Application of USP 4 in Dissolution Testing of Complex Parenterals and IVIVC

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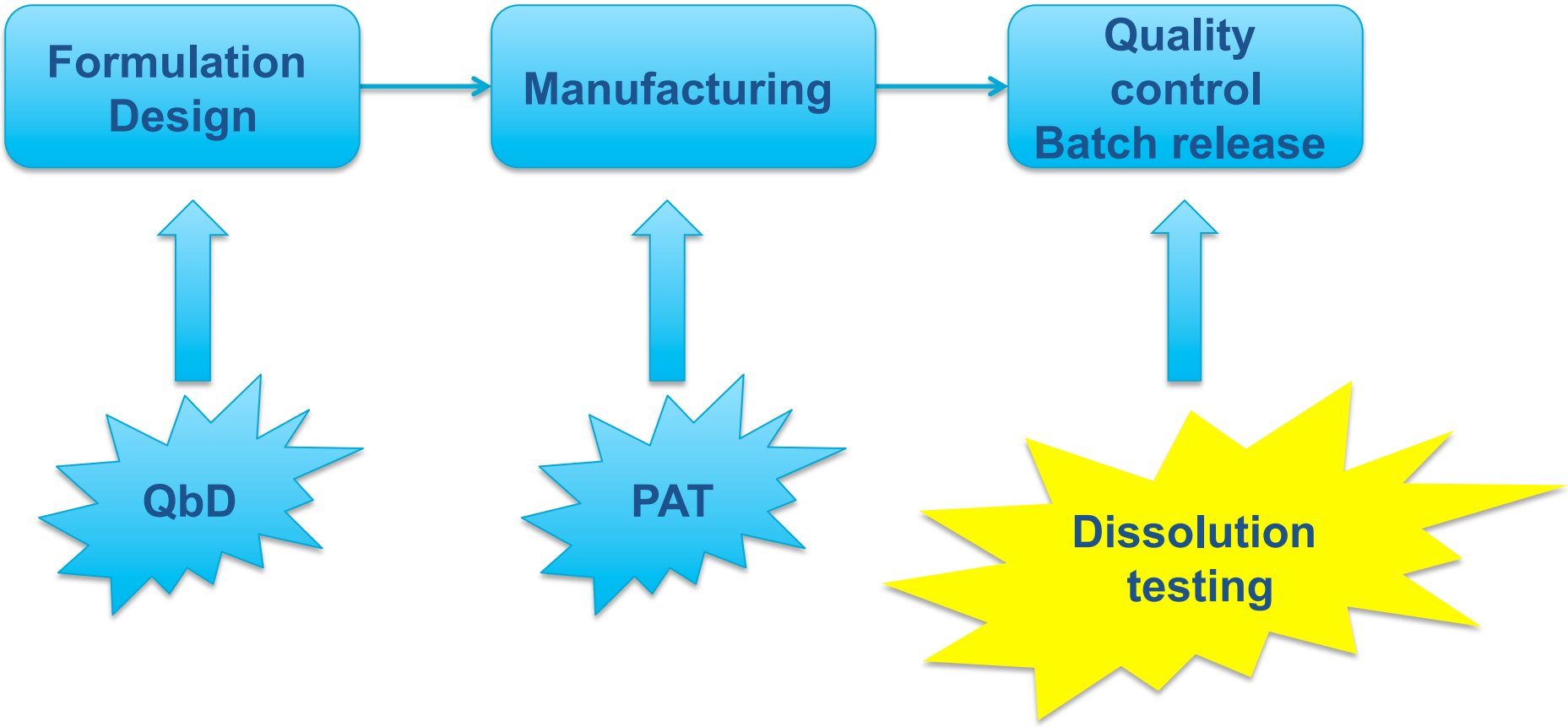
SPDS
DISSO INDIA- Hyderabad 2018
International Symposium

Product Development



A good *in vitro* release method

- ✓ Reproducibility
- ✓ Discriminatory ability- Manufacturing process and/or formulation changes
- ✓ Biorelevant
- ✓ Standardized
- ✓ Predict *in vivo* performance -IVIVC

Complex Parenterals

- Long-acting injectable (LAI) (parenteral) drug products

Microspheres

Implants/inserts

Multivesicular liposomes

Suspensions

- Injectable drug products with nanotechnology

Nano size liposomes

Iron complex

Nanosuspensions

- Semi-solids

Lotion

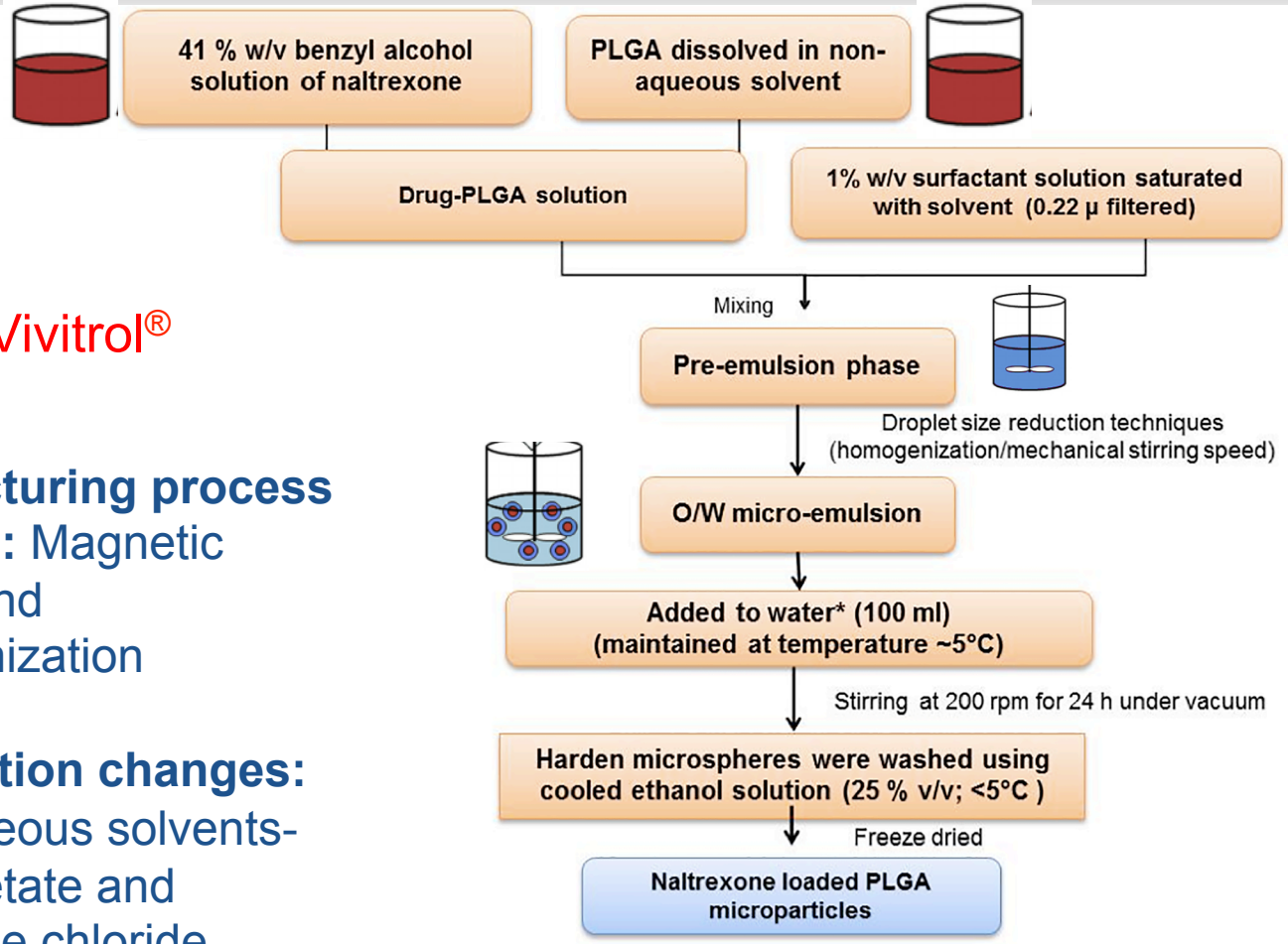
Ointments

Cream

- Emulsions

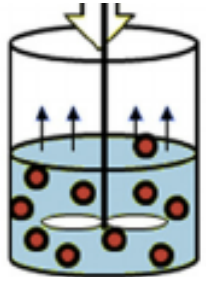
Microspheres

Preparation of Naltrexone Q1/Q2 equivalent microspheres



RLD: Vivitrol®

- **Manufacturing process changes:** Magnetic stirring and homogenization
- **Formulation changes:** Non-aqueous solvents- Ethyl acetate and methylene chloride



