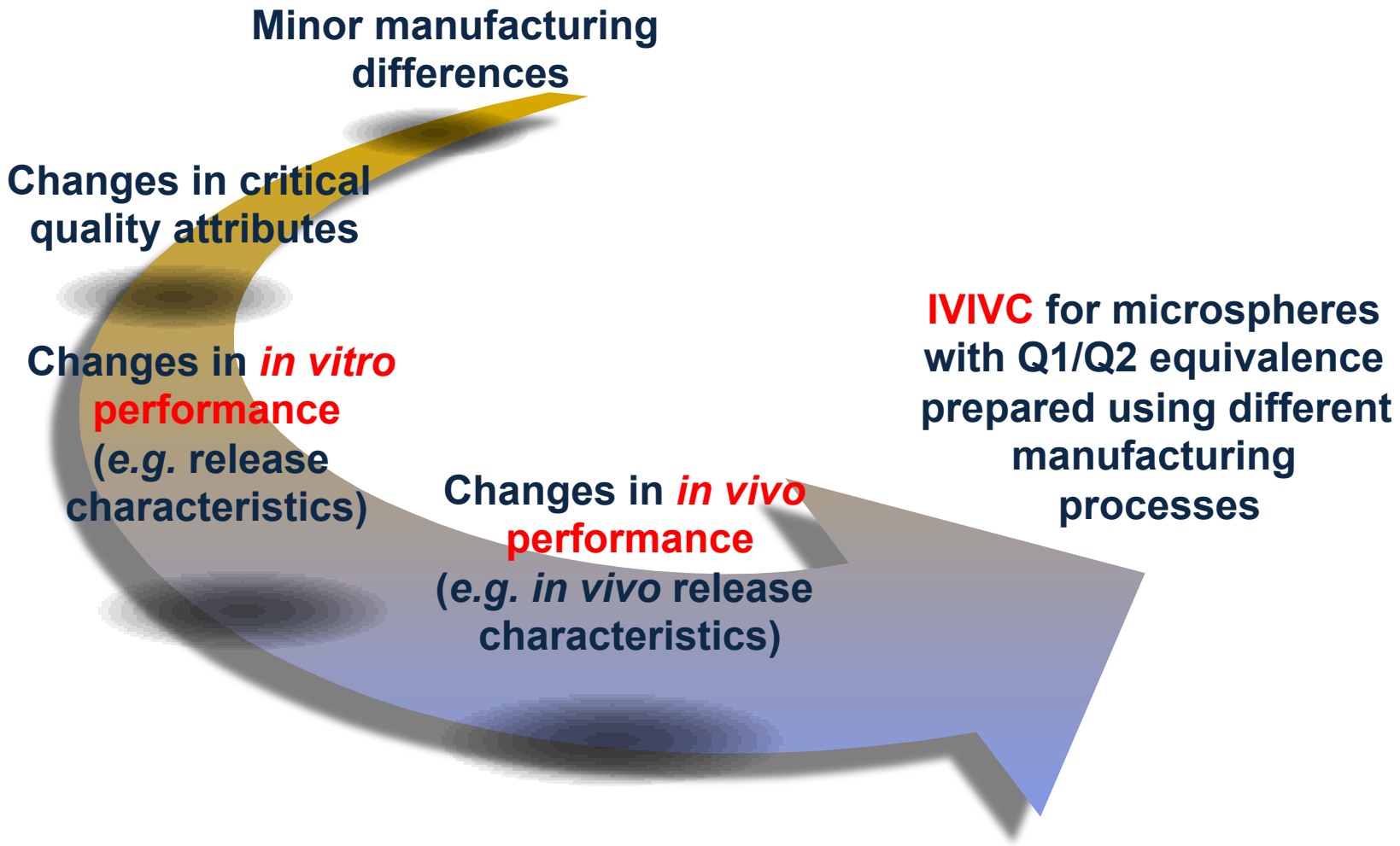
In Vitro-In Vivo Correlation for Complex Drug Products and *In Vitro/In Vivo* Stability Issues

Diane J. Burgess, Ph.D.
Board of Trustees Distinguished Professor of Pharmaceutics
University of Connecticut
May 2016

Parenteral Microsphere Drug Products



Case I: 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

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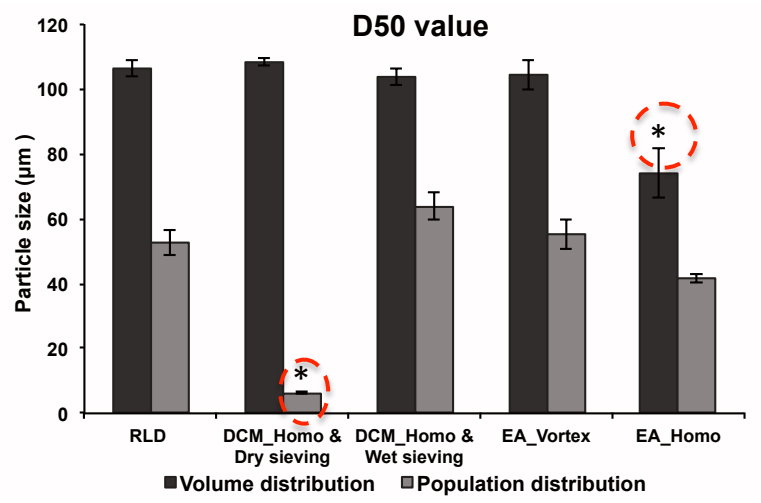
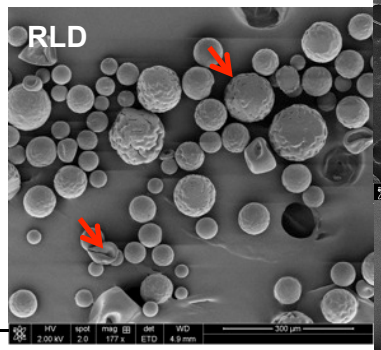
Case I: Compositionally Equivalent Risperidone Microspheres

