Optimization of *in vitro* release setup for *in situ* forming depot technology

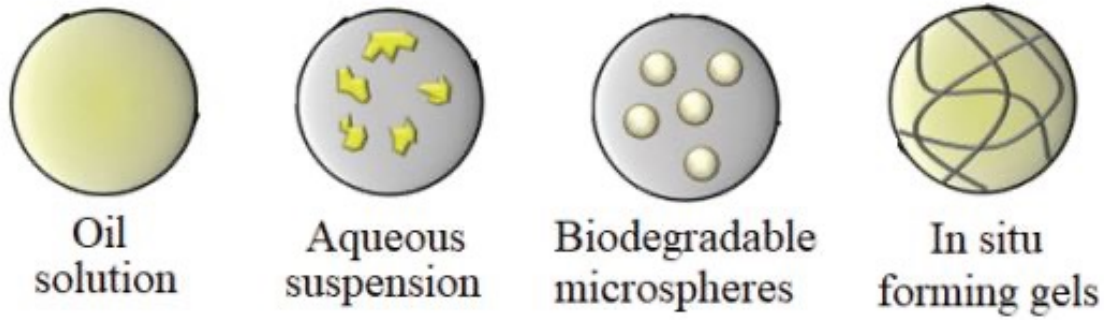
Charlotte PELOSO

CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
JULY 8-12, 2024 • BOLOGNA, ITALY

INTEGRATING
Delivery Science
ACROSS DISCIPLINES

World of Long Acting Injectables (LAI)

Main LAI strategies



R. Holm et al., AAPS J. 25, 2023

ACTIVE PHARMACEUTICAL INGREDIENTS
Pharmacological activity
Small molecules
Macromolecules possible

SOLVENT
Pharmaceutically acceptable
Make the system Injectable

COPOLYMERS
Bioresorbable
Controlled release

bepo®

Gaudriault, G. EP3257498B1, 2011
C. Roberge et al., J. Control Release 319, 2020

Session: Technical Session III

Long-Acting Drug Delivery Formulations II

Dr. Adolfo Lopez-Noriega

Wednesday, July 10, 2024

9:00 AM – 11:00 AM CET

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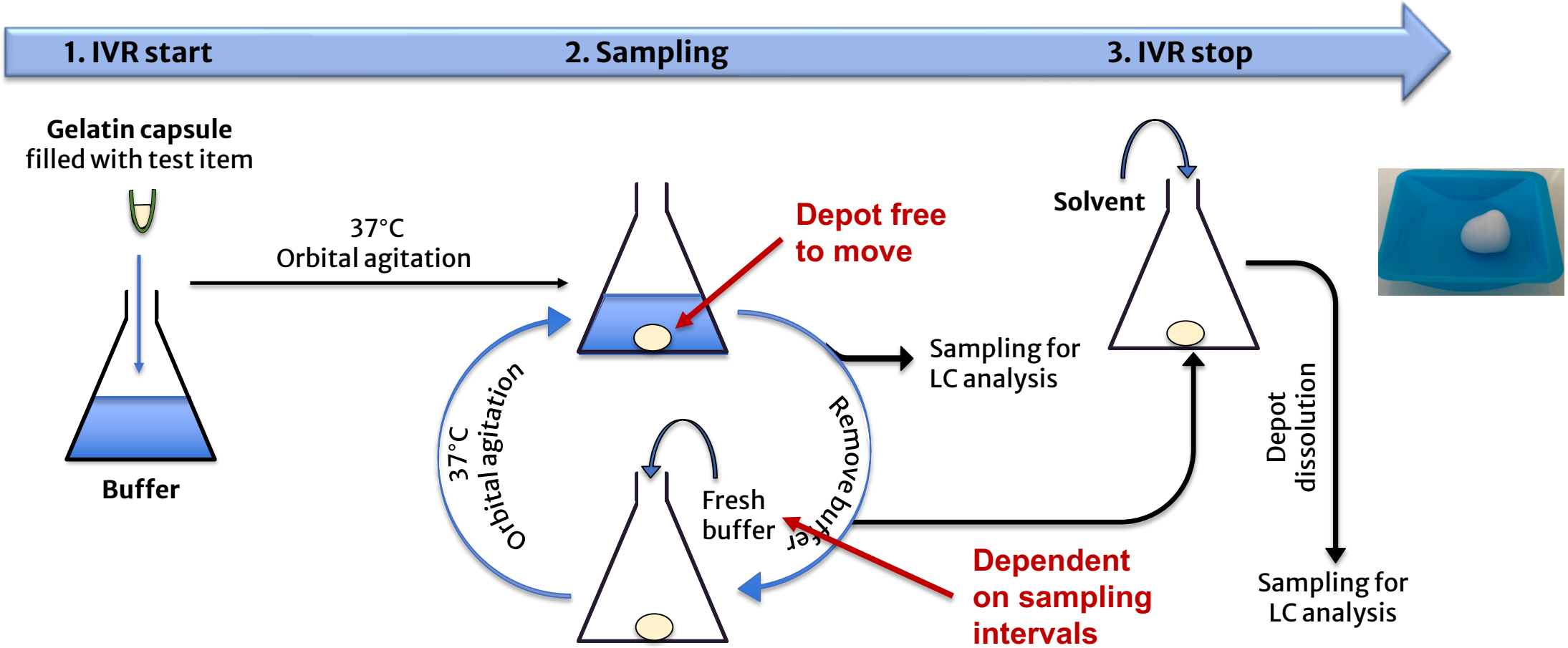
INTEGRATING Delivery Science ACROSS DISCIPLINES