Freeze dried microspheres

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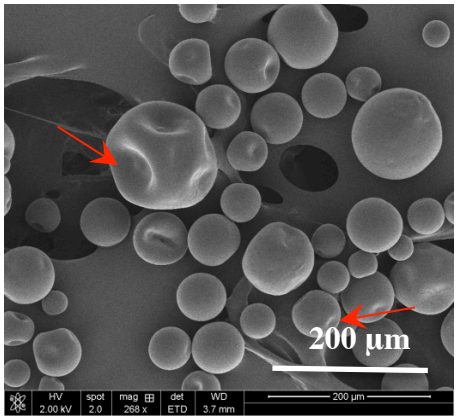
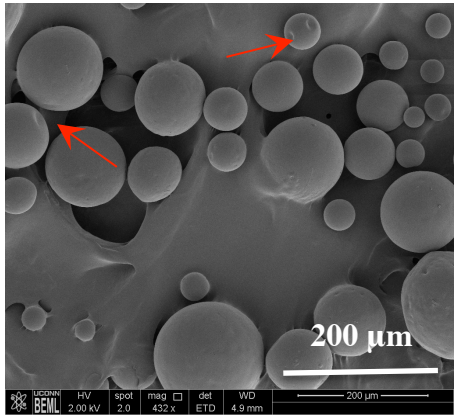
Physicochemical properties

Q1/Q2 equivalent Naltrexone microspheres

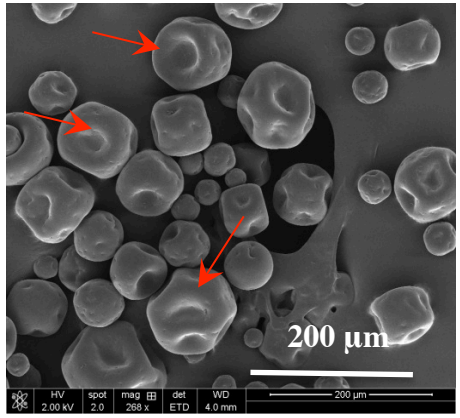
Sample	Solvent system	Preparation Method	Drug loading (%, w/w)	Porosity (%, w/w)	Mean Particle Size (μm)
Formulation 1	DCM&BA	Magnetic Stirring	28.74±1.64	49.83	121.11 ± 3.61
Formulation 2	EA&BA	Magnetic Stirring	29.7±1.11	58.32	105.49 ± 8.63
Formulation 3	EA&BA	Homogenization	29.57±1.75	65.08	68.56 ± 1.52
Vivitrol®	-	-	33.50±1.43	50.21	108.40 ± 7.4



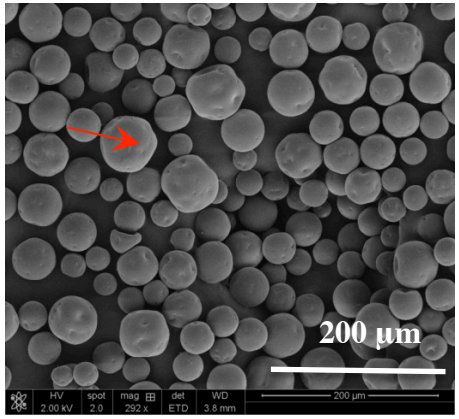
Vivitrol®



Formulation 1



Formulation 2



Formulation 3

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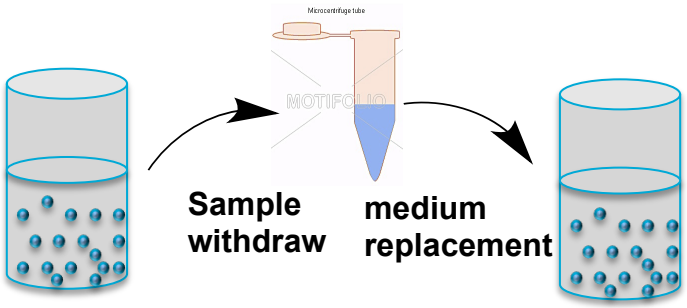
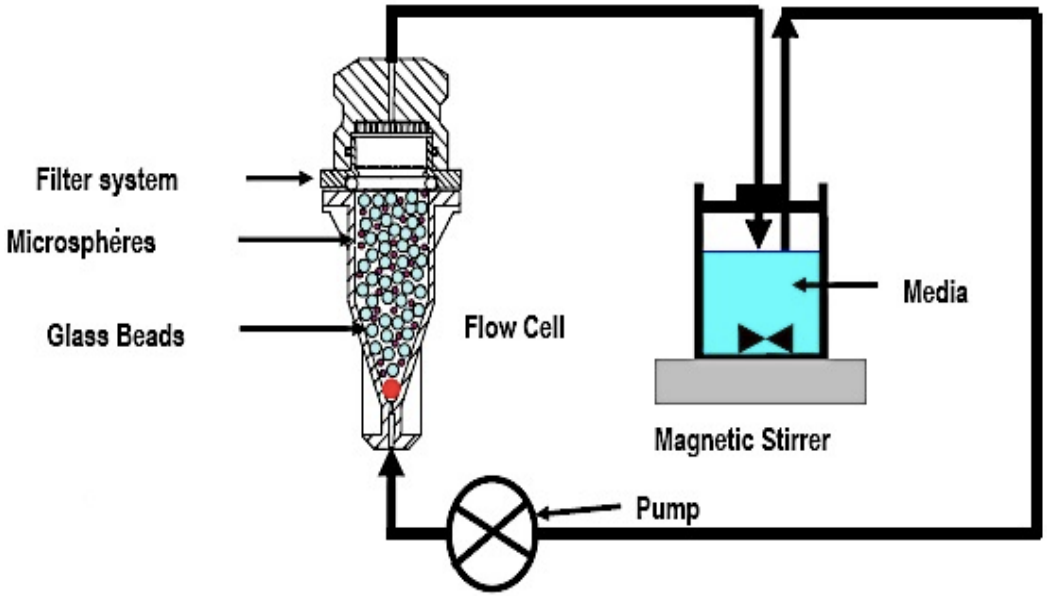
In vitro Release Testing: Methods

Sample-and-separate



Modified USP Apparatus 4



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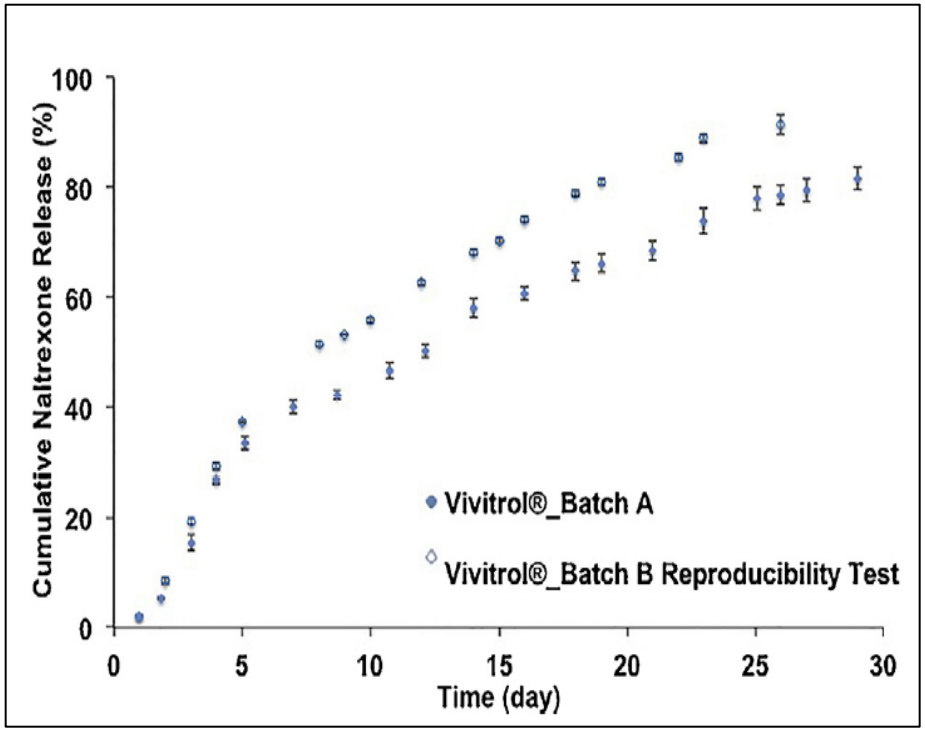
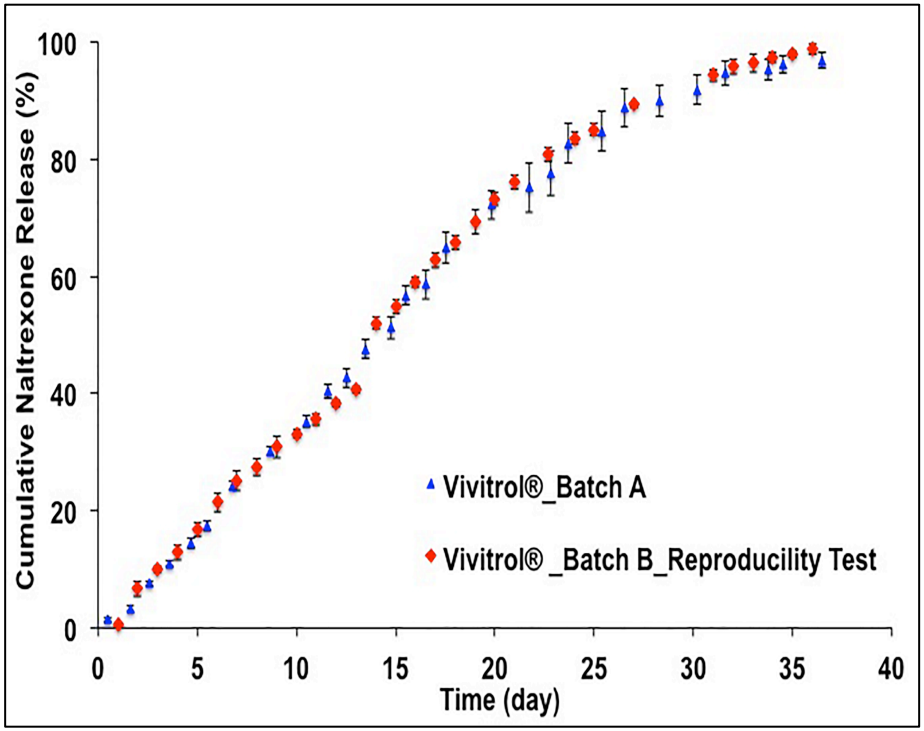
In vitro Release Testing: Reproducibility