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



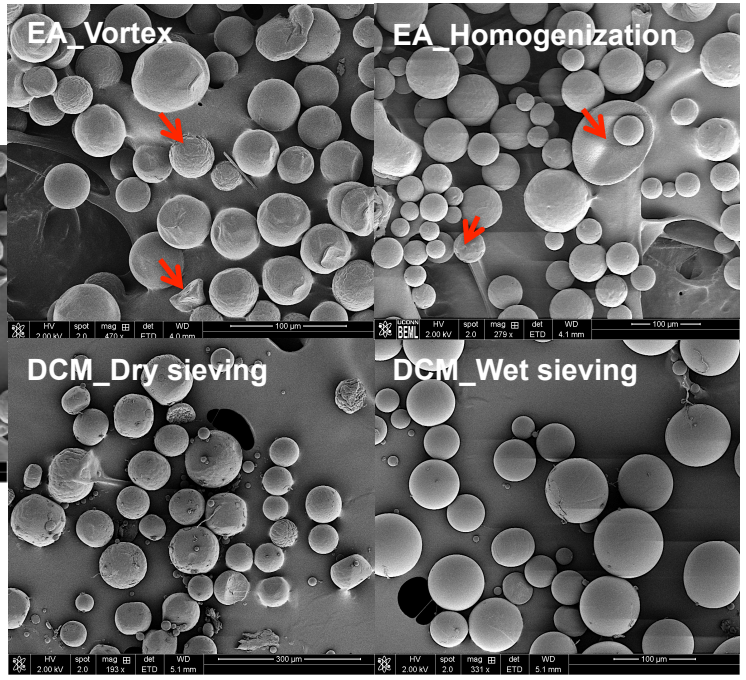
Sample	Solvent	Preparation Method
Risperdal® Consta®	-	-
Formulation_1	DCM	Homogenization & dry sieving
Formulation_2	DCM	Homogenization & wet sieving
Formulation_3	EA	Vortex & wet sieving
Formulation_4	EA	Homogenization & wet sieving



Porosity 43.97%

Porosity 54.98%

61.75%



Porosity 43.19%

46.04%

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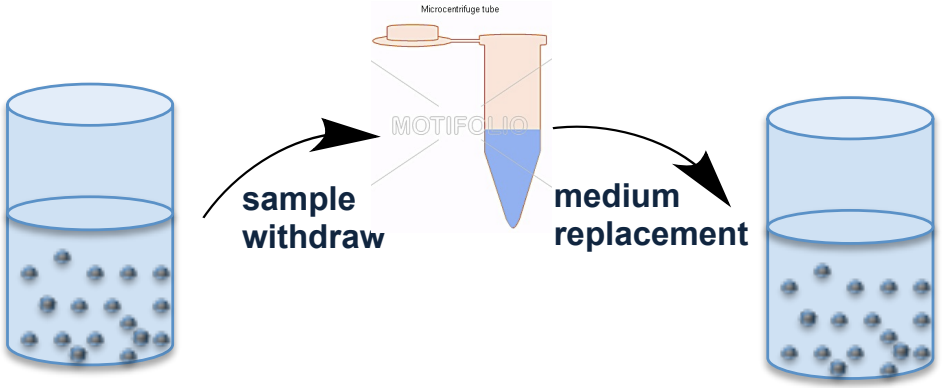
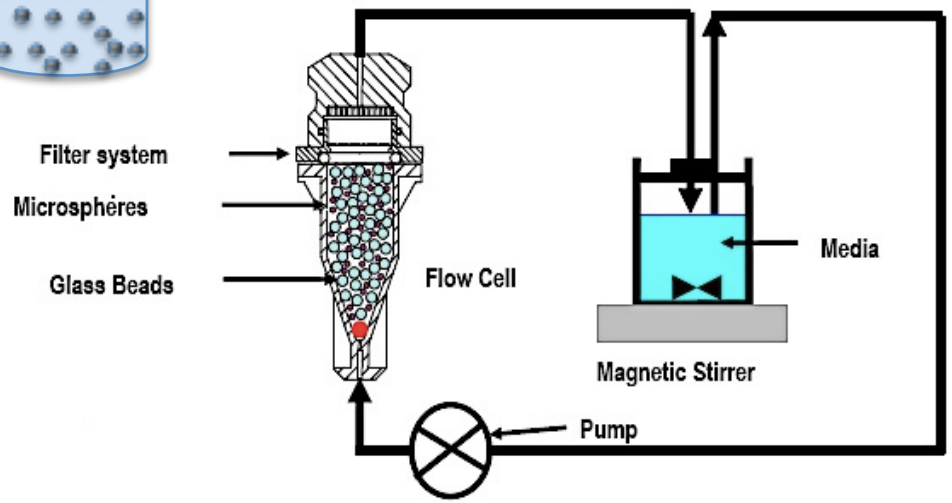
Case I: Compositionally Equivalent Risperidone Microspheres

