Understanding *In Situ* Forming Implants and Development of Appropriate *In Vitro* Testing Methods

Diane J. Burgess, Ph.D.
Pfizer Distinguished Professor of Pharmaceutical Technology
Board of Trustees Distinguished Professor of Pharmaceutics
University of Connecticut

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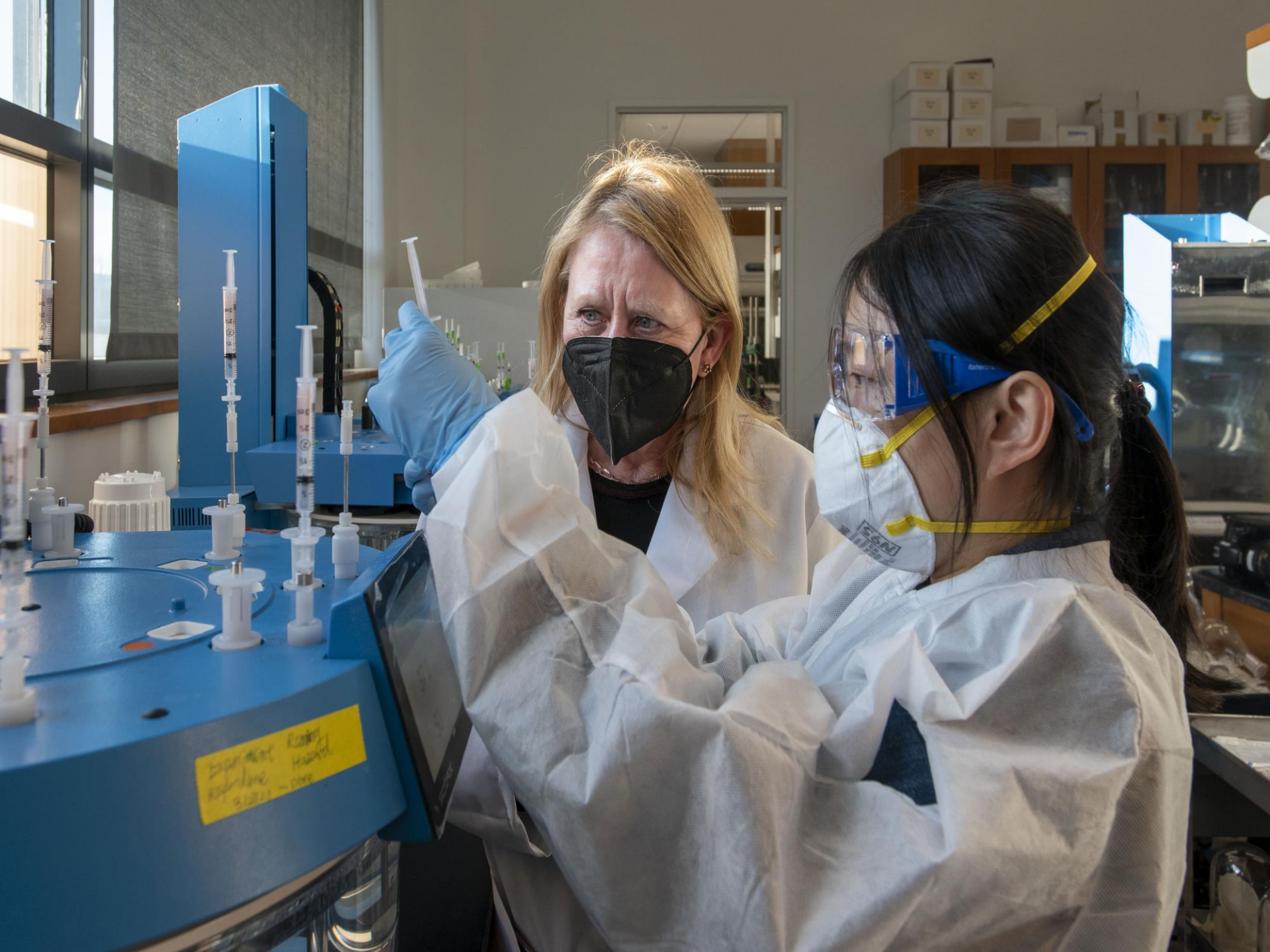
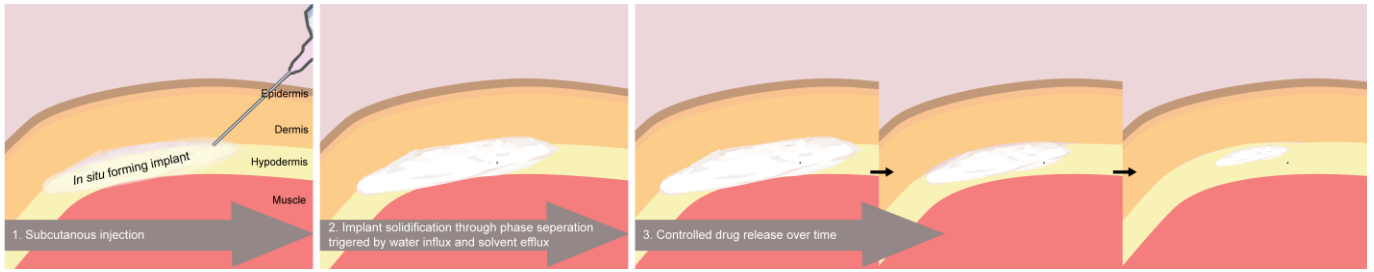
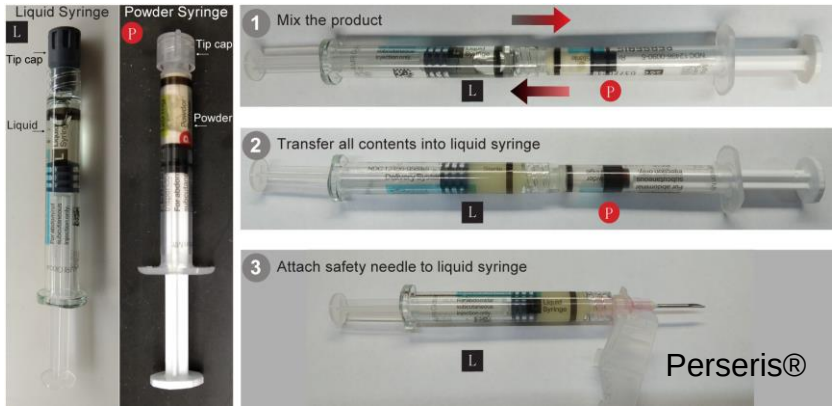
Rockville, MD



In situ forming implants
-Definition and advantages





- **Localized/systemic drug delivery**
- **Sustained drug release over periods of days to months**
- **Injectable and less invasive compared to traditional solid implants**
- **Improved patient compliance**

X. Wang, D.J. Burgess, Drug release from in situ forming implants and advances in release testing, Adv. Drug Deliv. Rev., (2021) 113912.

In situ forming implants
- Commercial products

Product /Approval date	Manufacturer	Indication	Powder Syringe	Liquid Syringe	Duration
Atridox® 1988	Tolmar	Chronic adult periodontitis	50 mg doxycycline hyclate	450 mg (36.7% PLA dissolved in 63.3% NMP)	7 days
Eligard® 2002	Tolmar	Advanced prostate cancer	7.5 mg leuprolide acetate	0.25 ml: 82.5 mg PLGA (L/G 50:50), 160 mg NMP	1 month
			22.5 mg leuprolide acetate	0.375 ml: 158.6 mg PLGA (L/G 75:25), 193.9 mg NMP	3 months
			30 mg leuprolide acetate	0.5 ml: 211.5 mg PLGA (L/G 75:25), 258.5 mg NMP	4 months
			45 mg leuprolide acetate	0.375 ml: 165 mg PLGA (L/G 85:15), 165 mg NMP	6 months
Sublocade® 2017	Indivior	Opioid addiction	N/A	0.5 ml: 100 mg buprenorphine, 178 mg PLGA (L/G 50:50), 278 mg NMP	1 month
				1.5 ml: 300 mg buprenorphine, 533 mg PLGA (L/G 50:50), 833 mg NMP	
Perseris® 2018	Indivior	Schizophrenia	90 mg risperidone	0.6 ml: 228 mg PLGA (L/G 80:20), 282 mg NMP	1 month
			120 mg risperidone	0.8 ml: 304 mg PLGA (L/G 80:20), 376 mg NMP	
Fensovi® 2020	Tolmar	Pediatric patients with central precocious puberty	45 mg Leuprolide acetate	165 mg PLGA (L/G ratio, 85:15), 165 mg NMP	6 months
Camcevi® 2021	Accord BioPharma	Advanced prostate cancer	N/A	42 mg Leuprolide mesylate, 184 mg PLA/136 mg NMP	6 months

X. Wang, D.J. Burgess, Drug release from in situ forming implants and advances in release testing, Adv. Drug Deliv. Rev., (2021) 113912.

In situ forming implants
-Issues

- **Limited commercial products**
- **Lack of FDA guidance on *in vitro* release testing**

Objectives

1. **Develop reproducible, biorelevant *in vitro* release testing method for risperidone *in situ* forming implants**

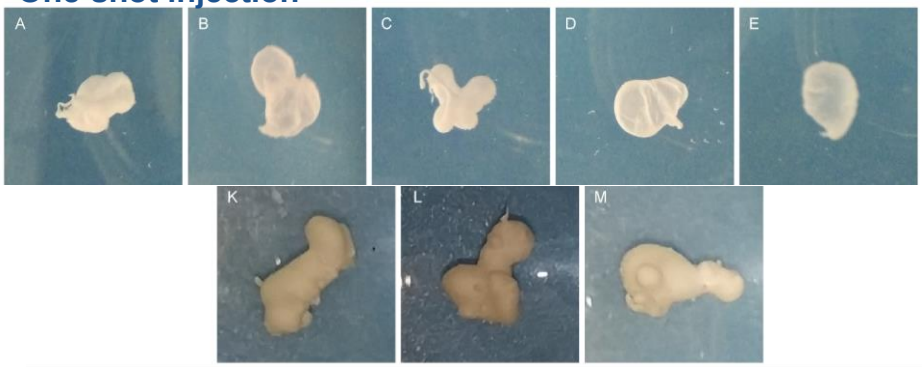
2. **Investigate impact of polymer attributes on performance of *in situ* forming implants**

3. **Develop bioequivalence recommendations for *in situ* forming implants through an *in vitro* only approach**

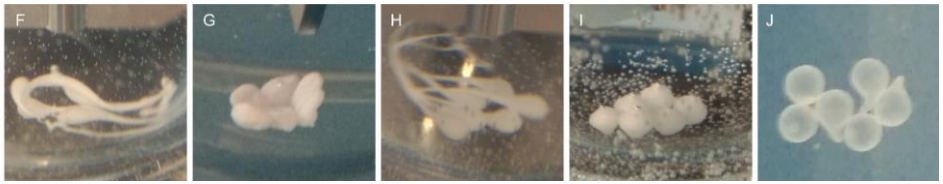
In situ forming implants
-Development of reproducible *in vitro* release testing method

Irregular shape of implants formed by direct injection

One-shot injection



Drop-by-drop injection

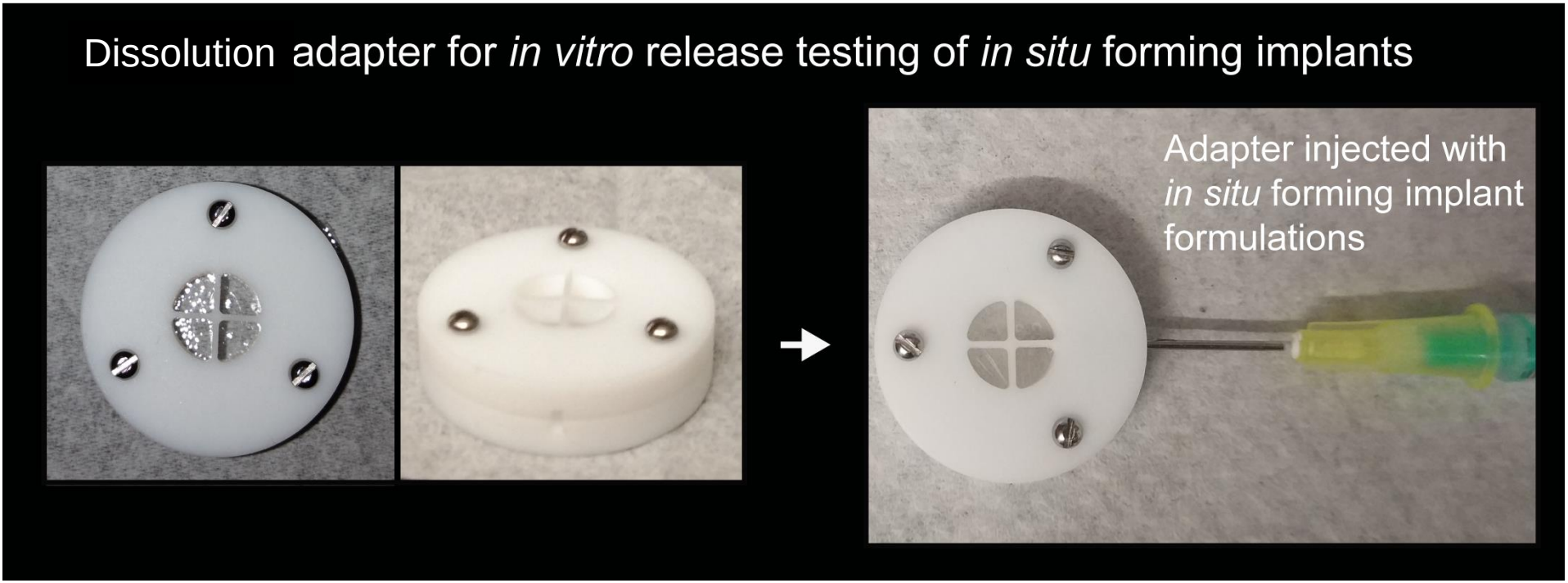


X. Wang, Q. Bao, M. S. Suh, M. Kastellorizios, R. Wang, D. J. Burgess. Novel adapter method for in vitro release testing of in situ forming implants. Int. J. Pharm., 2022, 621:121777.

