Development of *In Vitro-In Vivo* Correlation for Complex Parenteral Microsphere Drug Products – Effect of Burst Release

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PURPOSE

To understand the effect of differences in the burst release % of compositionally equivalent PLGA microspheres on the modeling and predictability of *in vitro-in vivo* correlation (IVIVC)

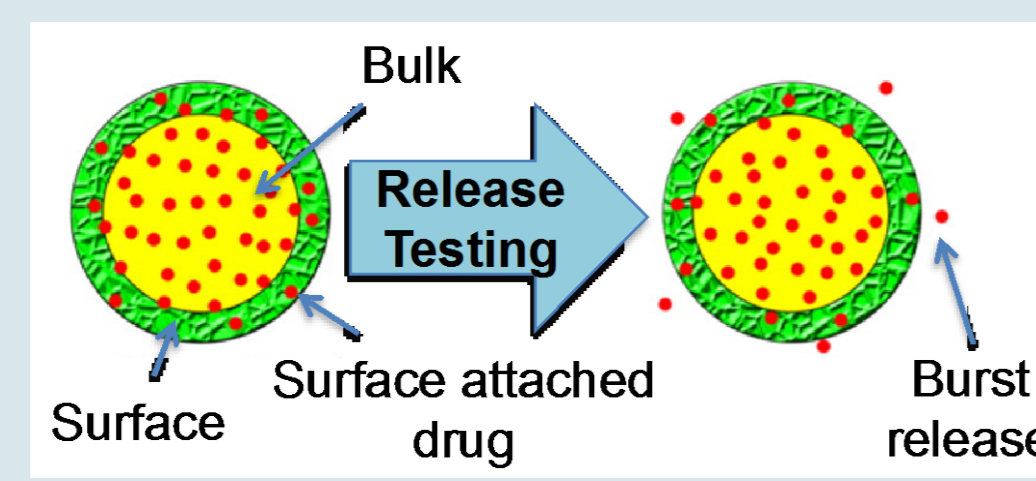### *In vitro-in vivo* correlation (IVIVC):

In vitro response ←→ **IVIVC** ←→ *In vivo response*

Predictive mathematical model

Burst release:

Initial fast release of drug from the surface of microspheres

- Highly variable – difficult to to model mathematically
- *In vivo* burst release is absorption rate limited– IVIVC predictability?

METHOD(S)

Model Drug: Risperidone

Polymer: Poly(lactic-co-glycolic acid) (PLGA) with similar molecular weight to that of the commercially available risperidone microsphere product (Risperdal® Consta®, one Month formulation).

Preparation Method: PLGA microspheres were prepared *via* a single emulsion-solvent extraction/evaporation method.

Process variables: Solvent systems (type and composition), sieving method.

Characterization of microspheres:

1. **Critical quality attributes:** Drug loading, particle size, size distribution, porosity and morphology

2. *In Vitro* Release Testing:
- Method: Developed USP apparatus 4 method
- Cell Preparation: Briefly, ~ 10 mg of microspheres mixed with glass beads were put into flow through cells
- Medium: 10 mM phosphate buffer with 0.01% w/v sodium azide, pH 7.4
- Testing Temperature: 37°C
- Flow Rate: 8 mL/min
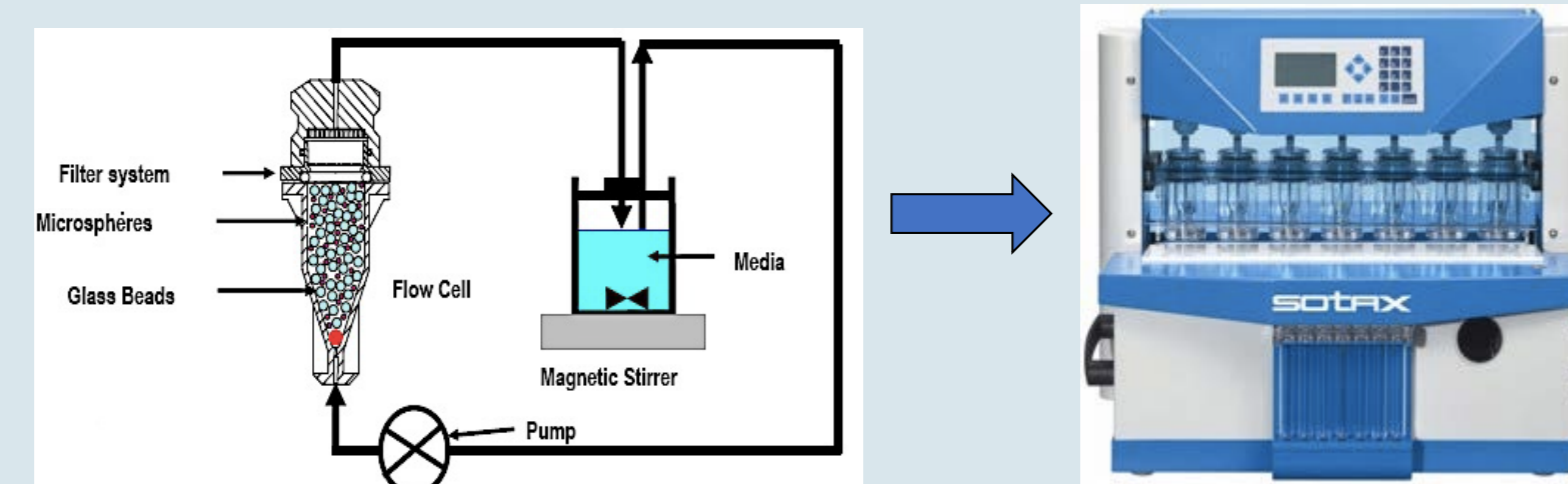
3. *In Vivo* Release Testing:
- Model: Rabbit
- Route: IM injection
- Blood Sample collection

4. *In vitro-in vivo* correlation (IVIVC):
- 2- Stage deconvolution Approach (Loo-Riegelman method)
- Validation of the model: Internal as well as external
- Estimation of % Prediction Error (%PE)

RESULT(S)