- ***In vitro* release testing**

Sample-and-Separate method



Continuous flow method

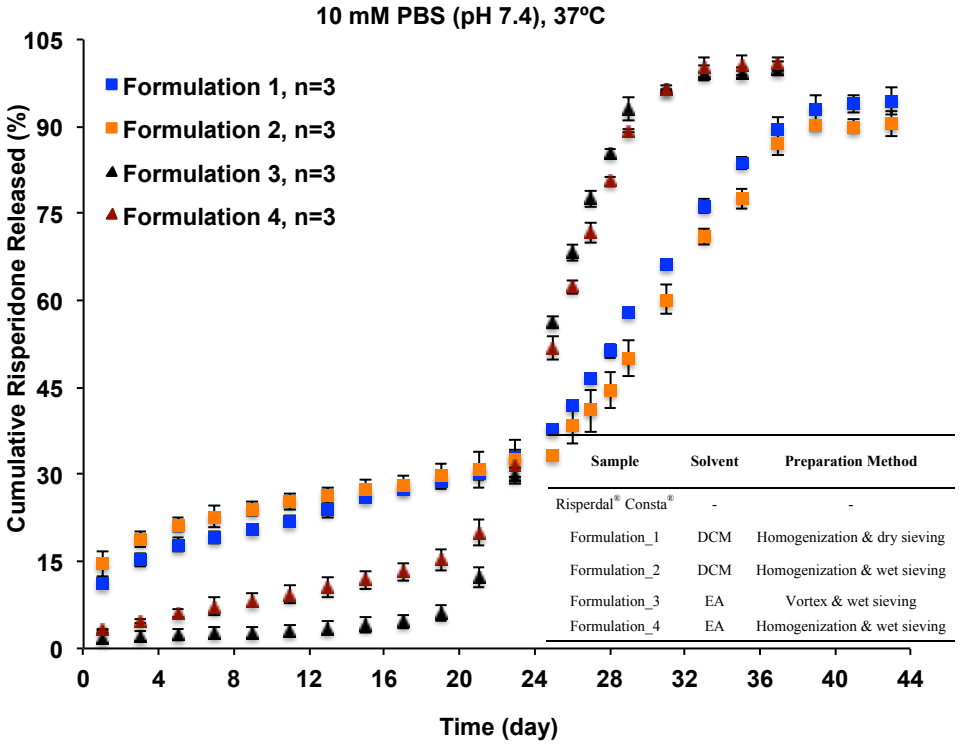


Zolnik B.S., Burgess D.J., *Dissolu. Technol., 2005*

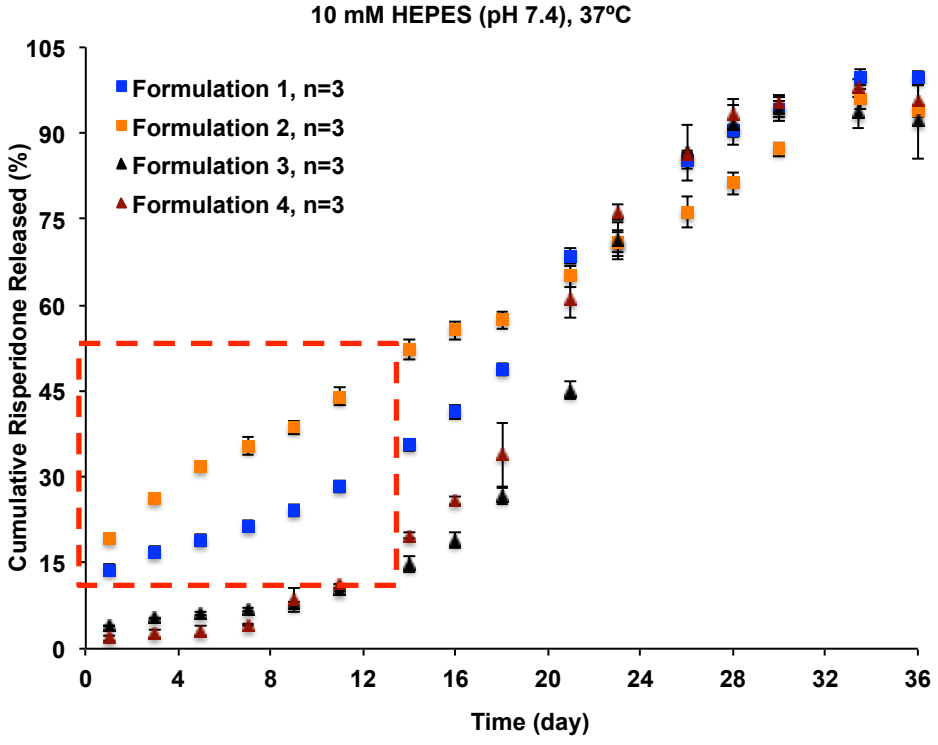
Case I: Compositionally Equivalent Risperidone Microspheres

- ***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.

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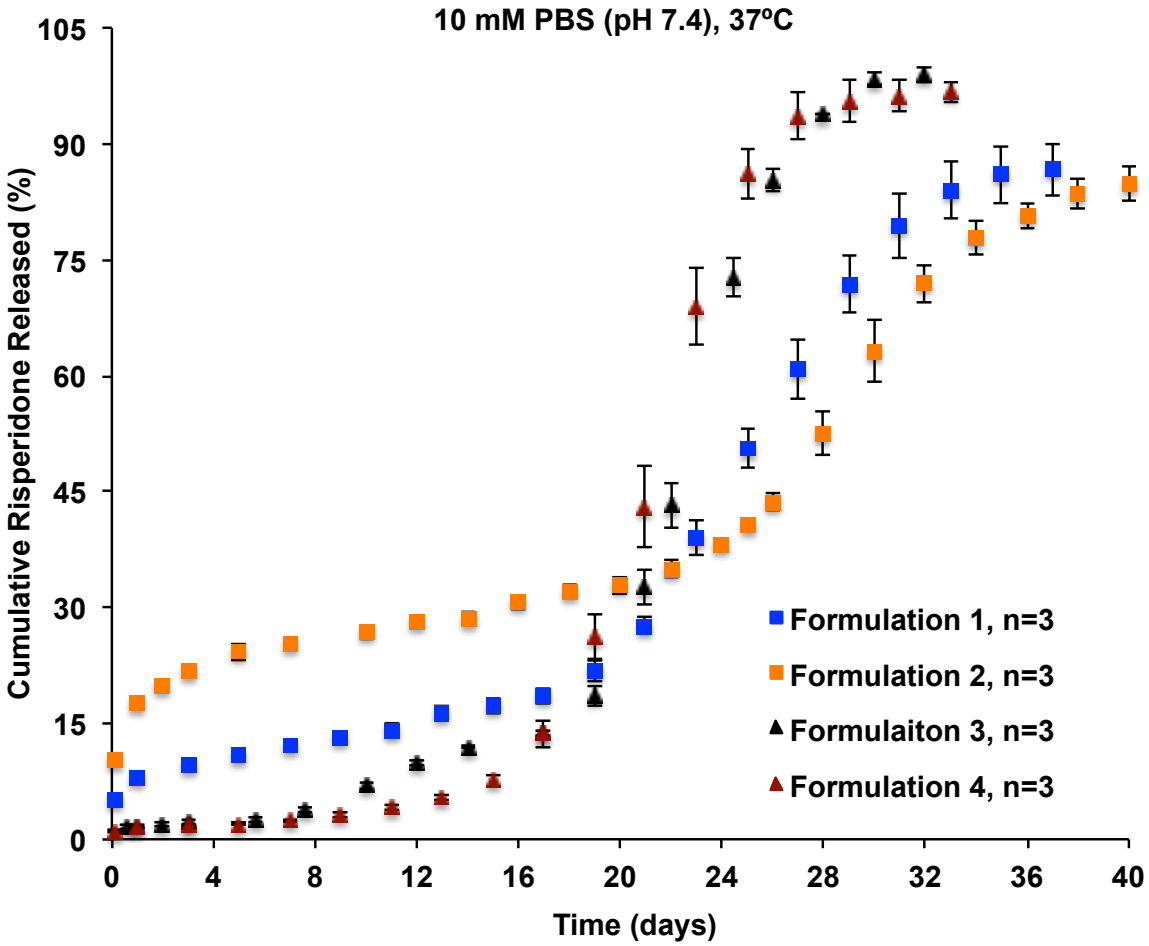
Case I: Compositionally Equivalent Risperidone Microspheres