In situ forming implants

-Development of reproducible *in vitro* release testing method

Novel shape-controlling adapter with PVA film



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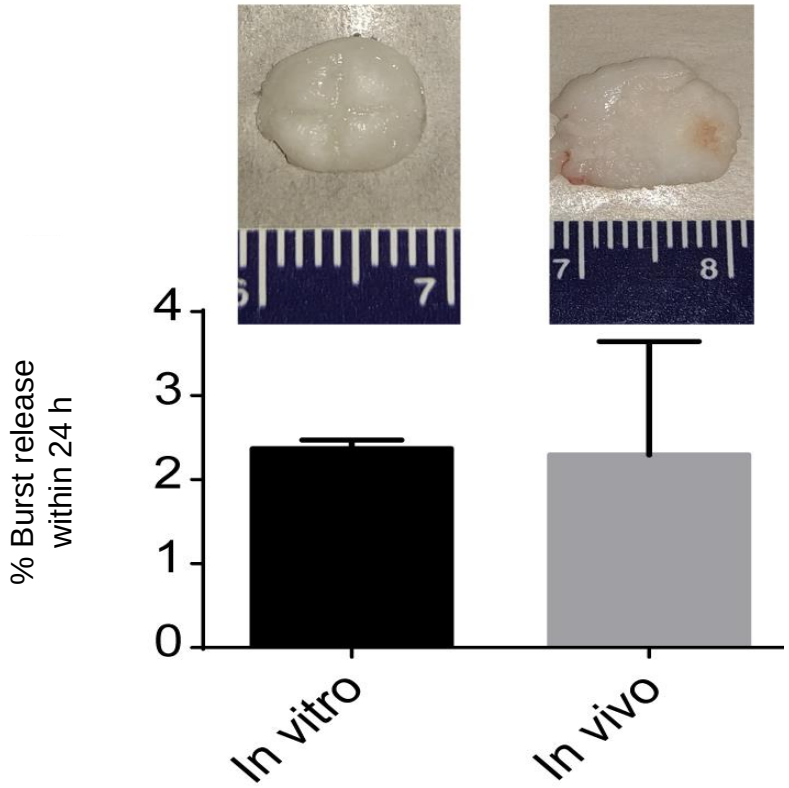
In situ forming implants

-Development of reproducible *in vitro* release testing method

Bio-mimicking and reproducible



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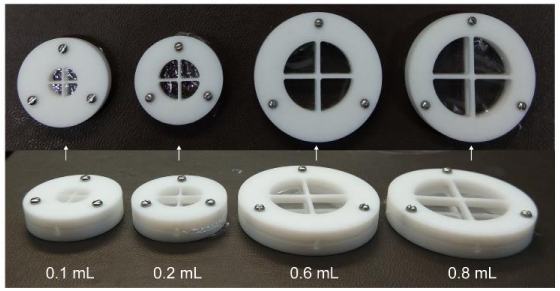
In situ forming implants

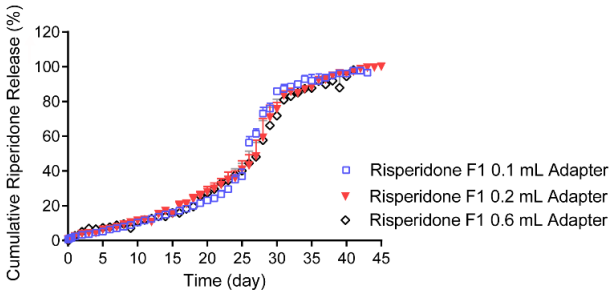
-Development of reproducible *in vitro* release testing method

Volume-independent drug release

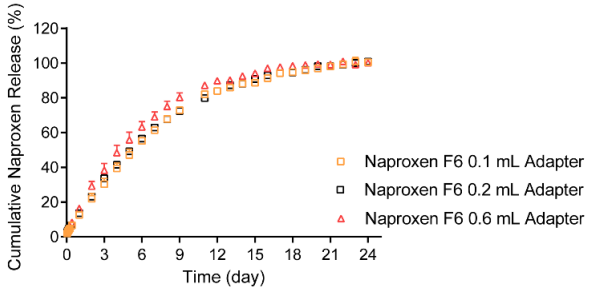
A



B



C



Formulation	Drug	PLGA	NMP
Risperidone F1	90 mg risperidone	228 mg PLGA (L/G 80/20, 24.2 KDa)	282 mg
Naproxen F6	100 mg naproxen	228 mg PLGA (L/G 80/20, 24.2 KDa)	282 mg

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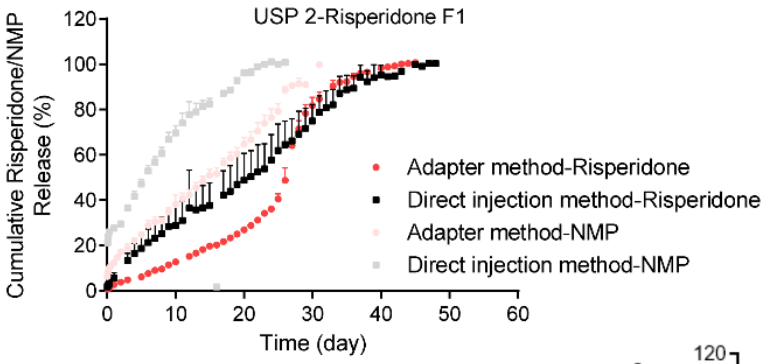
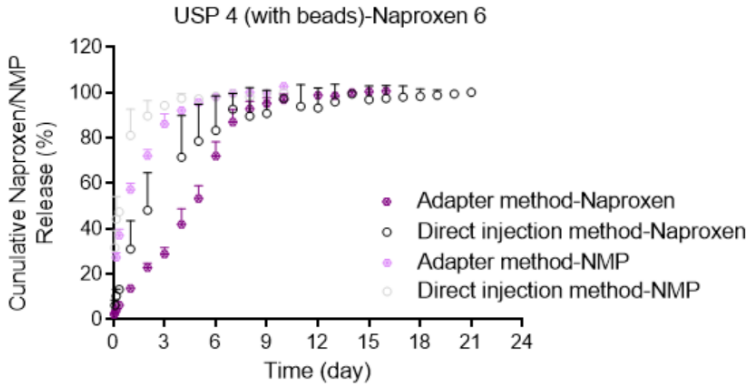
In situ forming implants

-Development of reproducible *in vitro* release testing method

Consistent release data and capacity to distinguish different release phases





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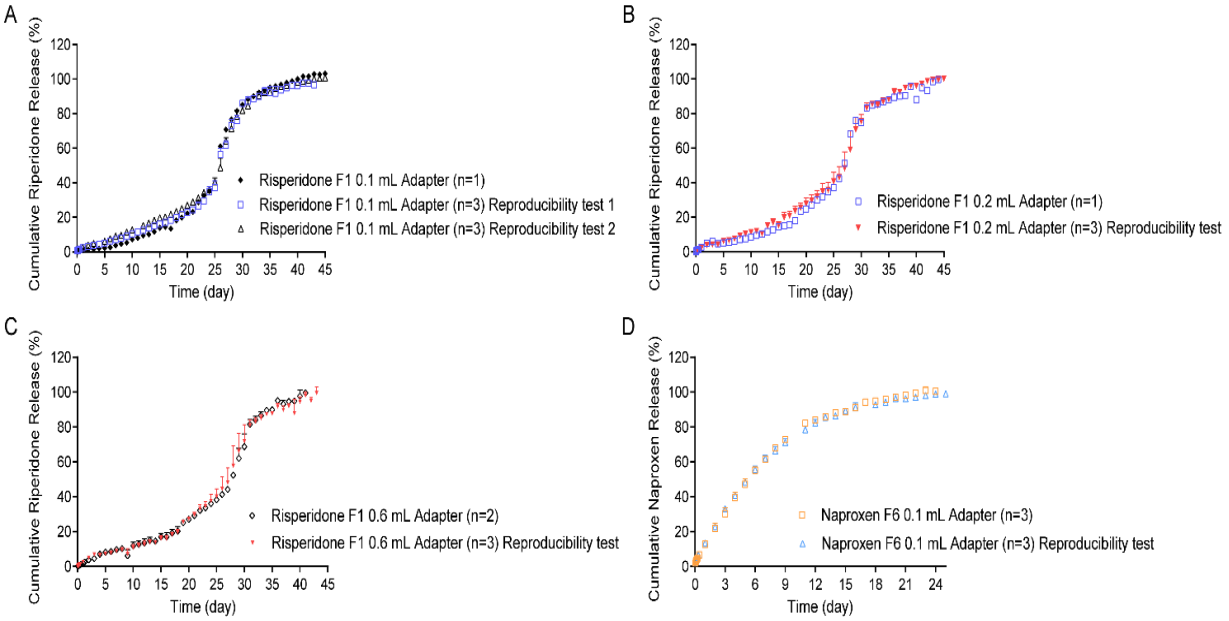
In situ forming implants
-Development of reproducible *in vitro* release testing method

Desirable reproducibility



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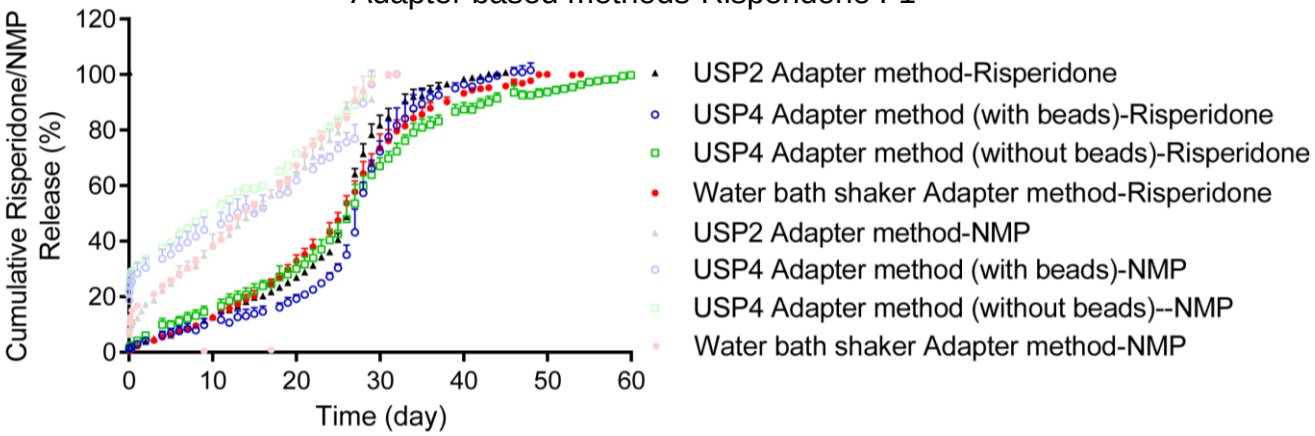
In situ forming implants

-Development of reproducible *in vitro* release testing method

Applicable to different dissolution apparati (USP 2, USP 4, water bath shaker)

Adapter based methods-Risperidone F1



➡ Discriminative in apparatus changes

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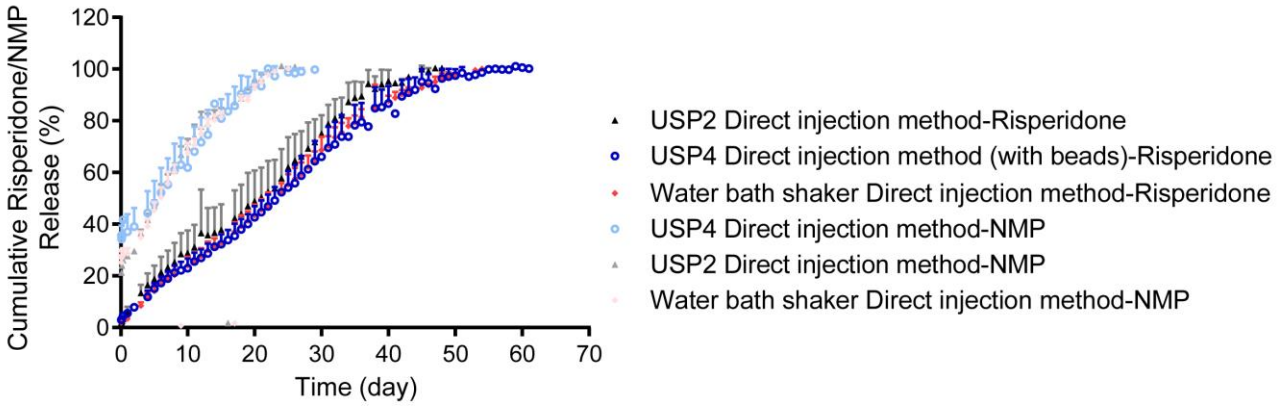
In situ forming implants
-Development of reproducible *in vitro* release testing method

Applicable to different dissolution apparati (USP 2, USP 4, water bath shaker)

Direct injection methods-Risperidone F1



➡ Failed to discriminate apparatus changes due to the large error bars

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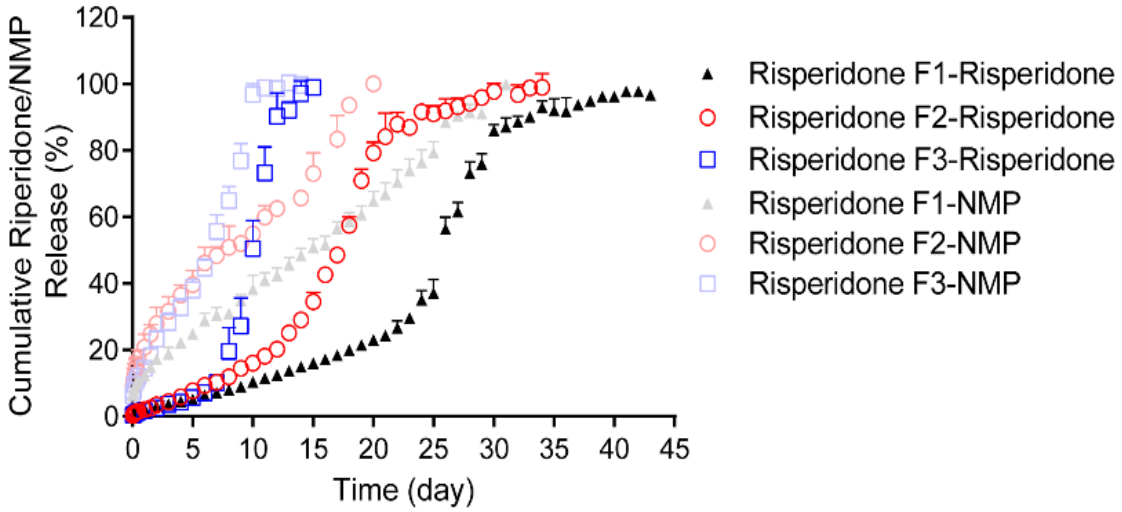
In situ forming implants

