In Vitro Drug Release from Complex Parenterals and Development of IVIVCs

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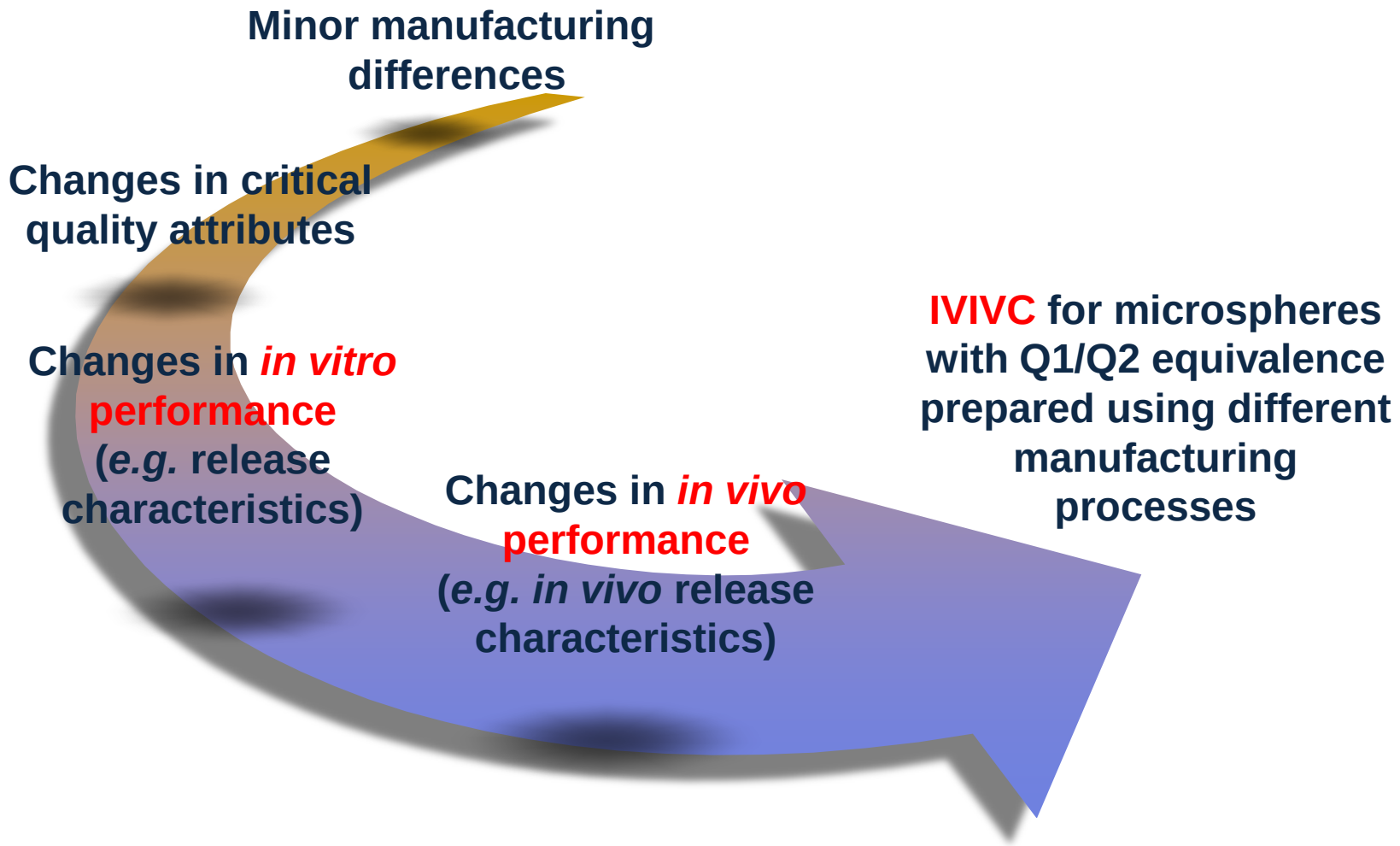
Motivation

Develop IVIVC for Q1/Q2 equivalent complex drug products using **compendial apparatus**

Faster approval of generic drug products

Safe and high quality generic drug product to patients

Parenteral Microsphere Drug Products



Case I: Compositionally Equivalent Risperidone Microspheres

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

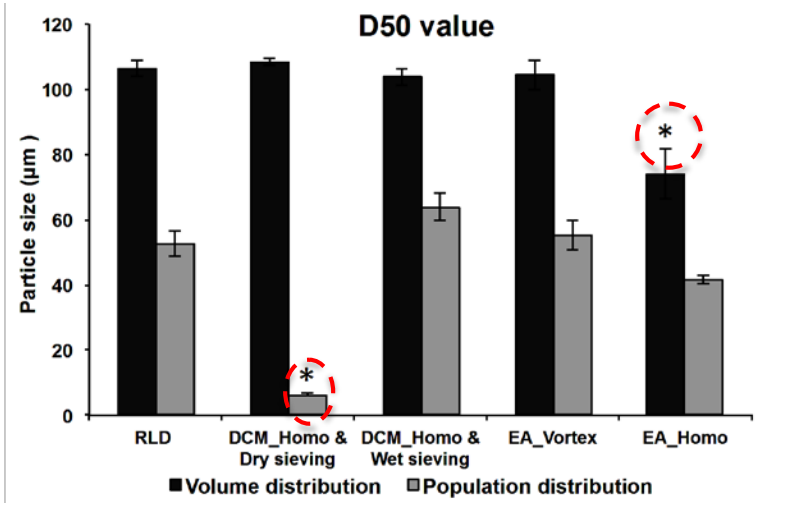
Table 1. Drug loading of the prepared risperidone microspheres.

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

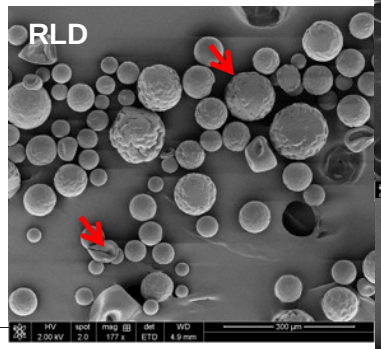
Shen J., Burgess D.J., *J. Control. Release, (2015)*

Case I: Compositionally Equivalent Risperidone Microspheres

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



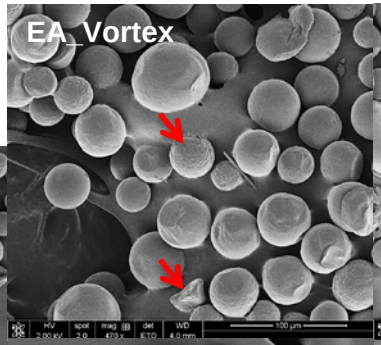
Sample	Solvent	Preparation Method
Risperdal® Consta®	-	-
Formulation_1	DCM	Homogenization & dry sieving
Formulation_2	DCM	Homogenization & wet sieving
Formulation_3	EA	Vortex & wet sieving
Formulation_4	EA	Homogenization & wet sieving

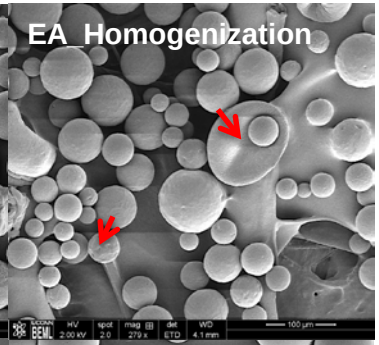


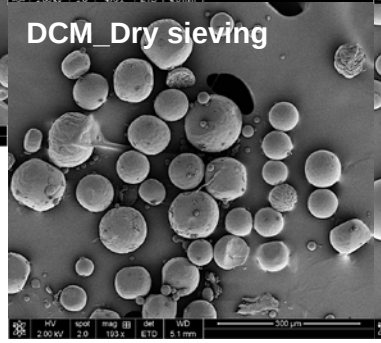
Porosity 43.97%

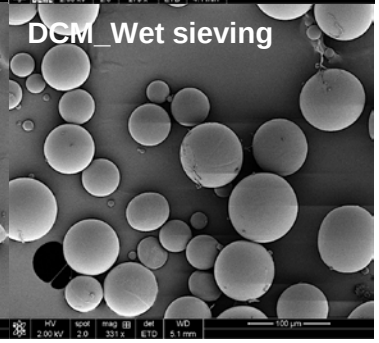
Porosity 54.98%

61.75%









Porosity 43.19%

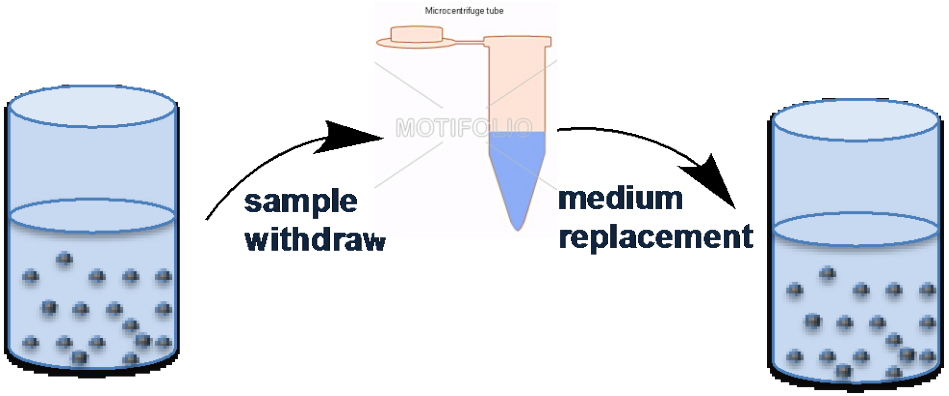
46.04%

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

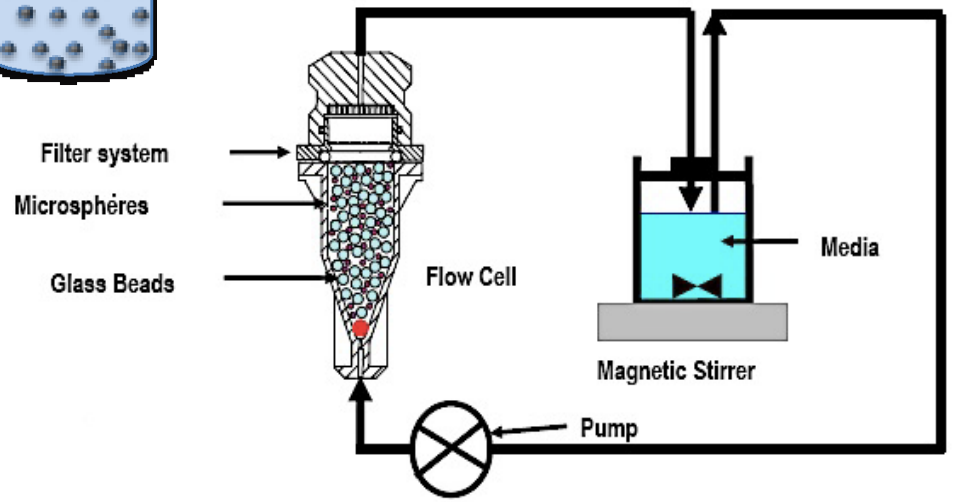
Case I: Compositionally Equivalent Risperidone Microspheres

- *In vitro* release testing

Sample-and-Separate method



Continuous flow method

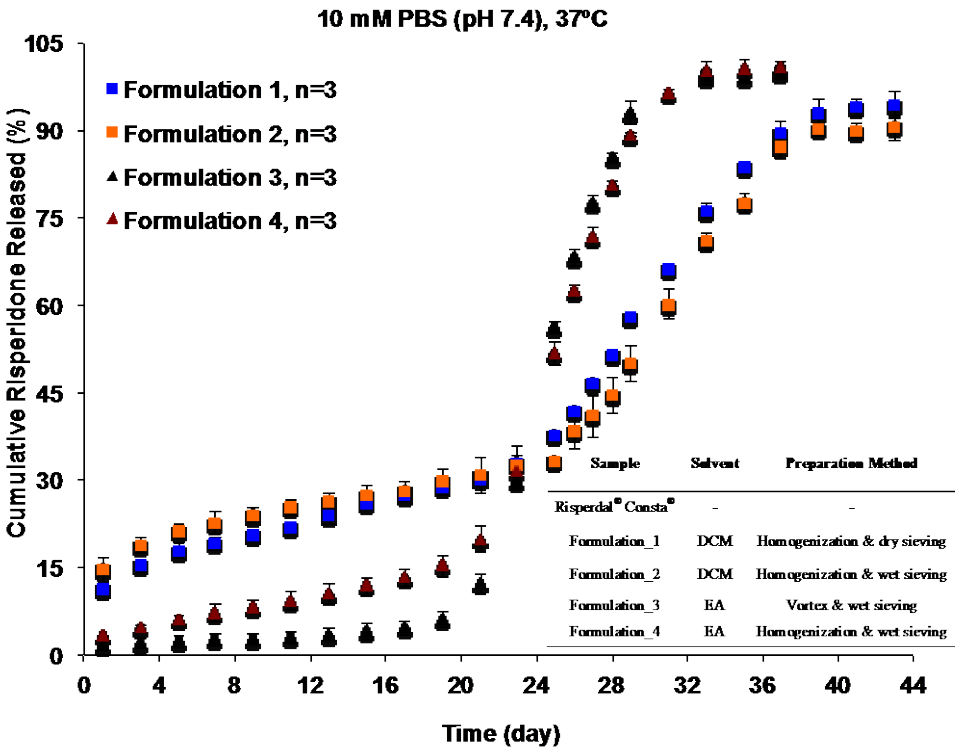


Zolnik B.S., Burgess D.J., *Dissolu. Technol., 2005*

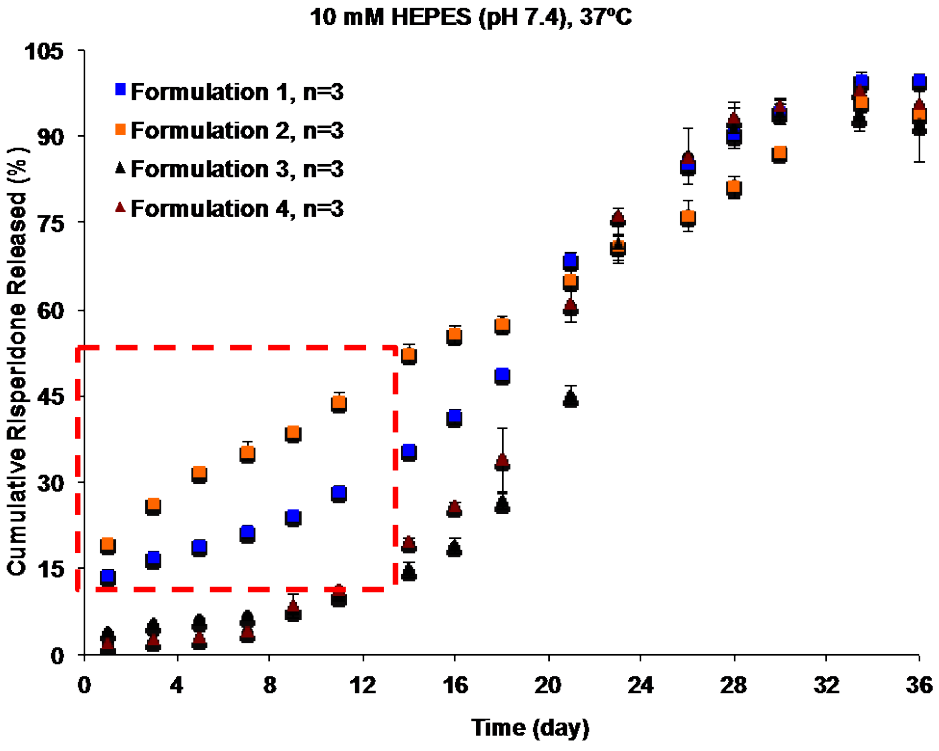
Case I: Compositionally Equivalent Risperidone Microspheres

- ***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

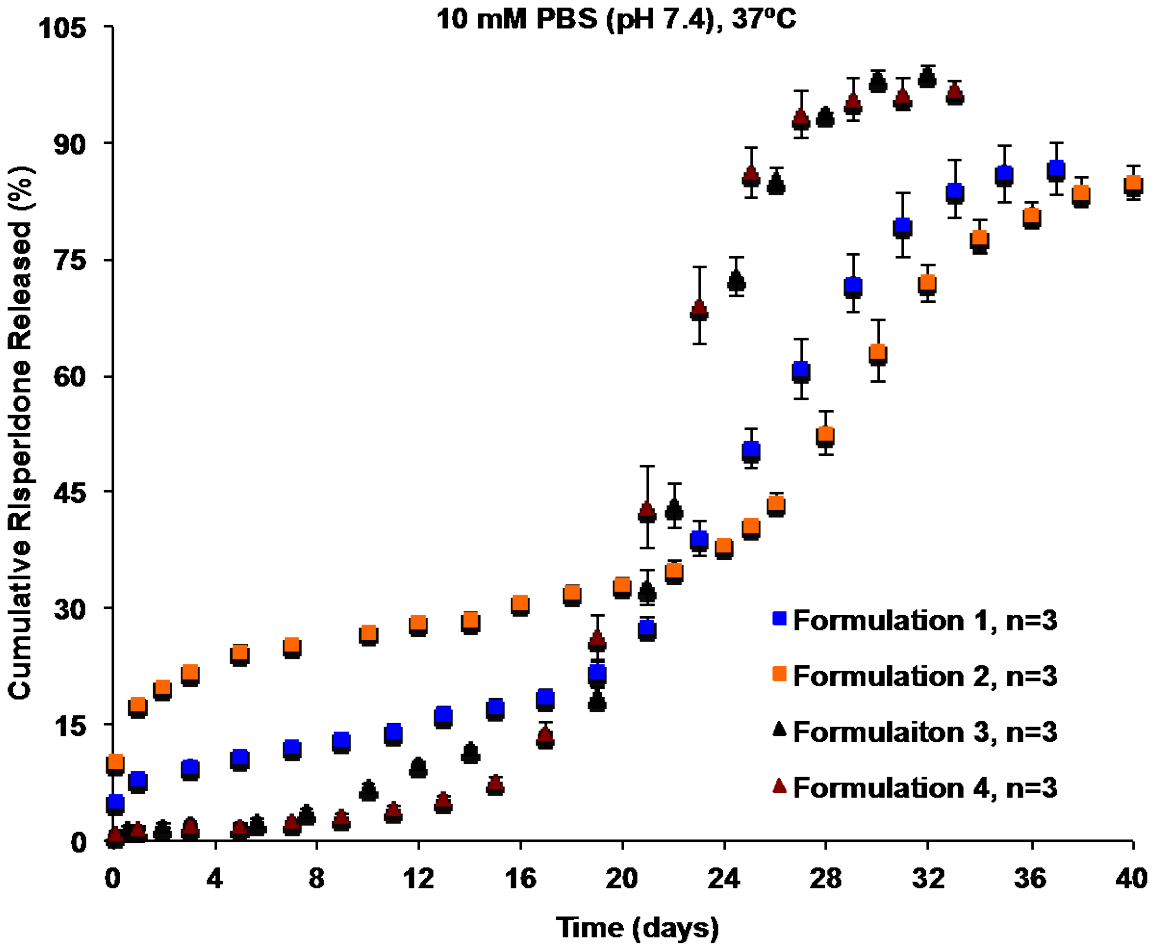


Microsphere aggregation was observed.