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



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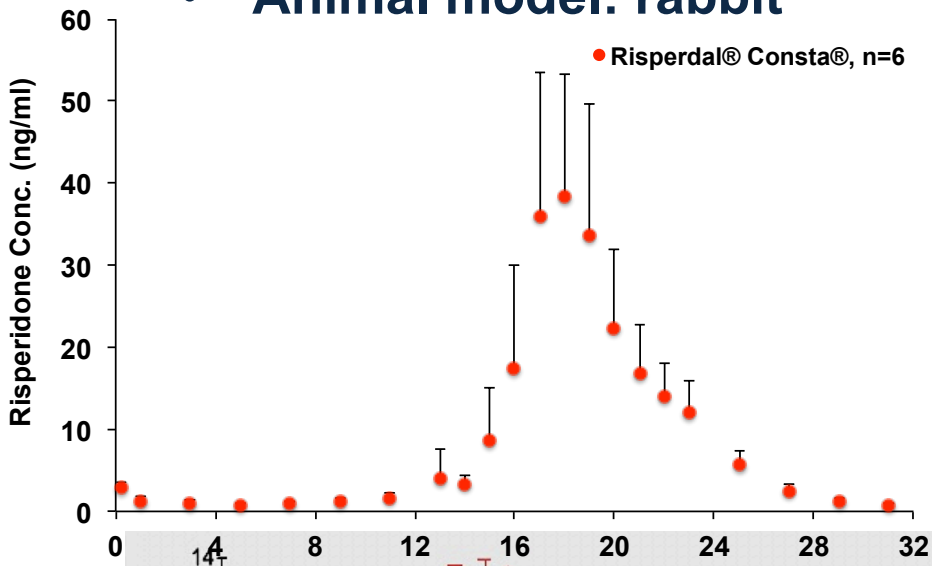
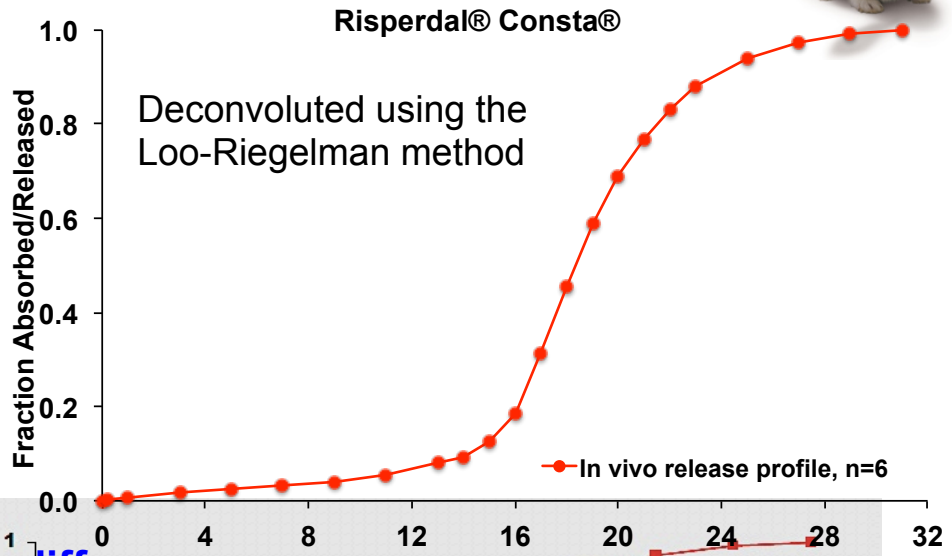
Case I: Compositionally Equivalent Risperidone Microspheres

- ***In vitro-in vivo* correlation (IVIVC):**
  - ✓ **Definition: A predictive mathematical model describing the relationship between an *in vitro* property of a dosage form (*e.g.* rate or extent of drug release) and a relevant *in vivo* response (*e.g.* plasma drug concentrations or amount of drug absorbed).**
  - ✓ **Approach: deconvolution**
    - **Numerical**
    - **Compartment method (*e.g.* Wagner-Nelson, and Loo-Riegelman)**
    - **Other methods**

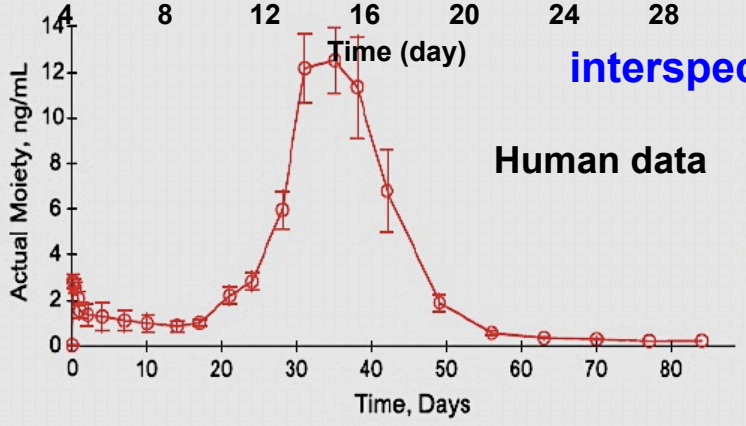
Case I: Compositionally Equivalent Risperidone Microspheres

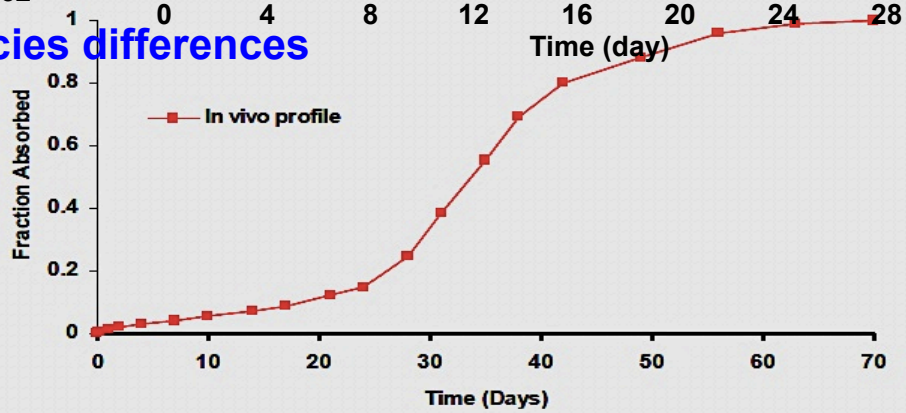
- ***In vivo* release testing**
  - **Animal model: rabbit**