-Development of reproducible *in vitro* release testing method

Ability to discriminate formulation changes with significant differences in PLGA attributes



Formulation	Drug	PLGA	NMP
Risperidone F1	90 mg risperidone	228 mg PLGA (L/G 80/20, 24.2 KDa)	282 mg
Risperidone F2	90 mg risperidone	228 mg PLGA (L/G 75/25, 16.8 KDa)	282 mg
Risperidone F3	90 mg risperidone	228 mg PLGA (L/G 50/50, 23.5 KDa)	282 mg

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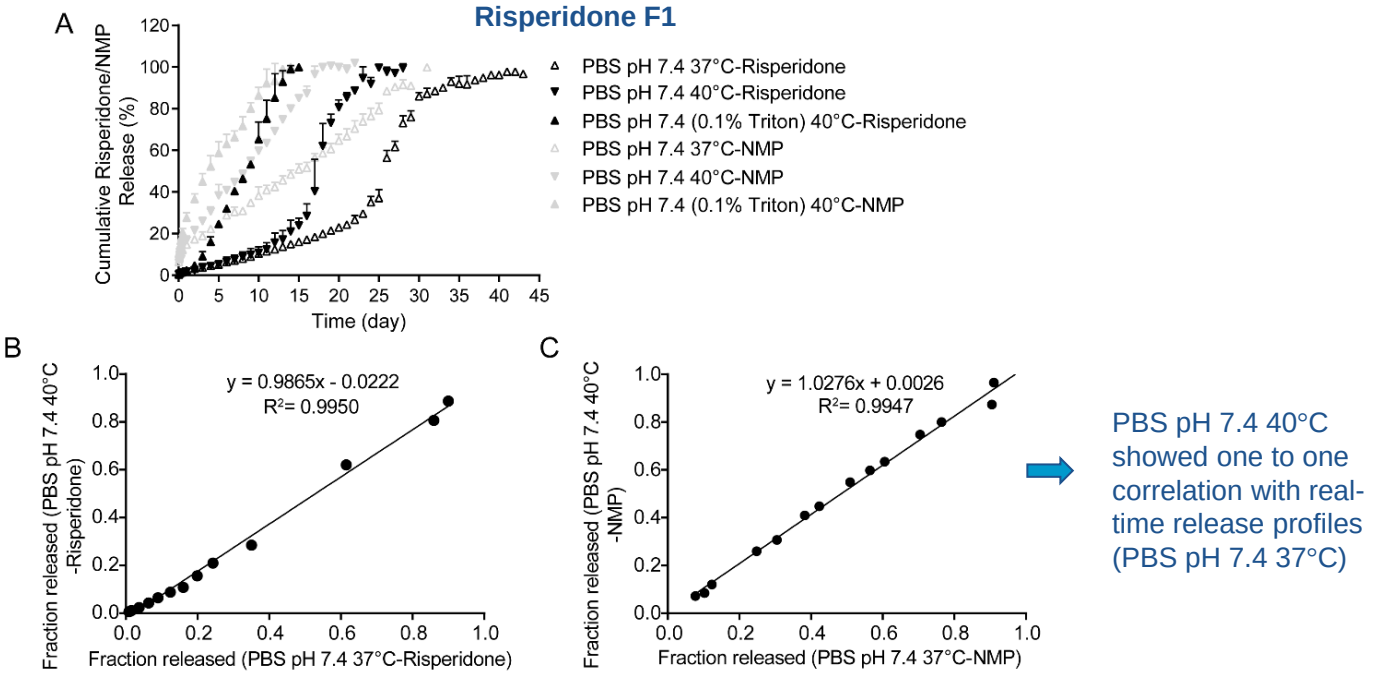
In situ forming implants
-Development of reproducible *in vitro* release testing method

Accelerated dissolution method based on the novel adapter



PBS pH 7.4 40°C showed one to one correlation with real-time release profiles (PBS pH 7.4 37°C)

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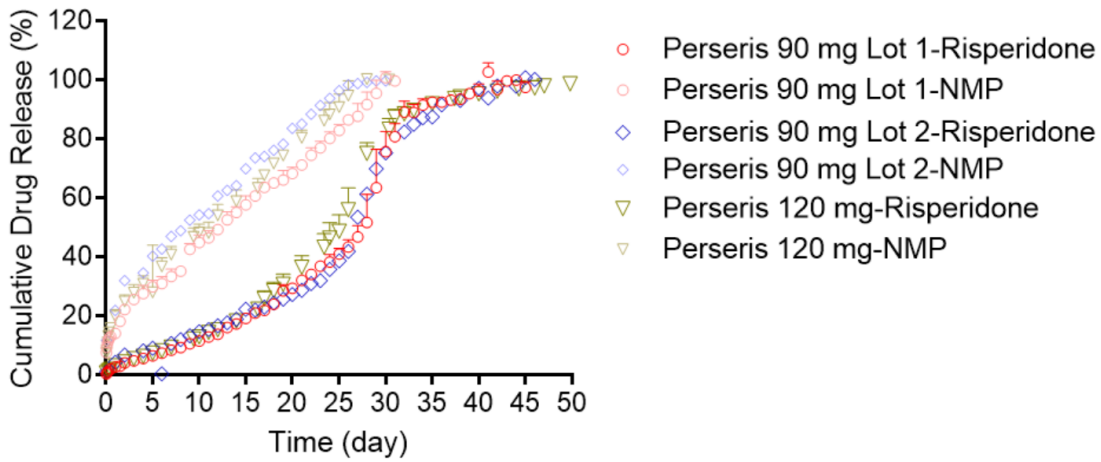
In situ forming implants
-Reverse engineering of RLD Perseris® and *in vitro*/ *in vivo* characterization

Formulation	Molecular weight (tested)	L/G ratio	End group	Blockiness (Rc)
Perseris® 90 mg	22.2 kDa	79.52/20.48	Acid	2.53
Perseris® 120 mg	21.7 kDa	78.48/21.52	Acid	2.48



In vitro release testing of Perseris in phosphate buffered saline (pH 7.4) at 37°C using 0.1 mL adapters, USP 2 (n=3).

Comparison	f2 value
	Risperidone
Perseris 90 mg Lot 1 vs Perseris 90 mg Lot 2	72.41
Perseris 90 mg Lot 1 vs Perseris 120 mg Lot 1	59.29

f2 test indicates high similarity between different strengths and between different lots of the same strength

X. Wang, Q. Bao, R. Wang, B. Wan[a], Y. Wang, B. Qin, D. J. Burgess. Reverse Engineering of Perseris and Development of Compositionally Equivalent Formulations. *Int. J. Pharm.*, 639: 122948.

In situ forming implants
-Reverse engineering of RLD Perseris® and *in vitro/ in vivo* characterization

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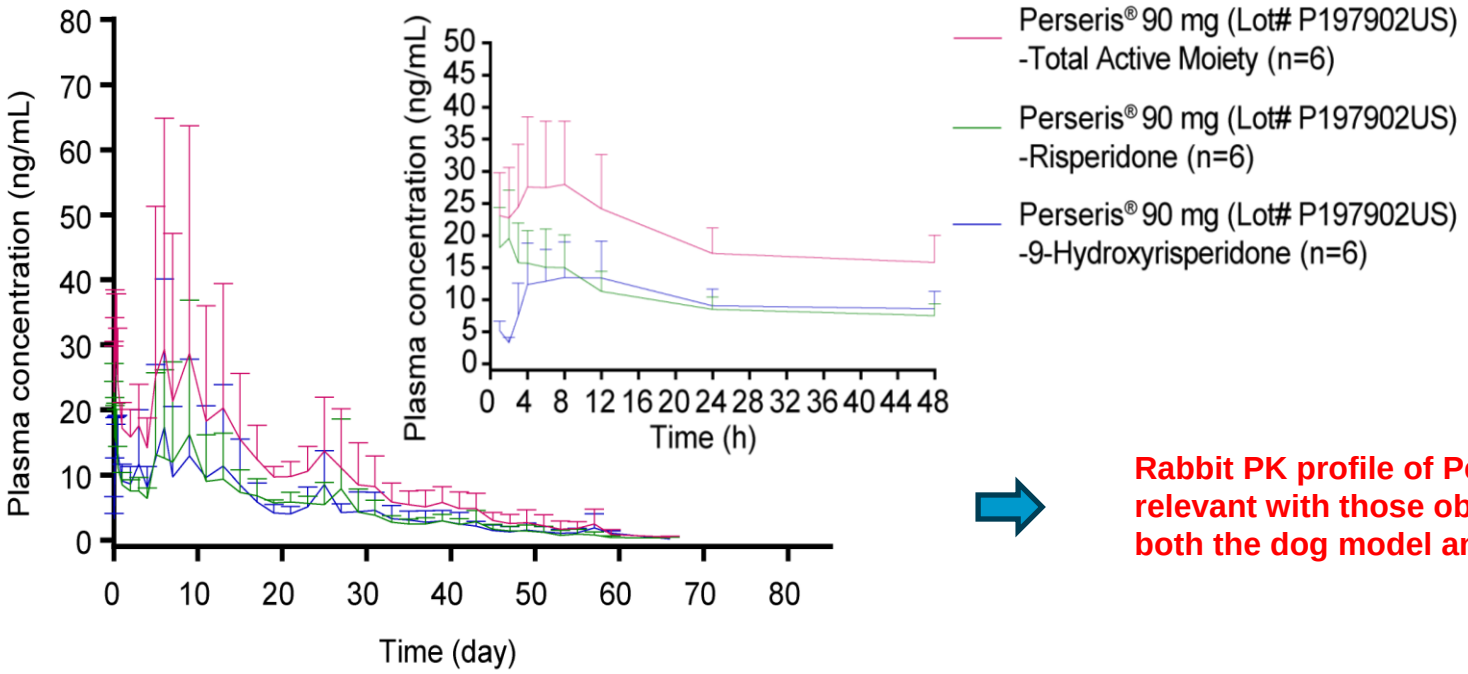
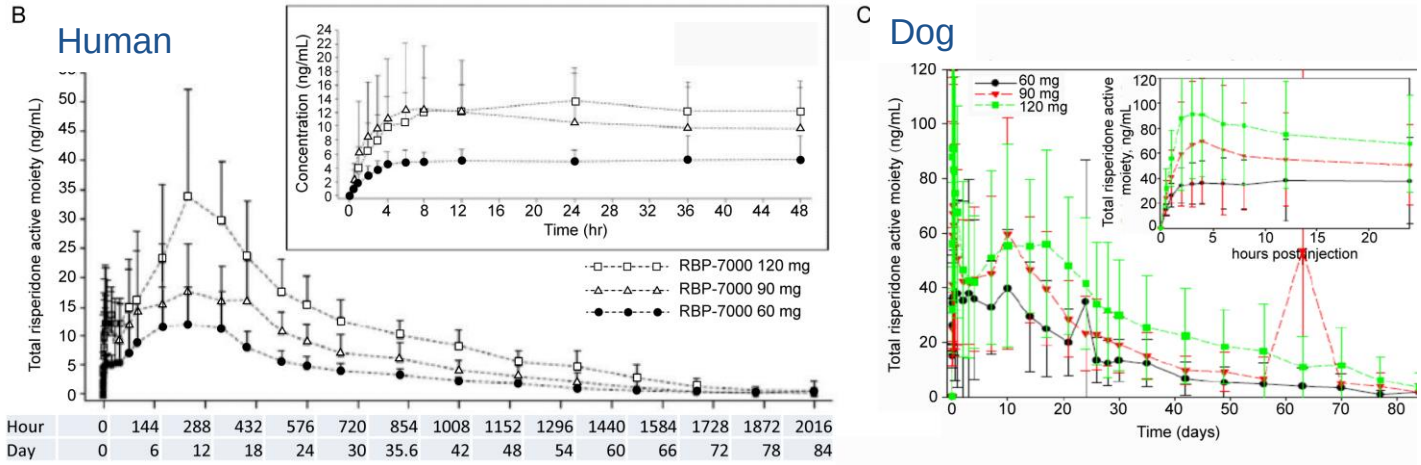
Rabbit



Rabbit PK profile of Perseris is relevant with those obtained from both the dog model and human

X. Wang, Q. Bao, R. Wang, T. Li, Y. Wang, B. Qin, Q. Li, D. J. Burgess, In Vivo Characterization of Perseris and Compositionally Equivalent Formulations. J. Control. Release. In submission.