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**



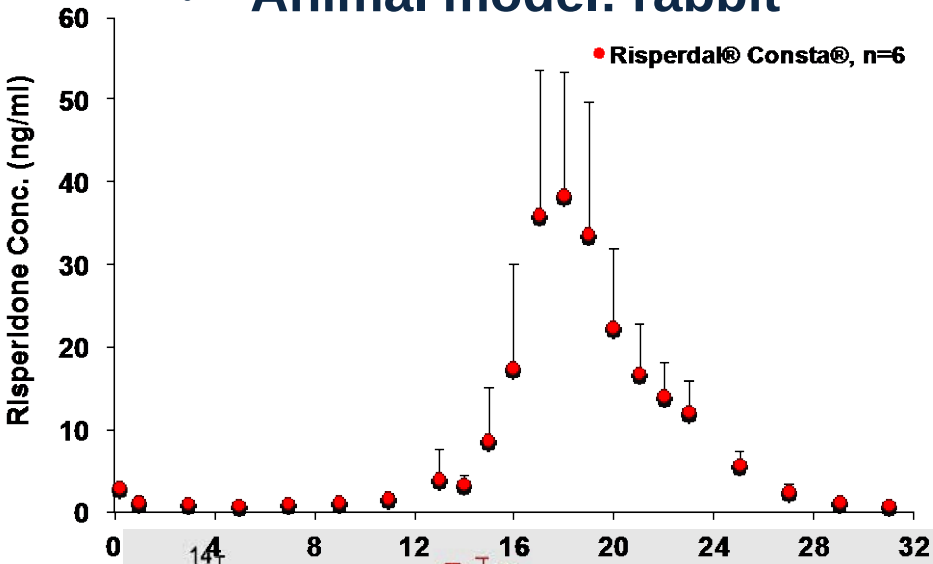
Shen J., Burgess D.J., *J. Control. Release, (2015)*

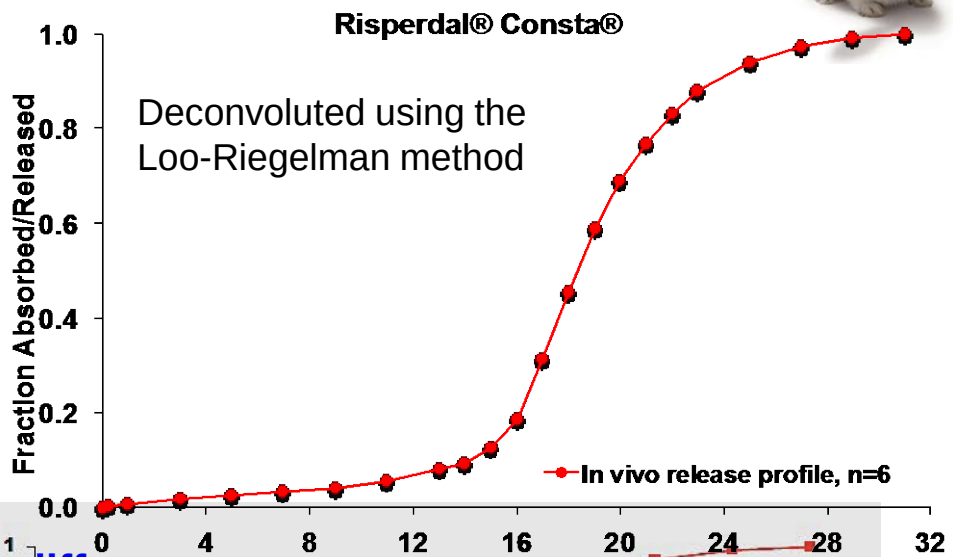
Case I: Compositionally Equivalent Risperidone Microspheres

- ***In 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**

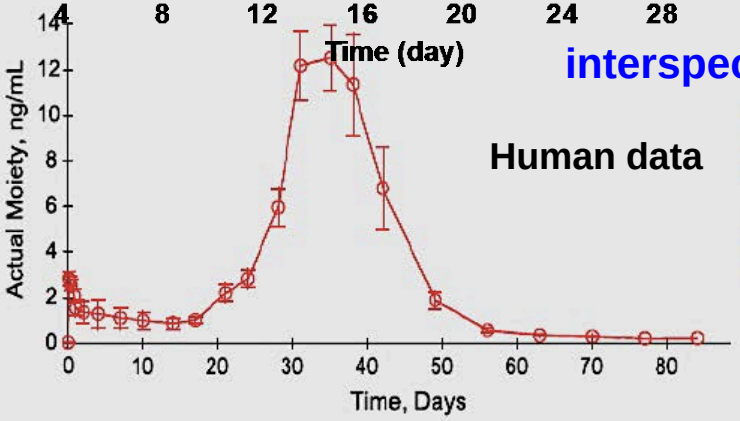
Case I: Compositionally Equivalent Risperidone Microspheres

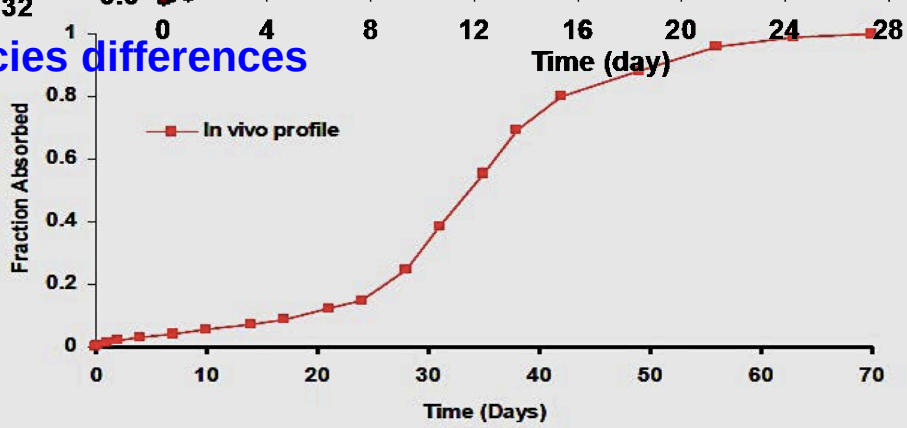
- ***In vivo* release testing**
  - **Animal model: rabbit**





interspecies differences

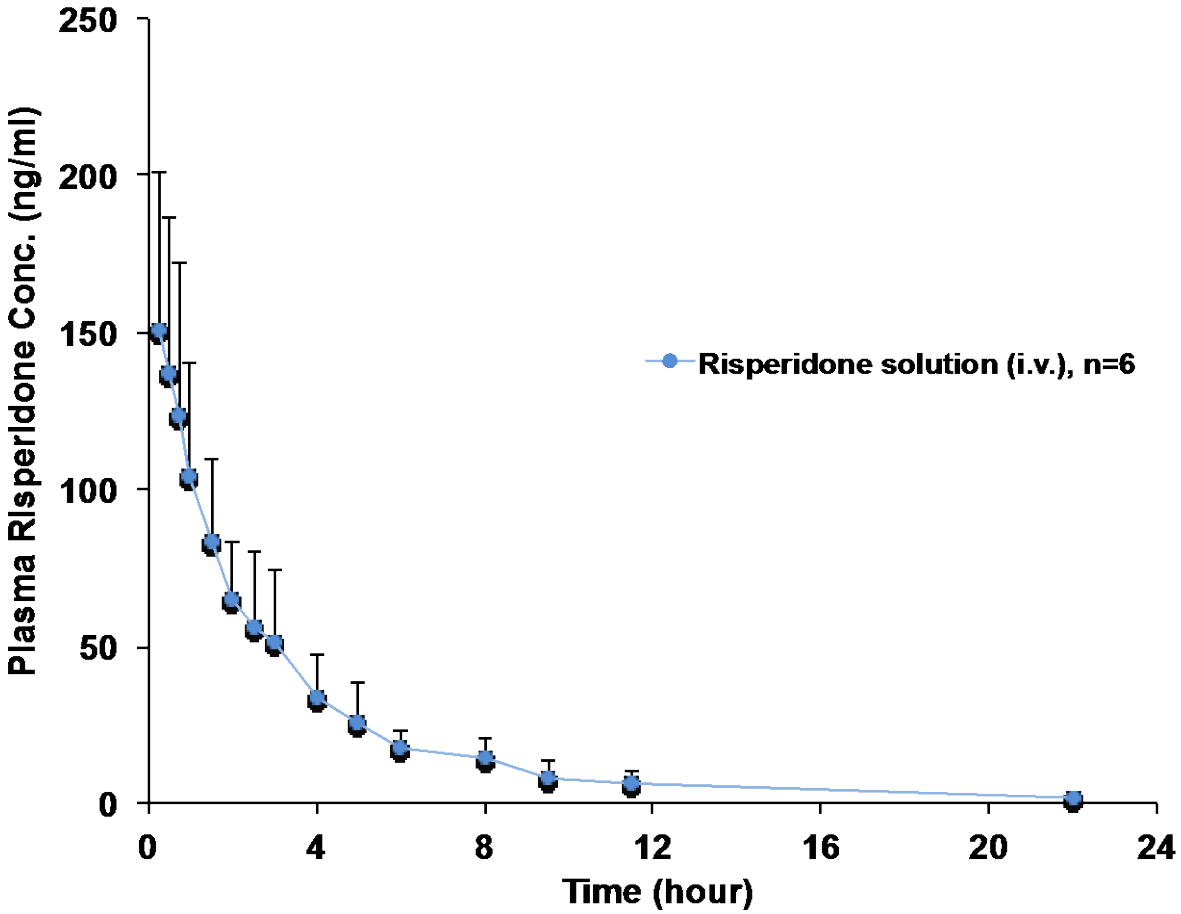




Rawat A., Burgess, D.J., *Int. J. Pharm., 2012*; Shen J., Burgess D.J., *J. Control. Release, (2015)*

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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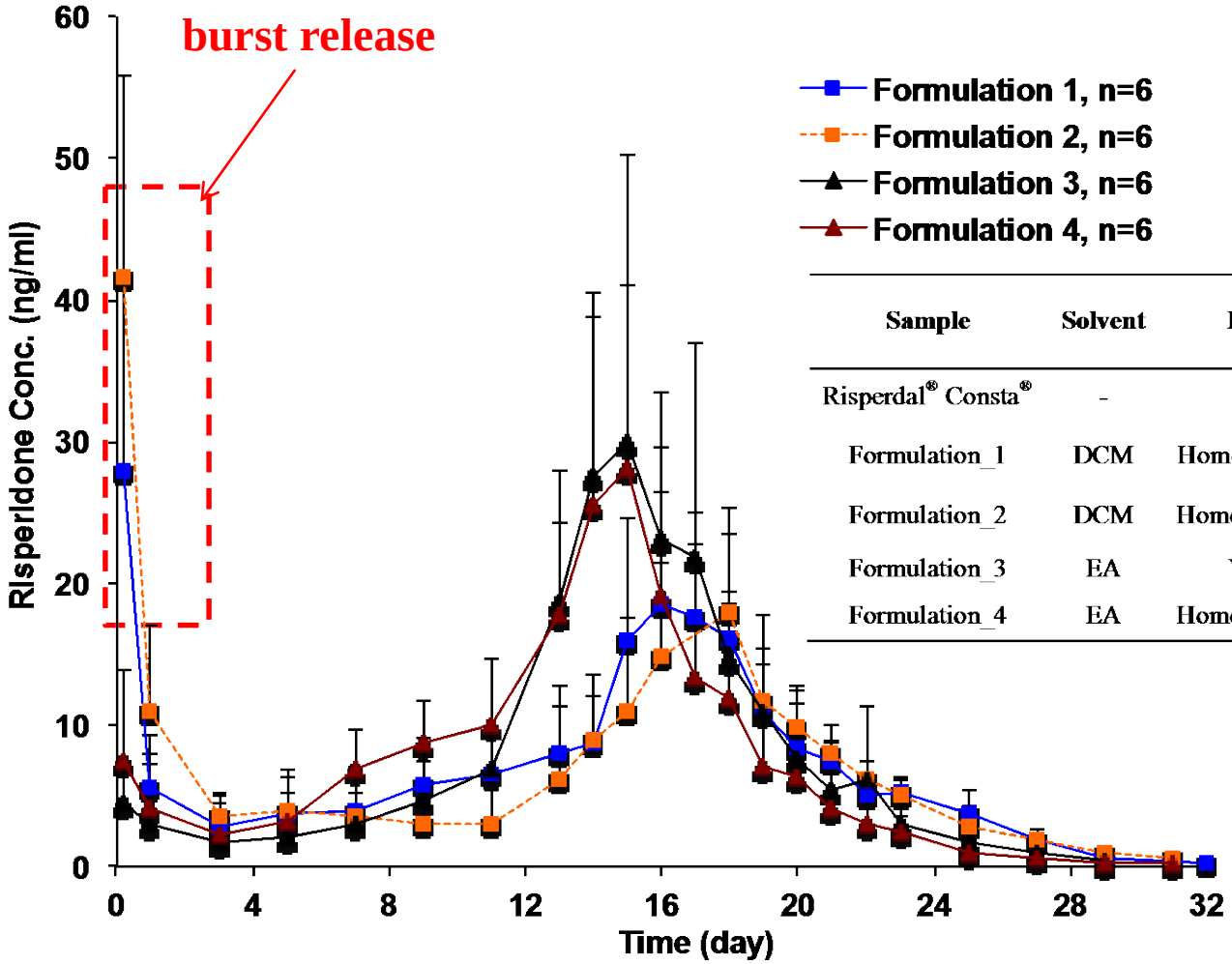
Case I: Compositionally Equivalent Risperidone Microspheres