interspecies differences

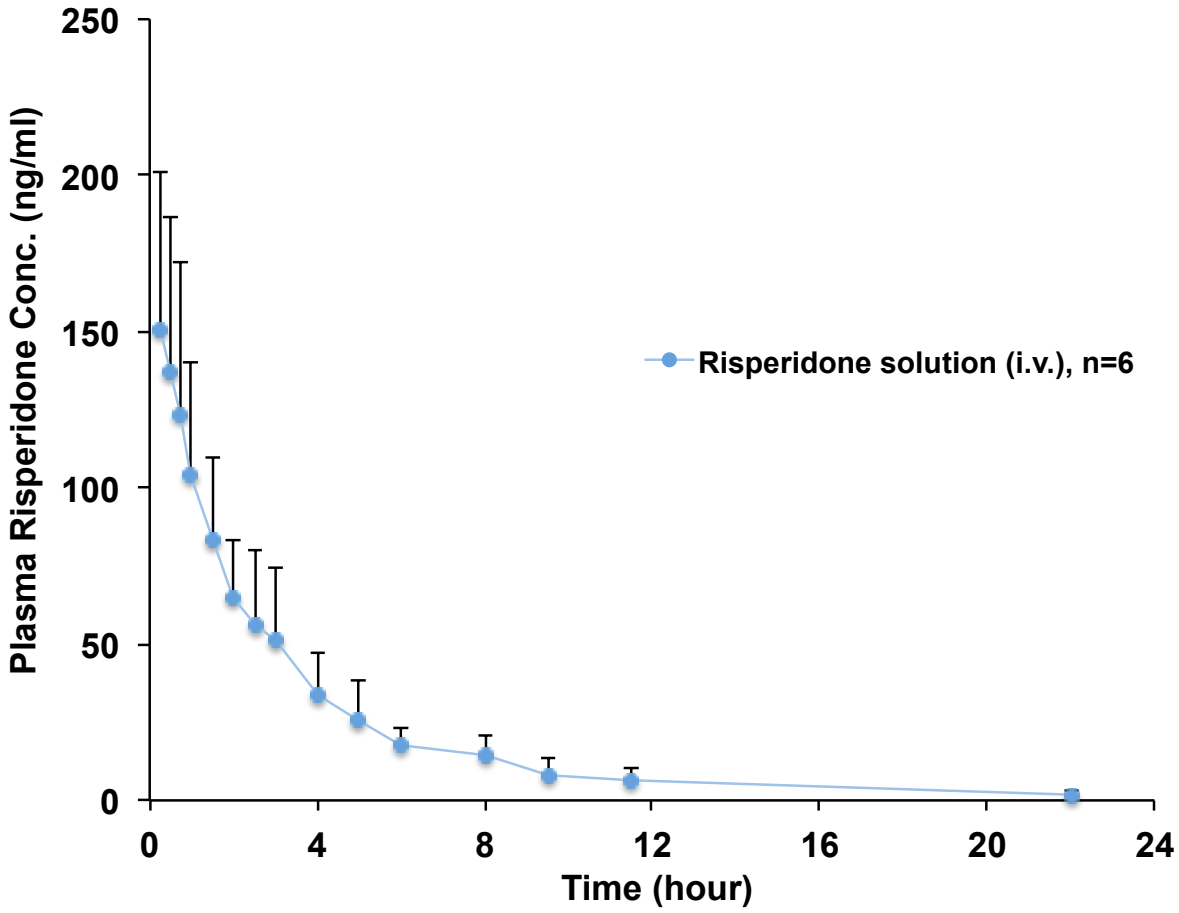




Rawat A., Burgess, D.J., *Int. J. Pharm., 2012*; Shen J., Burgess D.J., *J. Control. Release, (2015)*

Case I: Compositionally Equivalent Risperidone Microspheres

- ***In vivo* release testing**



Pharmacokinetic parameters	
A	128.33±31.91
B	46.80±34.68
α (h^{-1})	0.698±0.17
β (h^{-1})	0.152±0.03
K_{10} (h^{-1})	0.369±0.019
K_{21} (h^{-1})	0.181±0.075
K_{21} (h^{-1})	0.299±0.131

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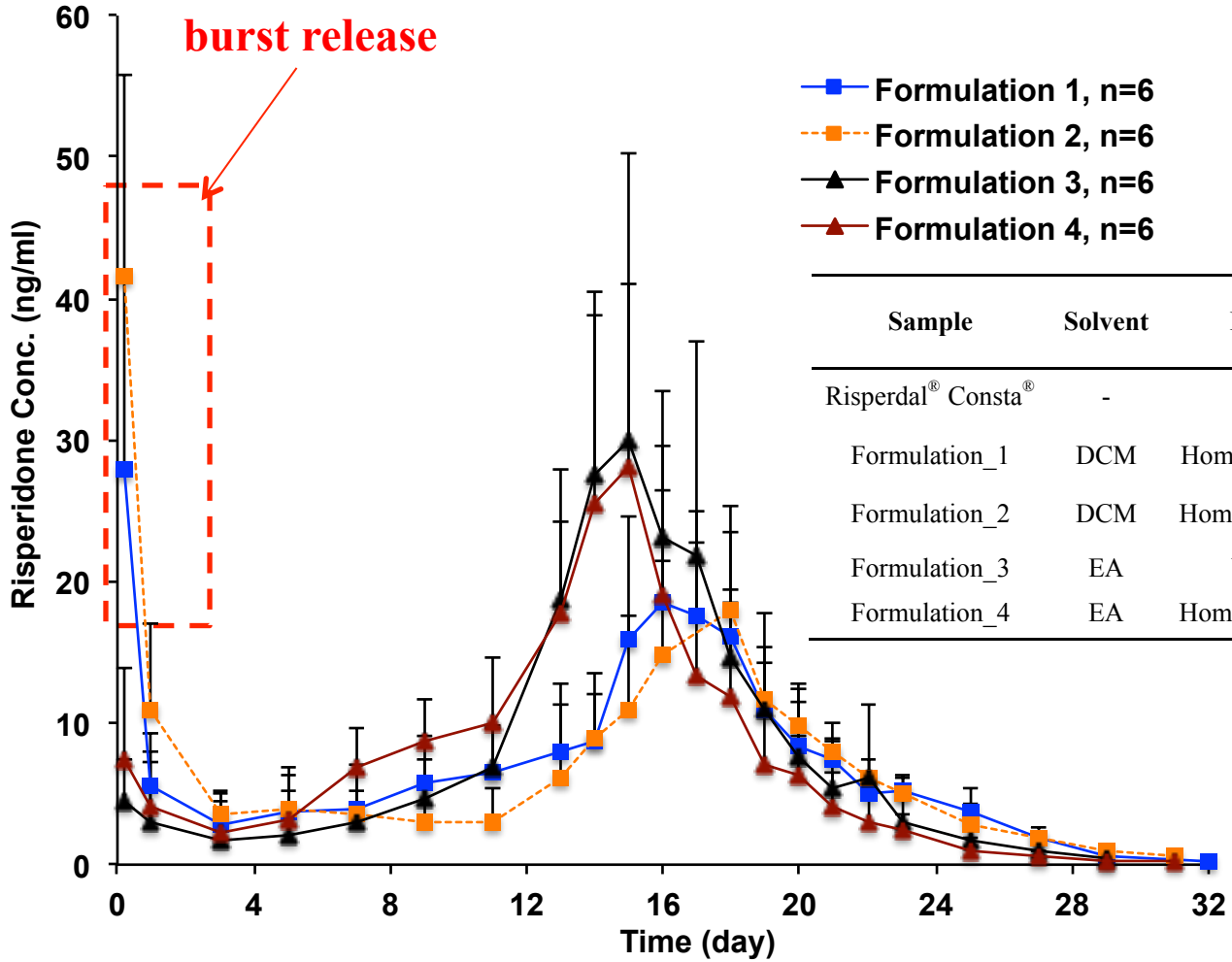
Case I: Compositionally Equivalent Risperidone Microspheres