In situ forming implants
-Reverse engineering of RLD Perseris® and *in vitro/ in vivo* characterization



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In situ forming implants

-Impact of polymer attributes on performance of *in situ* forming implants

PLGA No.	MW (kD)	Inherent Viscosity		L/G ratio		Blockiness		End group		T_g
	Target; Reported	Reported	Tested	Target; Reported	Tested	Target; Reported	Tested	Target; Reported	Tested	Tested (° C)
0	24.2; 24.2	0.28	0.281	80/20; 79/21	78:22	2.50; 2.15	2.20	Acid; Acid	Acid	45.30±0.76
1	19.2; 18.2	0.23	0.237	75/25; 74/26	73:27	2.10; 2.56	2.72	Acid; Acid	Acid	44.50±0.53
2	19.2; 17.8	0.23	0.252	80/20; 79/21	78:22	2.50; 2.42	2.41	Acid; Acid	Acid	45.36±0.93
3	19.2; 18.3	0.22	0.242	85:15; 84:16	83:17	2.90; 2.30	2.41	Acid; Acid	Acid	45.39±0.32
4	24.2; 25.4	0.28	0.287	75:25; 74:26	73:27	2.50; 2.51	2.59	Acid; Acid	Acid	46.84±0.31
5	24.2; 25.0	0.28	0.276	80:20; 79:21	78:22	2.90; 2.63	2.53	Acid; Acid	Acid	46.31±0.77
6	24.2; 26.4	0.29	0.271	85:15; 85:15	84:16	2.10; 2.08	2.10	Acid; Acid	Acid	46.91±0.71
7	29.2; 31.8	0.34	0.352	75:25; 74:26	73:27	2.90; 2.83	3.08	Acid; Acid	Acid	46.68±0.44
8	29.2; 31.1	0.33	0.357	80:20; 79:21	79:21	2.10; 2.38	2.52	Acid; Acid	Acid	47.79±0.54
9	29.2; 31.1	0.32	0.357	85:15; 85:15	84/16	2.50; 2.22	2.23	Acid; Acid	Acid	48.19±0.67
10	24.2; 26.7	0.29	0.285	80:20; 80:20	79:21	2.20; 1.82	1.69	Ester; Ester	Ester	42.08±0.85
11	24.2; 24.9	0.26	0.257	50:50; 50:50	49:51	2.50; 2.60	2.81	Acid; Acid	Acid	45.55±0.44
12	24.2; 27.1	0.29	0.285	50:50; 50:50	49:51	3.00; 2.67	3.12	Acid; Acid	Acid	44.44±0.32
13	24.2; 25.8	0.29	0.281	50:50; 50:50	49:51	3.50; 3.50	4.33	Acid; Acid	Acid	44.86±0.16

X. Wang, Q. Bao, R. Wang, O. Kwok, K. Maurus, Y. Wang, B. Qin, D. J. Burgess. In Situ Forming Risperidone Implants: Effect of PLGA Attributes on Product Performance. Journal of Controlled Release, 2023, 361: 777-791

In situ forming implants

-Impact of polymer attributes on performance of *in situ* forming implants

Formulation No.	PLGA	Solvent	Drug
Perseris	228 mg PLGA (Mw 22 kDa, L/G 80:20, Blockiness 2.50, Acid end-cap)	282 mg NMP	90 mg Risperidone
0	228 mg PLGA (Mw: 24.2; L/G ratio: 80/20; Blockiness: 2.15; Acid end-cap)	282 mg NMP	90 mg Risperidone
1	228 mg PLGA (Mw: 18.2; L/G ratio: 75/25; Blockiness: 2.56; Acid end-cap)	282 mg NMP	90 mg Risperidone
2	228 mg PLGA (Mw: 17.8; L/G ratio: 80/20; Blockiness: 2.42; Acid end-cap)	282 mg NMP	90 mg Risperidone
3	228 mg PLGA (Mw: 18.3; L/G ratio: 85/15; Blockiness: 2.30; Acid end-cap)	282 mg NMP	90 mg Risperidone
4	228 mg PLGA (Mw: 25.4; L/G ratio: 75:25; Blockiness: 2.51; Acid end-cap)	282 mg NMP	90 mg Risperidone
5	228 mg PLGA (Mw: 25.0; L/G ratio: 80/20; Blockiness: 2.63; Acid end-cap)	282 mg NMP	90 mg Risperidone
6	228 mg PLGA (Mw: 26.4; L/G ratio: 85/15; Blockiness: 2.10; Acid end-cap)	282 mg NMP	90 mg Risperidone
7	228 mg PLGA (Mw: 31.8; L/G ratio: 75:25; Blockiness: 2.83; Acid end-cap)	282 mg NMP	90 mg Risperidone
8	228 mg PLGA (Mw: 31.1; L/G ratio: 80/20; Blockiness: 2.38; Acid end-cap)	282 mg NMP	90 mg Risperidone
9	228 mg PLGA (Mw: 31.1; L/G ratio: 85/15; Blockiness: 2.22; Acid end-cap)	282 mg NMP	90 mg Risperidone
10	228 mg PLGA (Mw: 26.7; L/G ratio: 80/20; Blockiness: 1.82; Ester end-cap)	282 mg NMP	90 mg Risperidone
11	228 mg PLGA (Mw: 24.9; L/G ratio: 50/50; Blockiness: 2.60; Acid end-cap)	282 mg NMP	90 mg Risperidone
12	228 mg PLGA (Mw: 27.1; L/G ratio: 50/50; Blockiness: 2.67; Acid end-cap)	282 mg NMP	90 mg Risperidone
13	228 mg PLGA (Mw: 25.8; L/G ratio: 50/50; Blockiness: 3.50; Acid end-cap)	282 mg NMP	90 mg Risperidone

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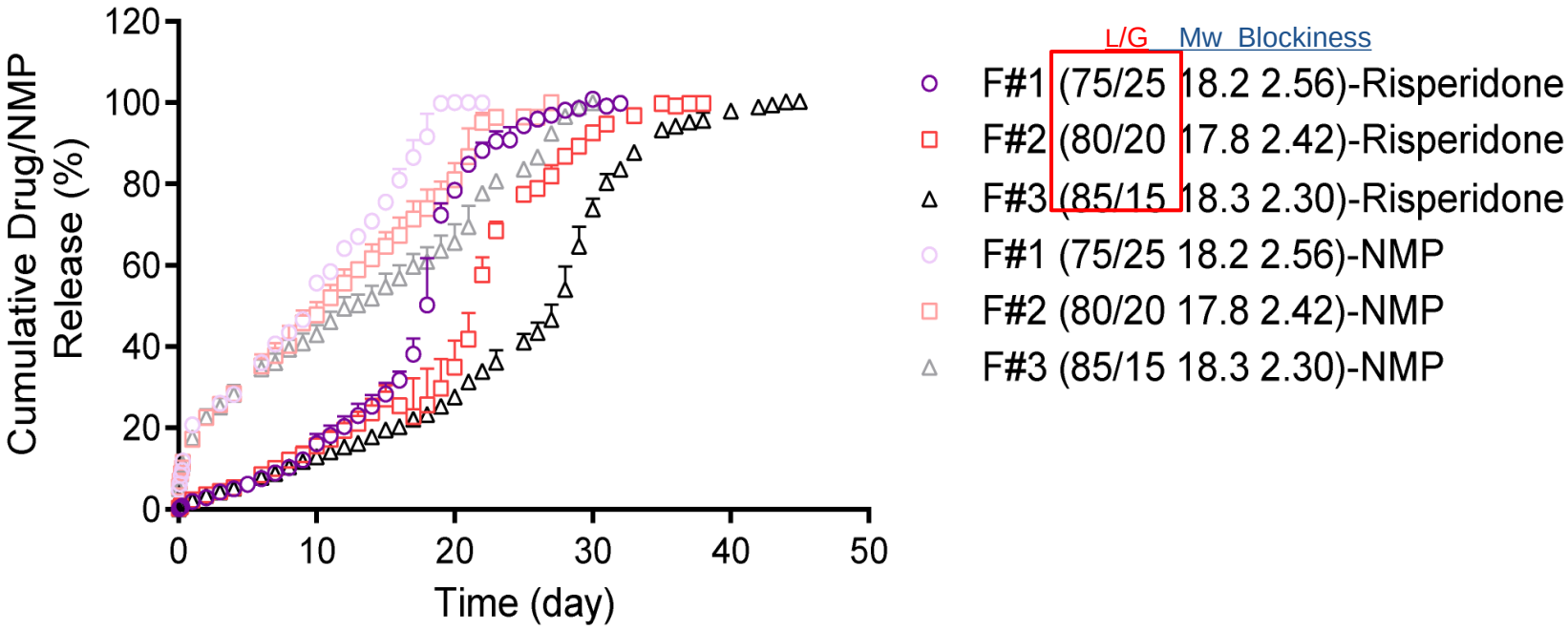
In situ forming implants

-Impact of polymer attributes on implant performance of *in situ* forming implants

In vitro drug release profiles (Adapter method)-Impact of L/G ratio at Mw 18 KDa



In vitro release testing of different risperidone/PLGA/NMP *in situ* forming implant formulations in phosphate buffered saline (pH 7.4) at 37°C using 0.1 mL adapters, USP 2 (n=3).

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In situ forming implants

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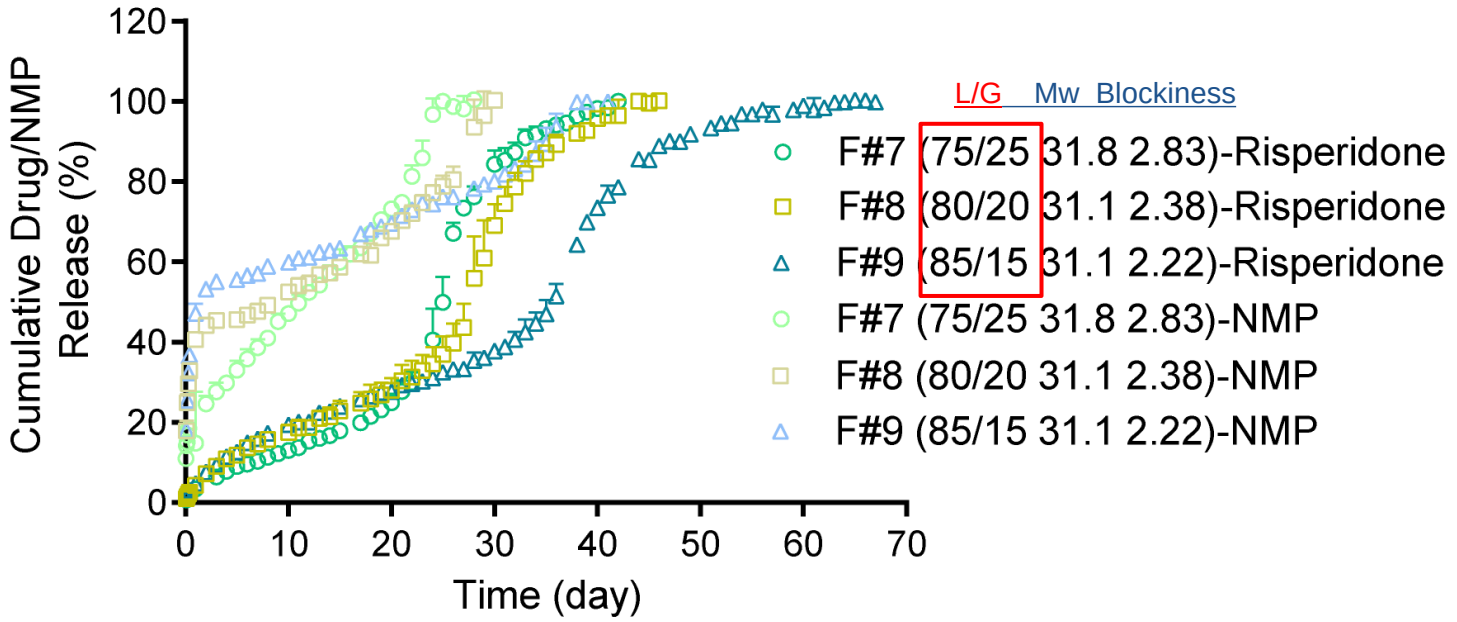
In vitro drug release profiles (Adapter method)-Impact of L/G ratio at Mw 31 KDa



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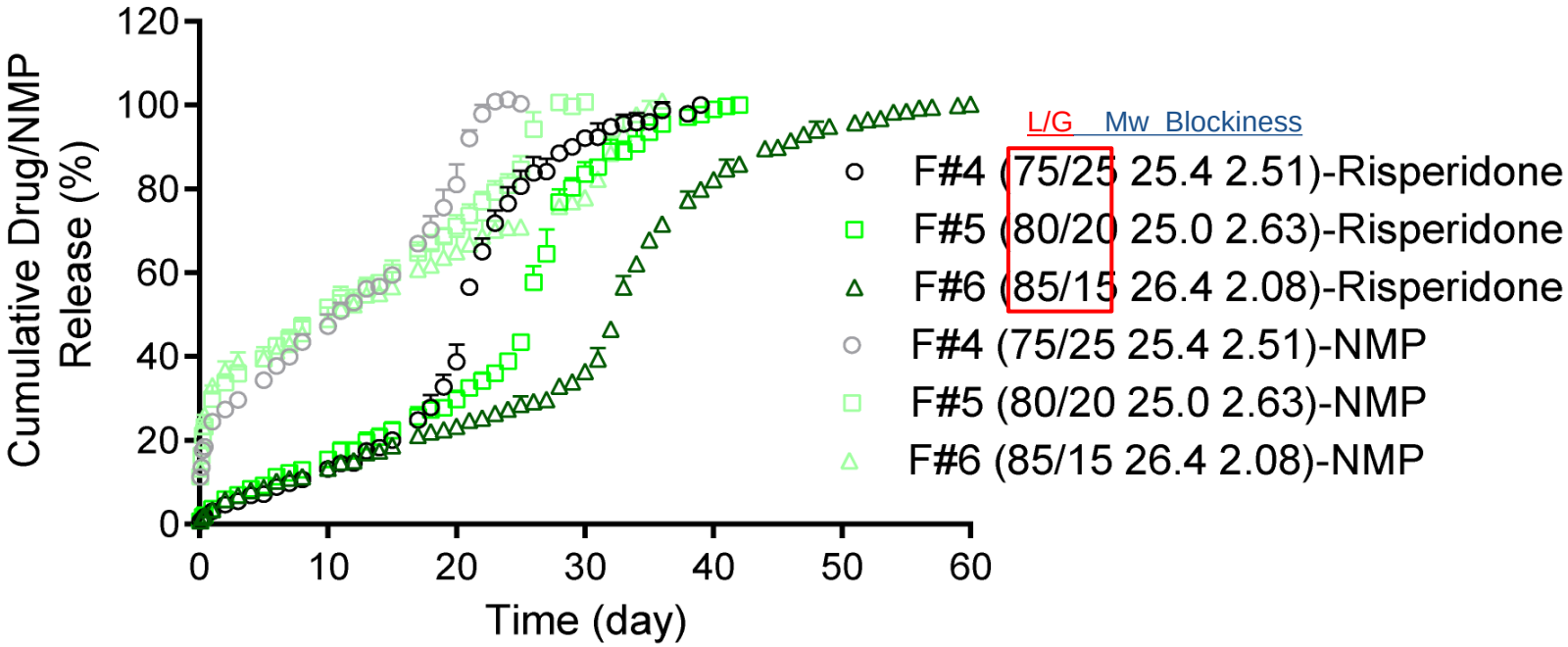
In situ forming implants

-Impact of polymer attributes on implant performance of *in situ* forming implants