- ***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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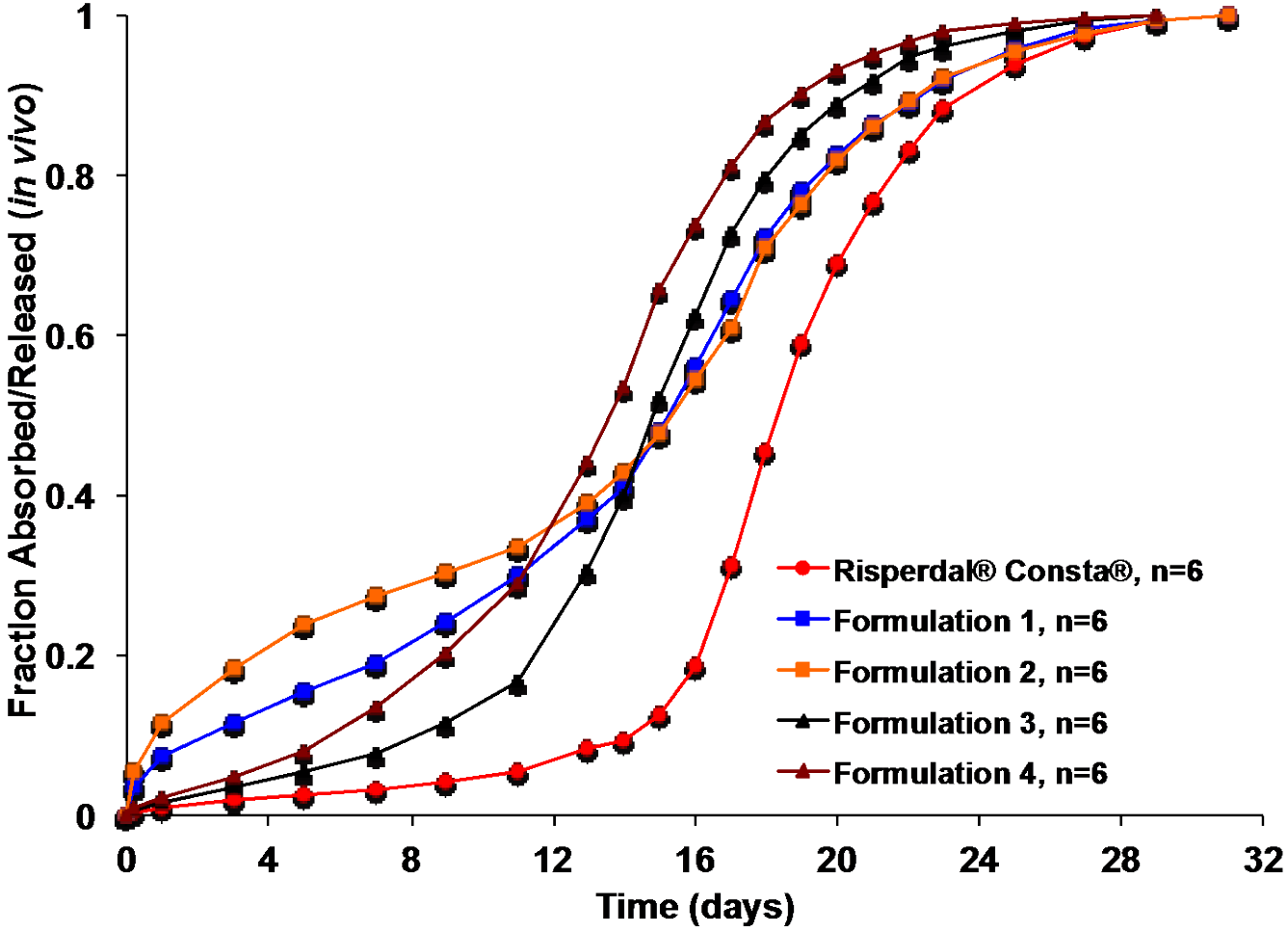
Case I: Compositionally Equivalent Risperidone Microspheres

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



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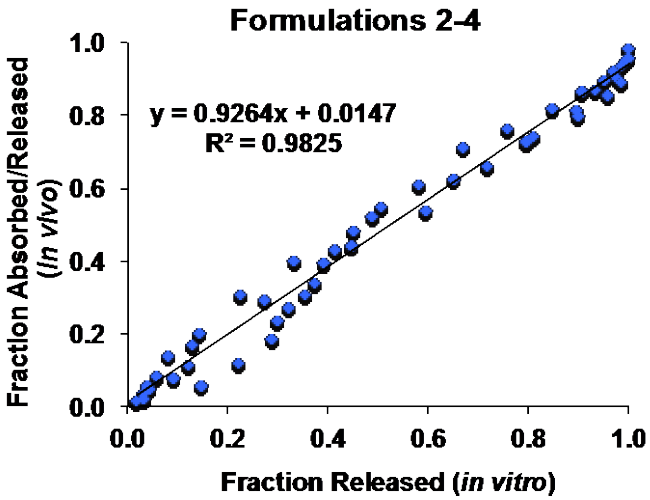
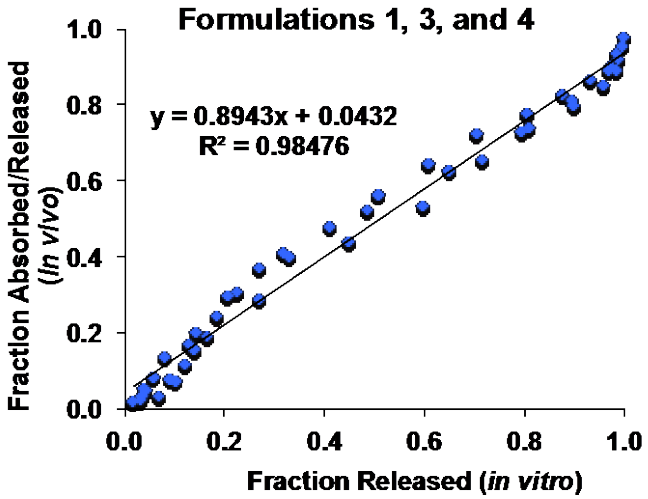
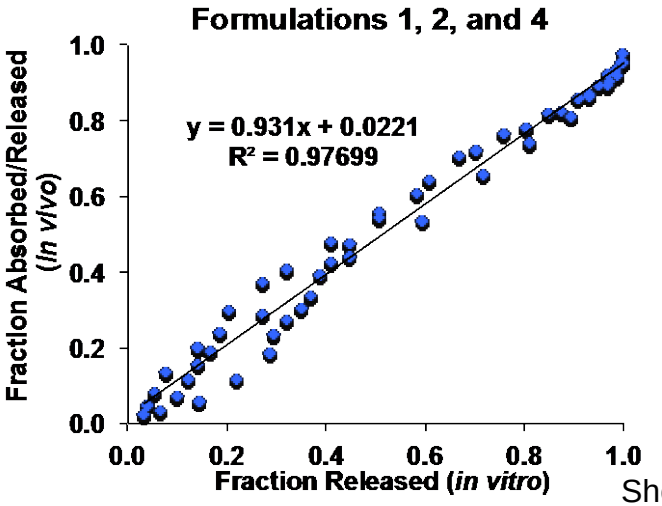
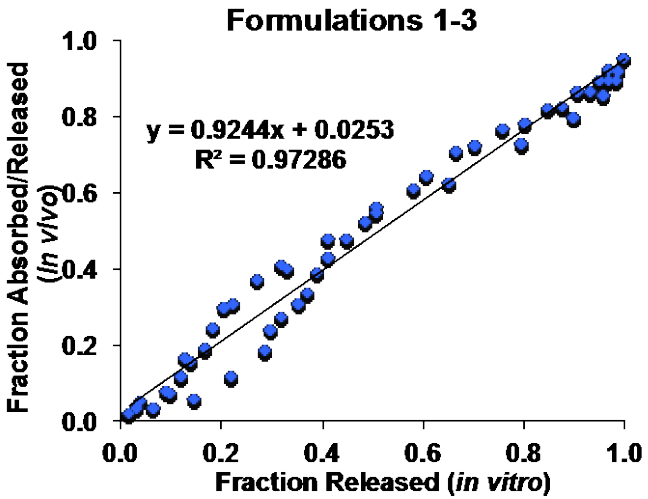
Case I: Compositionally Equivalent Risperidone Microspheres

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





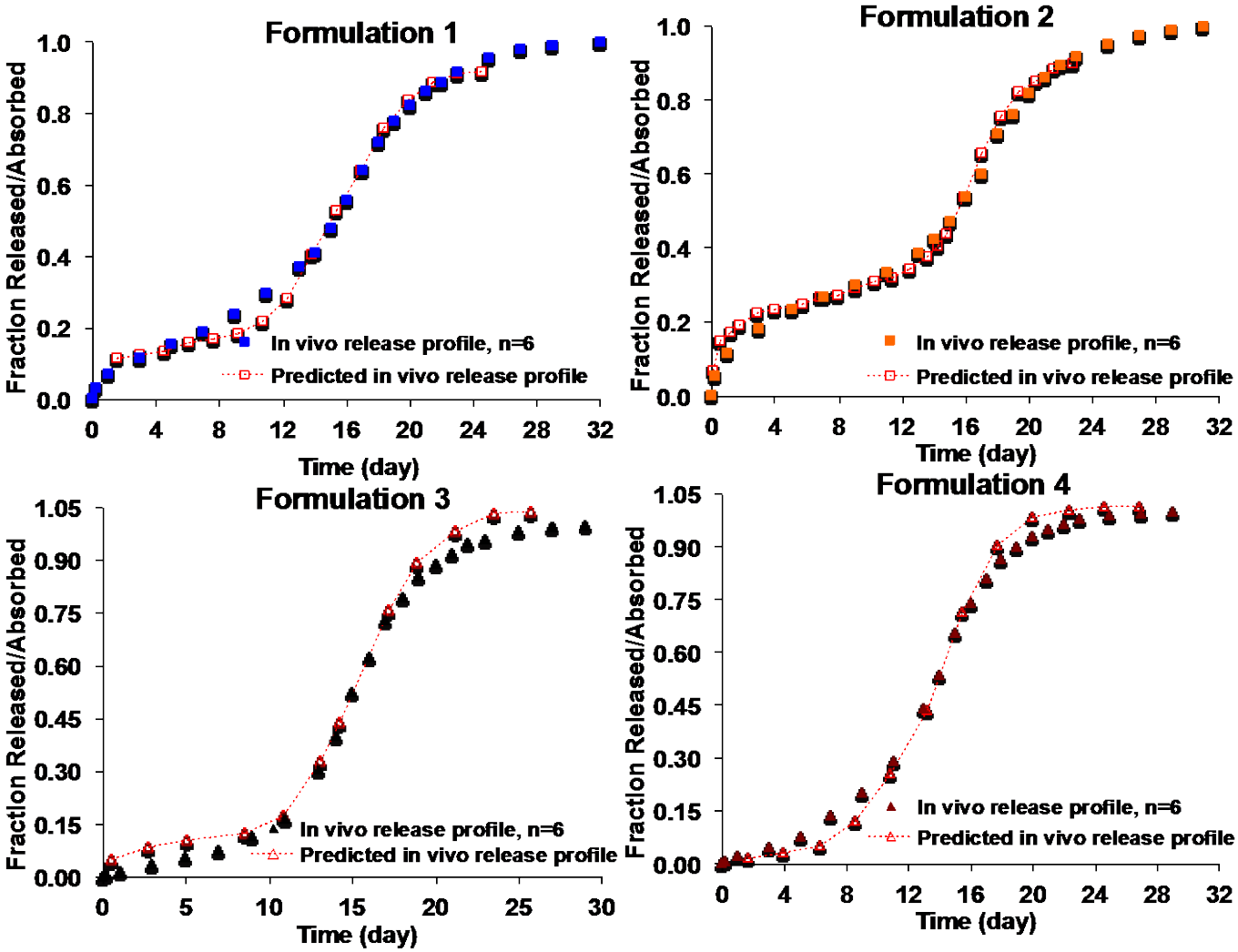




Shen J., Burgess D.J., *J. Control. Release, (2015)*

Case I: Compositionally Equivalent Risperidone Microspheres

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



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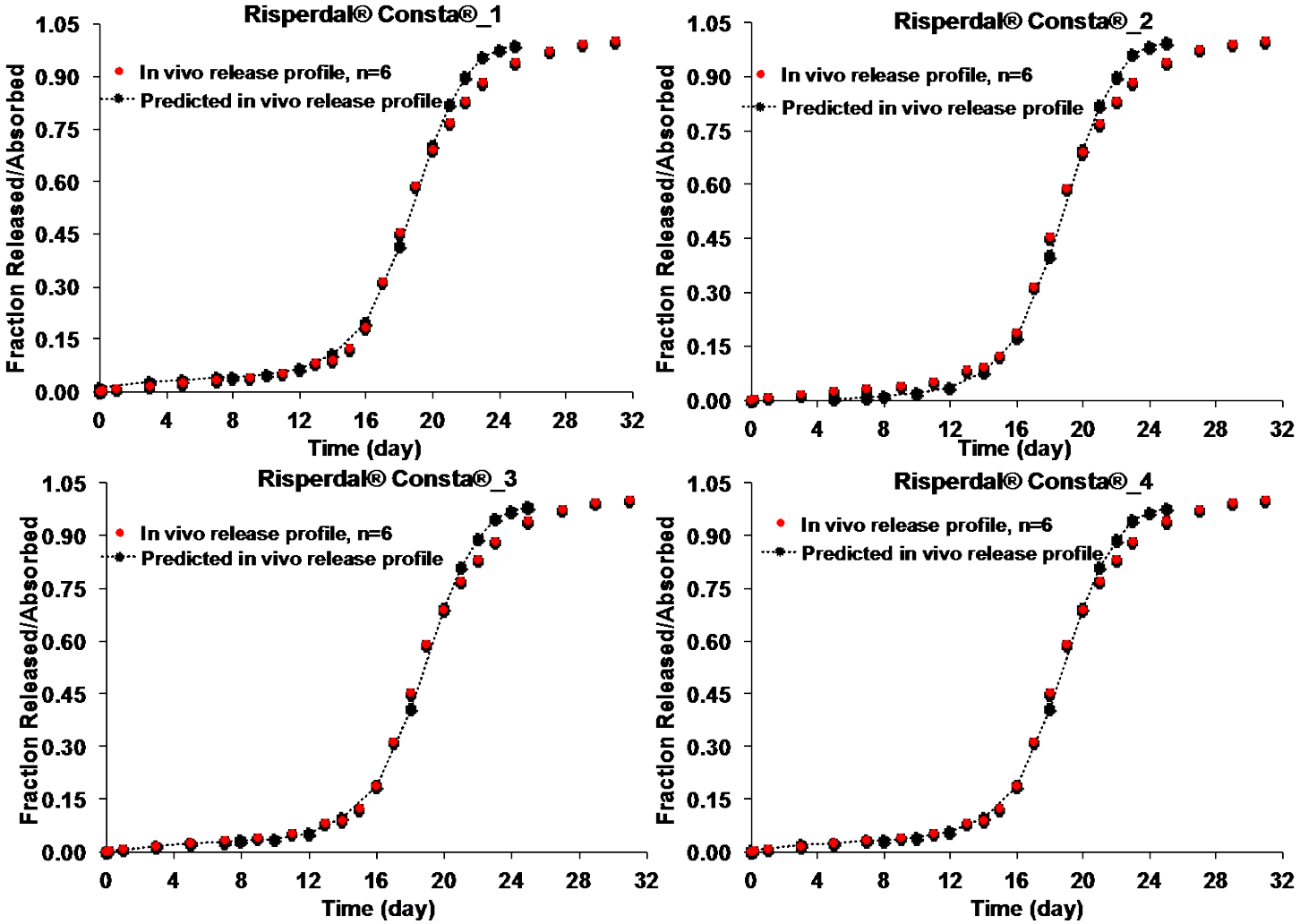
Case I: Compositionally Equivalent Risperidone Microspheres

➢ Prediction for the RLD product



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

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**.