Sample and separate



USP Apparatus 4



Dissolution conditions: PBS (10 mM, pH 7.4) + 0.02 % (v/v) Tween 20+ 0.02 % (w/v) sodium azide, 37 °C

The medium was replaced every five days

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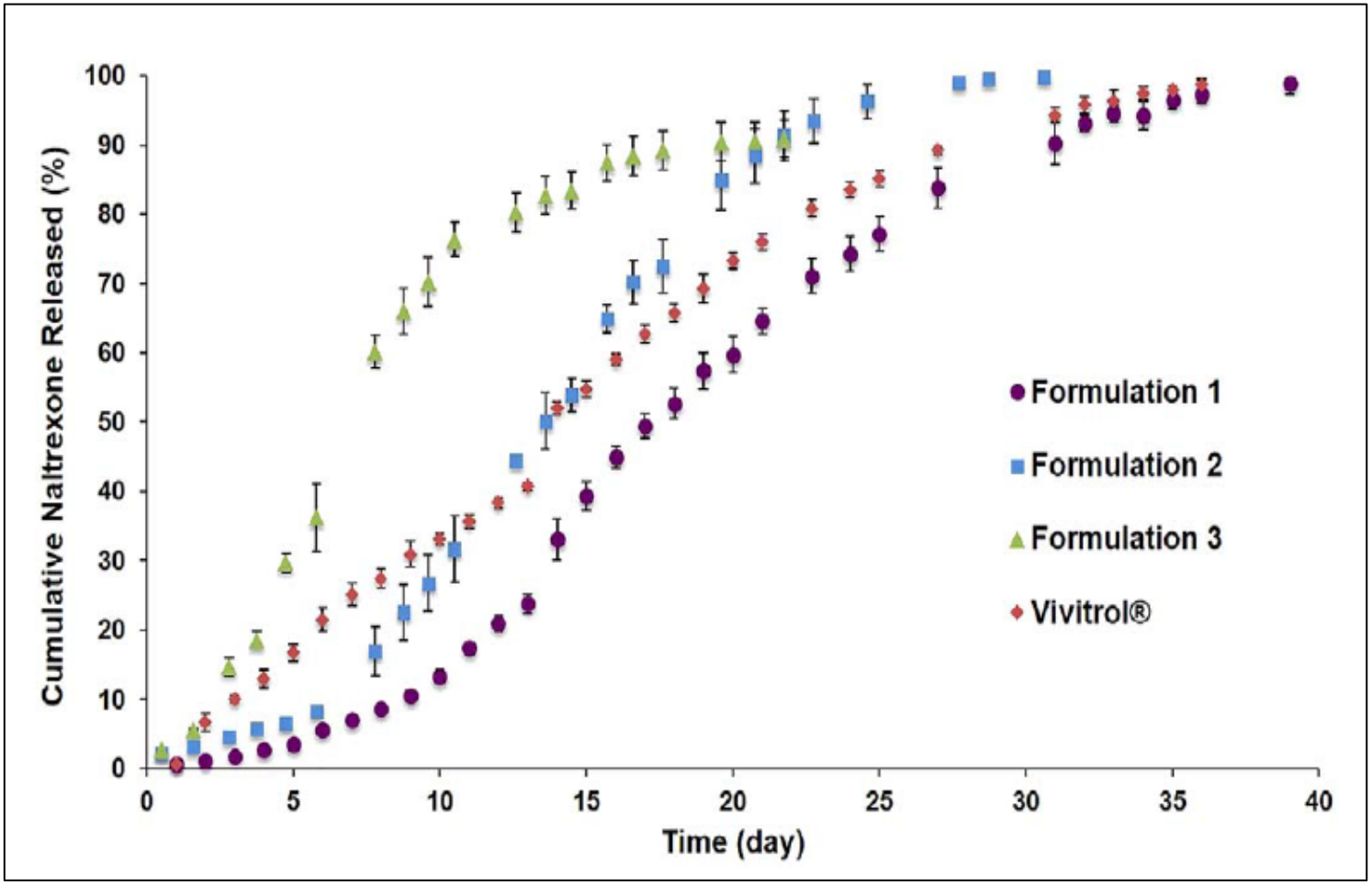
In vitro Release Testing: Discriminatory ability

USP Apparatus 4



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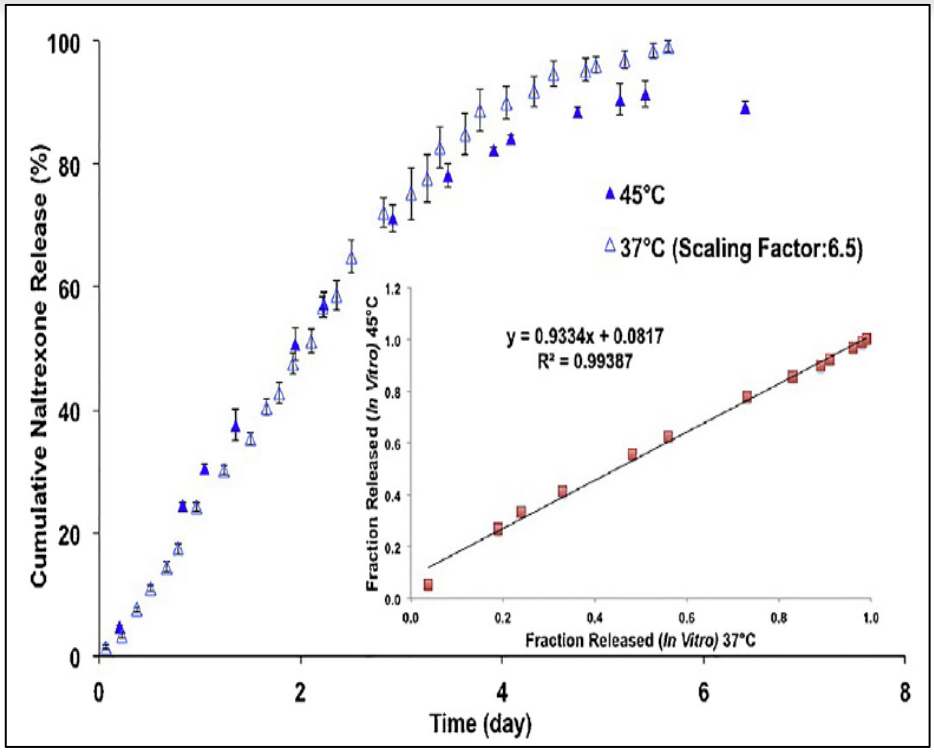
USP Apparatus 4: Accelerated Release Testing

"Real-time" *in vitro* release testing

- ✓ Extended periods of time
- ✓ Delayed batch release- can reduce product shelf-life

"Accelerated" *in vitro* release testing

- ✓ Shortens testing duration
- ✓ Use in development of IVIVC



Parameters:

Temperature, solvent, ionic strength, pH, enzymes, surfactants and agitation rate