In vitro drug release profiles (Adapter method)-Impact of L/G ratio at Mw 25 KDa



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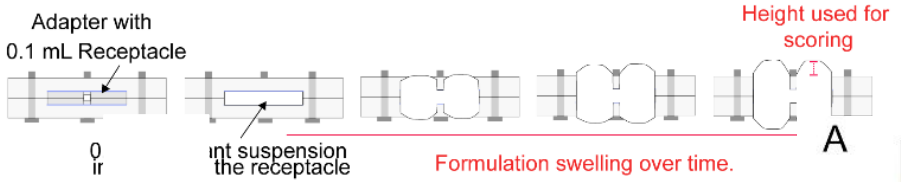
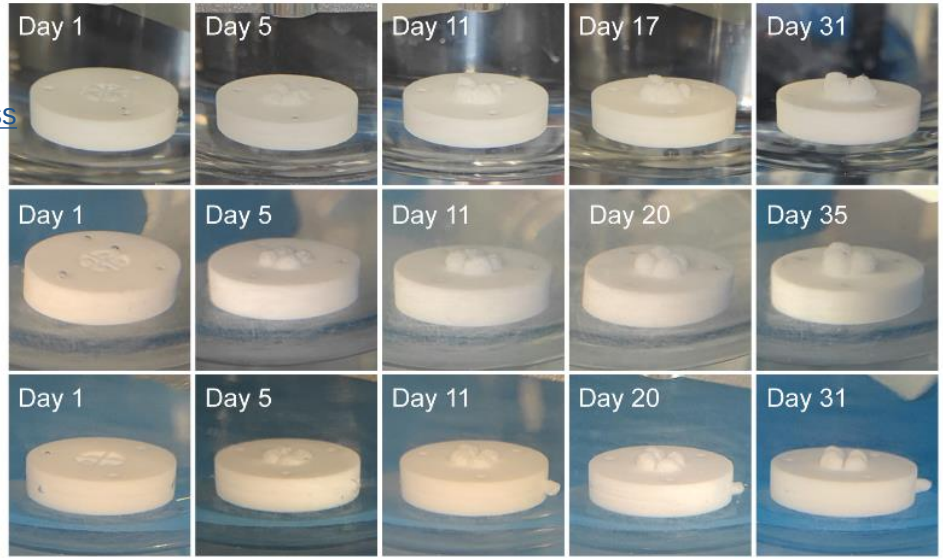
In situ forming implants

-Impact of polymer attributes on implant performance of *in situ* forming implants

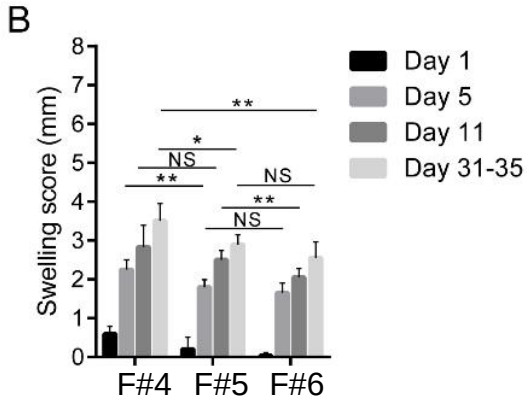


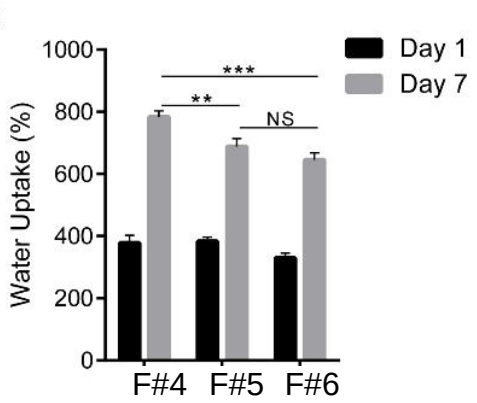
	L/G	Mw	Blockiness
F#4	(75/25	25.4	2.51)
F#5	(80/20	25.5	2.63)
F#6	(85/15	26.4	2.08)



L/G ratio ↑

Swelling and water uptake ↓



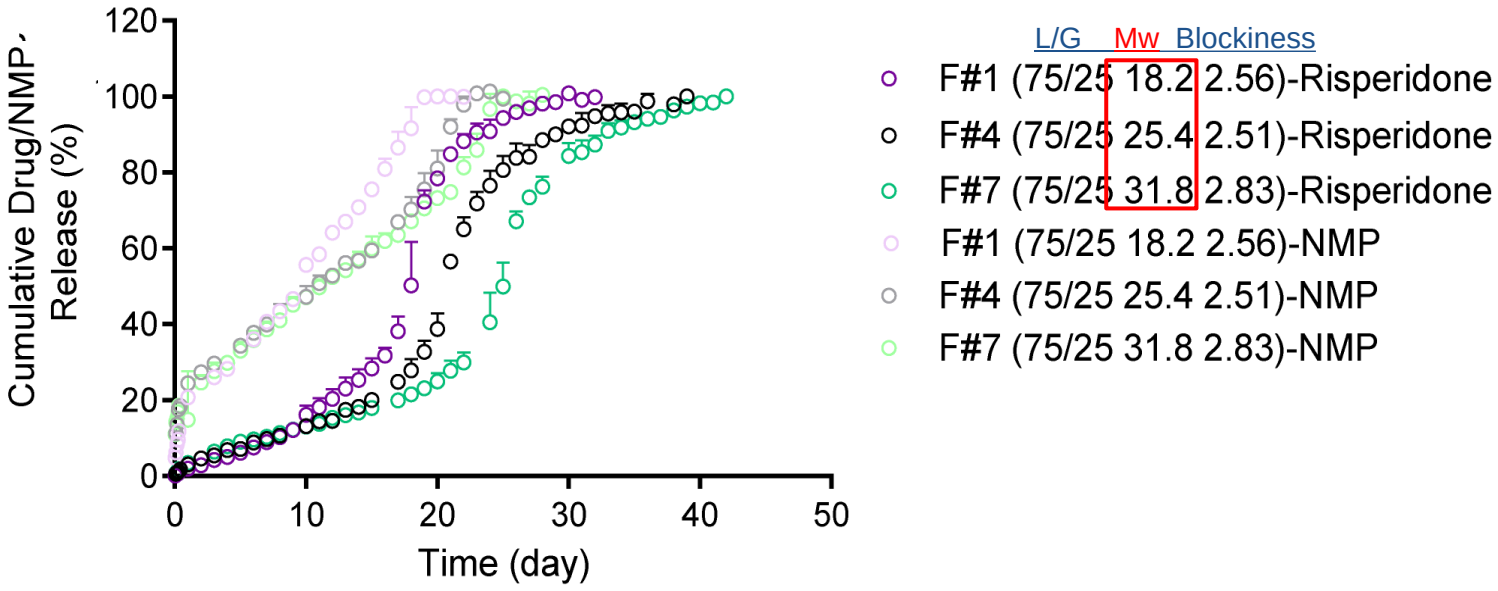


X. Wang, Q. Bao, R. Wang, O. Kwok, K. Maurus, Y. Wang, B. Qin, D. J. Burgess. In Situ Forming Risperidone Implants: Effect of PLGA Attributes on Product Performance. Journal of Controlled Release, 2023, 361: 777-791

In situ forming implants

-Impact of polymer attributes on performance of *in situ* forming implants

In vitro drug release profiles (Adapter method)- Impact of Mw at L/G ratio 75/25



In vitro release testing of different risperidone/PLGA/NMP *in situ* forming implant formulations in phosphate buffered saline (pH 7.4) at 37°C using 0.1 mL adapters, USP 2 (n=3).

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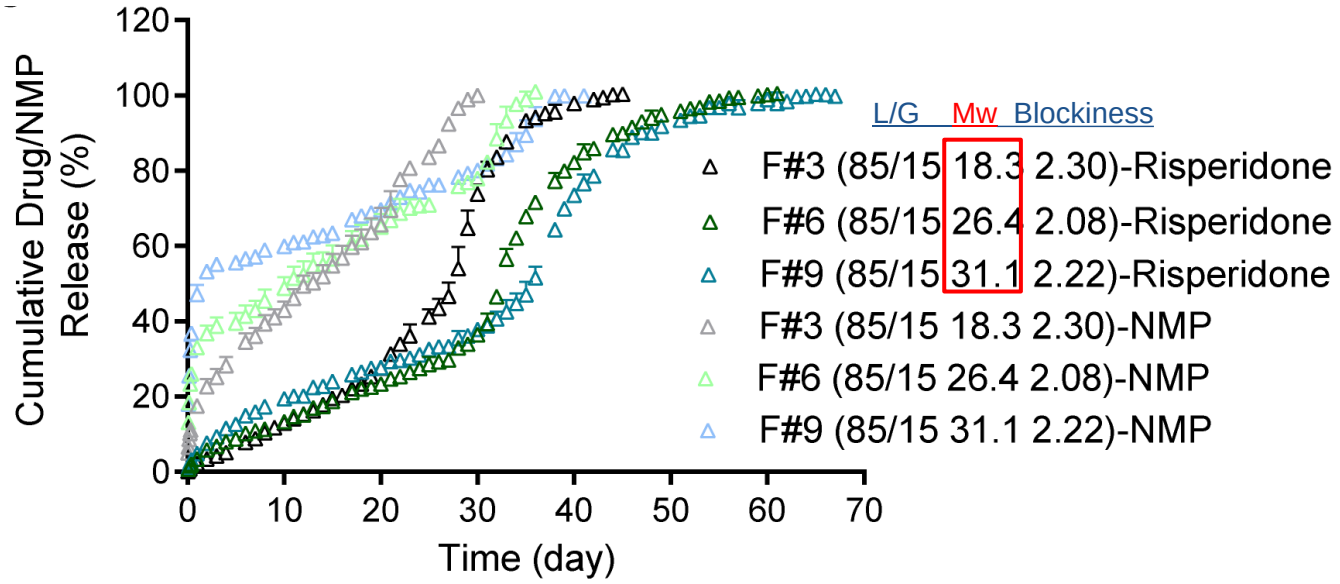
In situ forming implants

-Impact of polymer attributes on performance of *in situ* forming implants

In vitro drug release profiles (Adapter method)- Impact of Mw at L/G ratio 85/15



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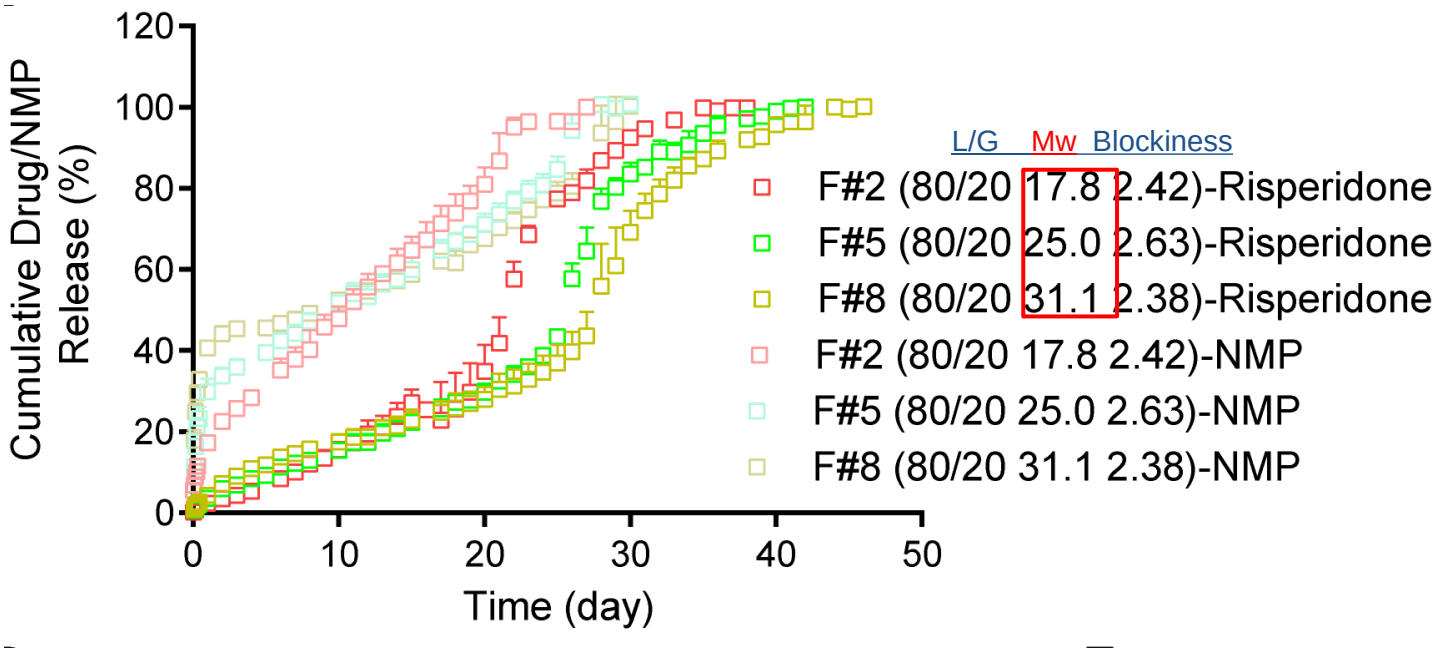
In situ forming implants

-Impact of polymer attributes on performance of *in situ* forming implants

In vitro drug release profiles (Adapter method)- Impact of Mw at L/G ratio 80/20



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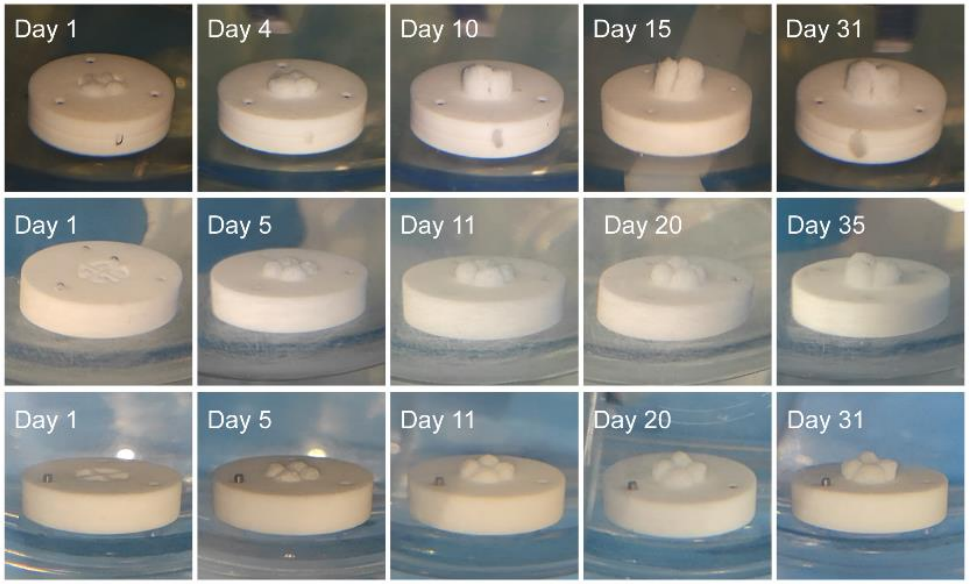
In situ forming implants

-Impact of polymer attributes on performance of *in situ* forming implants

	L/G	Mw	Blockiness
F#2	(80/20	17.8	2.42)
F#5	(80/20	25.5	2.63)
F#8	(80/20	31.1	2.38)

A



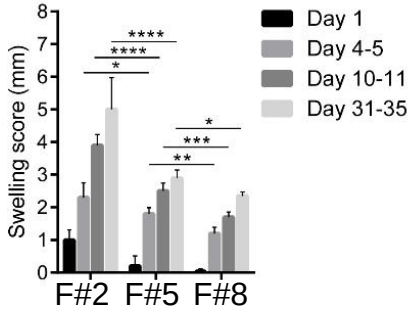
injected into the receptacle

Formulation swelling over time.