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

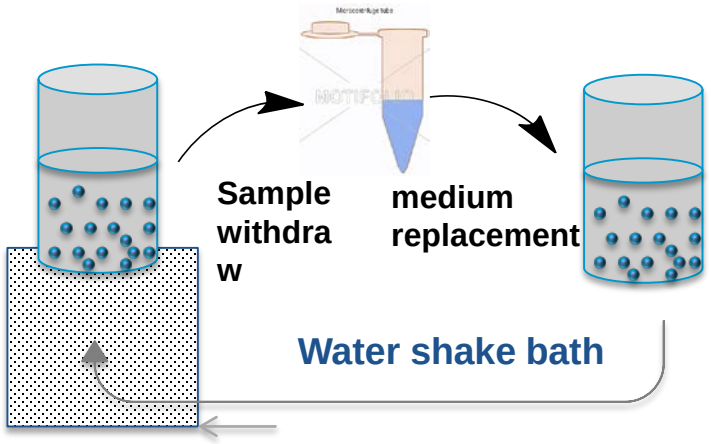

GIANT
COMPOSITE
BONTRAGER
Bianchi

Case II:

Naltrexone Microspheres

In vitro release testing methods used for naltrexone microspheres

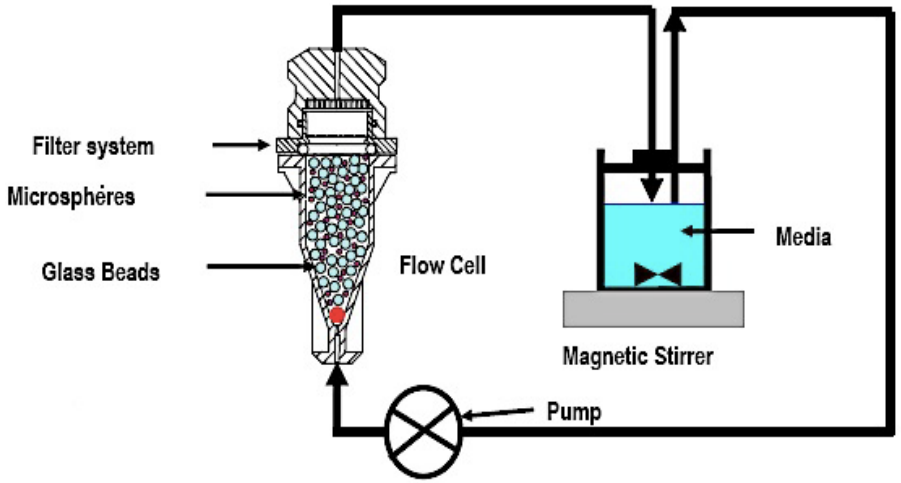
Sample-and-separate method



Advantages: Very simple set –up

Disadvantages: Non-standard size
Aggregation
Sample loss
Poor hydrodynamic control

USP apparatus IV - Continuous flow method



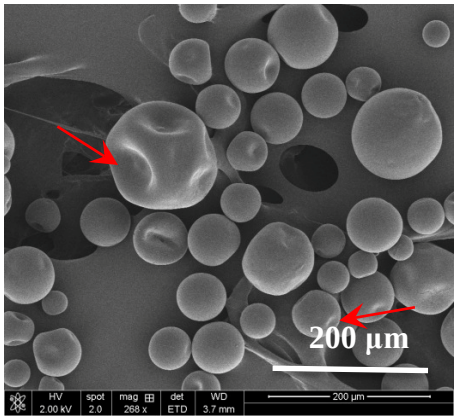
Advantages:

- ✓ No sample aggregation
- ✓ No sample loss
- ✓ Better geometric and hydrodynamic control
- ✓ Mimics *in vivo* conditions

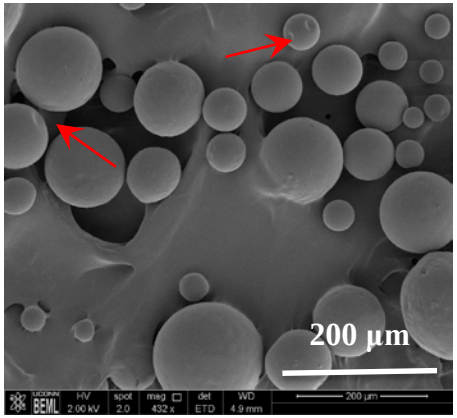
Physicochemical Properties

Q1/Q2 equivalent Naltrexone microspheres

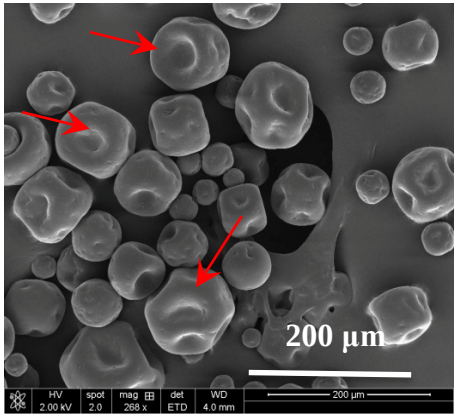
Sample	Solvent system	Preparation Method	Drug loading (%, w/w)	Porosity (%, w/w)
Formulation 1	DCM&BA	Magnetic Stirring	28.74±1.64	**49.83**
Formulation 2	EA&BA	Magnetic Stirring	29.7±1.11	58.32
Formulation 3	EA&BA	Homogenization	29.57±1.75	**65.08**
Vivitrol®	-		33.50±1.43	50.21



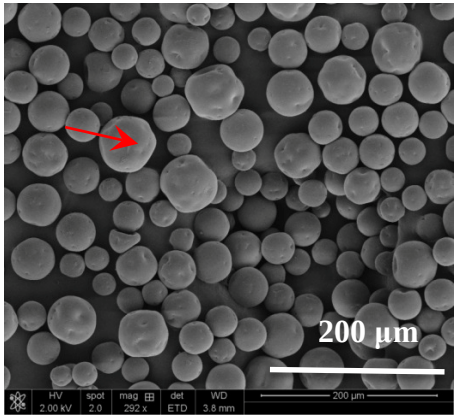
Vivitrol®



Formulation 1



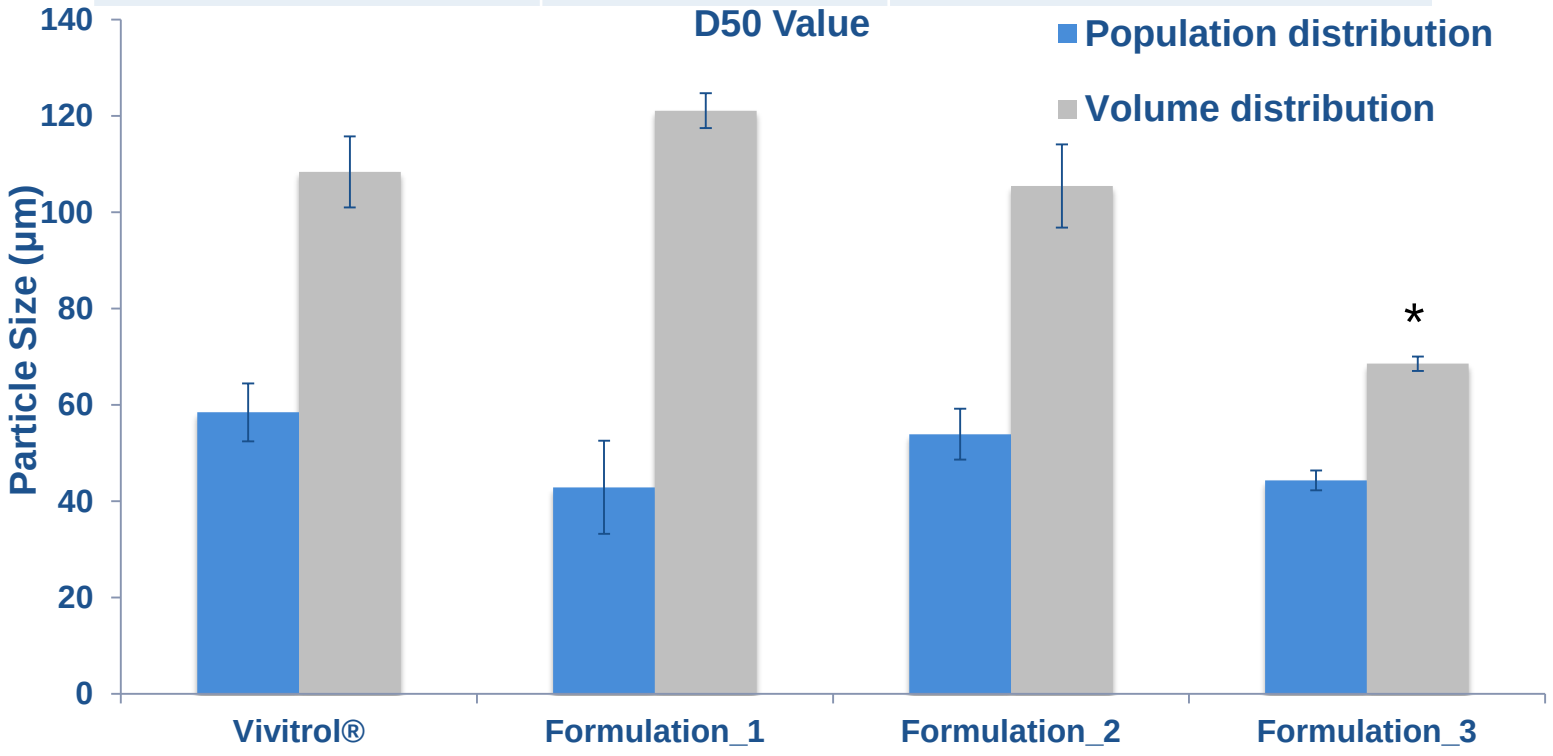
Formulation 2



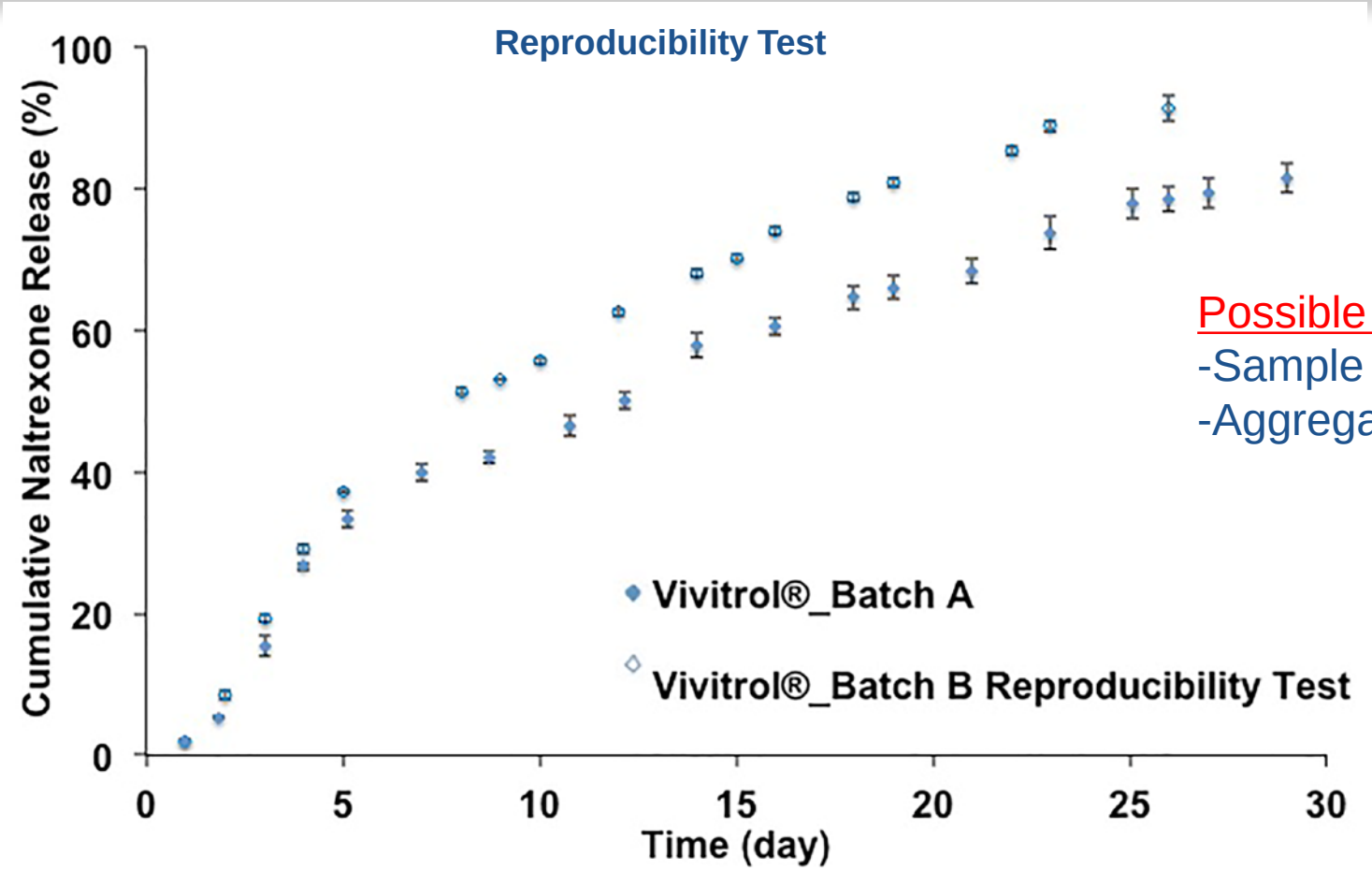
Formulation 3

Physicochemical Properties

Sample	Solvent system	Preparation Method
Formulation 1	DCM&BA	Magnetic Stirring
Formulation 2	EA&BA	Magnetic Stirring
Formulation 3	EA&BA	Homogenization
Vivitrol®	-	