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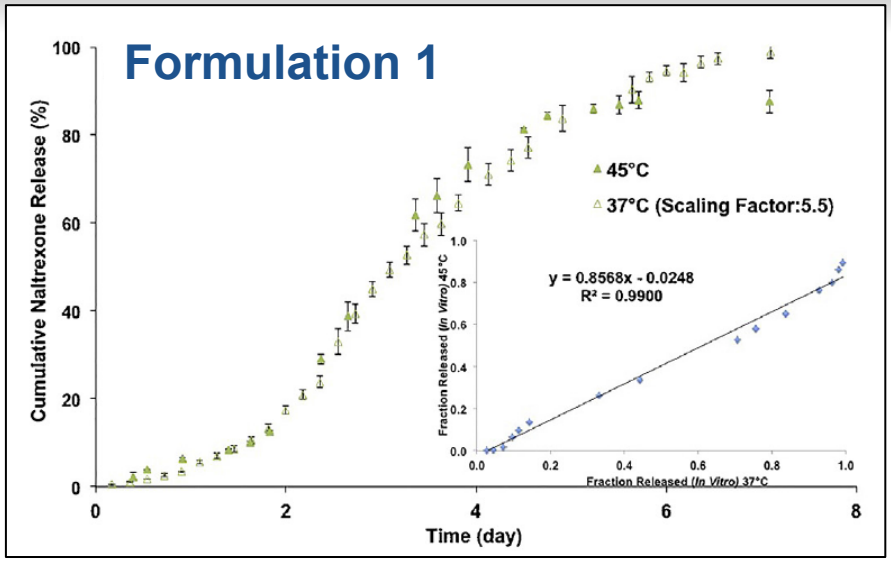
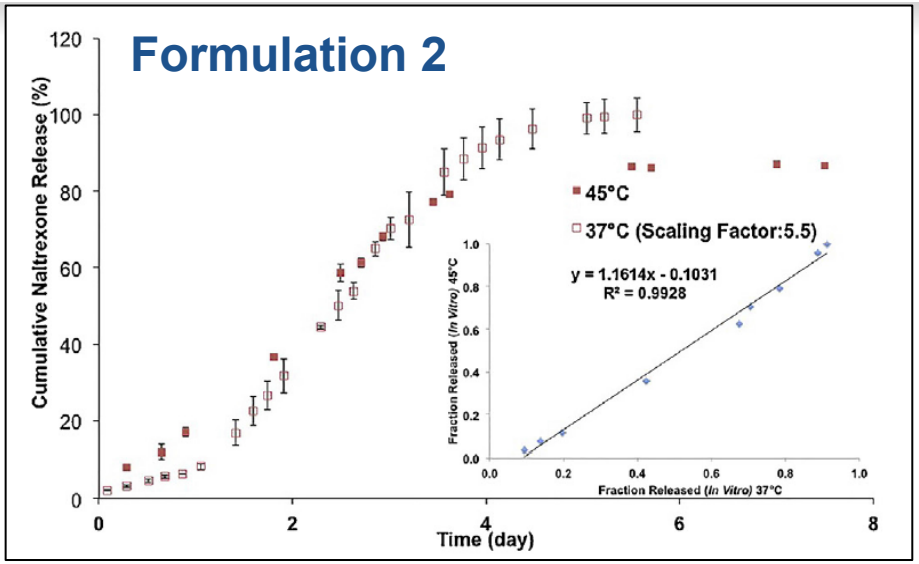
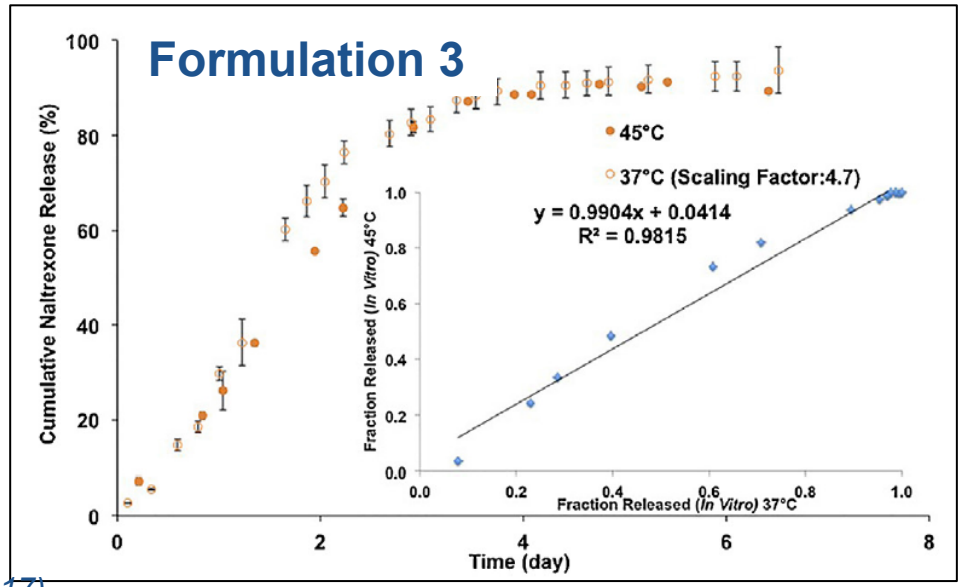
USP Apparatus 4: Accelerated Release Testing





In vitro release profiles at 37 °C (time-scaled) and at 45 °C

Linear correlation between real-time and accelerated release



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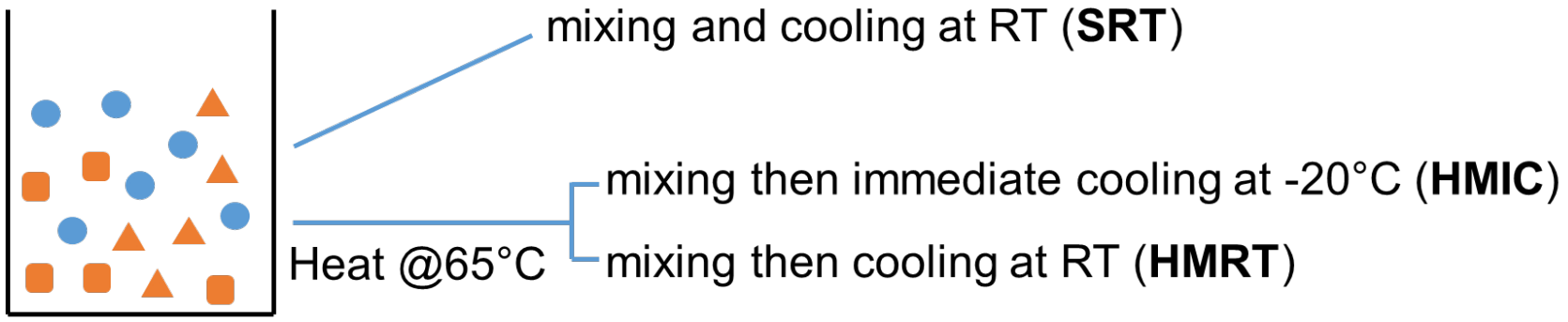
Ointments

Preparation of LE Q1/Q2 equivalent ointments



- White petrolatum
- Mineral oil
- **API: Loteprednol etabonate**

RLD: Lotemax®

- Four petrolatum sources: OWP (Fisher®, non-USP), NWP (Fougera®, USP), VWP (Vaseline®, USP) and PWP (Penreco®, USP)
- Three manufacturing processes: SRT, HMIC, HMRT

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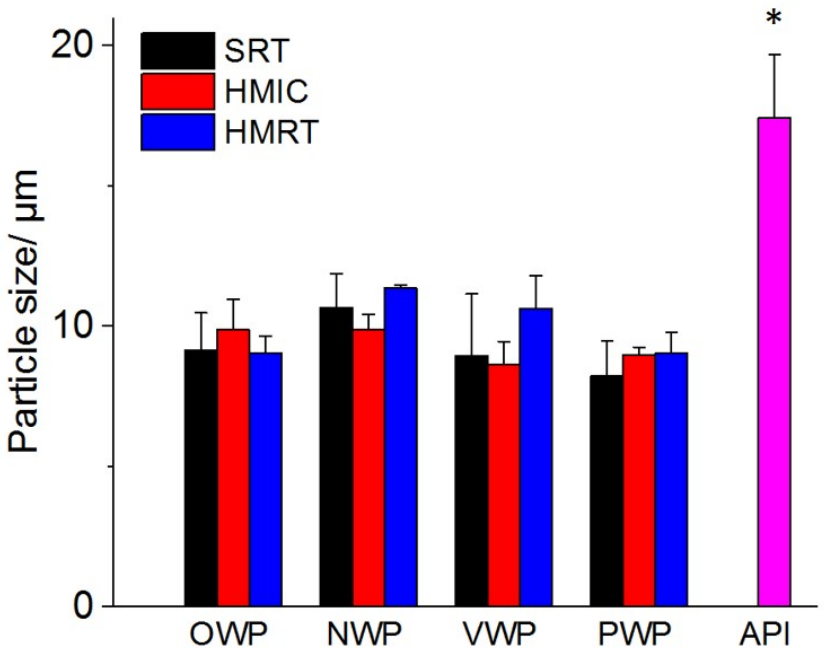
Physicochemical properties