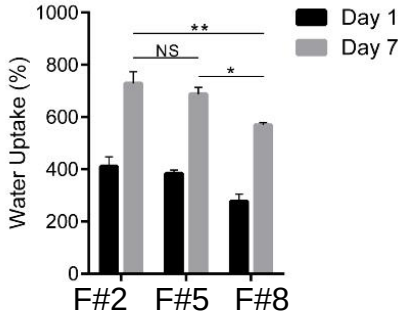
Mw ↑

Swelling and water uptake ↓

C



D



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In situ forming implants

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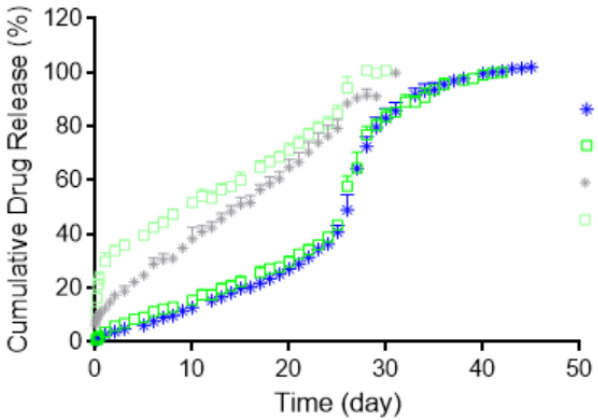
In vitro drug release profiles (Adapter method)- Impact of Blockiness



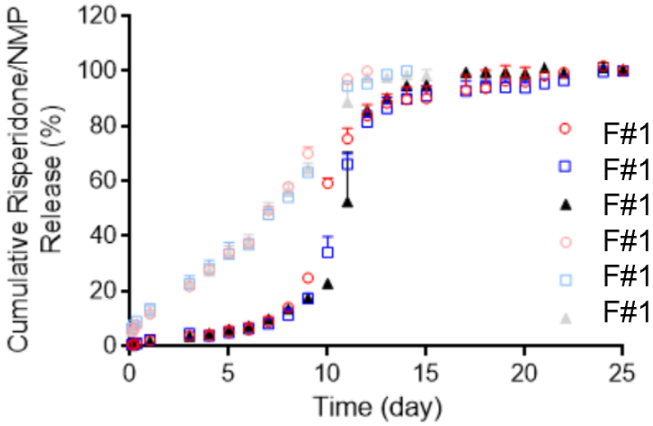
L/G Mw Blockiness

F#0 (80/20 24.2 2.15)-Risperidone

F#5 (80/20 25.0 2.63)-Risperidone

F#0 (8020 24.2 2.15)-NMP

F#5 (80/20 25.0 2.63)-NMP



L/G Mw Blockiness

F#11 (50/50 24.9 2.81)-Risperidone

F#12 (50/50 24.9 3.12)-Risperidone

F#13 (50/50 24.9 4.33)-Risperidone

F#11 (50/50 24.9 2.81)-NMP

F#12 (50/50 24.9 3.12)-NMP

F#13 (50/50 24.9 4.33)-NMP

In vitro release testing of different risperidone/PLGA/NMP *in situ* forming implant formulations in phosphate buffered saline (pH 7.4) at 37°C using 0.1 mL adapters, USP 2 (n=3).

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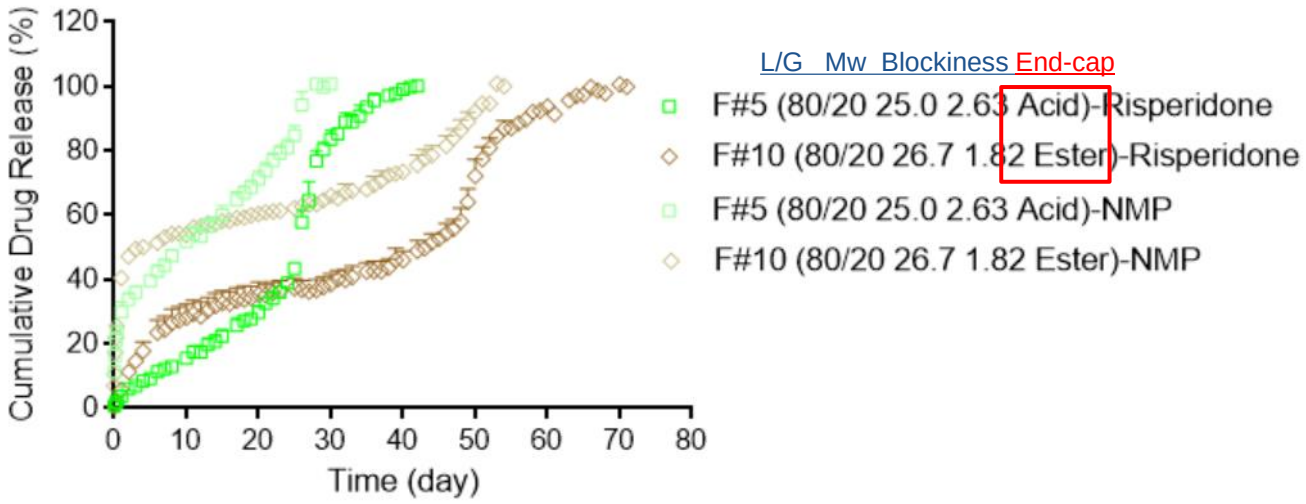
In vitro drug release profiles (Adapter method)- Impact of End-cap (acid vs ester)



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In situ forming implants

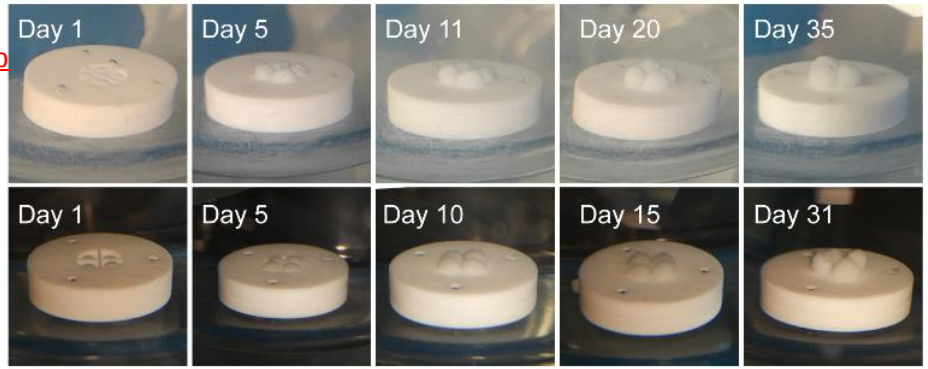
-Impact of polymer attributes on performance of *in situ* forming implants

A

L/G Mw Blockiness End-cap

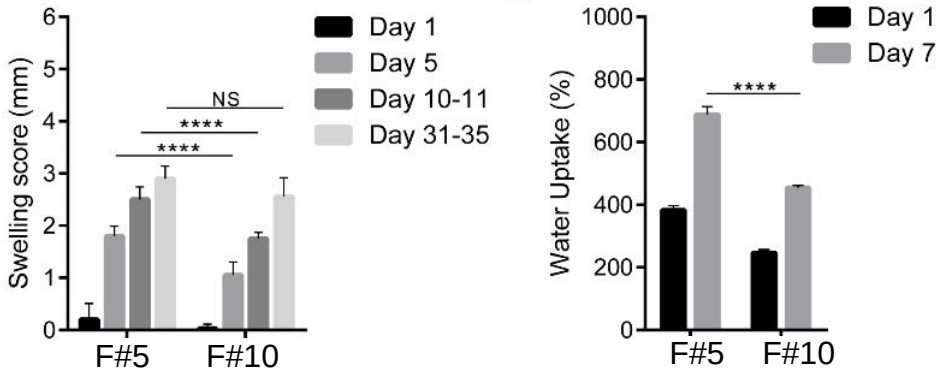
F#5 (80/20 25.5 2.63 Acid)

F#10 (80/20 26.7 1.82 Ester)



Ester end-cap resulted in less swelling and less water uptake of the formulation depot

C



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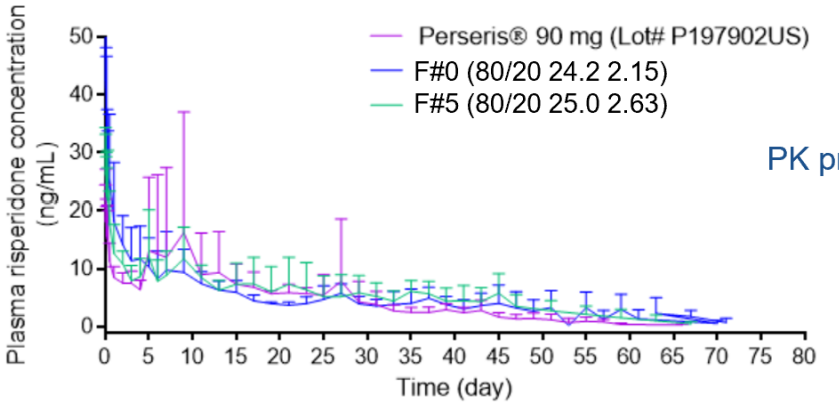
In Vivo Rabbit Model

Rabbit model

- ***In vivo* PK Profiles and Deconvoluted Drug Absorption Profiles**
- **Factors Contributing to the *In Vitro-In Vivo* Differences**
- **Improving the *In Vitro* Release Profiles**

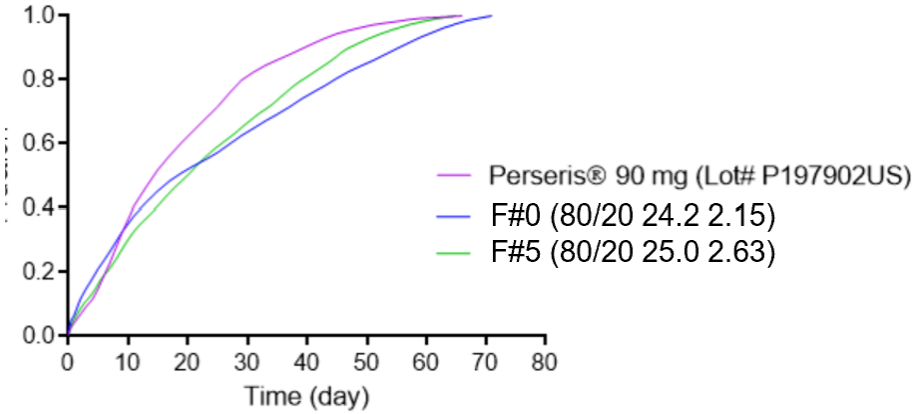
In Vivo PK Profiles and Deconvoluted Drug Absorption Profiles

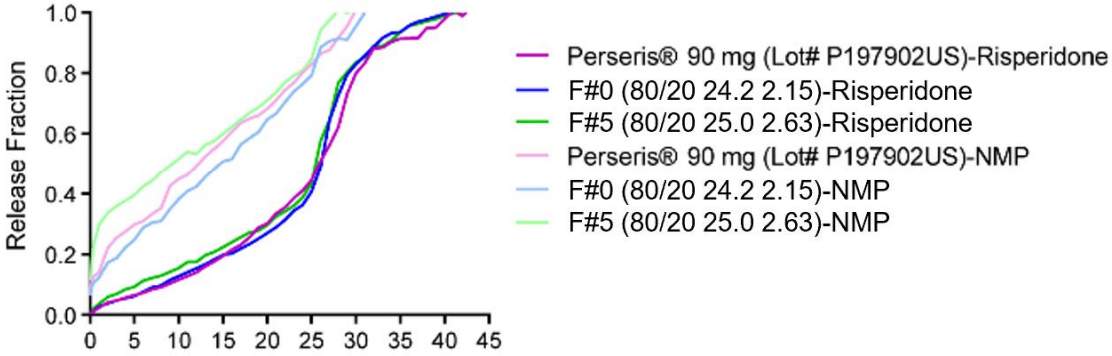
RLD and compositional equivalent formulations (F#0 & F#5) & impact of blockiness (F#0 vs F#5)



PK profiles

Deconvoluted *in vivo* absorption profiles (Loo–Riegelman method)