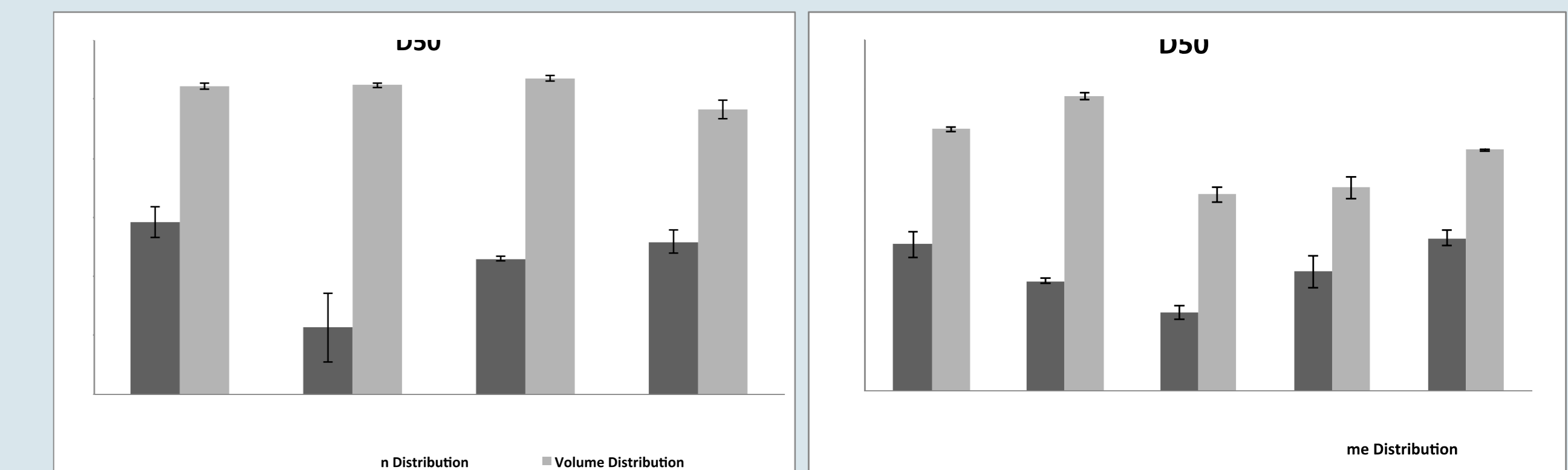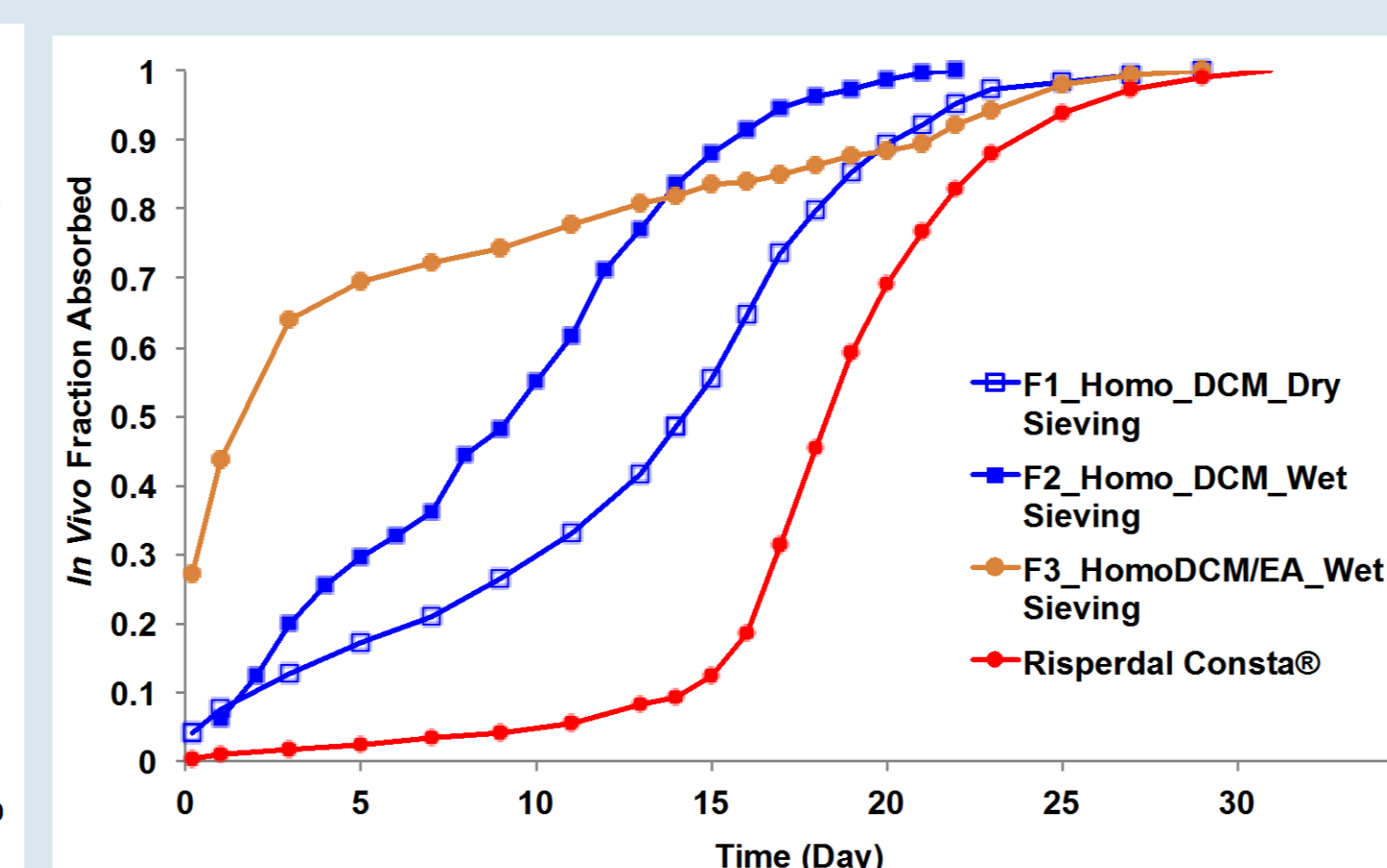| Formulations (Q1/Q2) ~ 36 % DL	F1	F2	F3	F4	F5	F6	F7	Risperdal Consta®
	High Burst Release Formulations			Low Burst Release Formulations				RLD
Solvent System	DCM		DCM/EA	EA/BA		DCM/BA	DCM/Methanol	
Preparation Method	Homogenization & Dry sieving	Homogenization & wet sieving		Vortex & wet sieving	Homogenization & wet sieving			
%Porosity	43.19	46.04	61.01	54.98	61.75	48.43	47.18	43.97