Drug content and uniformity

Formulations	Average Drug Loading ± SD (%, w/w)	RSD (%)
SRTOWP19	0.48 ± 0.01	2.87
SRTNWP19	0.49 ± 0.01	1.60
SRTVWP19	0.54 ± 0.02	3.00
SRTPWP19	0.49 ± 0.02	3.47
HMICOWP19	0.49 ± 0.01	1.22
HMICNWP19	0.47± 0.00	0.91
HMICVWP19	0.52 ± 0.01	1.94
HMICPWP19	0.51 ± 0.01	2.62
HMRTOWP19	0.51 ± 0.02	3.27
HMRTNWP19	0.48 ± 0.01	1.05
HMRTVWP19	0.50 ± 0.01	2.43
HMRTPWP19	0.50 ± 0.01	1.16

Particle size



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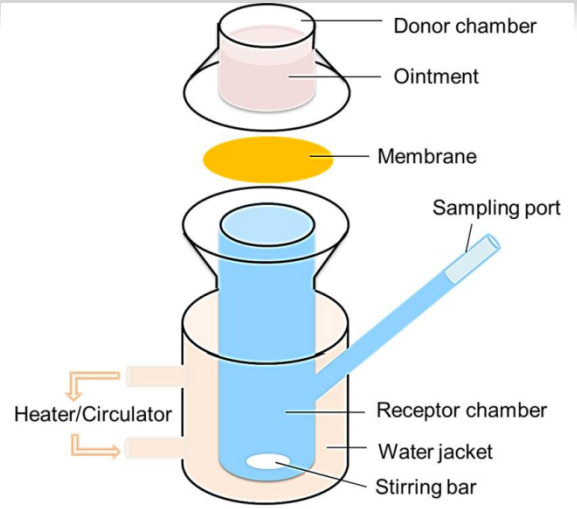
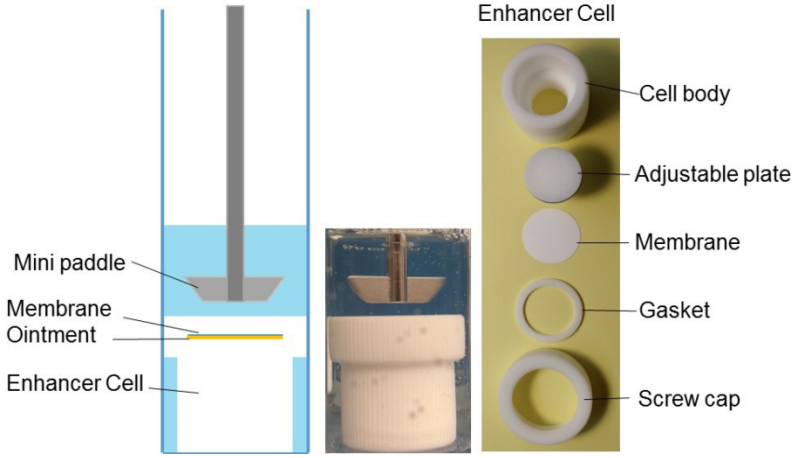
In vitro Release Testing: Methods

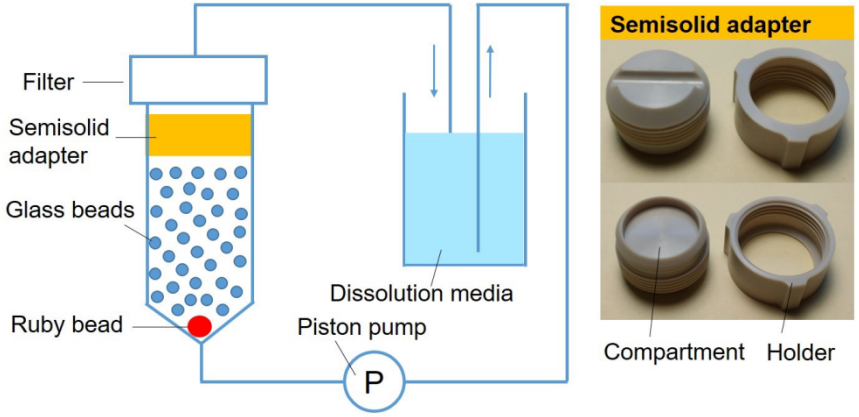


Franz diffusion cells (FDC)



USP Apparatus 2 with enhancer cells

USP Apparatus 4 with semisolid adapters



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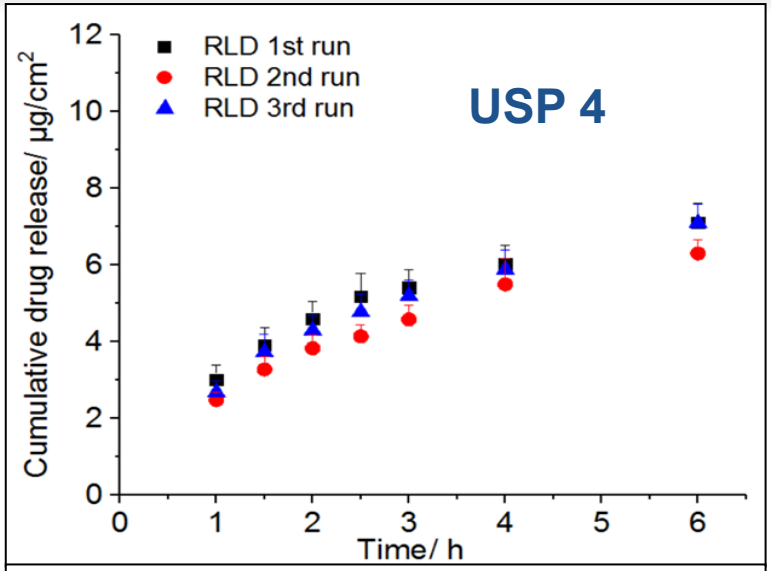
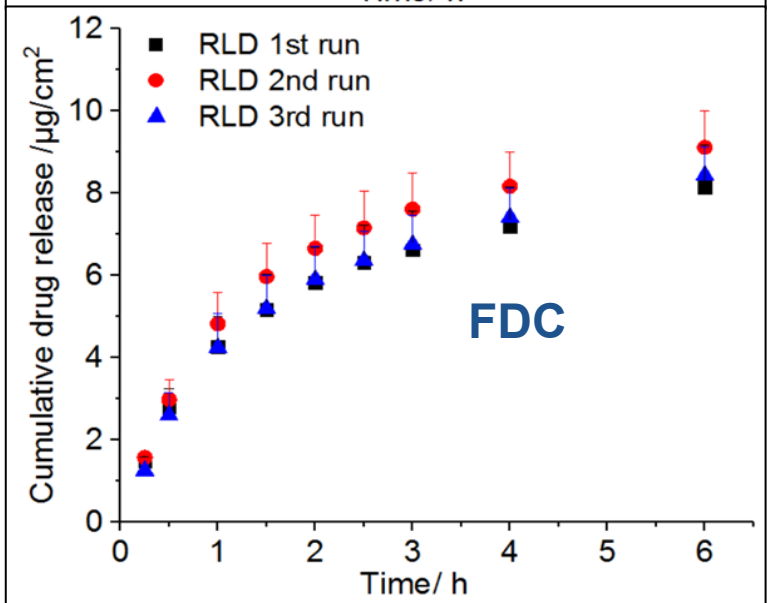
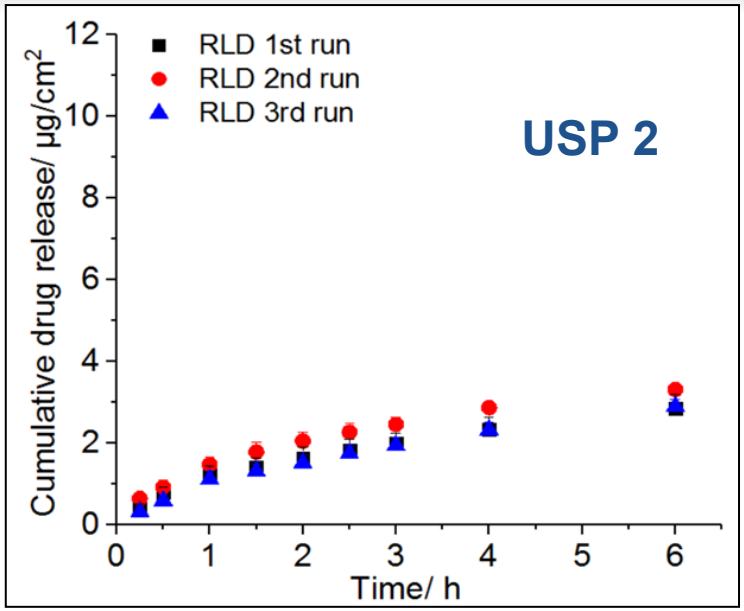
In vitro Release Testing: Reproducibility