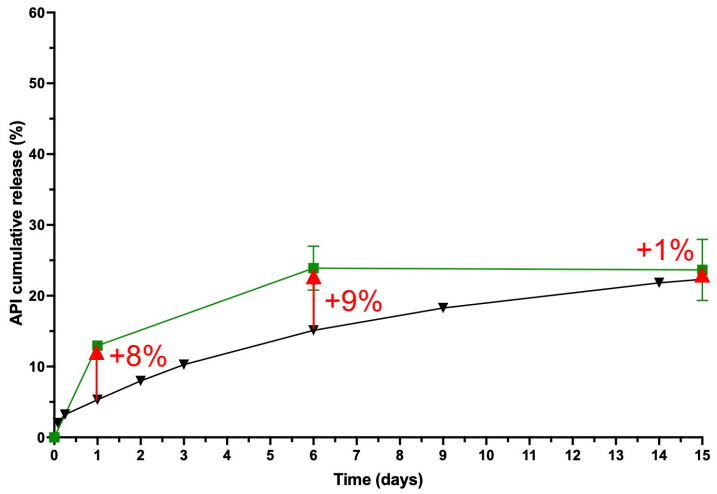
Classic *in vitro* release (IVR) setup

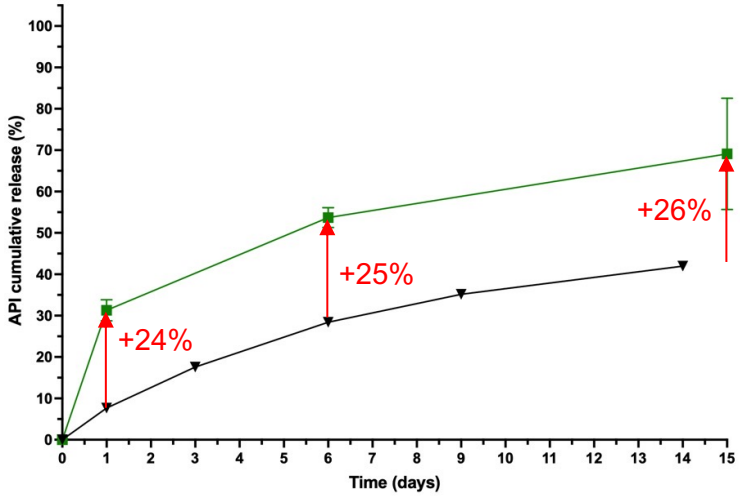


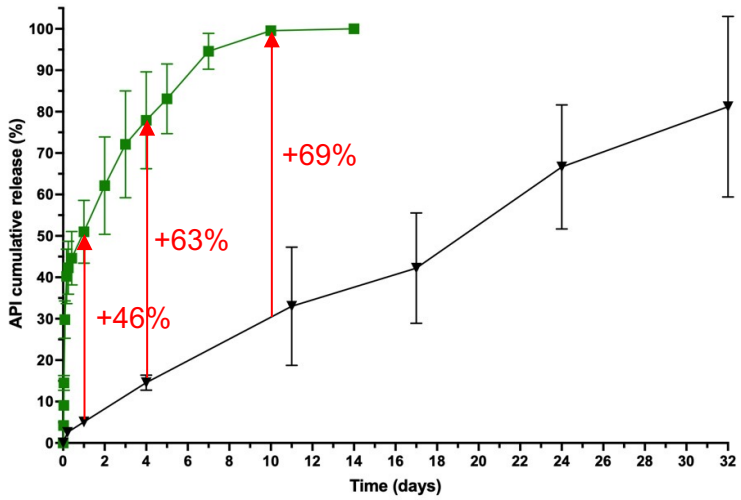
M. S. Suh et al., Int. J. Pharma. 592, 2021