Figure 1. Mean Particle Size of the prepared risperidone microspheres with variable burst release phase (Mean±SD, μm)
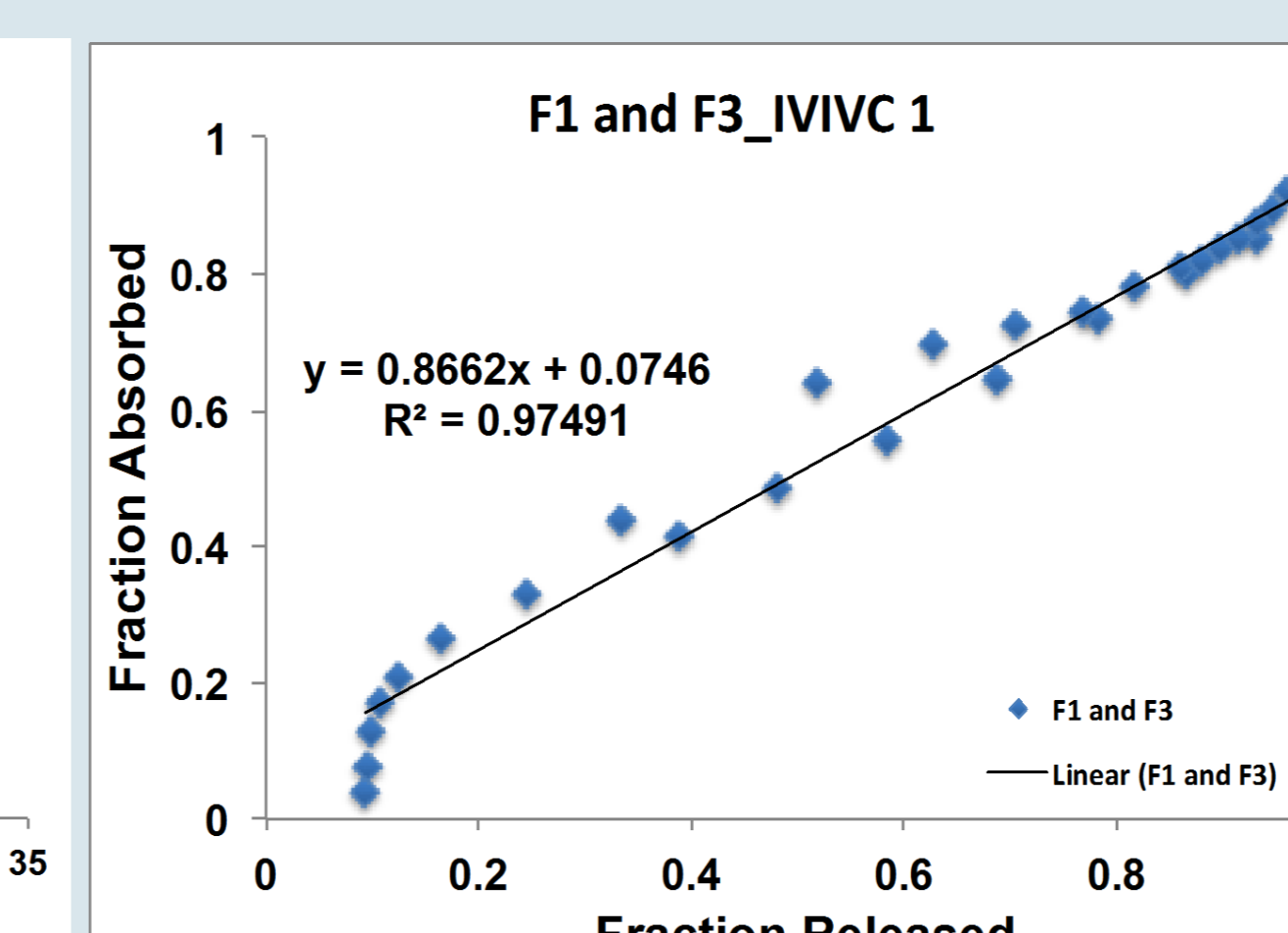