Dissolution conditions: pH 7.4 artificial tear fluid with 0.5% SDS at 37°C

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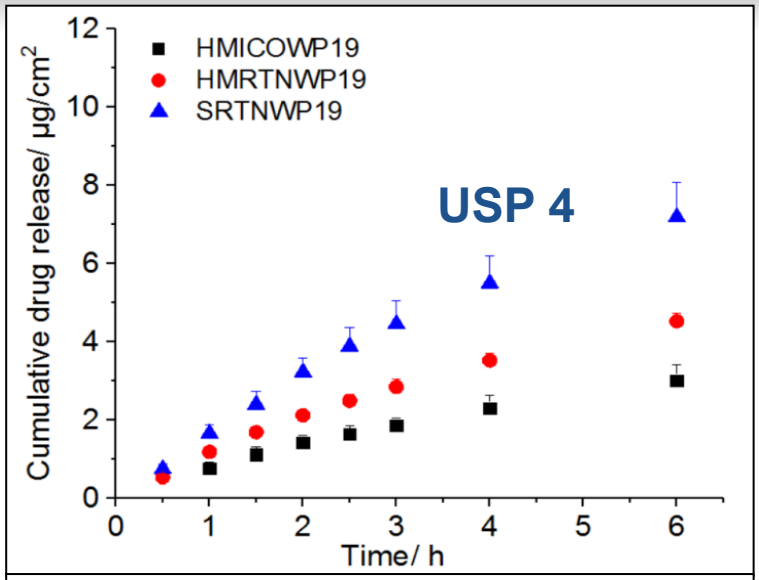
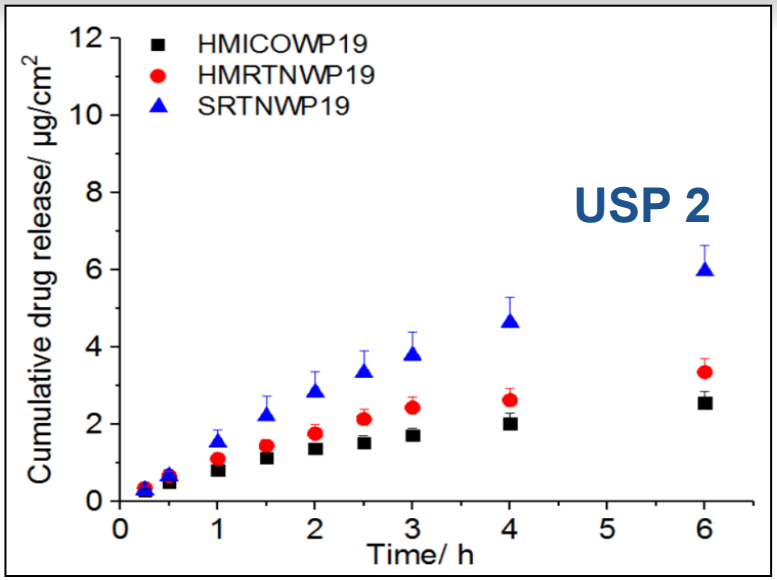
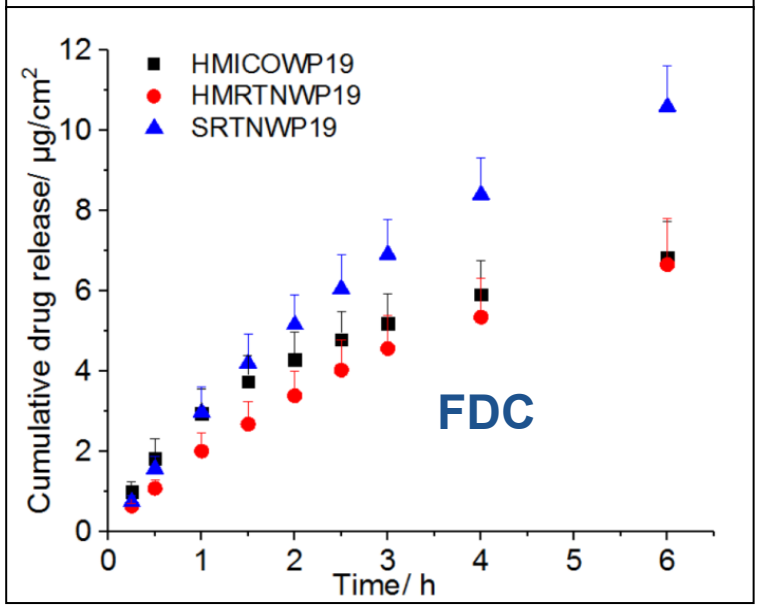
In vitro Release Testing: Discriminatory ability







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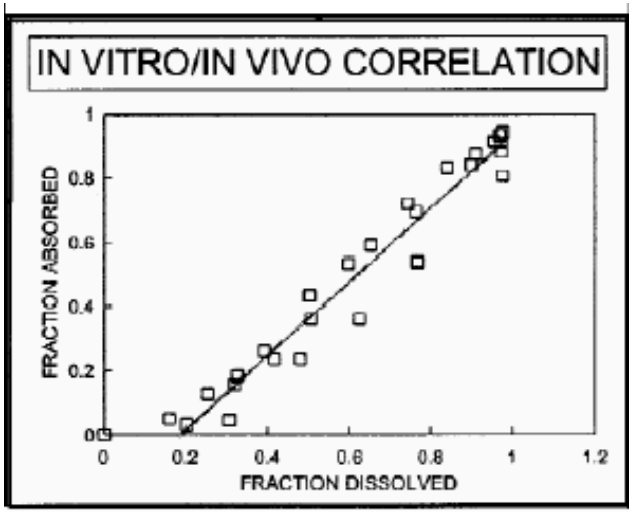
IVIVC

IVIVC

"Predictive mathematical model which describes relationship between an *in vitro* property of a dosage form and an *in vivo* response"



Level A

- ✓ Point to point correlation
- ✓ Most informative
- ✓ FDA requirement for bio-waiver

Other levels:

Level B: Mean property derived from entire profile (MRT *vs* MDT)

Level C: One dissolution time point and one PK parameter

Multiple level C: Same as C but with multiple time points.

Level D: Rank order relationship

- Less informative, Not for bio waivers, Only for research purpose

IVIVC: Applications

- ✓ To guide formulation and/or manufacturing process changes at various stages of drug product development
- ✓ To support and/or validate the use of an *in vitro* release method and to set clinically relevant dissolution specifications
- ✓ Level A IVIVC- *in vitro* release method can be used as a surrogate for bioequivalence studies

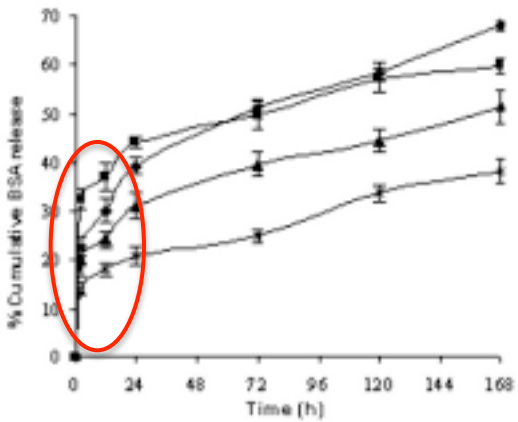
Challenges to the development of IVIVC

1) Lack of compendial *in vitro* release testing methods

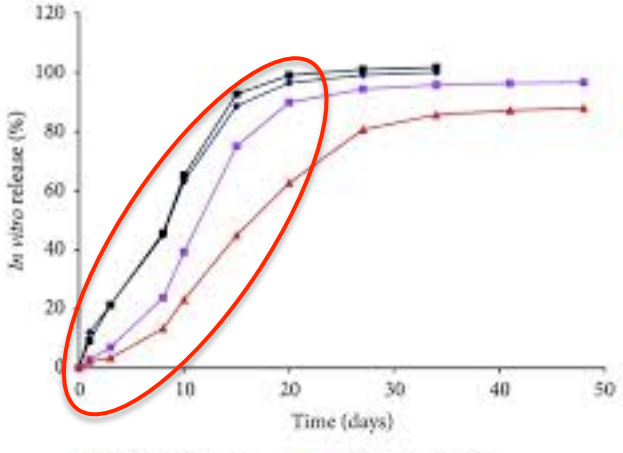
- ✓ Non compendial methods - sample and separate, dialysis sac *etc.*
- ✓ Not discriminative as well as biorelevant