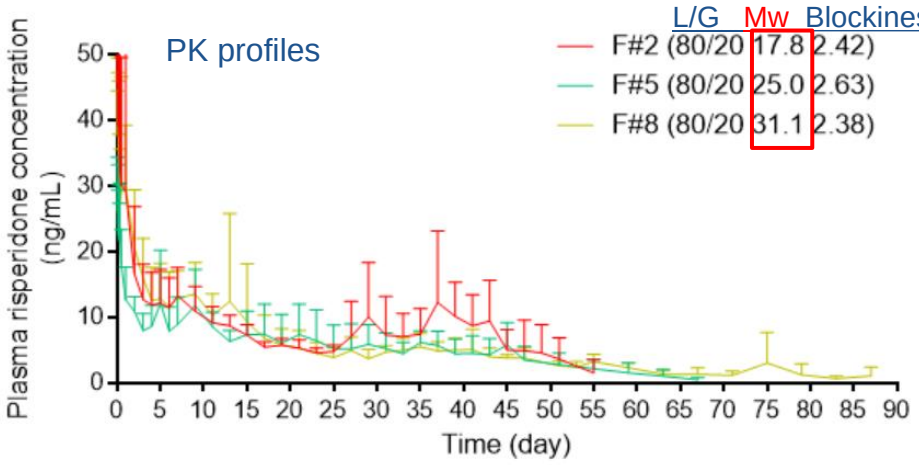


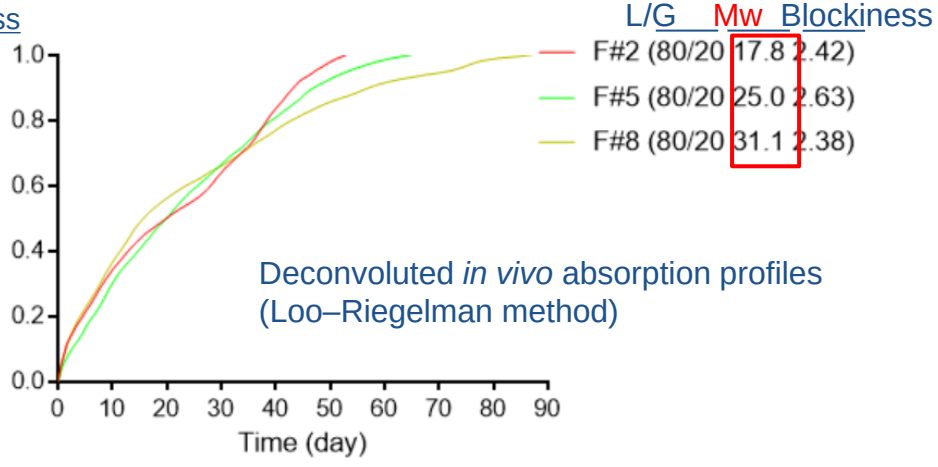


In vitro (Adapter method)

Comparison (*in vivo*)	f2 value
	Risperidone
Perseris vs F#0	53.35
Perseris vs F#5	51.22

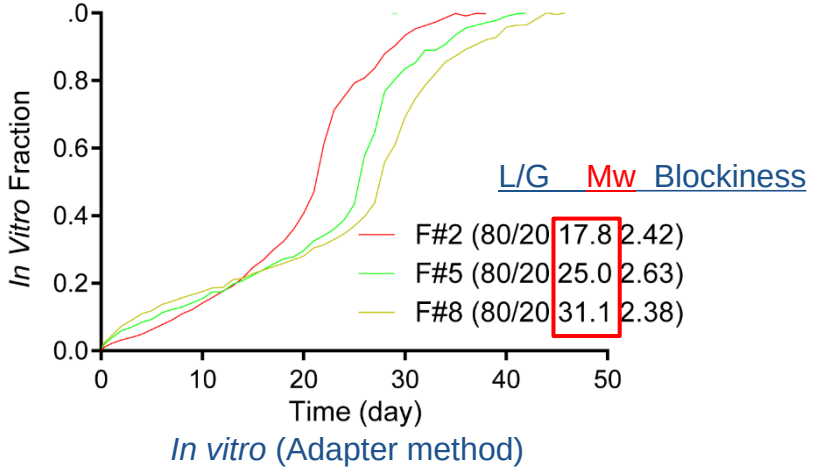
Impact of Mw





The same rank order between *in vivo* and *in vitro*

Comparison (*in vivo*)	f2 value
	Risperidone
F#2 vs F#5	72.78
F#5 vs F#8	63.36
F#2 vs F#8	62.62



In vitro (Adapter method)

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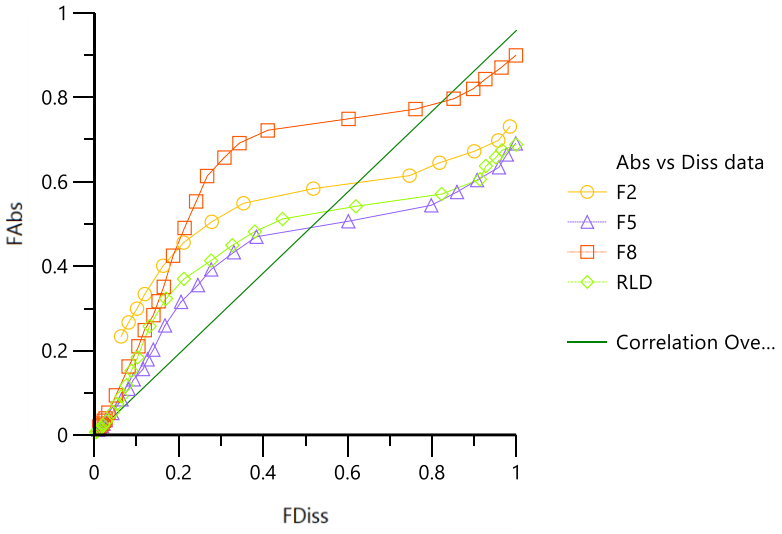
Undesirable IVIVC; Mw differences

F#2, F#5, F#8, Perseris®

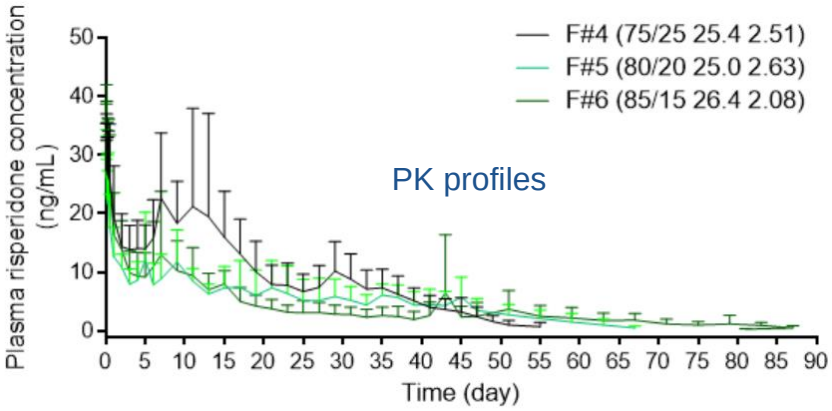


Dissolution: Double Webull

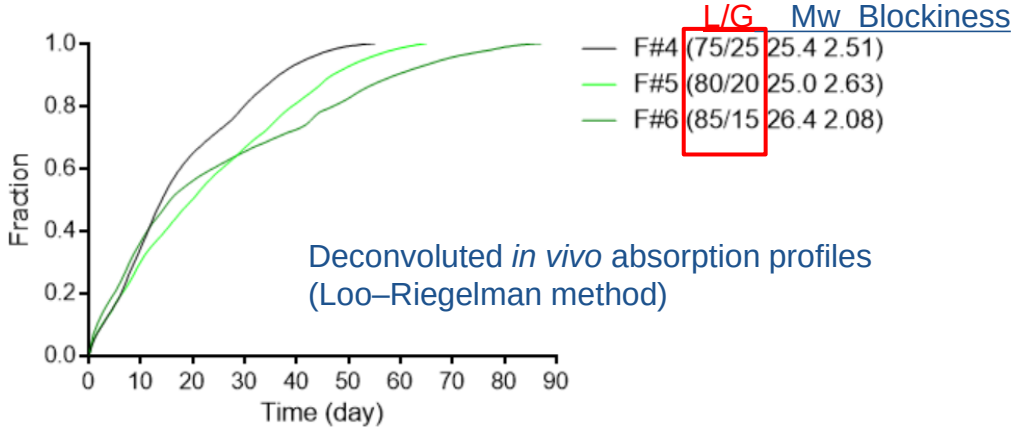
Correclation:
Fabs=AbsScale*(Diss(Tscale*Tvivo)

Formulation	Parameter	Predicted	Observed	%PE	Ratio
F#2 Internal	AUClast	399.2589	456.2263	-12.4867	0.875133
F#2 Internal	Cmax	32.54044	47.97764	-32.1758	0.678242
F#5 Internal	AUClast	375.1248	358.9916	4.49404	1.04494
F#5 Internal	Cmax	30.69467	26.31322	16.65112	1.166511
F#8 Internal	AUClast	340.9851	453.3219	-24.7808	0.752192
F#8 Internal	Cmax	26.68653	39.31681	-32.1244	0.678756
RLD External	AUClast	388.2078	306.9998	26.45211	1.264521
RLD External	Cmax	29.53408	19.54009	51.14606	1.511461
Avg Internal	AUClast	371.7896	422.8466	13.9205	0.879254
Avg Internal	Cmax	29.97388	37.86923	26.98377	0.79151

Impact of L/G ratio



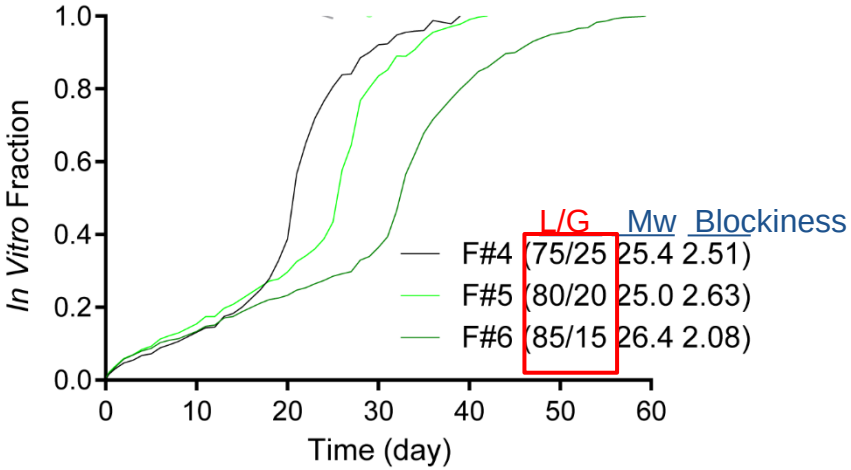
PK profiles



Deconvoluted *in vivo* absorption profiles (Loo–Riegelman method)

The same rank order between *in vivo* and *in vitro*

Comparison (*in vivo*)	f2 value
	Risperidone
F#4 vs F#5	48.54
F#5 vs F#6	63.69
F#4 vs F#6	29.50



In vitro (Adapter method)

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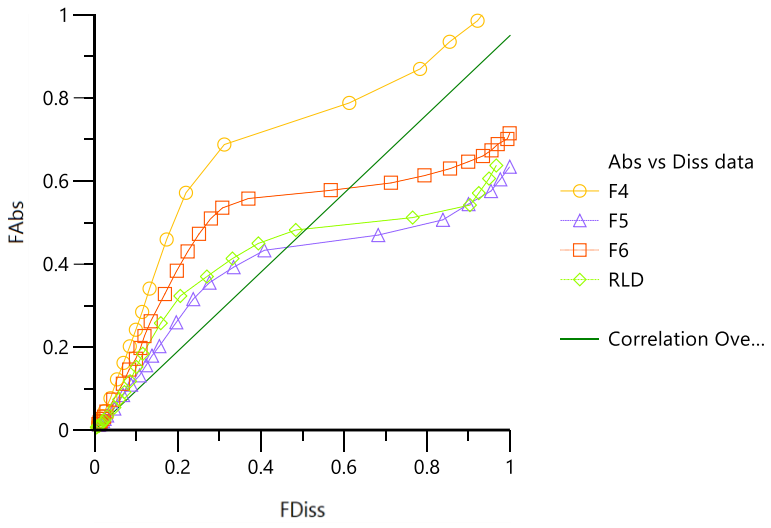
Undesirable IVIVC; L/G ratiio

F#4, F#5, F#6, Perseris®

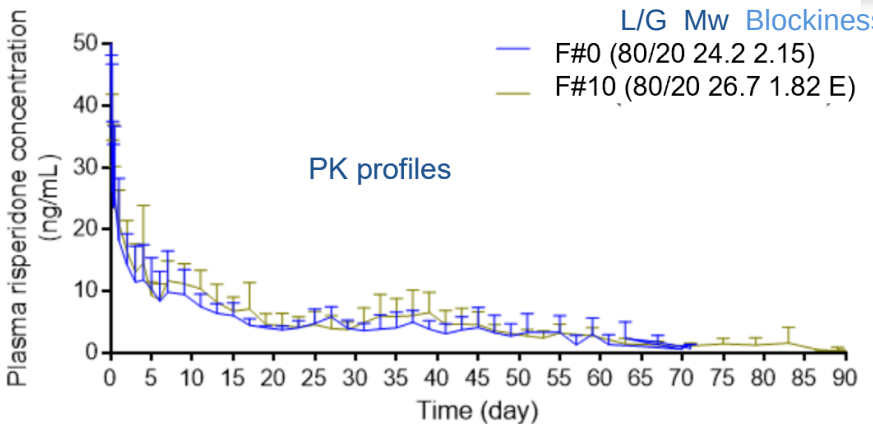


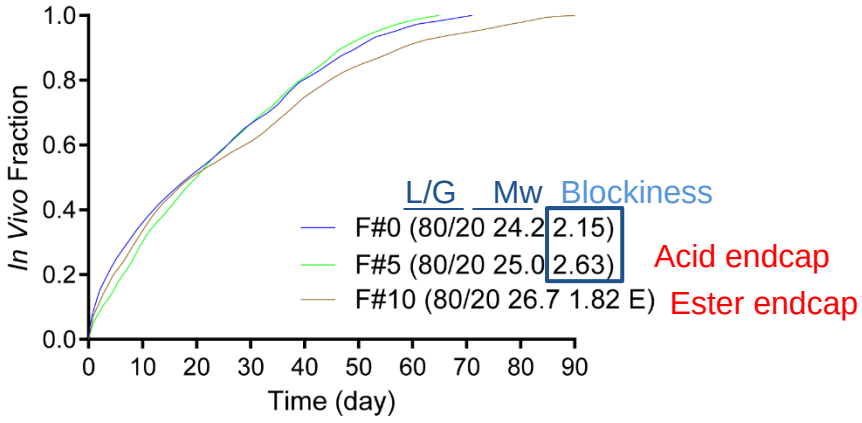
Dissolution: Double Webull

Correclation:
Fabs=AbsScale*(Diss(Tscale*Tvivo)