Random *in vitro in vivo* predictability

- API dependent – Formulation dependent
- Species dependent





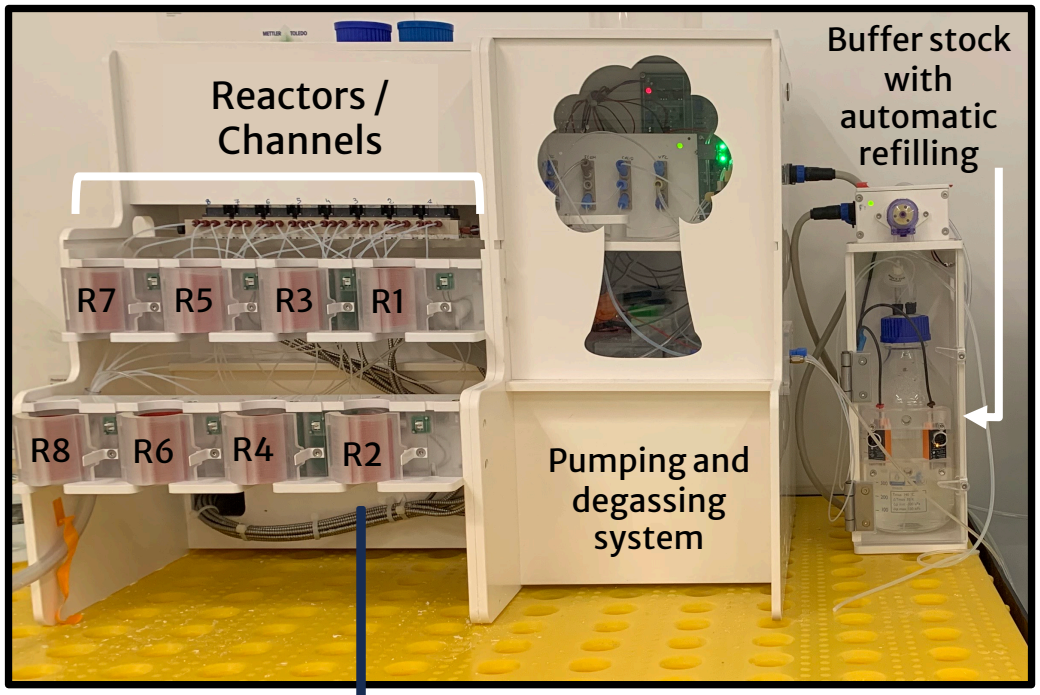


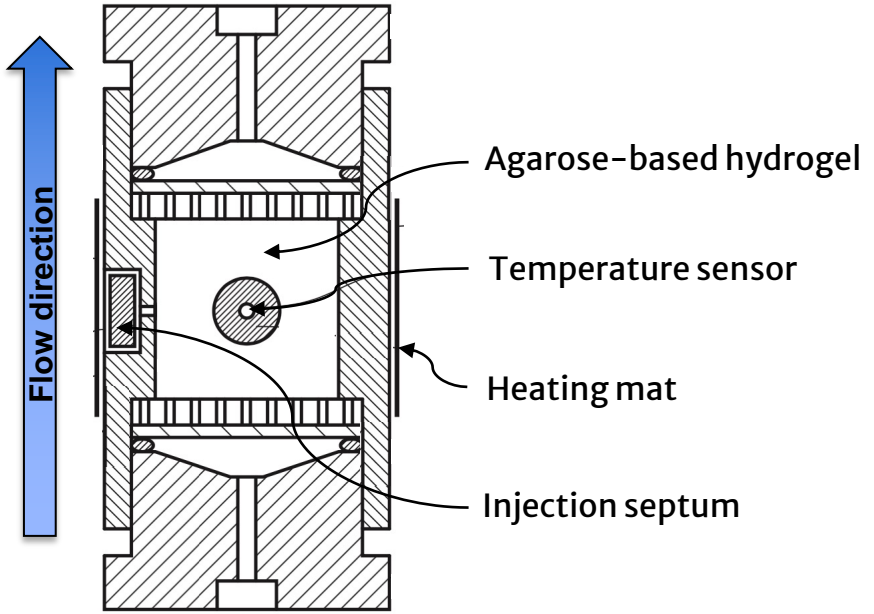
Classic capsule IVR
Preclinical data