Real-time *in vitro* release testing
Sample and separate method, 37° C

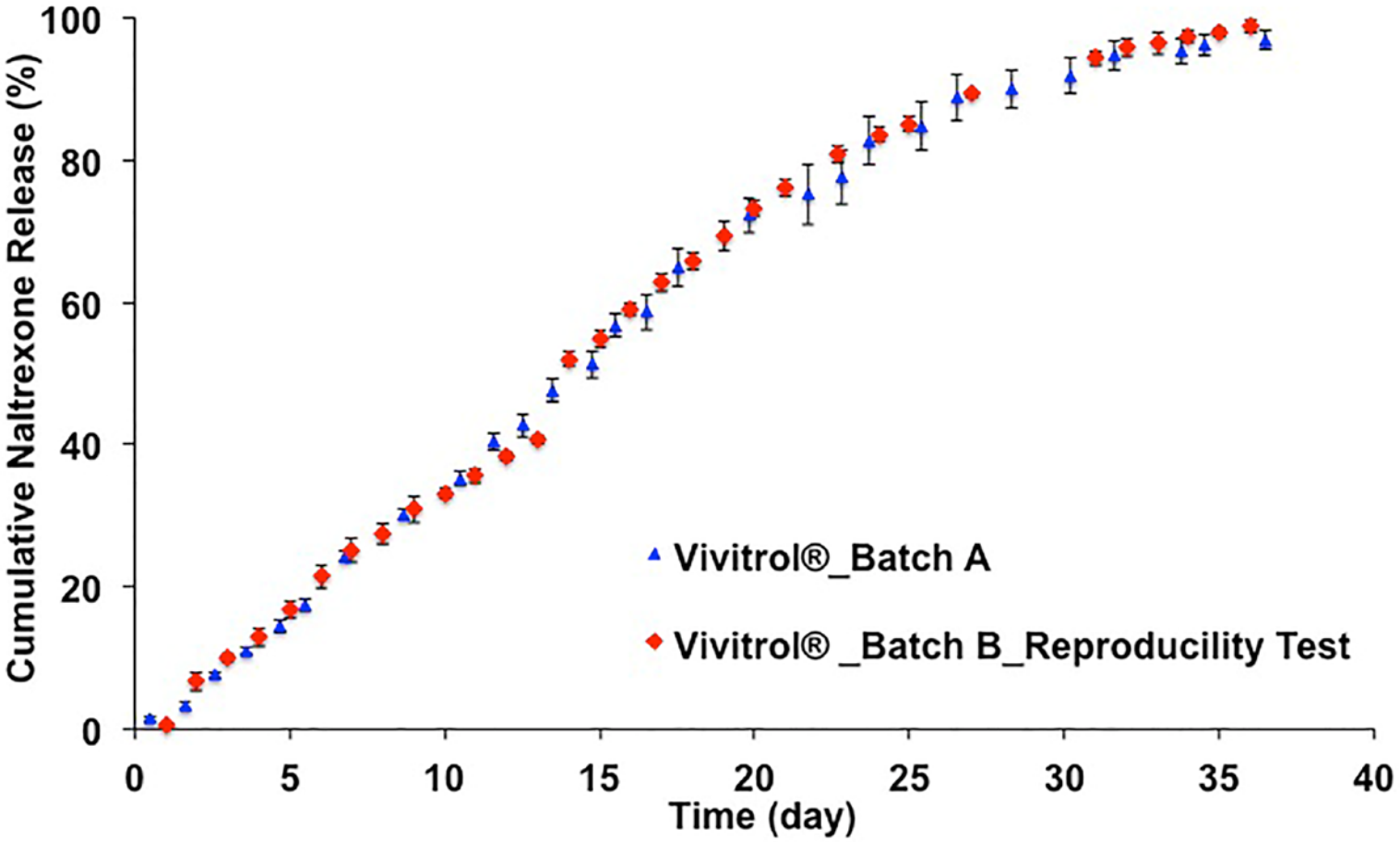


Possible reasons
-Sample loss
-Aggregation

Medium: PBS (10 mM, pH 7.4) + 0.02 % (v/v) Tween 20+ 0.02 % (w/v) sodium azide

The medium was replaced every five days at 37° C

Real-time *in vitro* release testing USP apparatus 4 method, 37° C



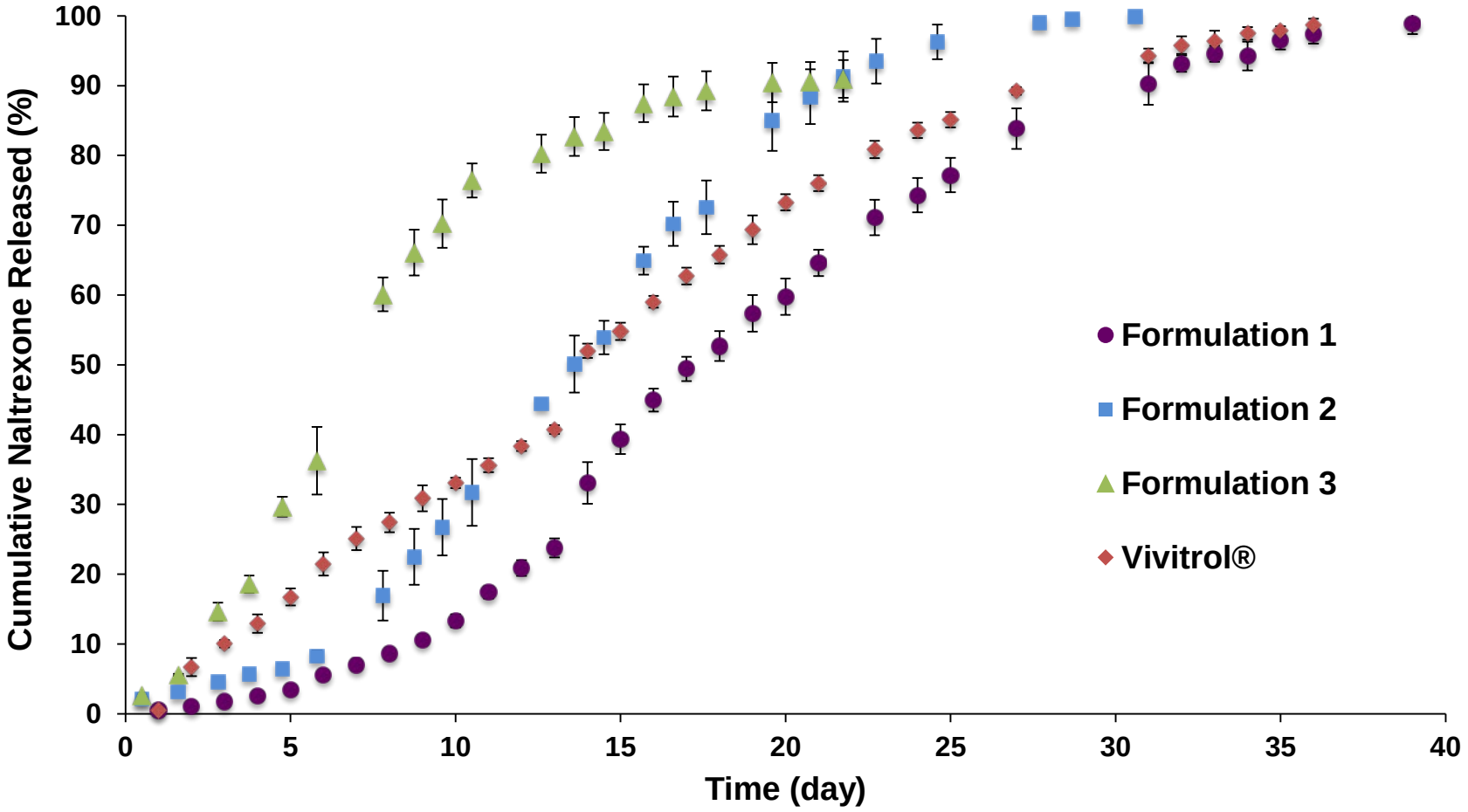
Medium: PBS (10 mM, pH 7.4) + 0.02 % (v/v) Tween 20+ 0.02 % (w/v) sodium azide

The medium was replaced every five days at 37° C

Real-time *in vitro* release testing

USP apparatus 4 method, 37°C

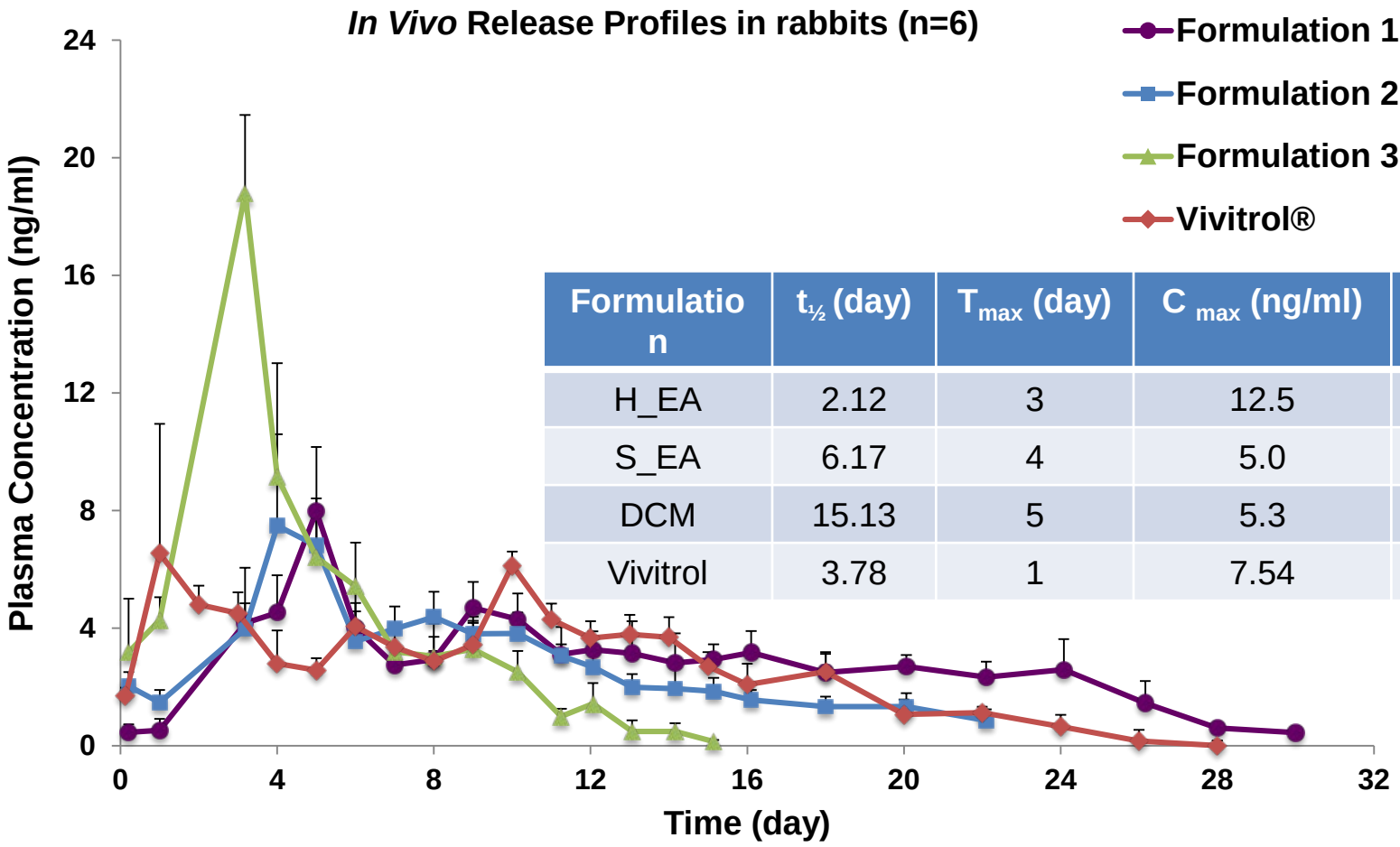
➢ Comparison of *In vitro* release profiles of naltrexone microspheres



- Note that the release medium was replaced every five days.

Development of IVIVC for naltrexone microspheres

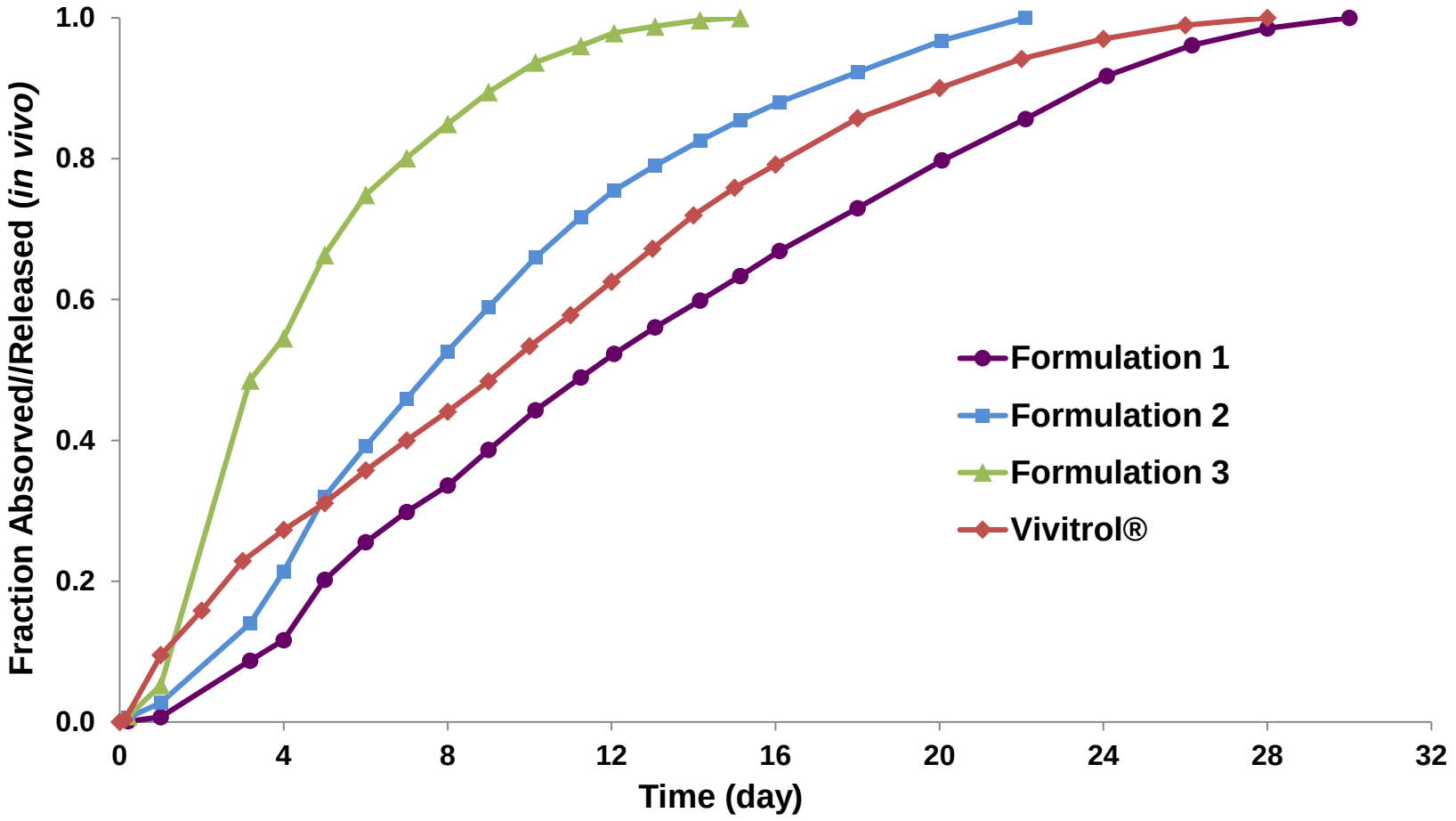
- *In vivo* release profiles of the prepared naltrexone microspheres (dose: 11.69 mg/kg) (rabbit, *n*=6)



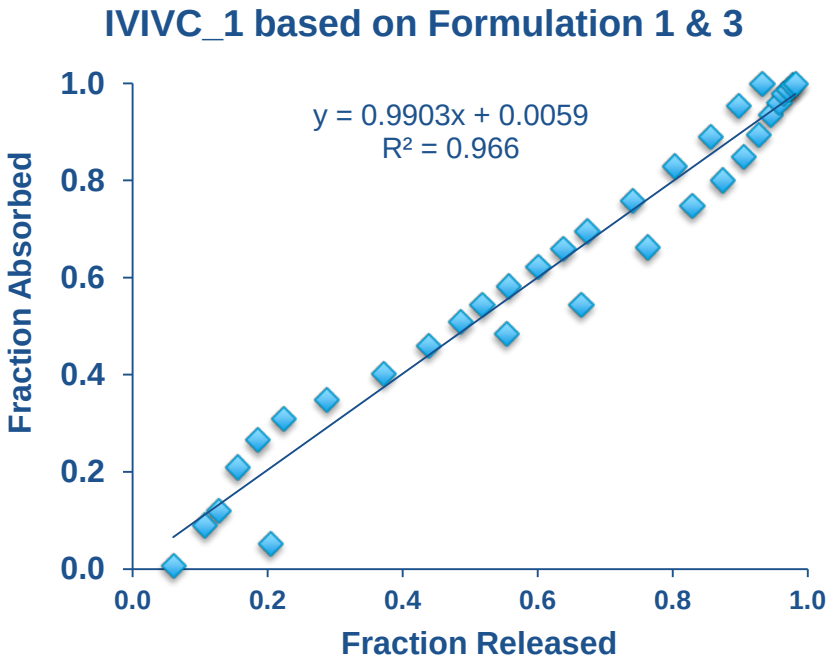
Formulation	$t_{½}$ (day)	T_{max} (day)	C_{max} (ng/ml)	AUC_{last}
H_EA	2.12	3	12.5	48.14
S_EA	6.17	4	5.0	41.92
DCM	15.13	5	5.3	53.41
Vivitrol	3.78	1	7.54	74.60

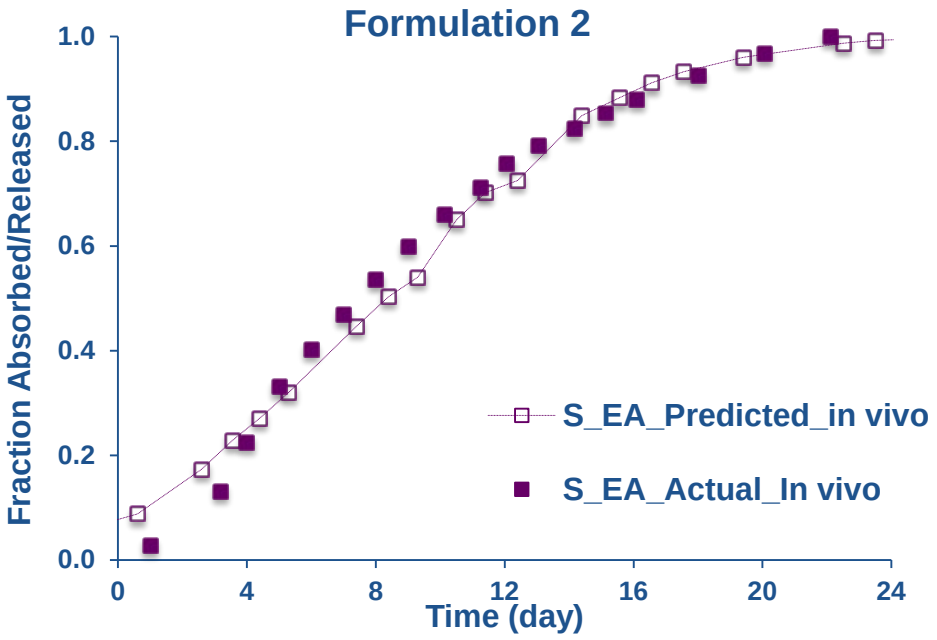
Development of IVIVC for naltrexone microspheres

- Deconvoluted *in vivo* release profiles of the prepared naltrexone microspheres (Loo-Riegelman method)

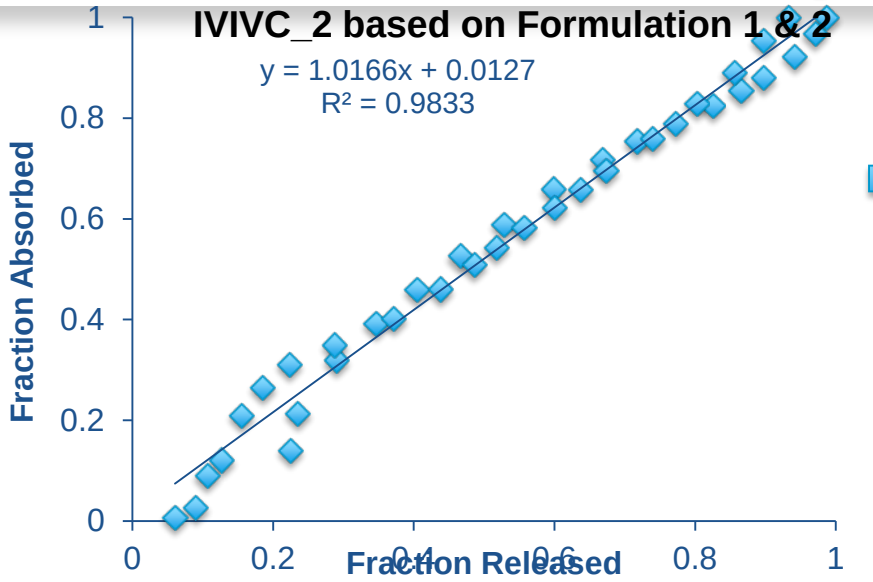


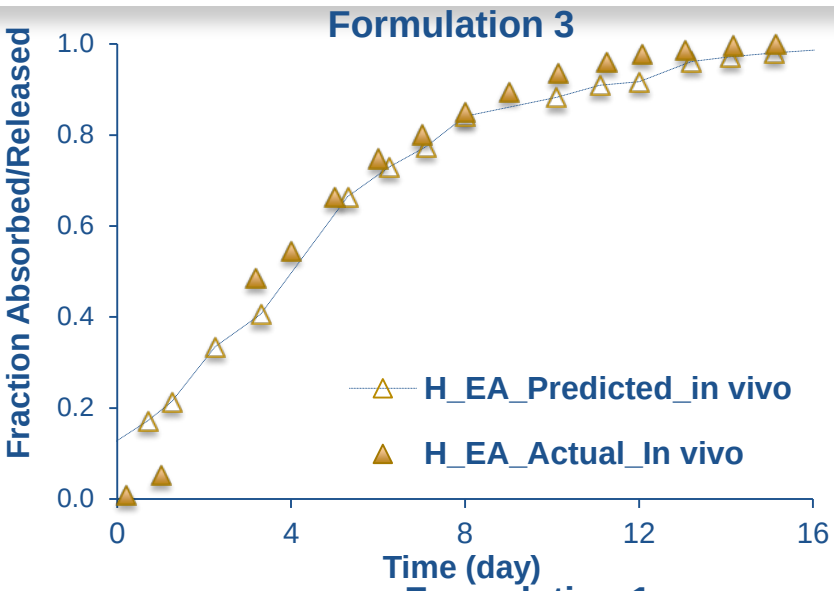
Development of IVIVC for naltrexone microspheres