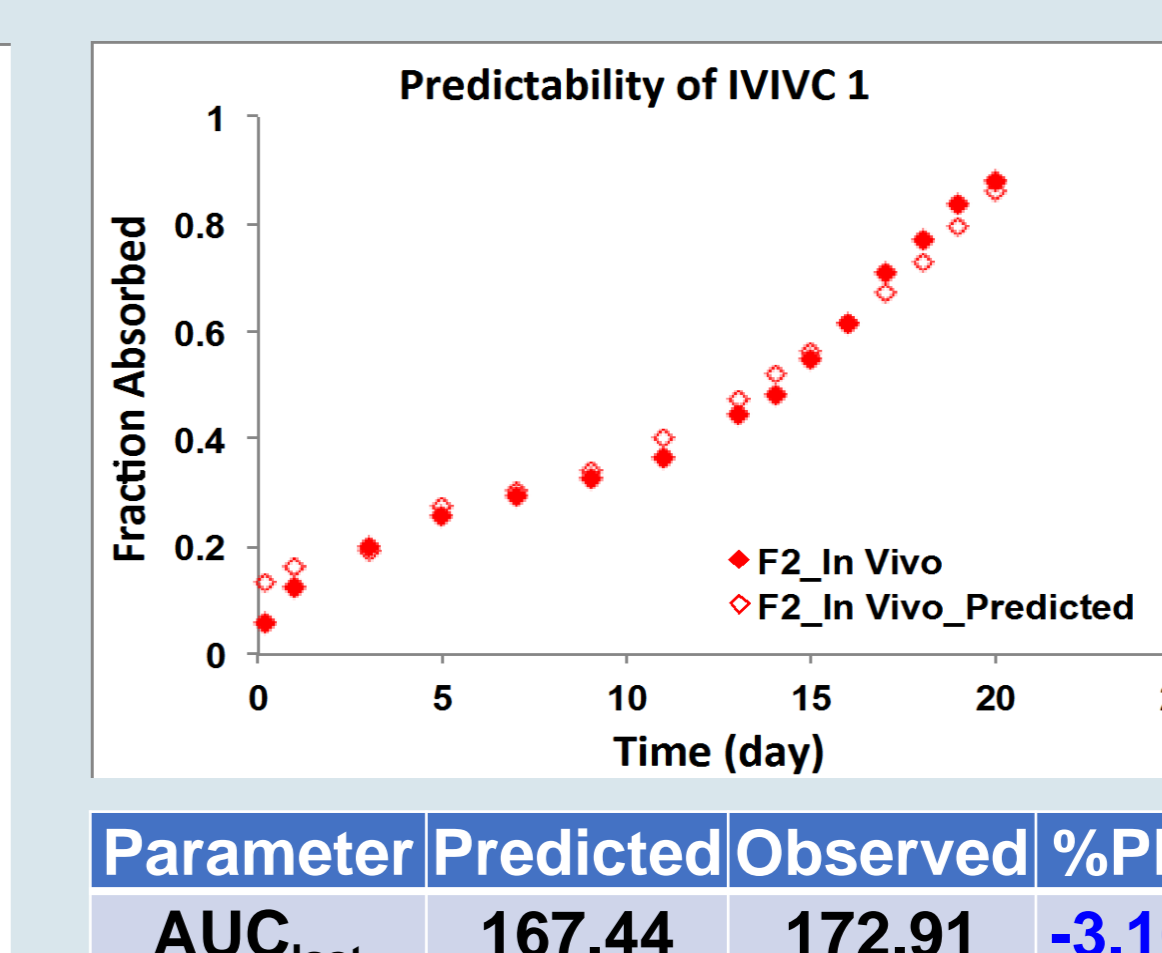
High Burst Release Formulations
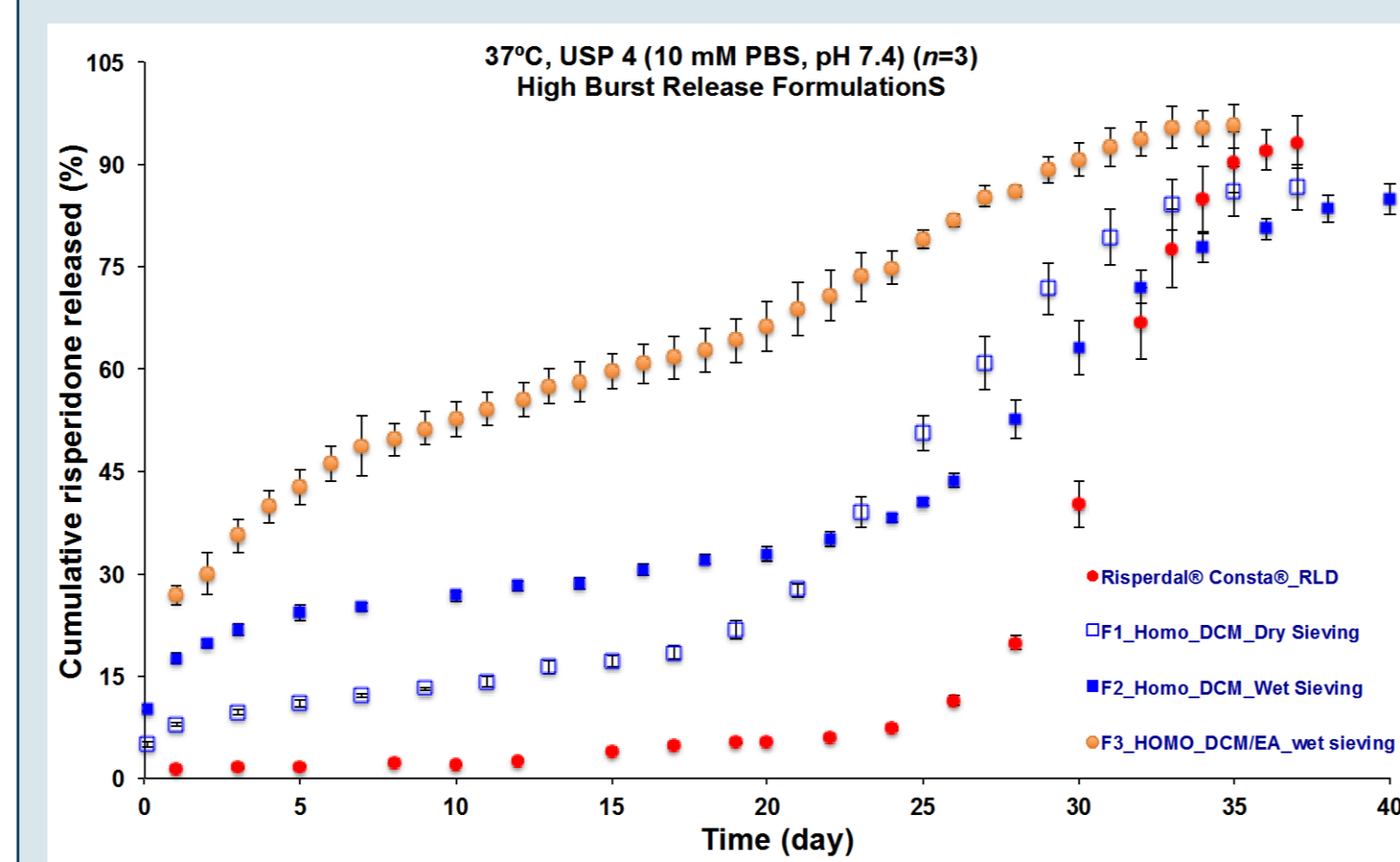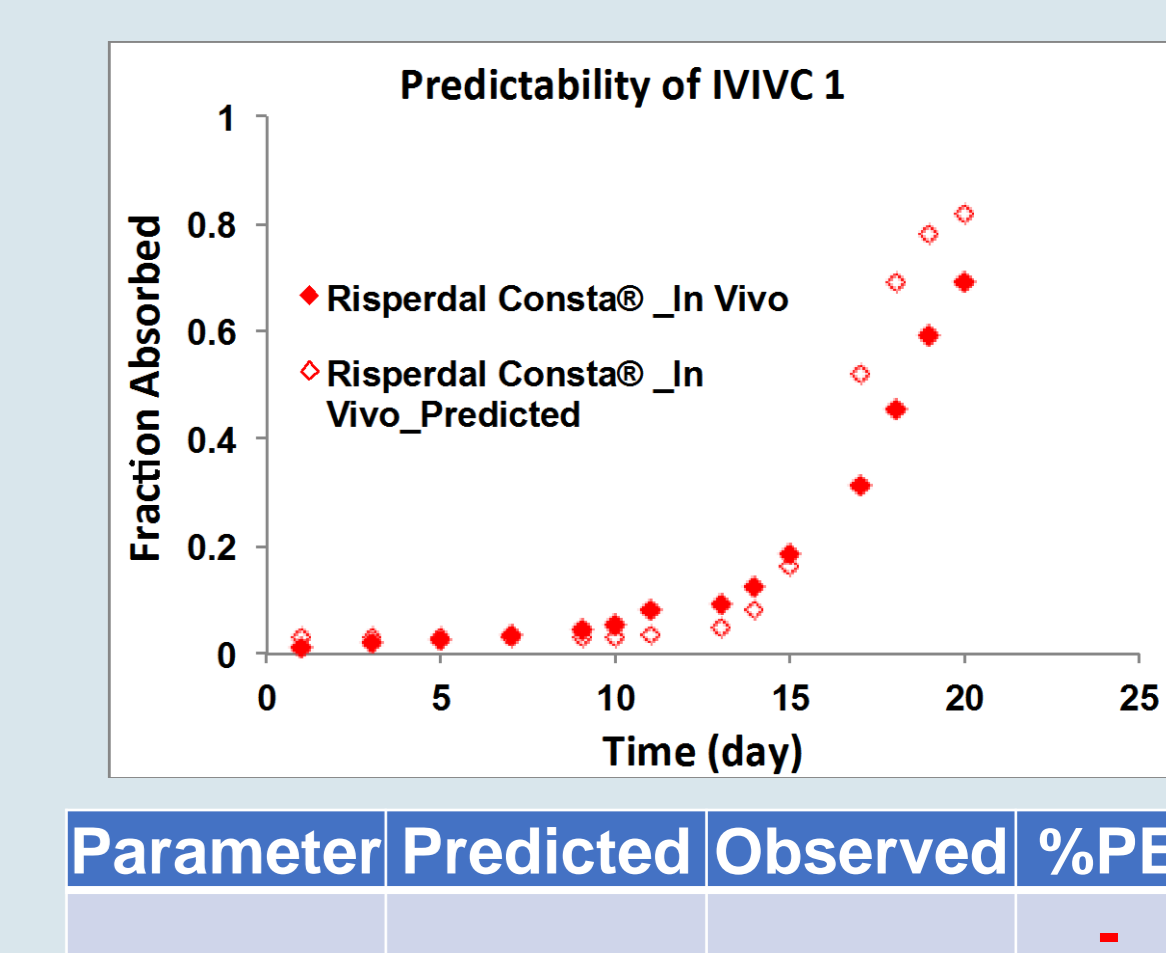