Main IVR profile deviation

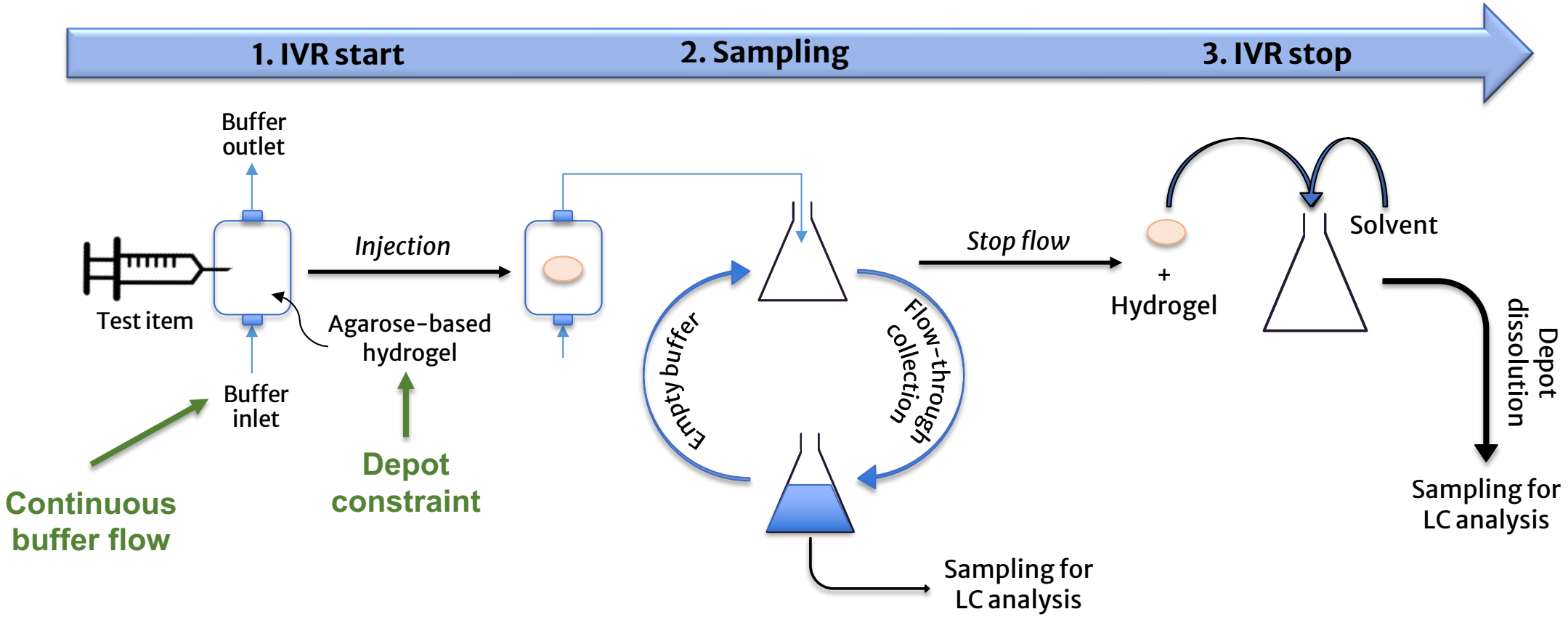
➢ **Initial burst**

MDC Flow-through IVR apparatus



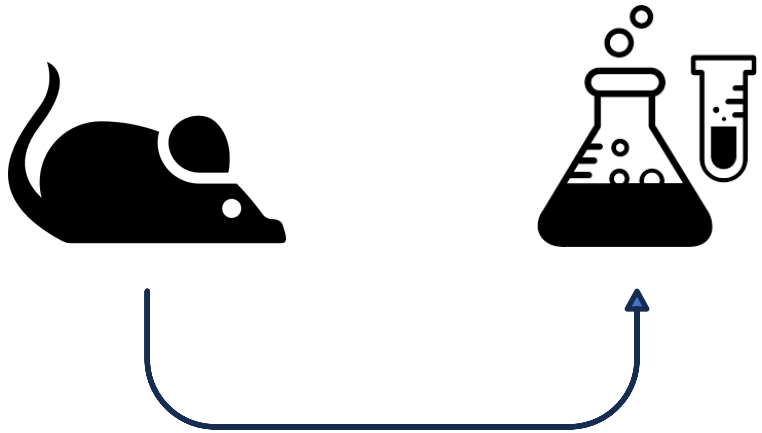


Flow-through IVR setup



From *vivo* to *vitro*

Optimizing IVR results