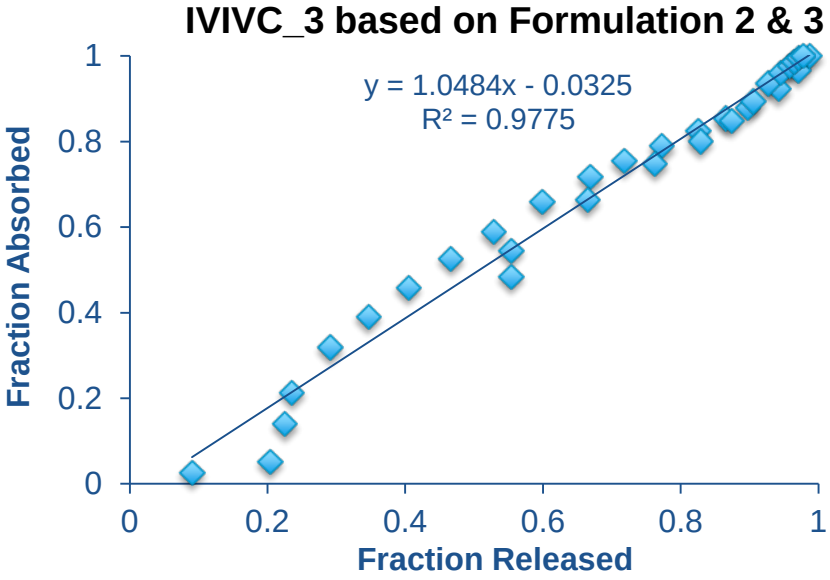


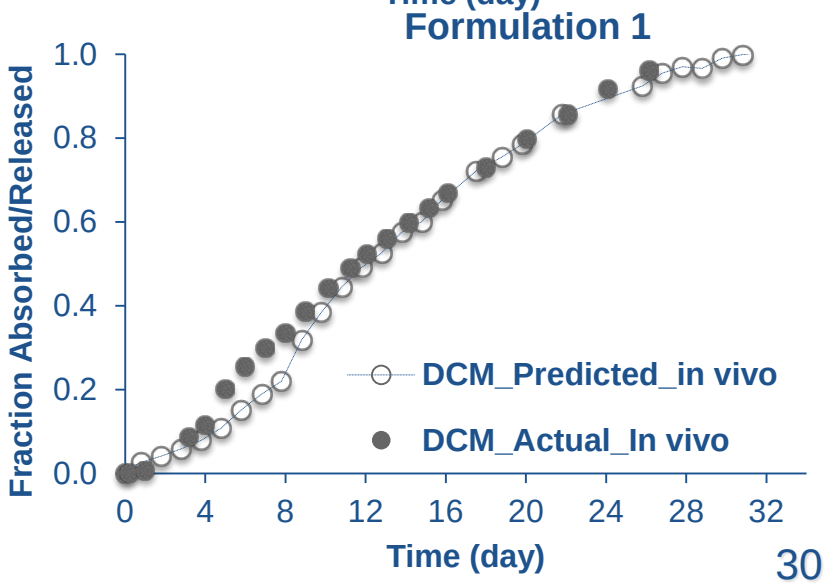


Development of IVIVC for naltrexone microspheres



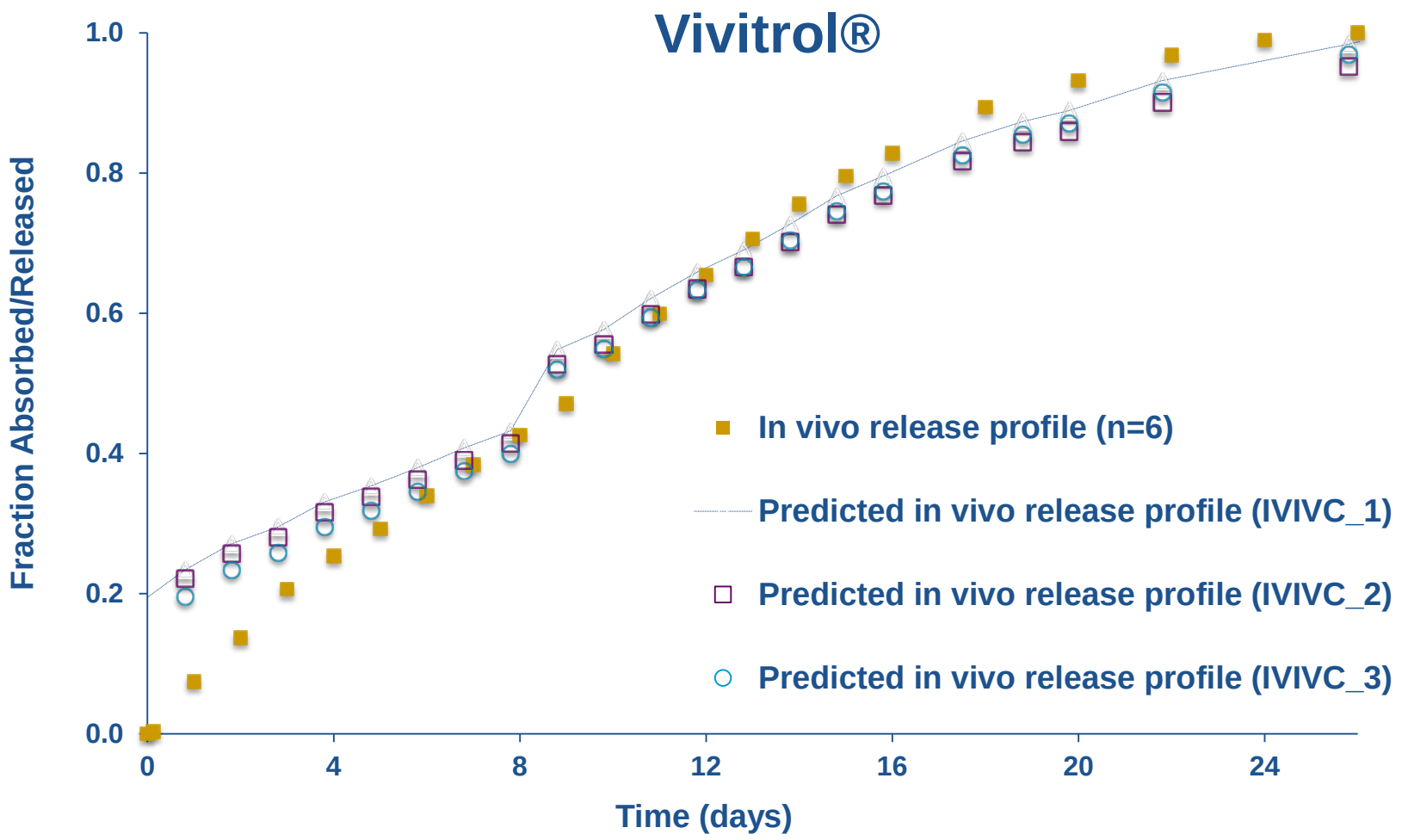






Development of IVIVC for naltrexone microspheres

- Predicted *in vivo* profiles of naltrexone microspheres using IVIVCs



Development of IVIVC for naltrexone microspheres

- Estimation of % prediction error (% PE) of the developed IVIVC model (IVIVC_1)

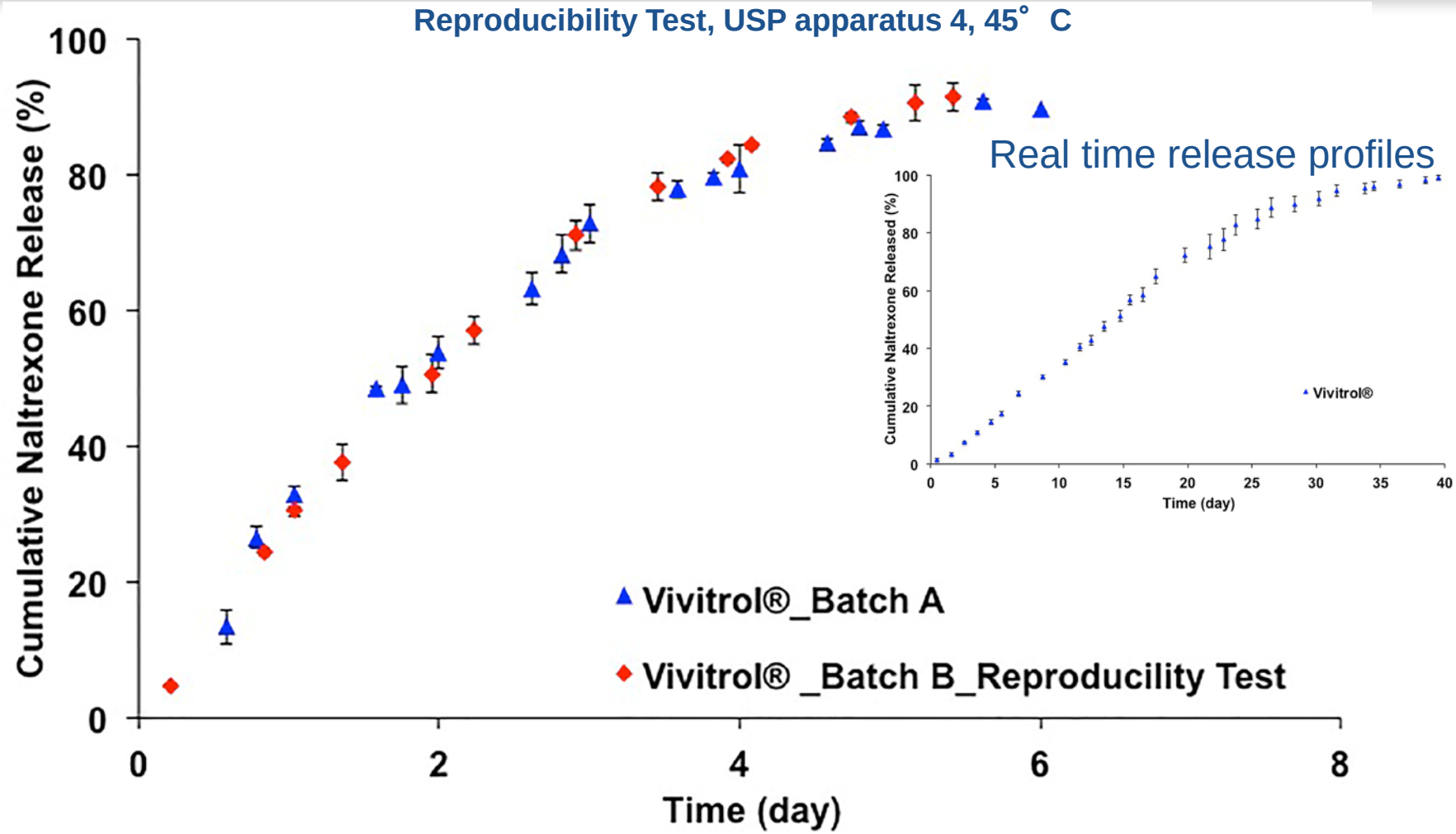
Formulation	Parameter	Observed	Predicted	%PE
Formulation 1 Internal	AUClast	70.99	80.82	-12.16
	Cmax	7.84	7.98	-1.68
Formulation 3 Internal	AUClast	70.79	72.17	-1.92
	Cmax	14.61	18.78	-22.24
Avg Internal	AUClast	70.89	76.50	7.04
	Cmax	11.22	13.38	11.96
Formulation 2 External	AUClast	69.14	62.78	10.13
	Cmax	7.74	7.49	3.38
Target	AUClast	81.70	74.60	9.53
	Cmax	6.84	7.54	-9.27

Conclusions

- An *in-vitro* release testing method using USP apparatus 4, a compendial apparatus, was developed.
- IVIVC for prepared naltrexone microspheres was successfully developed based on 3 formulations using developed USP apparatus 4 *in vitro* release testing method

- The developed real-time *in vitro* release testing method has a potential to predict *in vivo* performance of the prepared naltrexone microspheres.

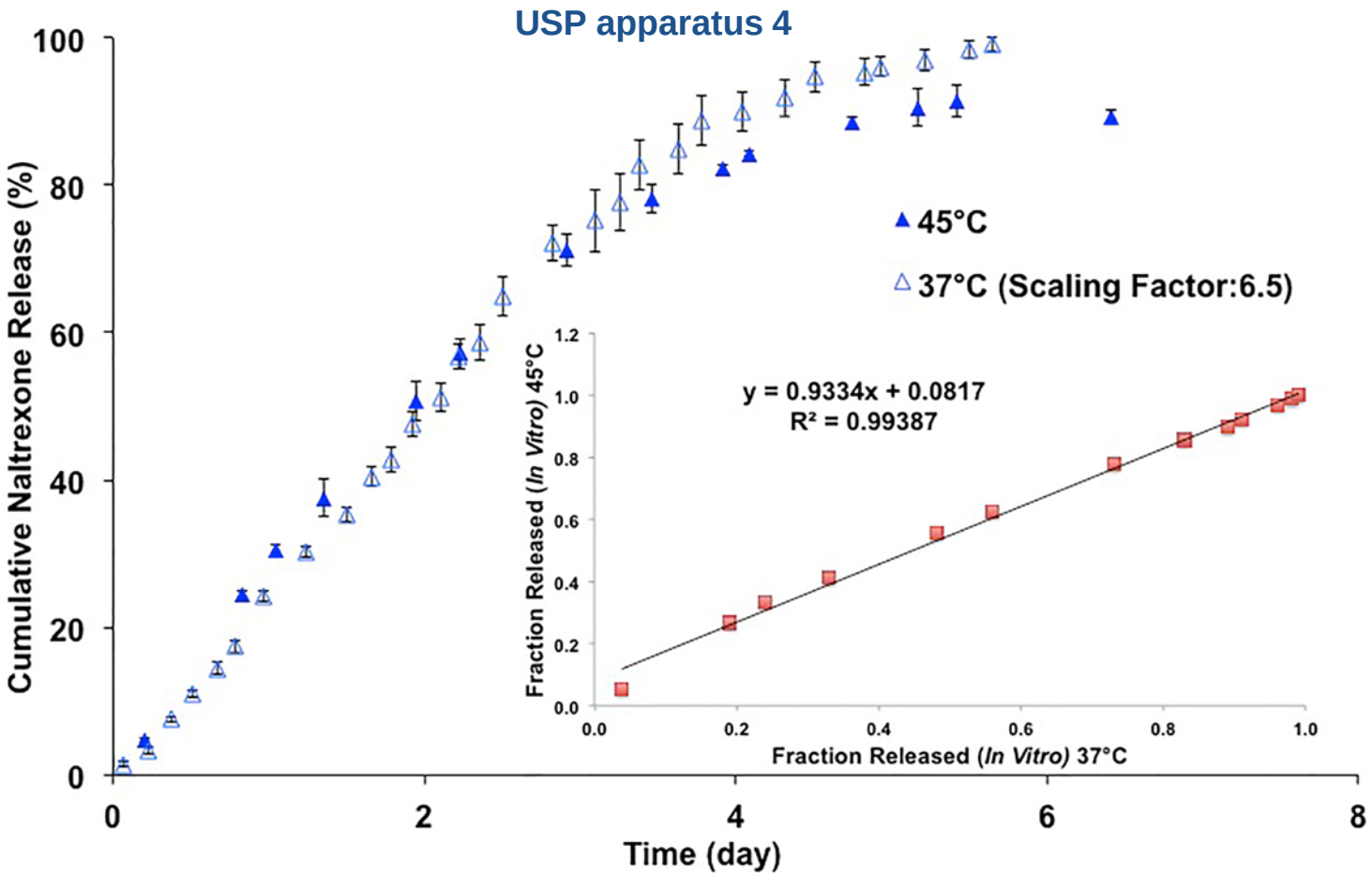
Development of accelerated *in vitro* release testing