In vitro release profiles

In vivo release profiles

F1 and F3_IVIVC 1

$y = 0.8662x + 0.0746$
$R^2 = 0.97491$

IVIVC

Predictability of IVIVC 1

Parameter	Predicted	Observed	%PE
AUC$_{last}$	167.44	172.91	-3.16
C$_{max}$	15.48	14.99	3.24

Predictability of IVIVC 1

Parameter	Predicted	Observed	%PE
AUC$_{last}$	188.82	247.14	23.59
C$_{max}$	39.62	38.29	3.48

Low Burst Release Formulations
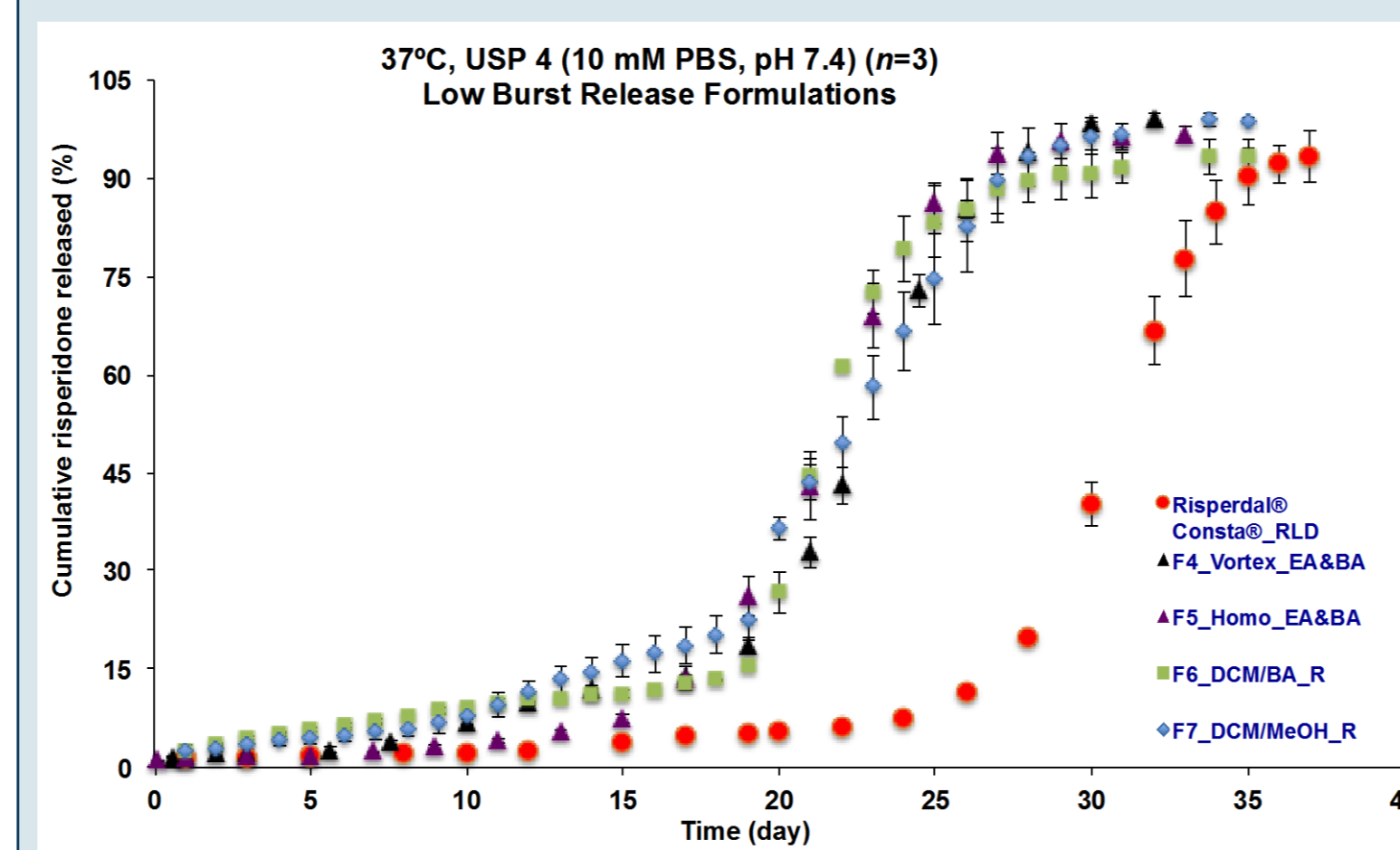
In vitro release profiles