- ***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

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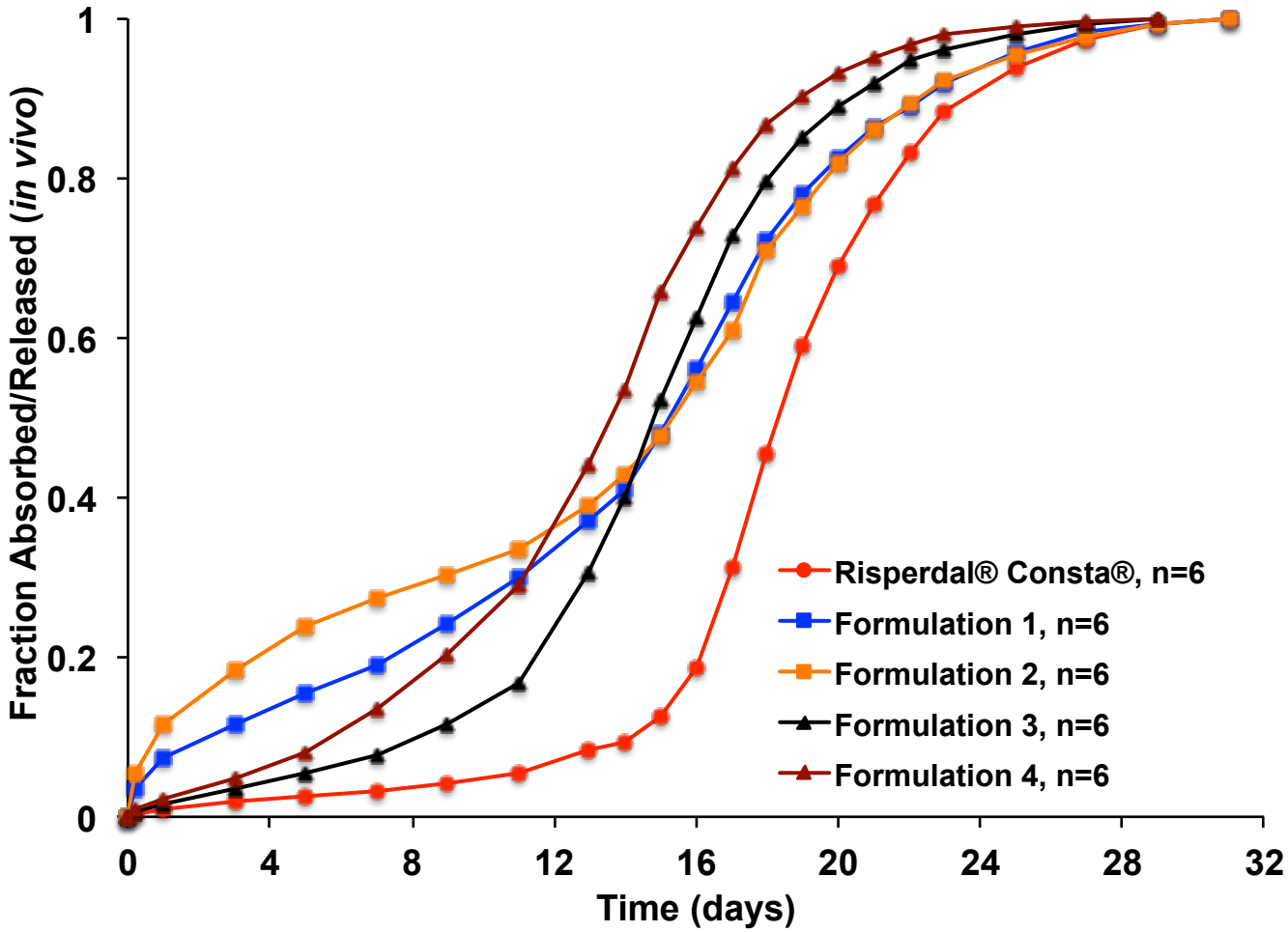
Case I: Compositionally Equivalent Risperidone Microspheres