Medium: PBS (10 mM, pH 7.4) + 0.02 % (v/v) Tween 20+ 0.02 % (w/v) sodium azide+ 0.0625 %w/v Sodium Ascorbate

Development of accelerated *in vitro* release testing

- Correlation between real-time and accelerated release profiles



Medium: PBS (10 mM, pH 7.4) + 0.02 % (v/v) Tween 20+ 0.02 % (w/v) sodium azide+ 0.0625 %w/v Sodium Ascorbate

Development of accelerated *in vitro* release testing

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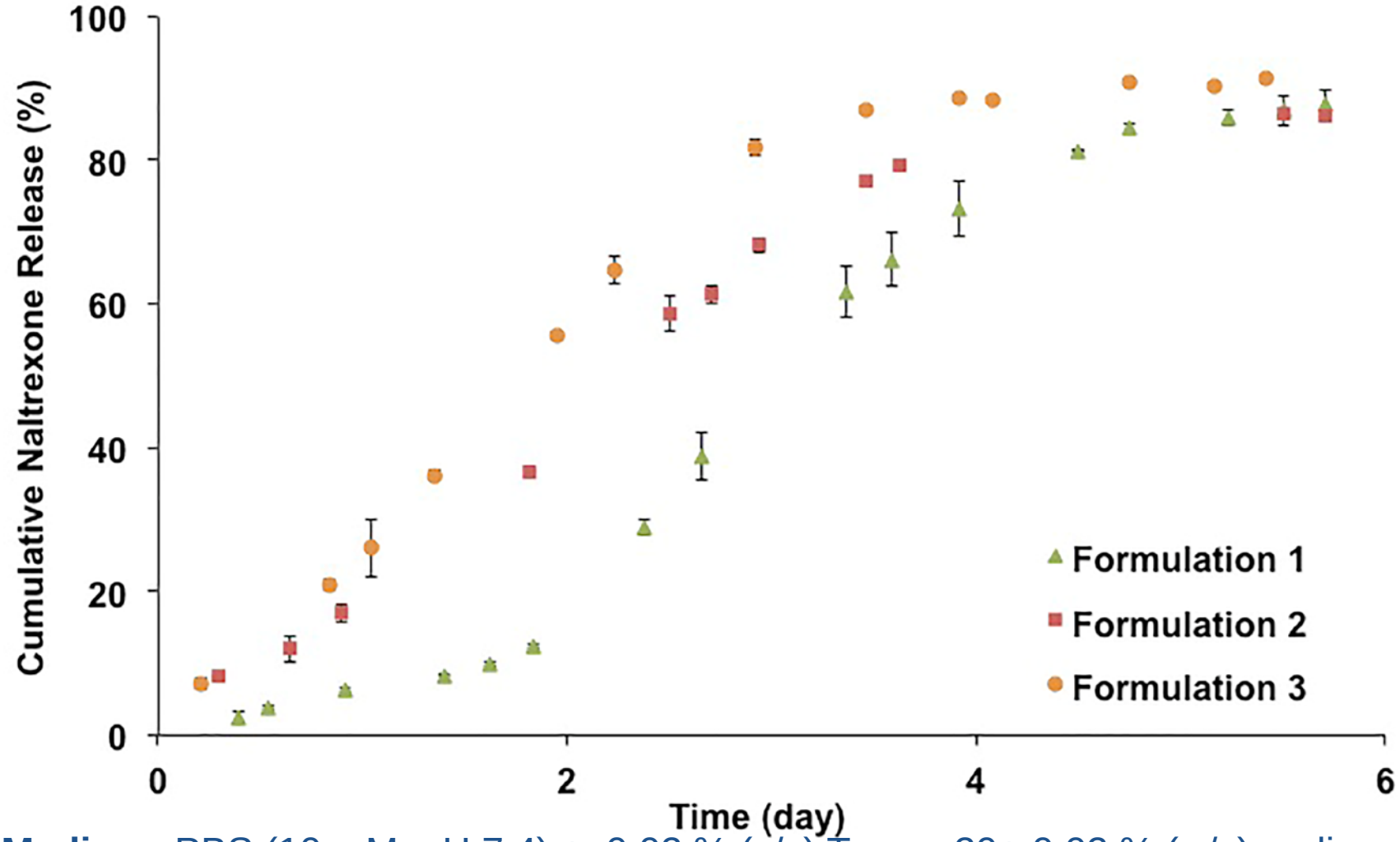
Discriminatory Test, USP apparatus 4, 45° C



Medium: PBS (10 mM, pH 7.4) + 0.02 % (v/v) Tween 20+ 0.02 % (w/v) sodium azide+ 0.0625 %w/v Sodium Ascorbate

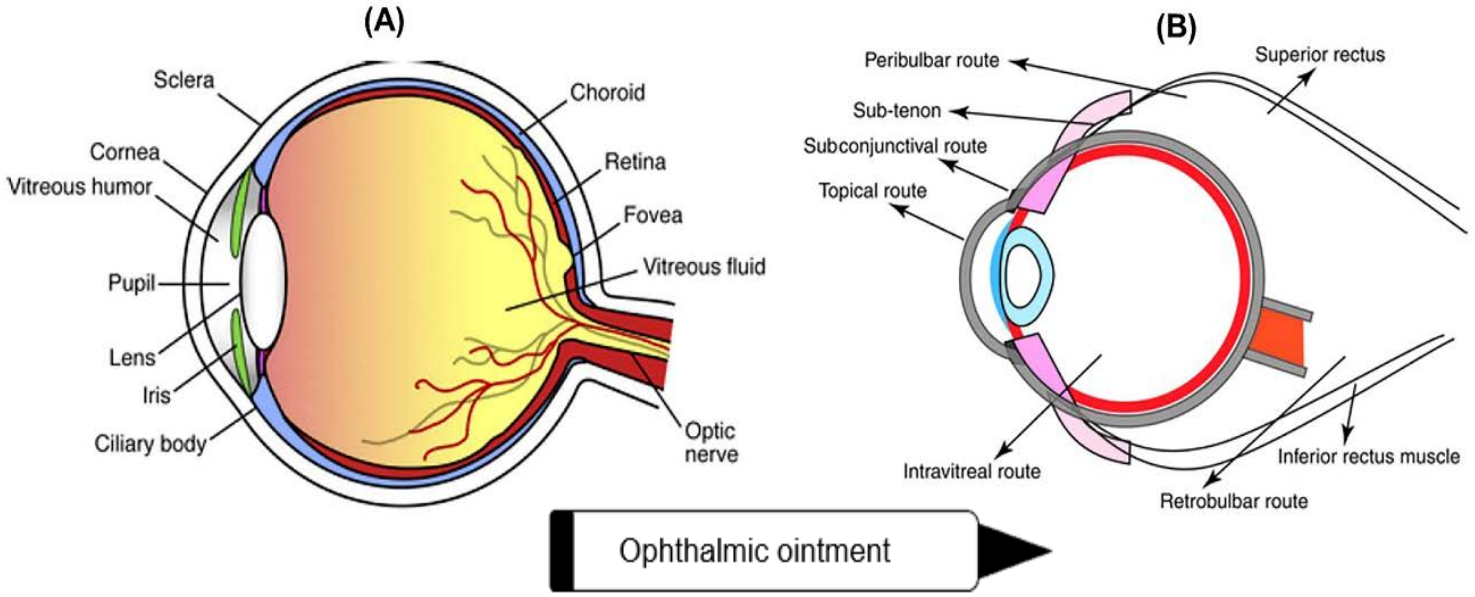
Conclusions

- Accelerated release testing method based on USP apparatus 4 using elevated temperature approach was developed.

- Developed accelerated *in-vitro* release testing method was
  1) Fast
  2) Reproducible,
  3) Able to differentiate manufacturing differences
  4) A 1:1 linear correlation with real-time release profiles.

In Vitro Release Testing of Ophthalmic Ointments

Ophthalmic Drug Delivery



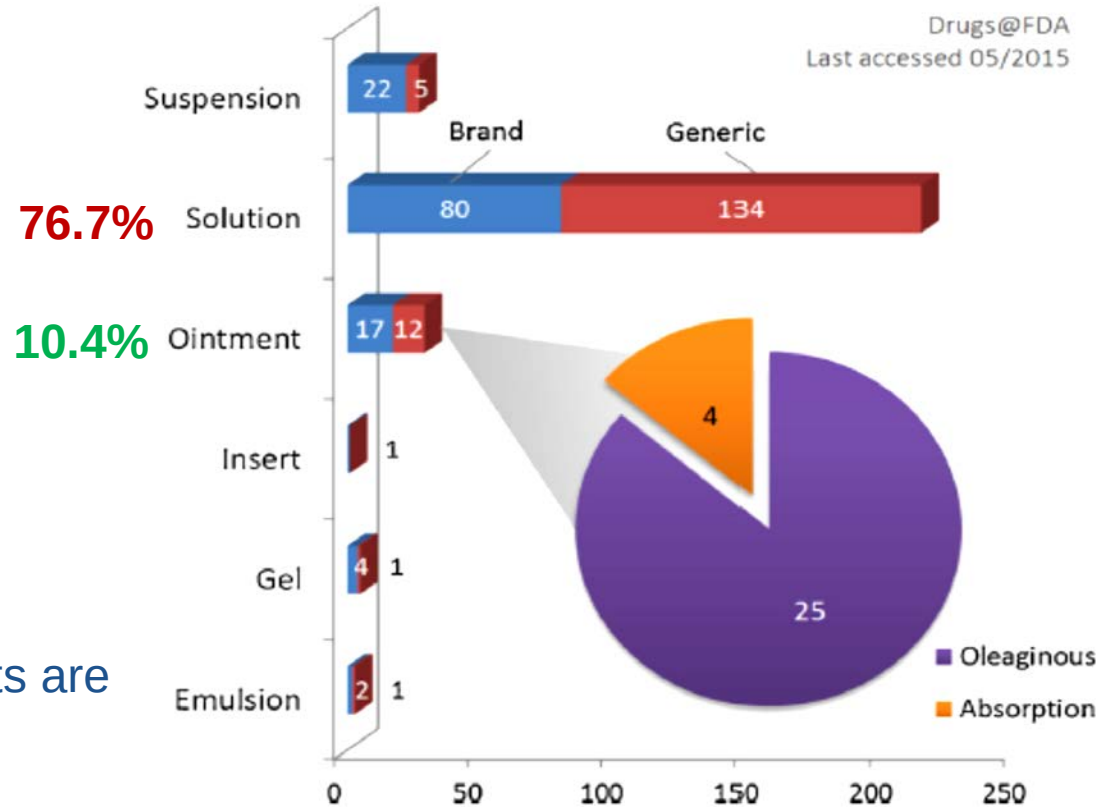
- **Topical route** (eye drops, ointments, suspensions, *etc.*)
- Periocular or intraocular routes of drug administrations (invasive)
- Systemic route (unwanted side effects)

Commercialization of Topical Ophthalmic Products

Major limitation of eye drops: Short residence time on the eye surface, resulting poor drug bioavailability.

Ointments can significantly prolong the drug residence time on the eye surface due to their rheological properties.

- Over 90% of market ointments are **white petrolatum** based.



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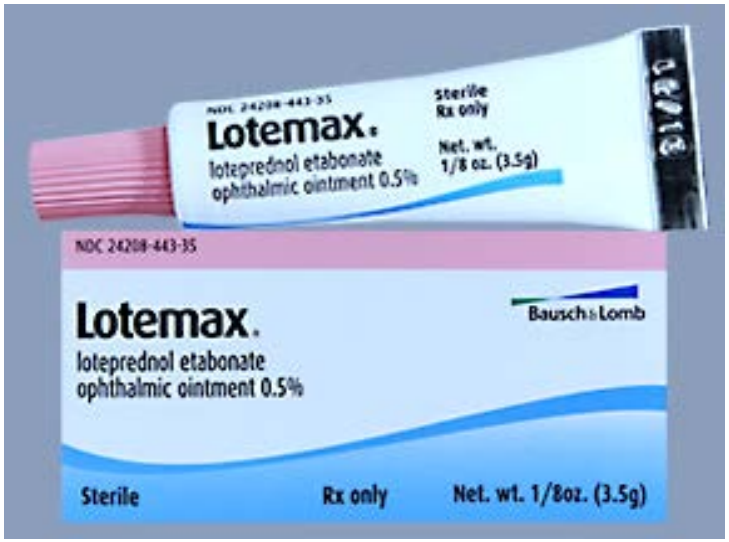
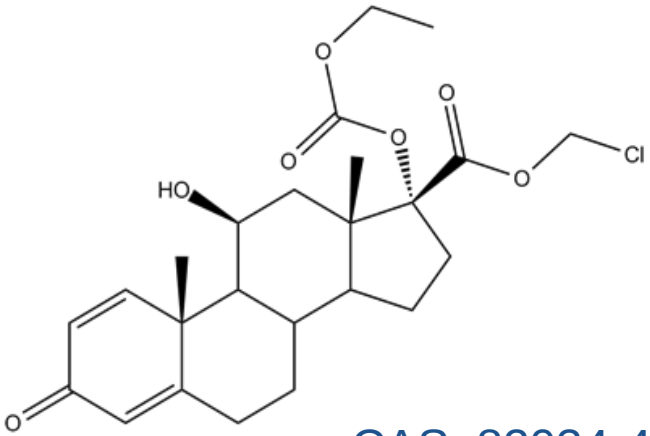
RLD: Loteprednol Etabonate ointment (Lotemax® , 0.5% w/w)

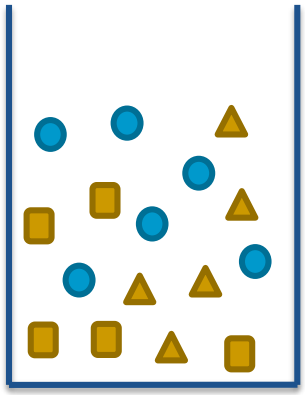




CAS: 82034-46-6
Formula: $C_{24}H_{31}ClO_7$
Mw: 466.95 g/mol

- Composed of white petrolatum and mineral oil.
- Approved by the FDA in 2011 for the treatment of **post-operative eye inflammation**

Preparation of Q1/Q2 LE ophthalmic ointments



mixing and cooling at RT (**SRT**)

Heat @65° C → mixing then immediate cooling at -20° C (**HMIC**)

Heat @65° C → mixing then cooling at RT (**HMRT**)

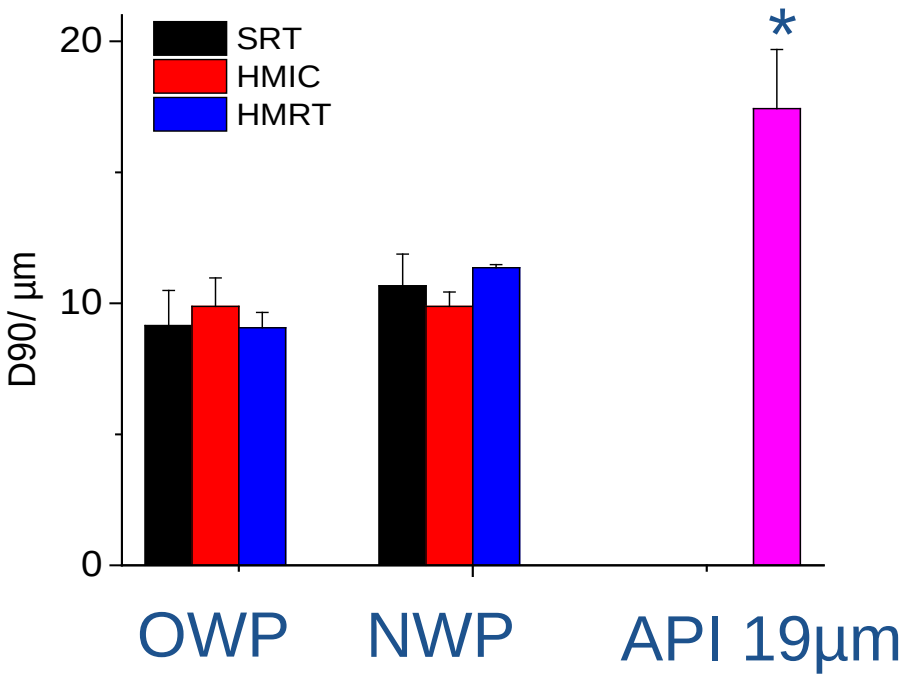
- White petrolatum (different sources: **OWP** or **NWP**)
- Mineral oil
- API **19** µm (crystalline)

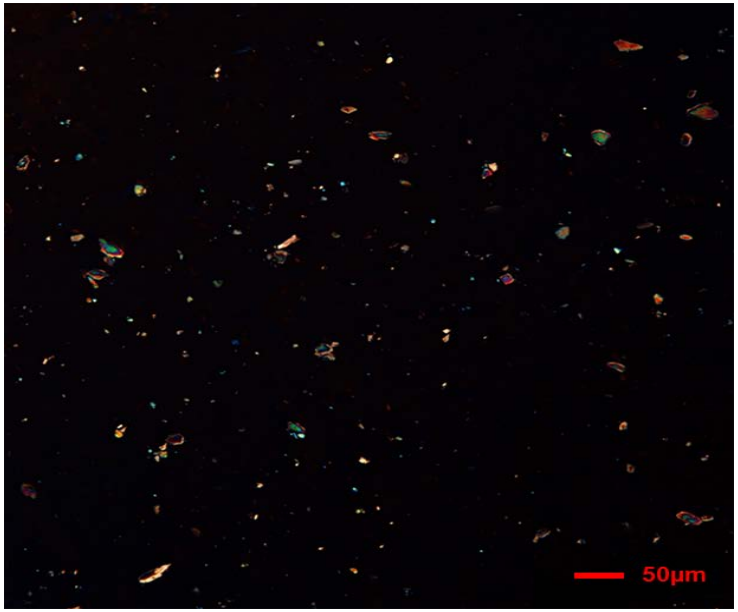
Drug content and uniformity

Formulations	Average Drug Loading ± SD (%, w/w)	RSD (%)
SRTOWP19	0.476 ± 0.014	2.94
SRTNWP19	0.492 ± 0.008	1.62
HMICOWP19	0.486 ± 0.006	1.23
HMICNWP19	0.473 ± 0.004	0.85
HMRTOWP19	0.506 ± 0.017	3.36
HMRTNWP19	0.476 ± 0.005	1.05

- The drug content of all the Q1/Q2 equivalent ointments was close to the target content 0.5% w/w. RSD was less than 3.5%, indication of good drug uniformity.