In vivo release profiles

F5, F6 and F7_IVIVC 2

$y = 0.9432x - 0.0006$
$R^2 = 0.95628$

IVIVC

Predictability of IVIVC 2
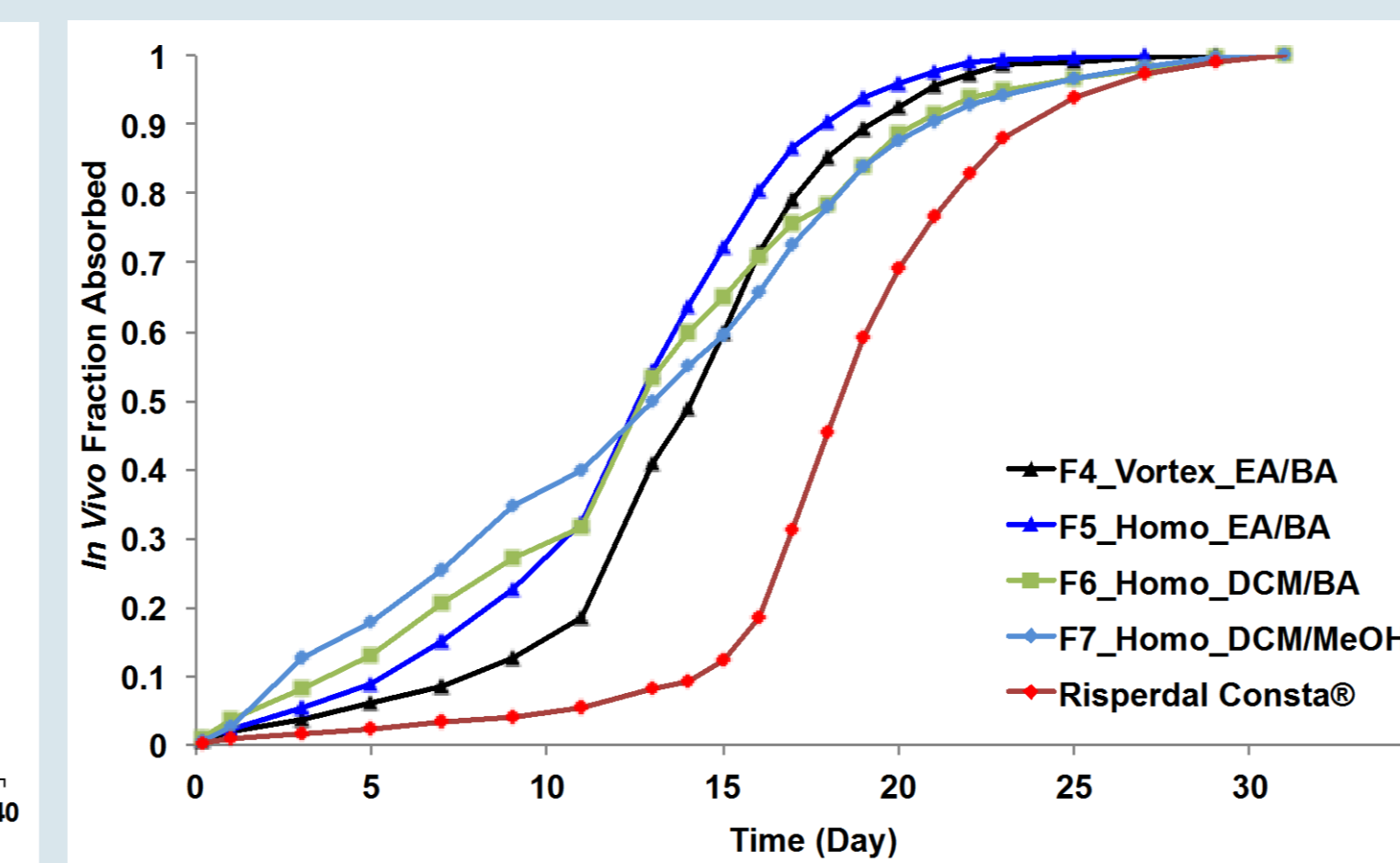