2) Complex multiphasic drug release profiles

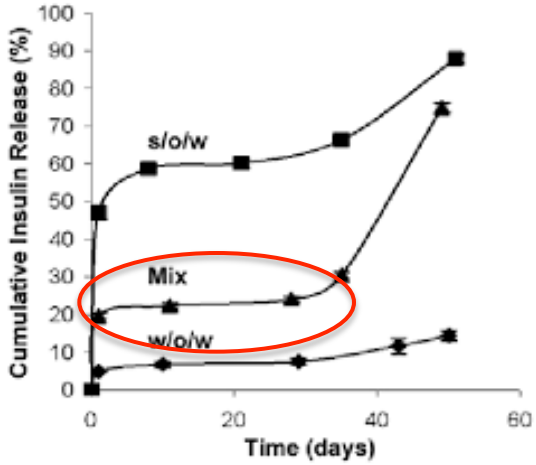
Type I



Type II



Type III



Challenges to the development of IVIVC

3) Various *in vivo* factors can also affect drug release

- Tissue response – foreign body reaction
- Presence of endogenous substances
- Enzymatic degradation
- pH
- Limited tissue fluid volume
- Muscle size and level of activity
- Drug permeability – burst release

Development of IVIVC

1. Develop two or more Q1/Q2 formulations with different release rate such as slow, medium and fast

Sample	Solvent system	Preparation Method	Drug loading (%, w/w)	Porosity (%, w/w)	Mean Particle Size (μm)
Formulation 1	DCM&BA	Magnetic Stirring	28.74±1.64	49.83	121.11 ± 3.61
Formulation 2	EA&BA	Magnetic Stirring	29.7±1.11	58.32	105.49 ± 8.63
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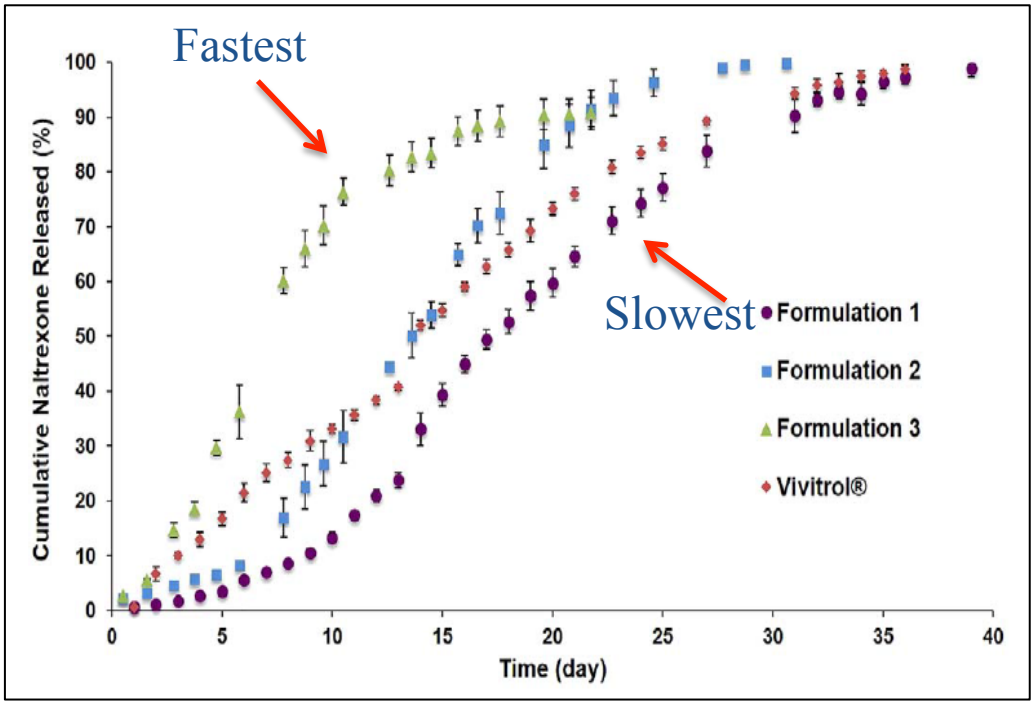
Development of IVIVC

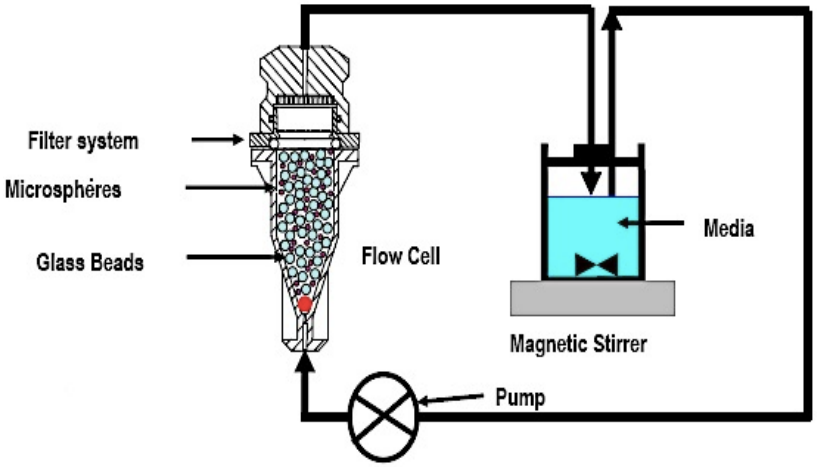
1. Develop two or more Q1/Q2 formulations with different release rate such as slow, medium and fast

- *In vitro* release testing – **Modified USP apparatus 4 method**

37°C, PBS (pH 7.4, *n=3)*



➢ **USP apparatus 4 – Continuous flow method**



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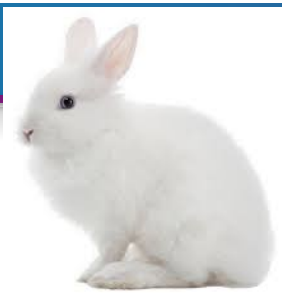
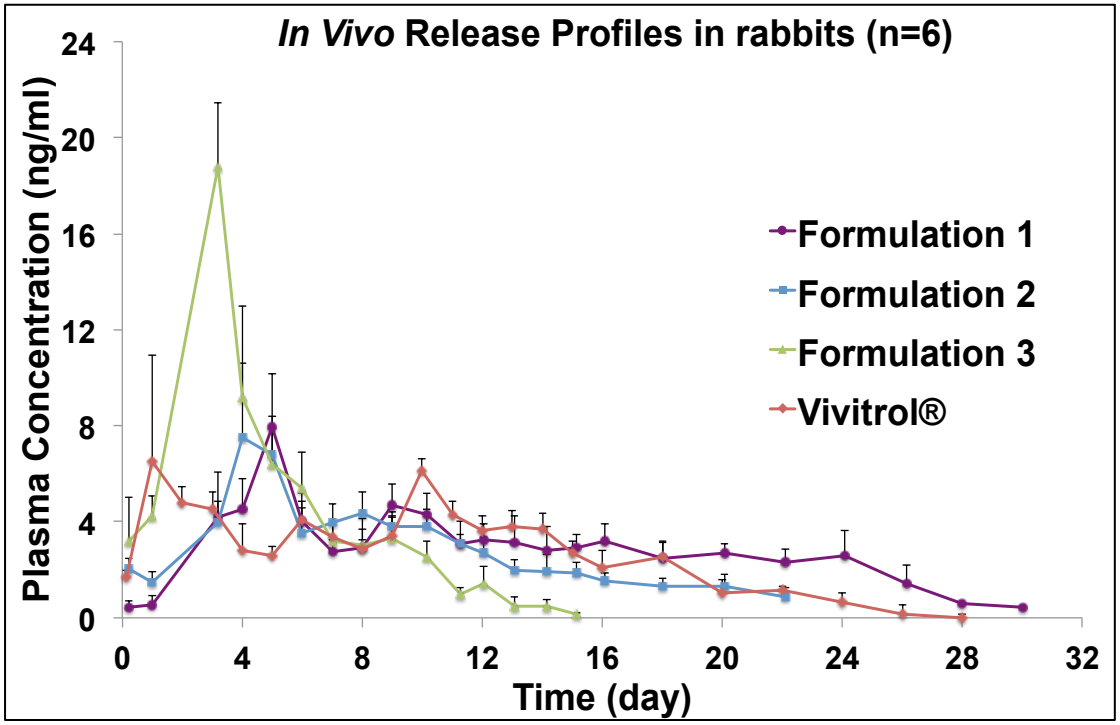
Development of IVIVC



2. Obtain *in vivo* release profile of selected formulations

✓ Evaluate syringeability/injectability - needle size, vehicle volume

- Animal model: Rabbit
- Route of administration: Intramuscular (IM)
- Blood sample collection
- LC-MS sample analysis



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Development of IVIVC

3. Establish *in vitro* and *in vivo* correlation

3.1 Deconvolute *in vivo* plasma concentration time profile to fraction absorbed profile

3.2 Develop correlation between fraction absorbed *in vivo* and fraction released *in vitro*

Development of IVIVC

3. Establish *in vitro* and *in vivo* correlation

3.1 Deconvolute *in vivo* plasma concentration time profile to fraction absorbed profile

Why?

Plasma conc. does not represent total fraction absorbed due to continuous drug distribution and elimination

How?