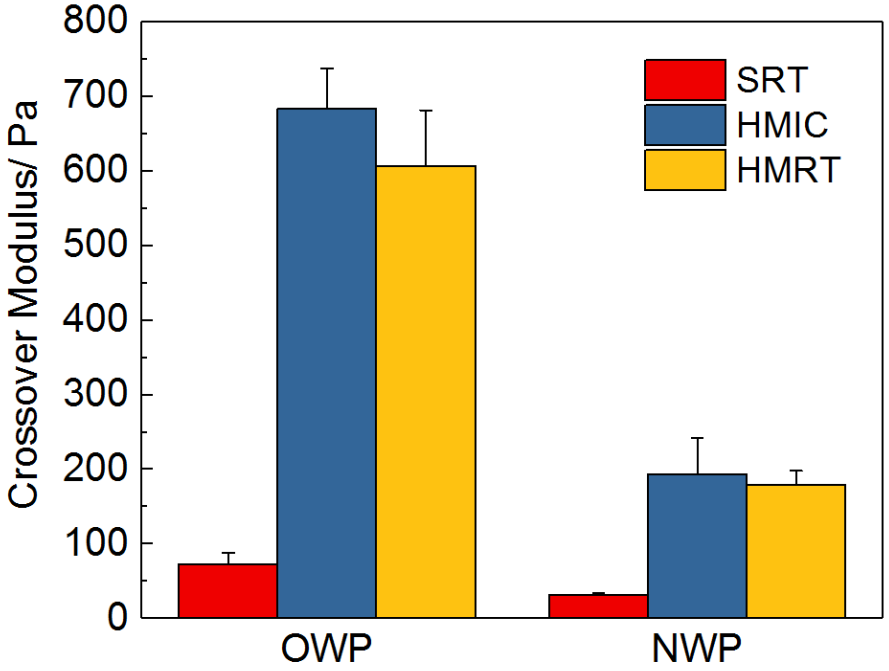
Particle size and distribution *via* PLM

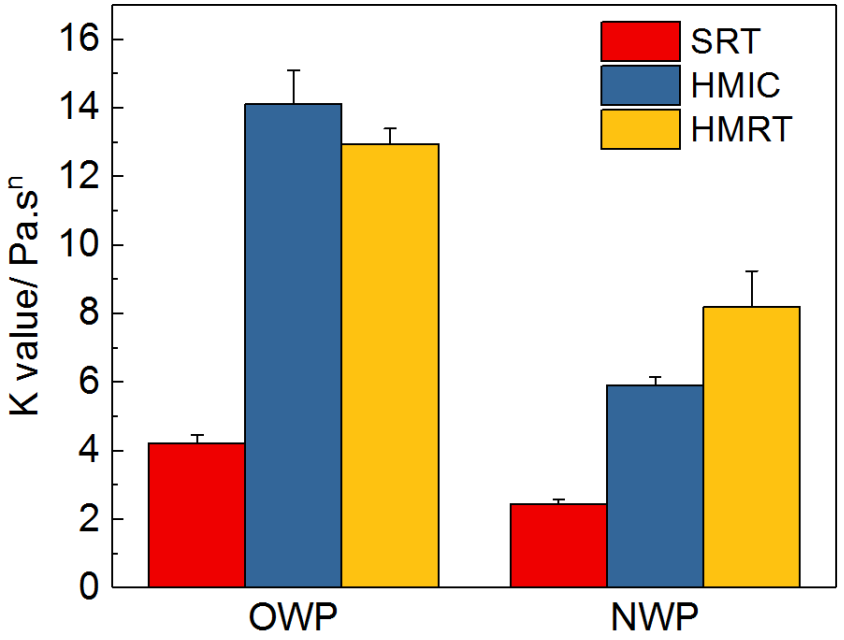




- All Q1/Q2 equivalent ointments showed an approximate particle size of 10 µm after manufacturing process.
- The API maintained the crystalline state in the ointment base.

Rheological parameters

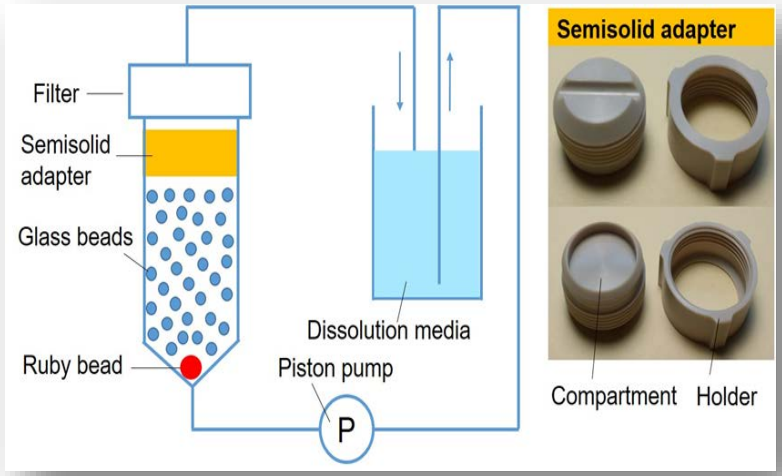




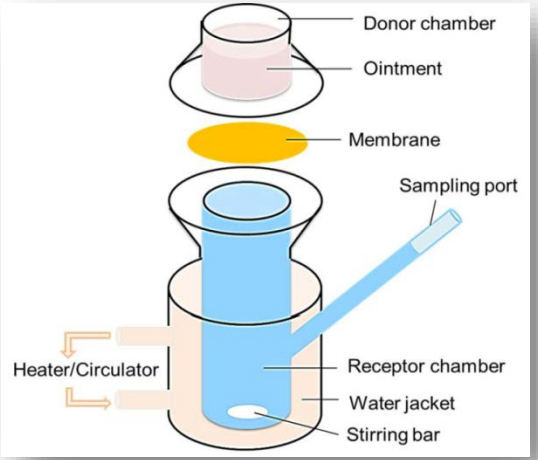
- Key parameters: crossover modulus (CM) and Power-law consistency index (K value).
- Ointments prepared using hot melt methods (HMIC and HMRT) showed higher rheological parameters compared to those prepared using simple mixing method (SRT).

In vitro release testing of LE ointments

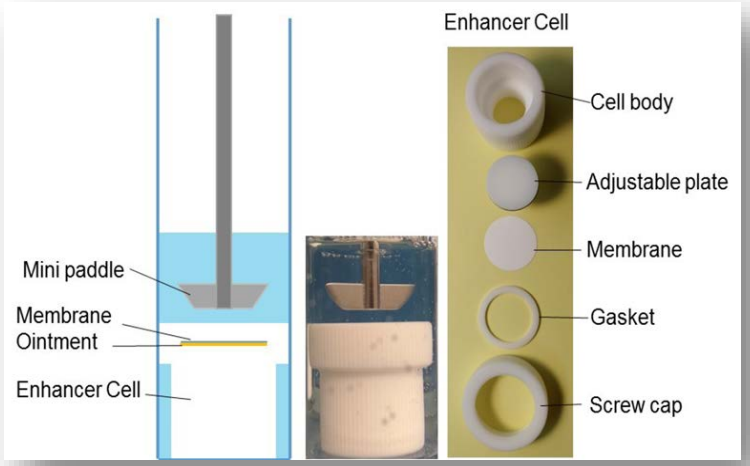
USP apparatus 4 with semisolid adapters



Franz diffusion cell

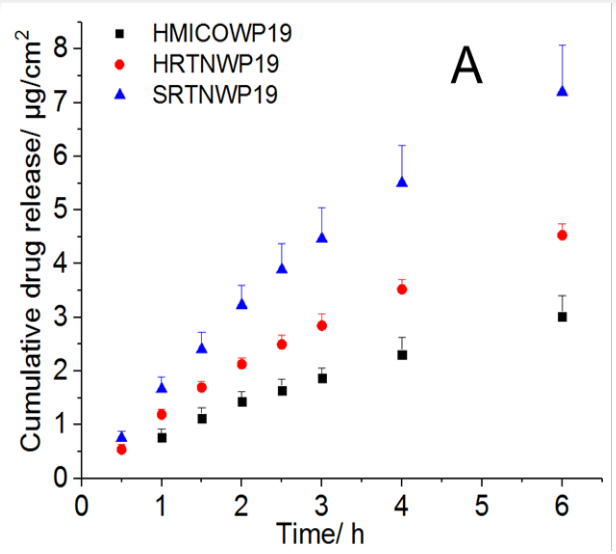


USP apparatus 2 with enhancer cells

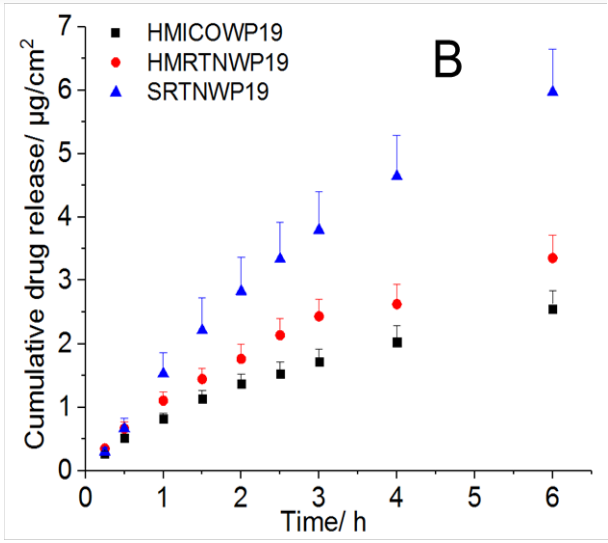


- Three release methods: USP apparatus 4, USP apparatus 2 and Franz diffusion cells.
- Dissolution condition: pH 7.4 artificial tear fluid with 0.5% w/v SDS at 37° C

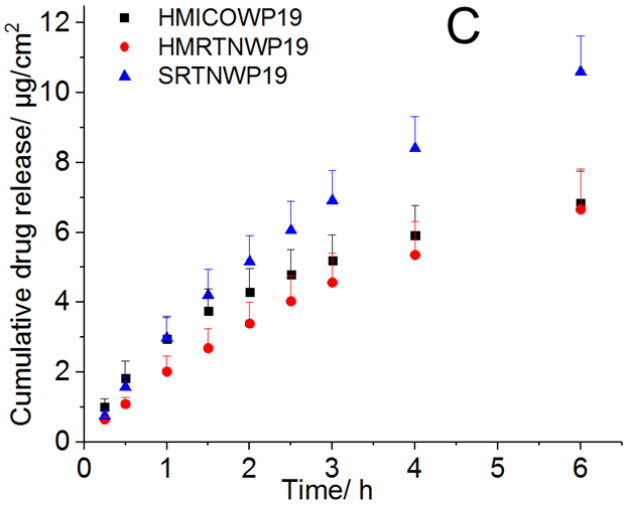
In vitro release profiles of LE ointments



USP apparatus 4 with semisolid adapters



USP apparatus 2 with enhancer cells

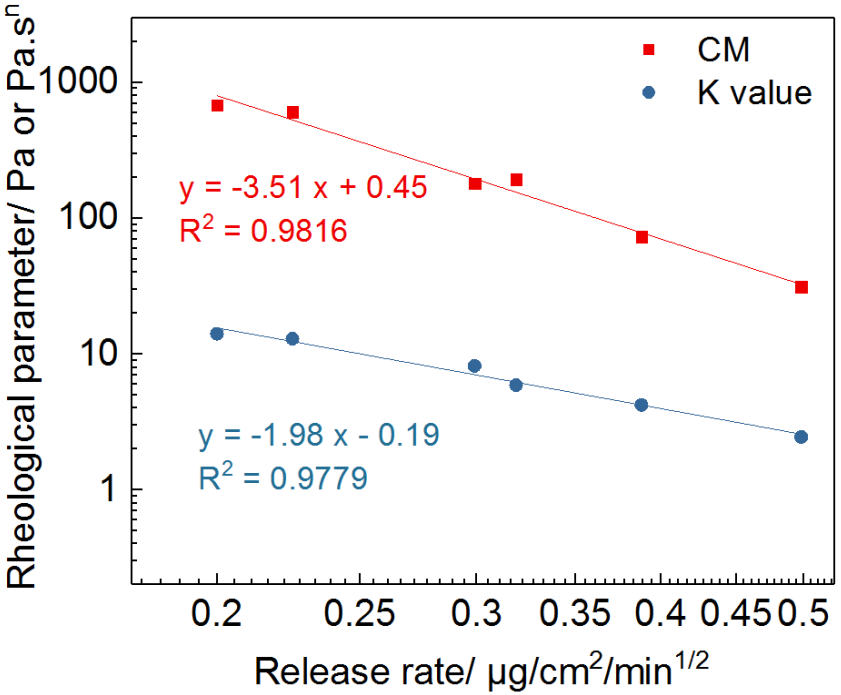


Franz Diffusion cells

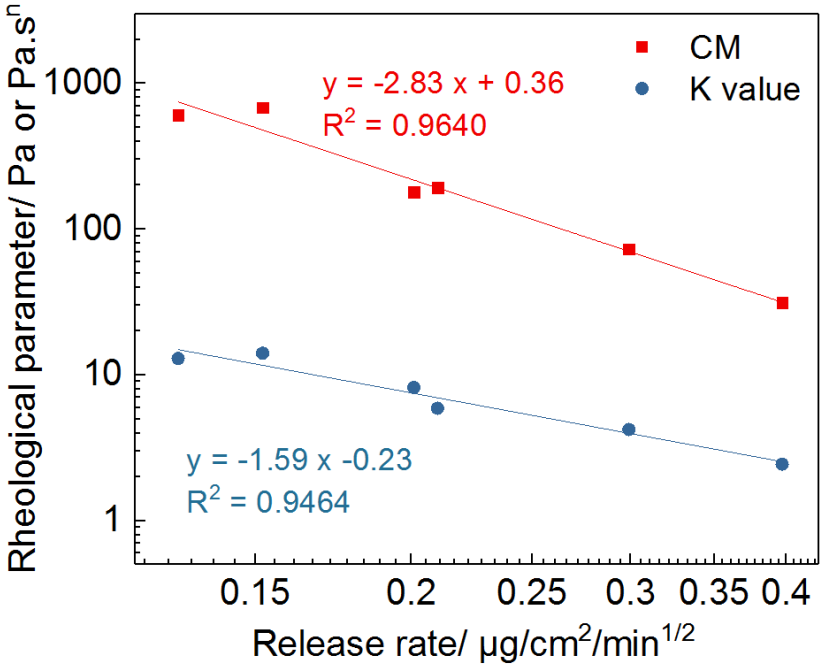
- Compared to USP apparatus 2 and Franz diffusion cell, USP apparatus 4 showed the best ability to discriminate the release profiles of the Q1/Q2 equivalent ophthalmic ointments with manufacturing differences.

Correlation between rheological parameters and *in vitro* release rate

USP apparatus 4



USP apparatus 2



- Strong logarithmic linear correlation between rheological parameters (CM and K value)
- USP apparatus 4 showed the best correlation among the three release testing methods. Compendial release methods displayed better correlation than the Franz diffusion cell method ($R^2 < 0.90$)

ACKNOWLEDGEMENTS

- **Risperidone and Naltrexone microspheres**:

  FDA grant # 1U01FD004931-01

- **Semisolid ophthalmic ointment**:

  FDA grant # 1U01FD005177-01

- **Sotax Corporation**


Thanks!
30/01/2009