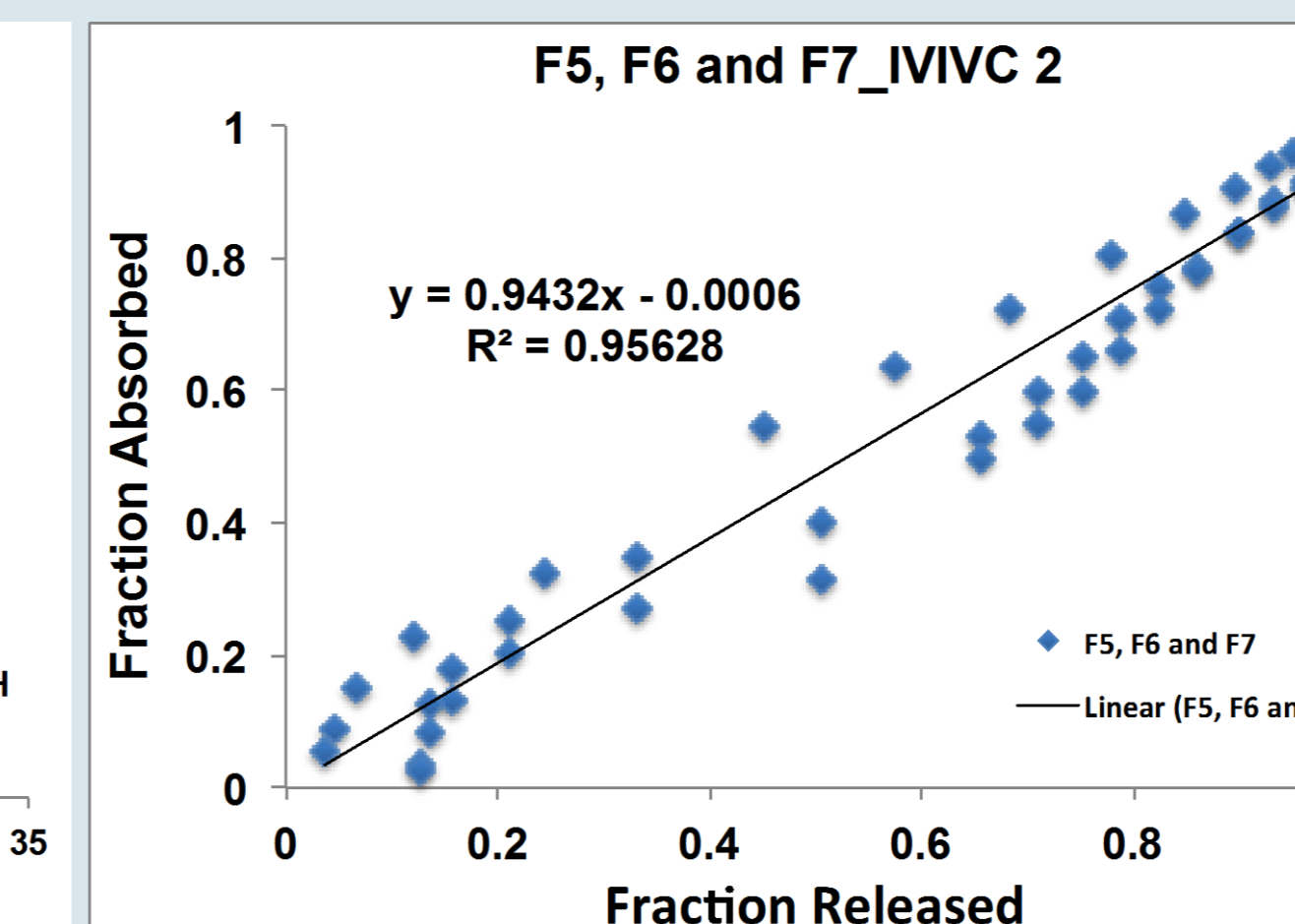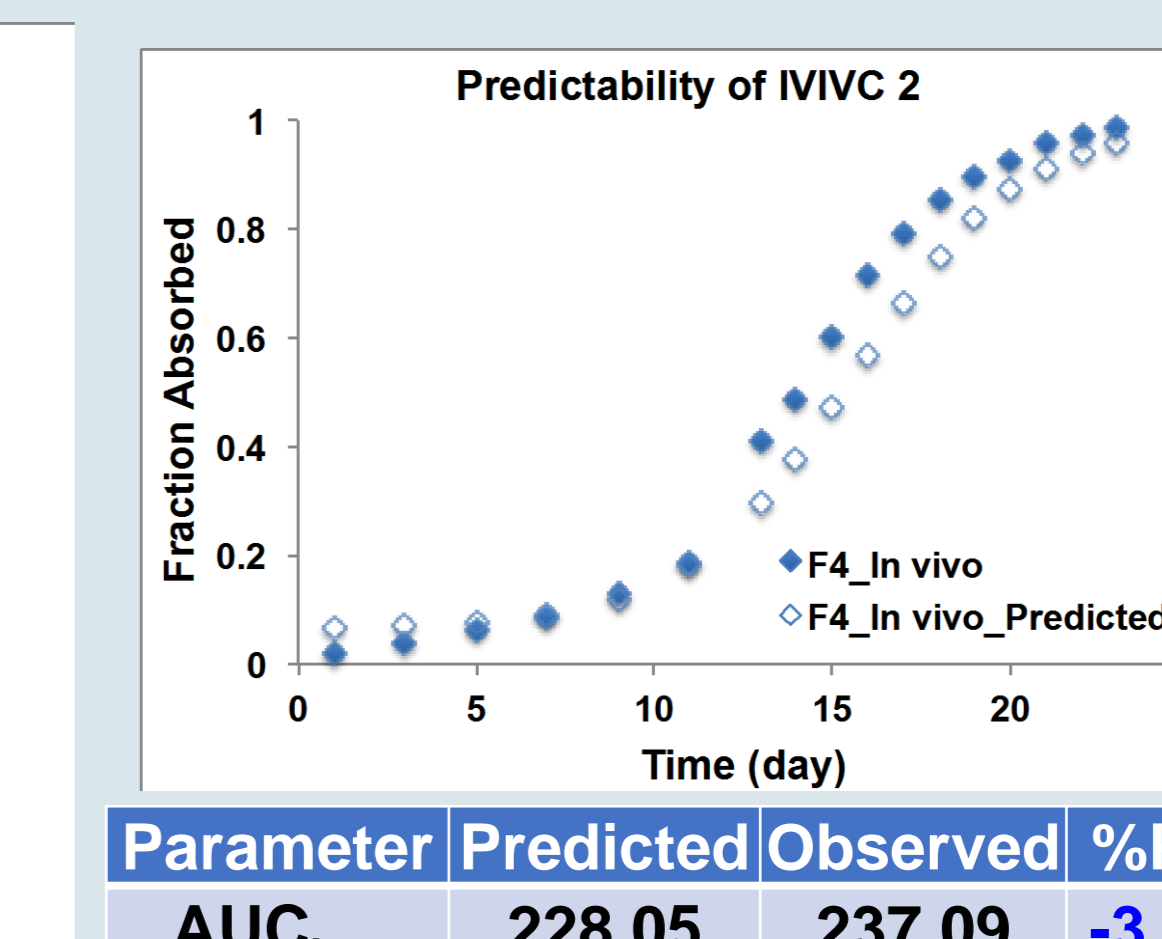
Parameter	Predicted	Observed	%PE
AUC$_{last}$	228.05	237.09	-3.81
C$_{max}$	41.27	39.98	3.24