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



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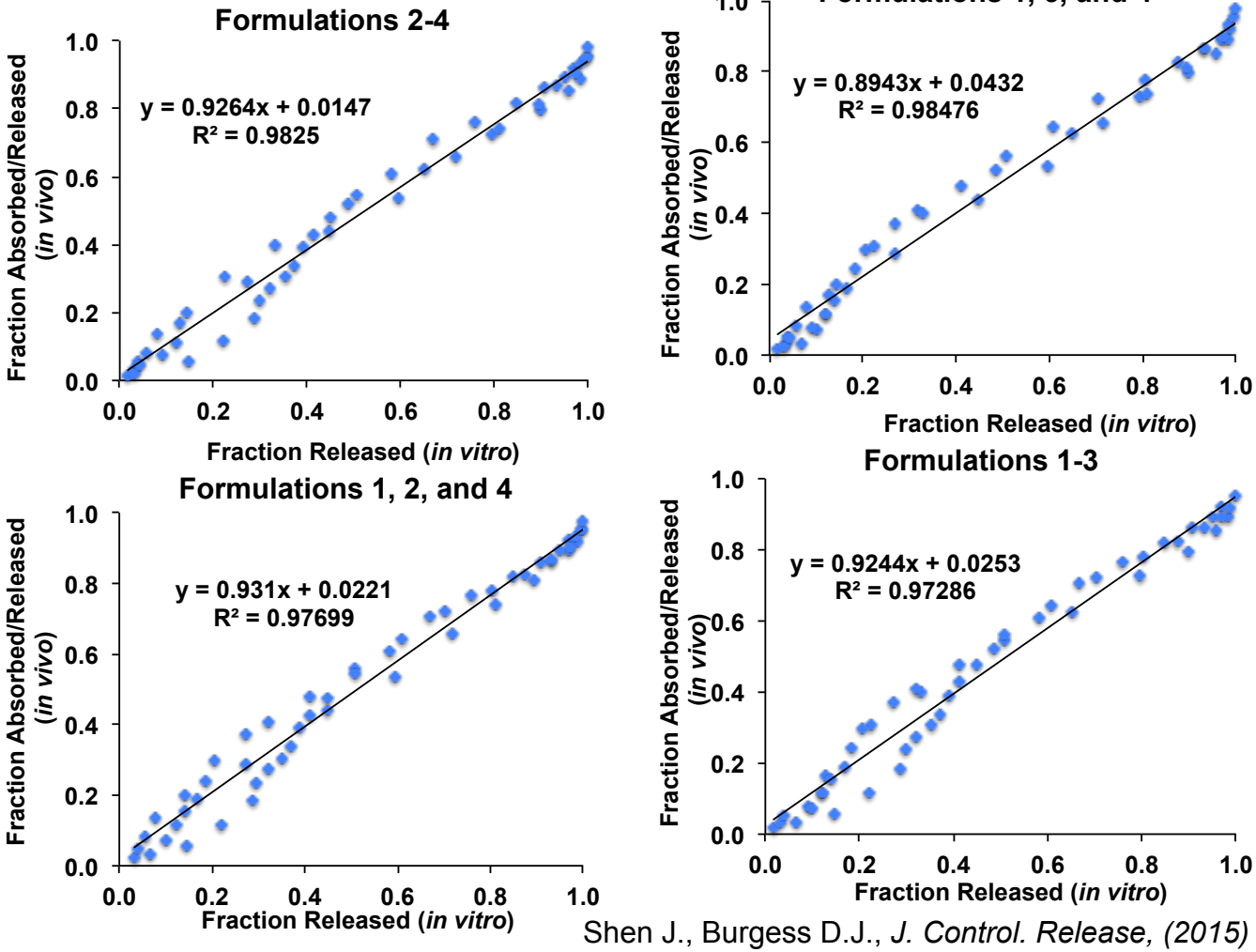
Case I: Compositionally Equivalent Risperidone Microspheres

- **Development of IVIVC (based on any combinations of three formulations)**



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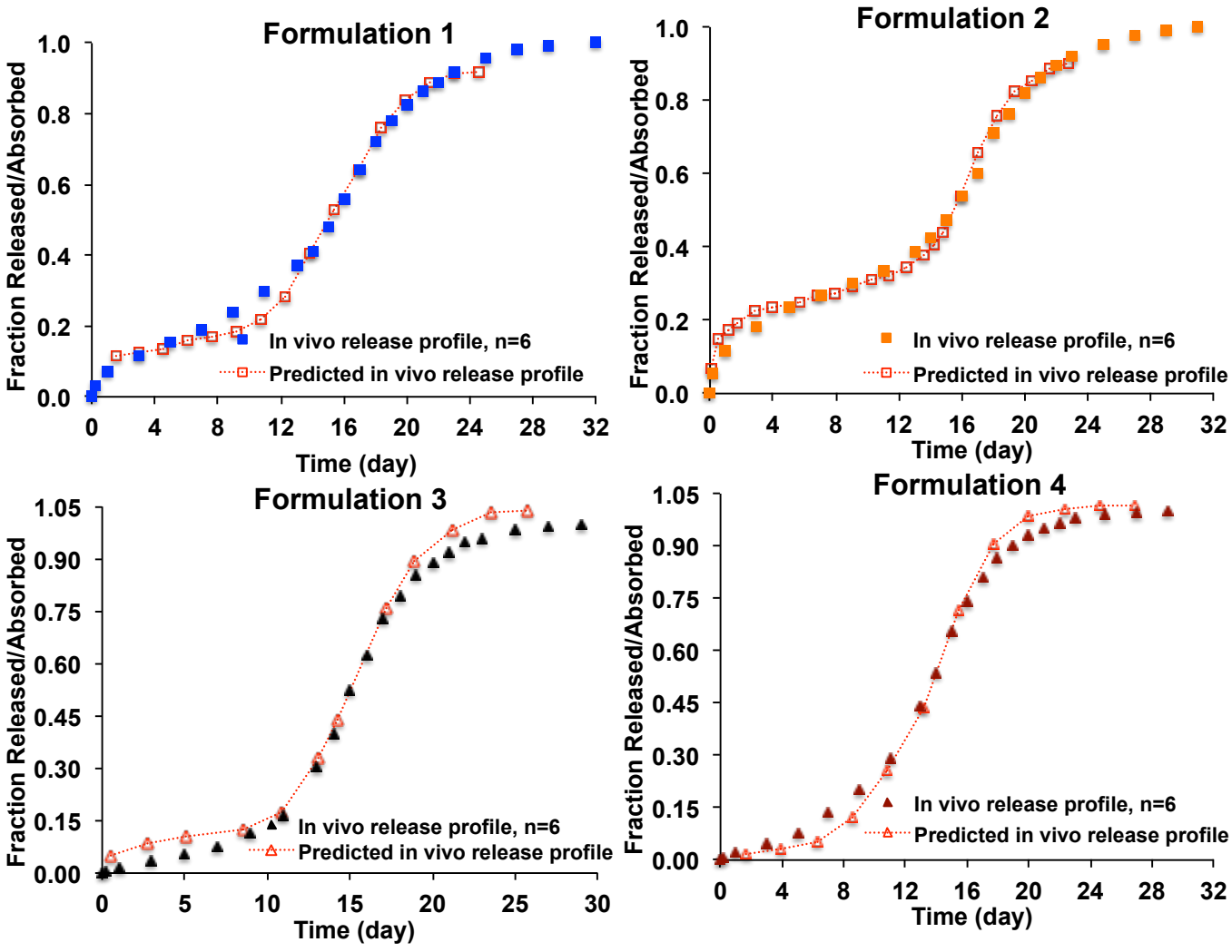
Case I: Compositionally Equivalent Risperidone Microspheres