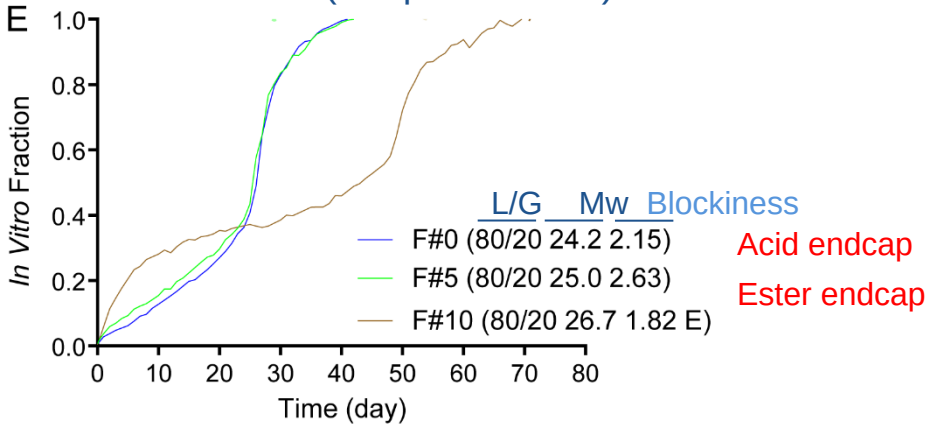
Formulation	Parameter	Predicted	Observed	%PE	Ratio
F#4 Internal	AUClast	333.8897	519.8985	-35.7779	0.642221
F#4 Internal	Cmax	45.88775	28.16312	62.93561	1.629356
F#5 Internal	AUClast	351.5489	358.9916	-2.07321	0.979268
F#5 Internal	Cmax	37.85684	26.31322	43.87001	1.4387
F#6 Internal	AUClast	346.5263	344.8982	0.47203	1.00472
F#6 Internal	Cmax	25.45798	29.31715	-13.1635	0.868365
RLD External	AUClast	371.7111	306.9998	21.07861	1.210786
RLD External	Cmax	37.52091	19.54009	92.0201	1.920201
Avg Internal	AUClast	343.9883	407.9295	12.77439	0.843254
Avg Internal	Cmax	36.40086	27.93116	39.98971	1.303235

Impact of End-cap





In vitro (Adapter method)



Comparison (*in vivo*)	f2 value
	Risperidone
F#5 vs F#10	65.22
F#0 vs F#5	64.03

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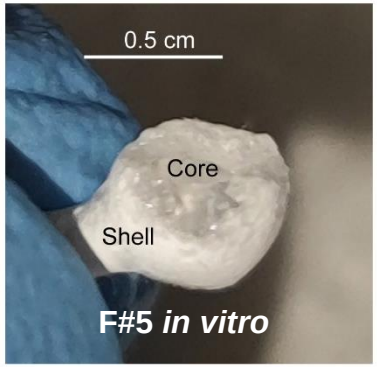
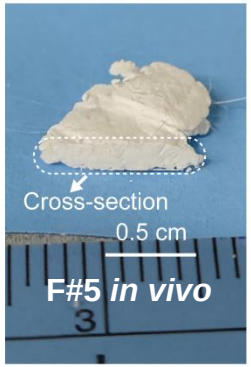
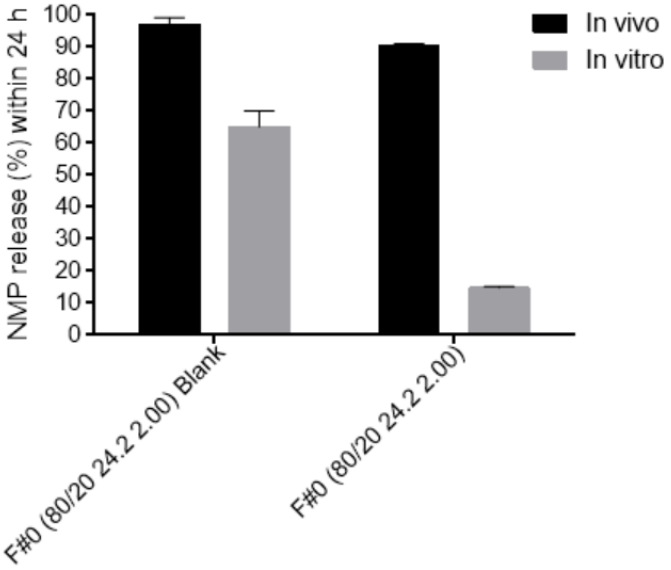
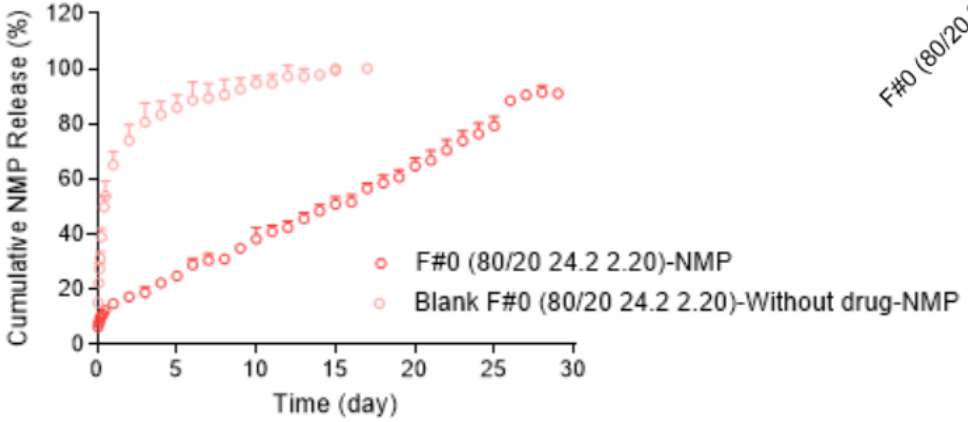
Factors contributing to the *in vitro-in vivo* differences:

- **Different phase separation rates**
- Different mechanical pressure
- Different water uptake





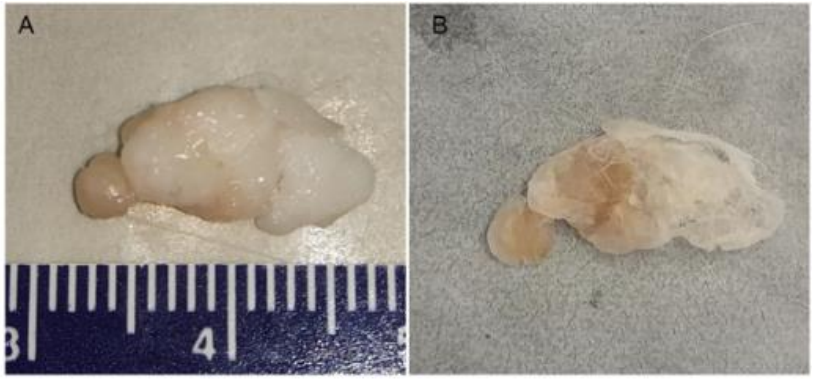




X. Wang, Q. Bao, R. Wang, T. Li, Y. Wang, B. Qin, Q. Li, D. J. Burgess, In Vivo Characterization of Perseris and Compositionally Equivalent Formulations. *Int. J. Pharm.*, 2023, 642: 123170.

Factors contributing to the *in vitro-in vivo* differences:

- Different phase separation rates
- **Different mechanical pressure**
- Different water uptake



Before extracting PLGA/NMP/drug using acetonitrile

Collagen/tissue shell left following extraction

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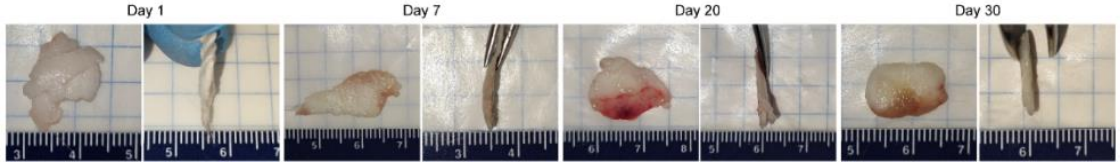
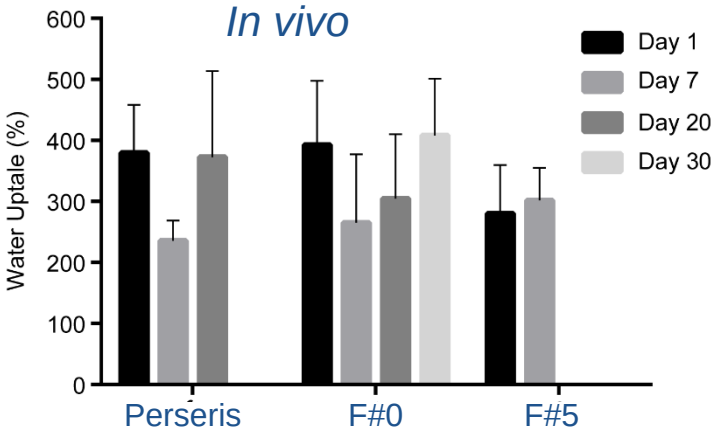
Factors Contributing to The *In Vitro-In Vivo* Differences:

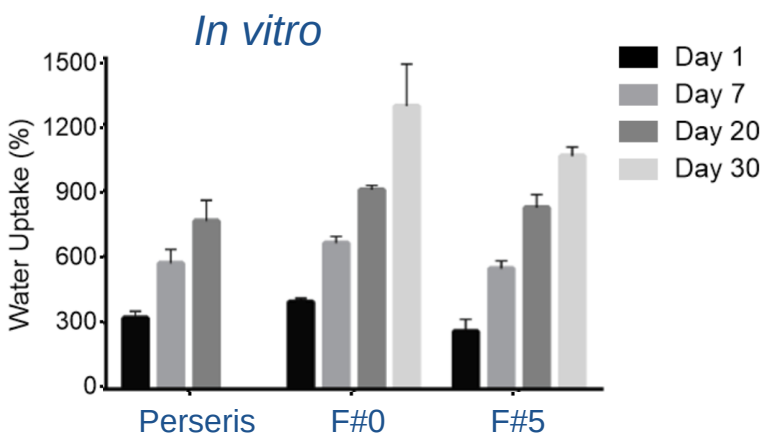
- Different phase separation rates
- Different mechanical pressure
- **Different water uptake**

F#0 *in vivo*



F#0 *in vitro*





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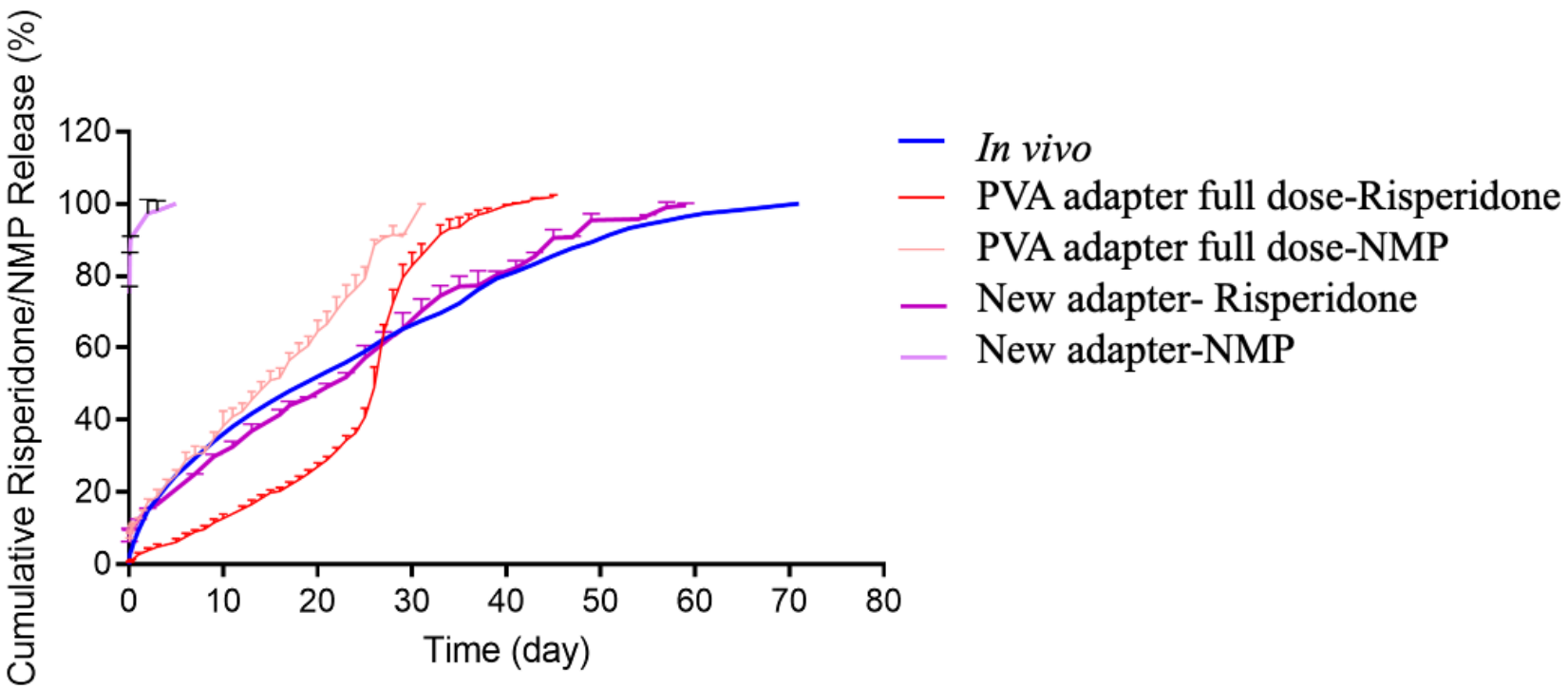
Improving the *In Vitro* Release Profiles:

F#0



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FDA Collaborators:

Dr. Bin Qin

Dr. Yan Wang

Dr. Qi Li

Dr. Qiangnan Zhang

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