Predictability of IVIVC 2
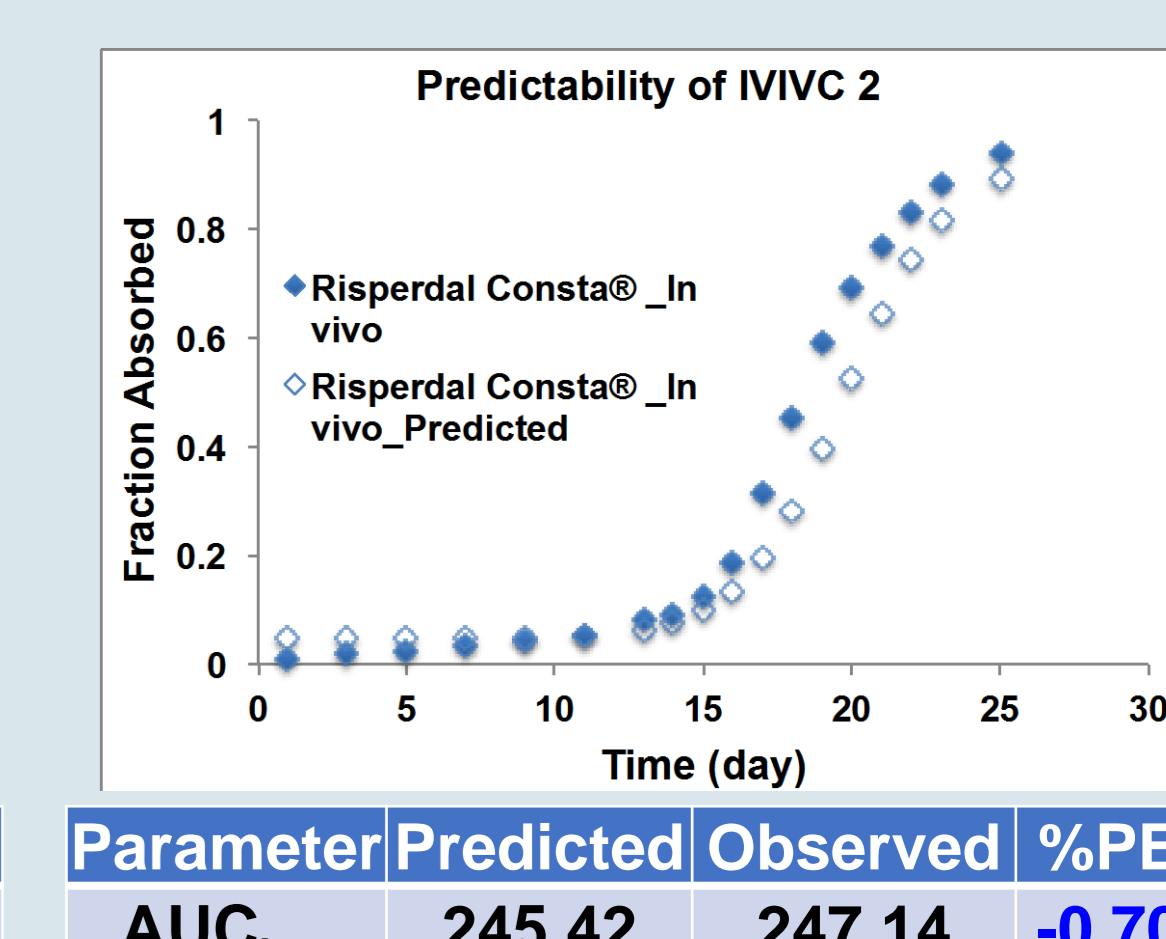
Parameter	Predicted	Observed	%PE
AUC$_{last}$	245.42	247.14	-0.70
C$_{max}$	39.51	38.29	10.30

CONCLUSION(S)

✓ The burst release phase of risperidone microspheres appeared to be sensitive to manufacturing changes such as the solvent system.

✓ An affirmative level A IVIVC was established between fraction released *in vitro* and fraction absorbed *in vivo* for the formulations with similar burst release characteristics using a rabbit model.

✓ This indicates that the developed USP Apparatus 4 based *in vitro* release testing method has the potential to be used as a biorelevant method.

FUNDING

- **Disclaimer:** This poster reflects the views of the authors and should not be construed to represent FDA'S views or policies.

REFERENCES:

1. Kastellorizios M., Burgess D., *Mol. Pharmaceutics* 2015, 12, 3332-38.

2. FDA Guidance for Industry: extended release oral dosage forms: development, evaluation and application of in vitro/in vivo correlation, Rockville, MD, 1997.