- **Predicted *in vivo* risperidone release profiles**



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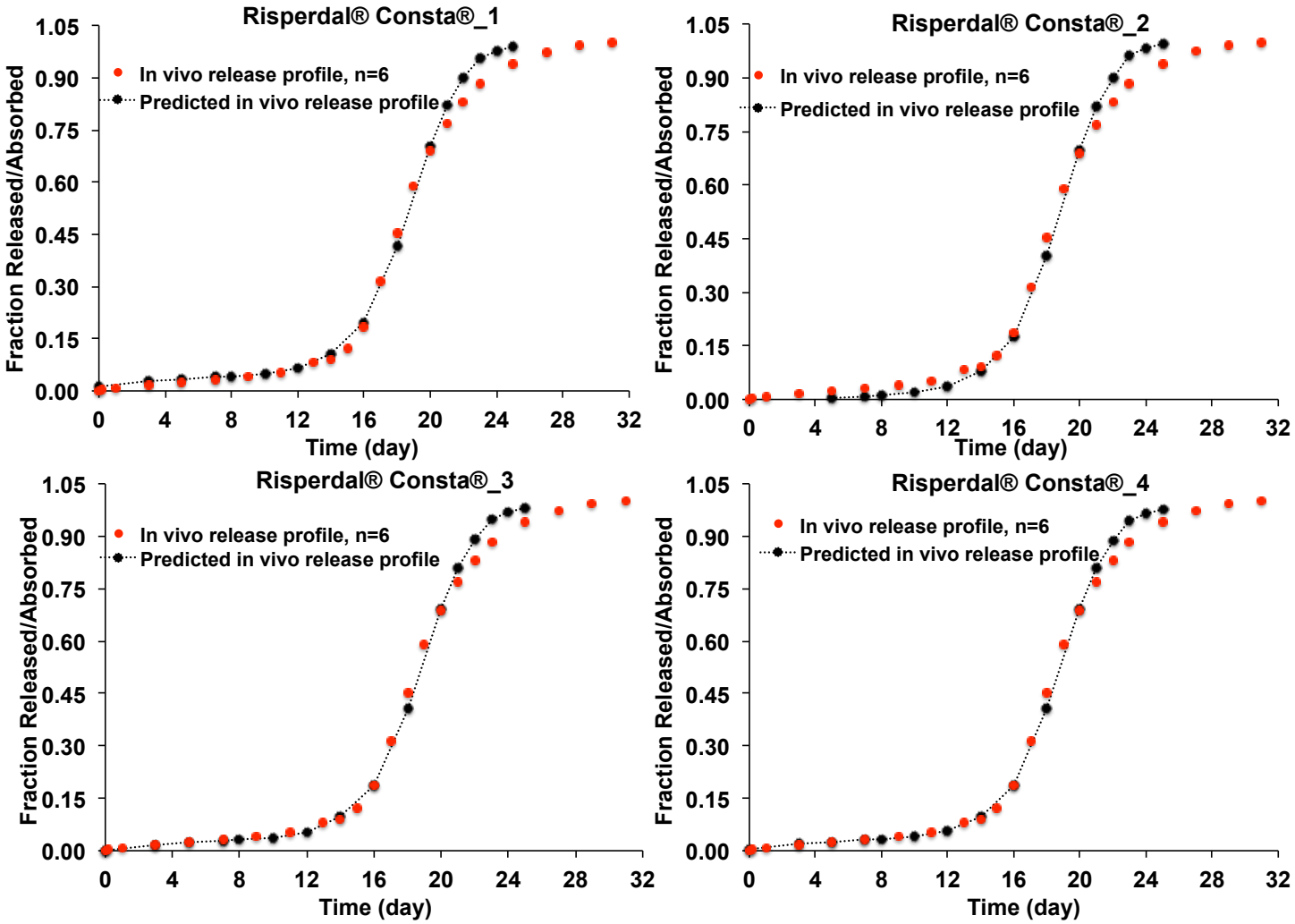
Case I: Compositionally Equivalent Risperidone Microspheres

- **Prediction for the RLD product**



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Case I: Compositionally Equivalent Risperidone Microspheres

➢ Validation of the developed IVIVC (based on the USP 4 method)

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

%PE: ~ 10% or less.

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Case I: Compositionally Equivalent Risperidone Microspheres

- **Validation of the developed IVIVC (based on the sample-and-separate method)**

PBS buffer

Internal validation	C_{max} (µg/L)			AUC (µg/L*day)		
	Pred.	Obs.	%PE	Pred.	Obs.	%PE
Formulation 2	22.06	41.62	-46.99	210.47	200.41	5.02
Formulation 3	28.61	29.98	-4.55	218.29	229.07	-4.70
Formulation 4	20.14	28.68	-29.76	195.64	220.95	-11.45
Average absolute %PE			27.10			7.06
External validation						
Formulation 1	16.93	27.99	-39.51	227.85	206.92	10.12
Prediction						
Risperdal® Consta®	33.06	38.29	-13.65	232.02	248.50	-6.63

HEPES buffer with Tween 20

Internal validation	C_{max} (µg/L)			AUC (µg/L*day)		
	Pred.	Obs.	%PE	Pred.	Obs.	%PE
Formulation 2	23.82	41.62	-42.77	206.17	200.41	2.87
Formulation 3	50.74	29.98	69.25	217.48	229.07	-5.06
Formulation 4	37.42	28.68	30.49	193.39	220.95	-12.47
Average absolute %PE			47.50			6.80
External validation						
Formulation 1	24.78	27.99	-11.47	236.91	206.92	14.49

%PE > 10%, the predictability of the developed IVIVCs based on the sample-and-separate method was **inconclusive**.

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Long Acting Suspensions

Drug Name	NDA No.	Active Ingredient	Strength/Dosing Frequency	Approval Date
Zyprexa Relprevv	022173	Olanzapine Pamoate	150 mg/2 wks, 300 mg/4 wks, 210 mg/2 wks, 405 mg/4 wks, or 300 mg/2 wks	12/11/2009
Depo-Provera	020246	Medroxyprogesterone Acetate	150 mg/mL/13 wks	10/29/1992
Depo-Provera	012541	Medroxyprogesterone Acetate	Initiation dose: 400 mg to 1000 mg/week Maintenance dose: 400 mg/month	9/23/1960
Abilify Maintena Kit	021866	Aripiprazole	300 mg or 400 mg/month	2/28/2013
Invega Sustenna	022264	Paliperidone Palmitate	39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, or 234 mg/1.5 mL/month	07/31/2009
Invega Trinza	207946	Paliperidone Palmitate	273 mg/0.875 mL, 410 mg/1.315 mL, 546 mg/1.75 mL, or 819 mg/2.625 mL/3 months	05/18/2015

In Vitro and In Vivo Stability Issues

- **Stability issues during product manufacturing *e.g.* drug excipient interactions**
- **Shelf-life stability of the drug, excipients and the drug product**
- ***In vivo* stability of the drug, excipients and drug product**

Acknowledgements

- NIH (1R01RR14171, 1R21HL090458-01, 1R43DK105627-01, 1R43EB011886-01)
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- Center for Pharmaceutical Processing Research
- USP
- Sotax Corp

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Thank You !