Loo-Riegelman Method → Fraction absorbed = $C_p + C_t + k_E$ AUC

- Where $\mathbf{C_t = ((k_{12}\,\Delta C_p\,\Delta t)/2) + ((Cp)_{tn-1}(k_{12}/k_{21}))*(1-e^{-k21\,\Delta t}) + ((Ct)tn-1)e^{(-k21*\Delta t)}}$

k_{12}, k_{21}, k_E ↓ WinNonlin PK analysis software

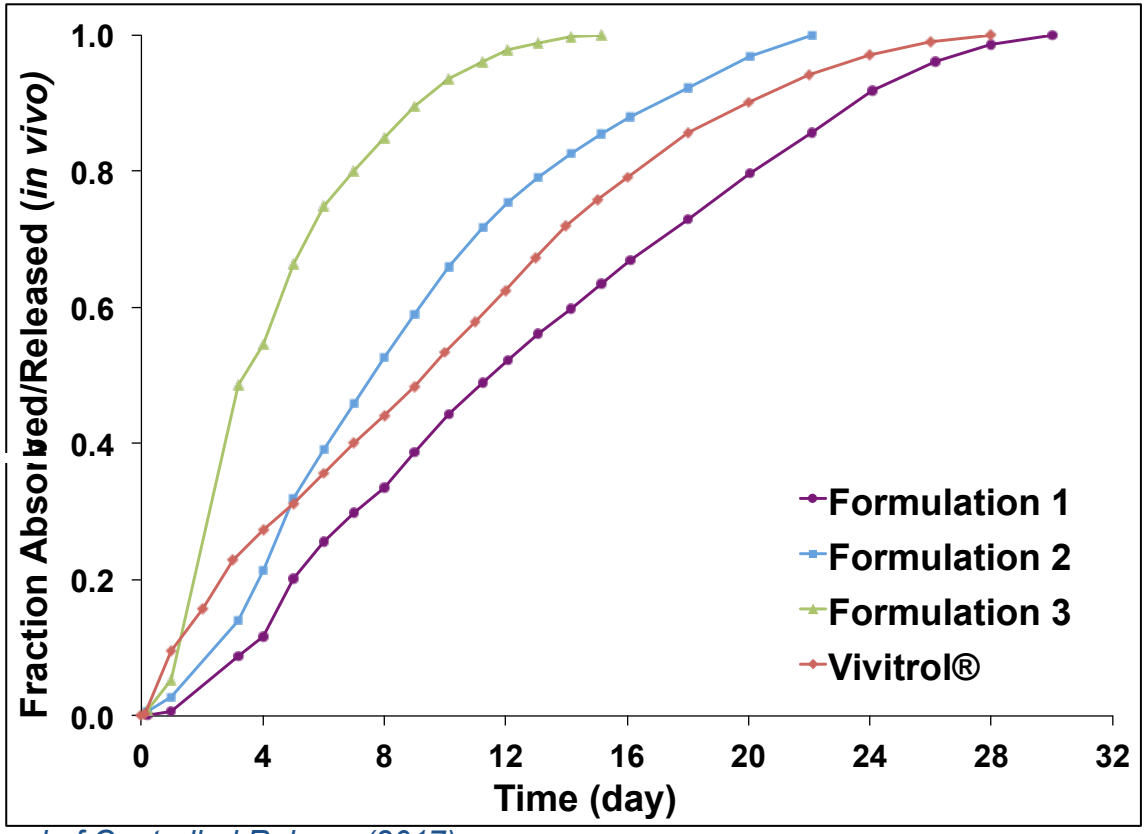
Need IV solution data to estimate PK parameters of drug itself

Development of IVIVC

3. Establish *in vitro* and *in vivo* correlation

3.1 Deconvolute *in vivo* plasma concentration time profile to fraction absorbed profile

Deconvoluted *in vivo* release profiles



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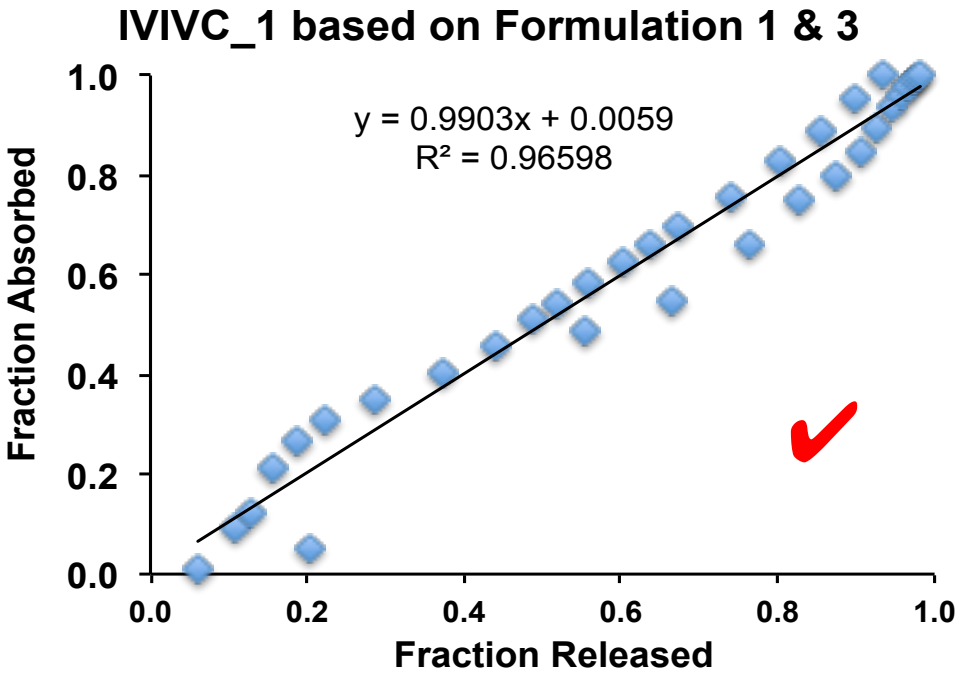
Development of IVIVC

3. Establish *in vitro* and *in vivo* correlation

3.2 Develop correlation between fraction absorbed *in vivo* and fraction released *in vitro*

- Correlation between different combination of formulations



Other Combinations

Combination_IVIVC	R^2 value
Formulations 1 & 2	0.97
Formulations 2 & 3	0.98

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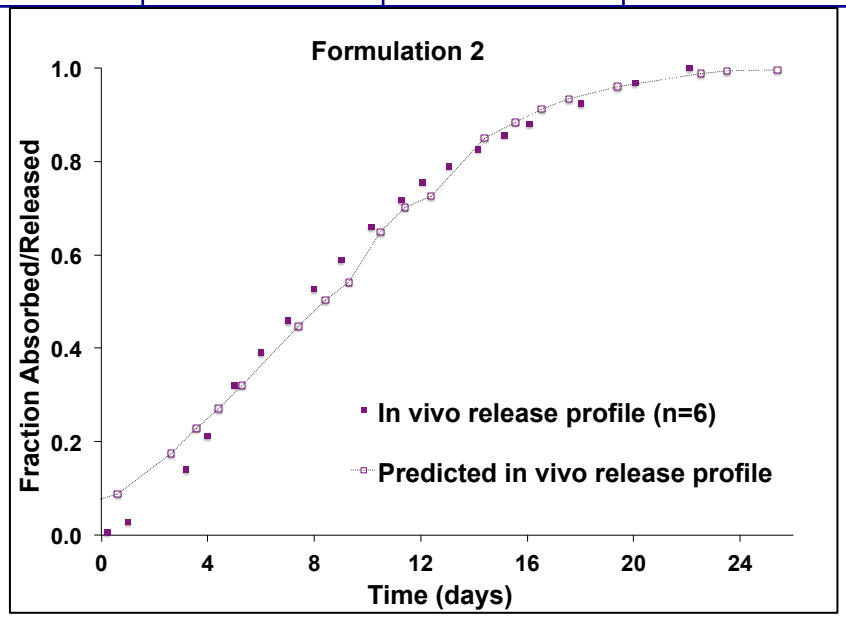
Validation of IVIVC

- Need one external formulation – not used to develop model
- Estimate % prediction error – predict *in vivo* profile using *in vitro* data- **WinNonlin IVIVC tool kit**

Formulation	Avg Internal		External		Vivitrol®	
Parameter	AUC_{last}	C_{max}	AUC_{last}	C_{max}	AUC_{last}	C_{max}
%PE	7.04	11.96	**10.13**	**3.38**	**9.53**	**-9.27**



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Summary

1. The developed modified USP apparatus 4 *in vitro* release testing methods were able to:

- Demonstrate reproducibility
- Discriminate the prepared naltrexone microspheres and LE ointments with manufacturing differences.
- Predict *in vivo* performance of microspheres.

↓

Modified USP apparatus 4 method has potential to be used as biorelevant, compendial in vitro release testing method for the development of IVIVC of complex parenteral drug products

2. Level A IVIVC was developed for the Q1/Q2 equivalent naltrexone microspheres prepared with manufacturing differences.

↓

Feasibility of developing level A IVIVC for complex parenteral drug product