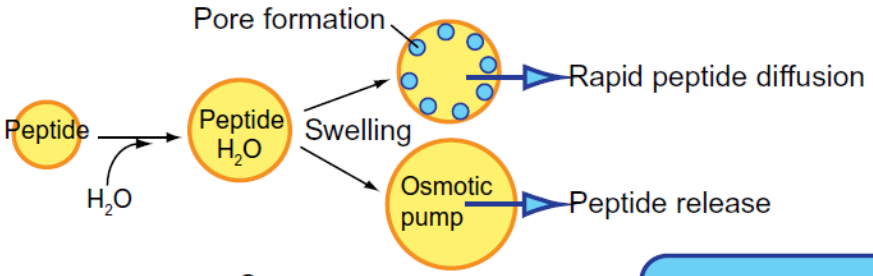
Release mechanisms

1. Erosion (mass loss)

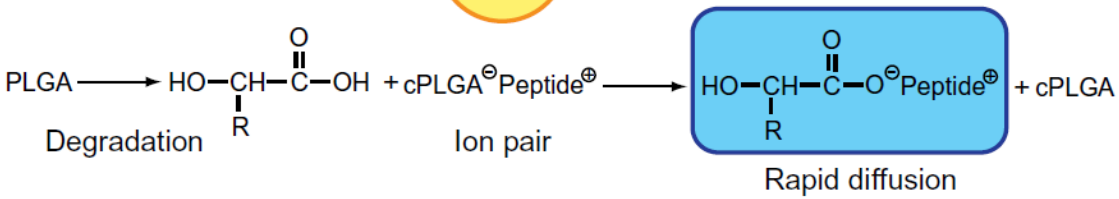
2. Diffusion/pore healing (early phase)



3. Water-mediated

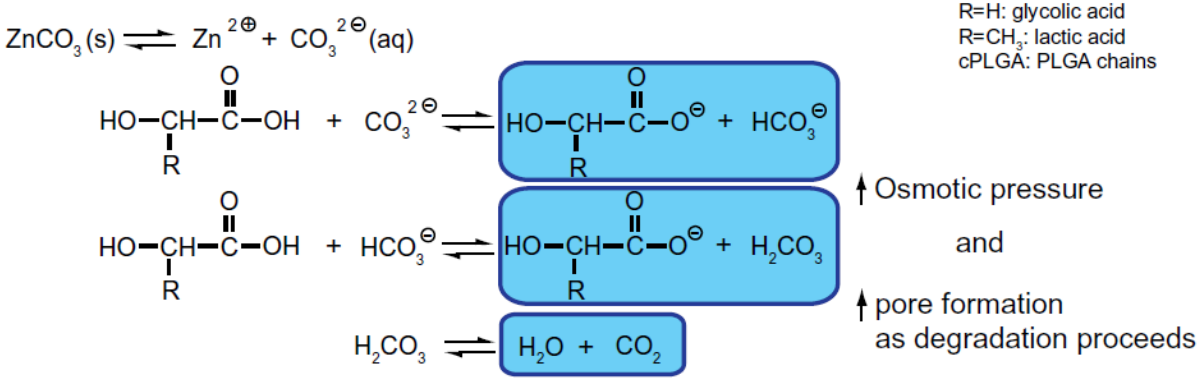


4. Desorption



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

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



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
- Several mechanisms contribute to the release of drugs from PLGA microspheres *in vitro* and *in vivo.* In addition to erosion, diffusion, and water-mediated processes, pore healing, drug-polymer interactions, and other dynamic microstructural changes to the polymer may affect the release mechanism.
- Development of a cage model has provided utility to facilitate mechanistic analysis of *in vivo* release by recovery of the microspheres
- Study results can be used to inform recommendations for product-specific guidances, pre-ANDA meeting requests, and Controlled Correspondence

Take Home Messages

- The effect of each parameter on the product performance is product specific. Therefore, the key physicochemical properties that are necessary for evaluation of Q1 sameness is on a ***case-by-case basis***.

- The key physicochemical properties of PLA/PLGA could be altered during manufacturing process. Therefore, in addition to the characteristics of the raw PLA/PLGA materials, it is critical to characterize PLA/PLGA using the finished product.

- The Q1/Q2 sameness of PLA/PLGA between the test product and reference listed drug should be determined using the finished microspheres rather than the raw materials.

Acknowledgements

FDA:

Bin Qin

Darby Kozak

Yuan Zou

Deyi Zhang

Xiaohui Jiang

Stephanie Choi

Markham Luke

Lei Zhang

Robert Lionberger

University of Connecticut: Dr. Diane Burgess; Dr. Jie Shen; Dr. Michael Kastellorizios; Dr. Min Sung Suh; M.S. Janki V. Andhariya

University of Michigan: Dr. Steven Schwendeman; Dr. Amy Doty; Dr. Keiji Kirota, Ms. Jia Zhou; Rose Ackermann; Karl Olsen; Dr. Anna Schwendeman

Akina Inc.: Dr. Kinam Park; John Garner; Sarah Skidmore; Justine Hadar