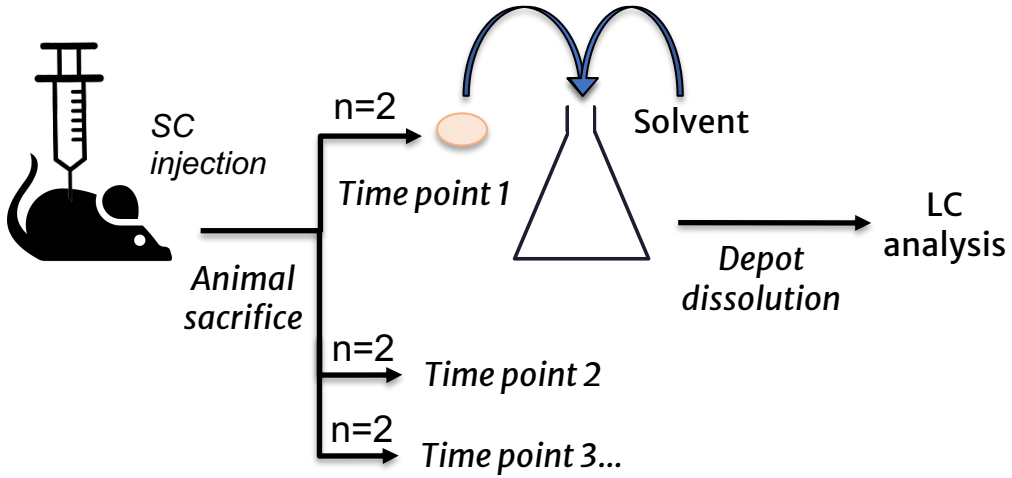


Test 1: formulations tested in Wistar rats

Study design: formulations tested in rats

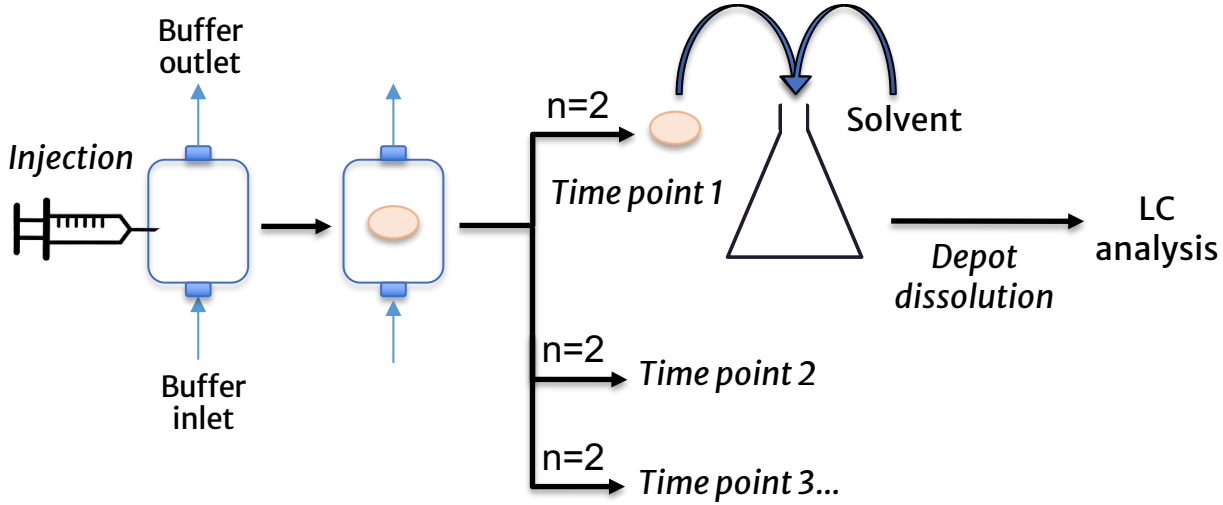
200 mg depot

In vivo design



Direct dosage of remaining API

In vitro design

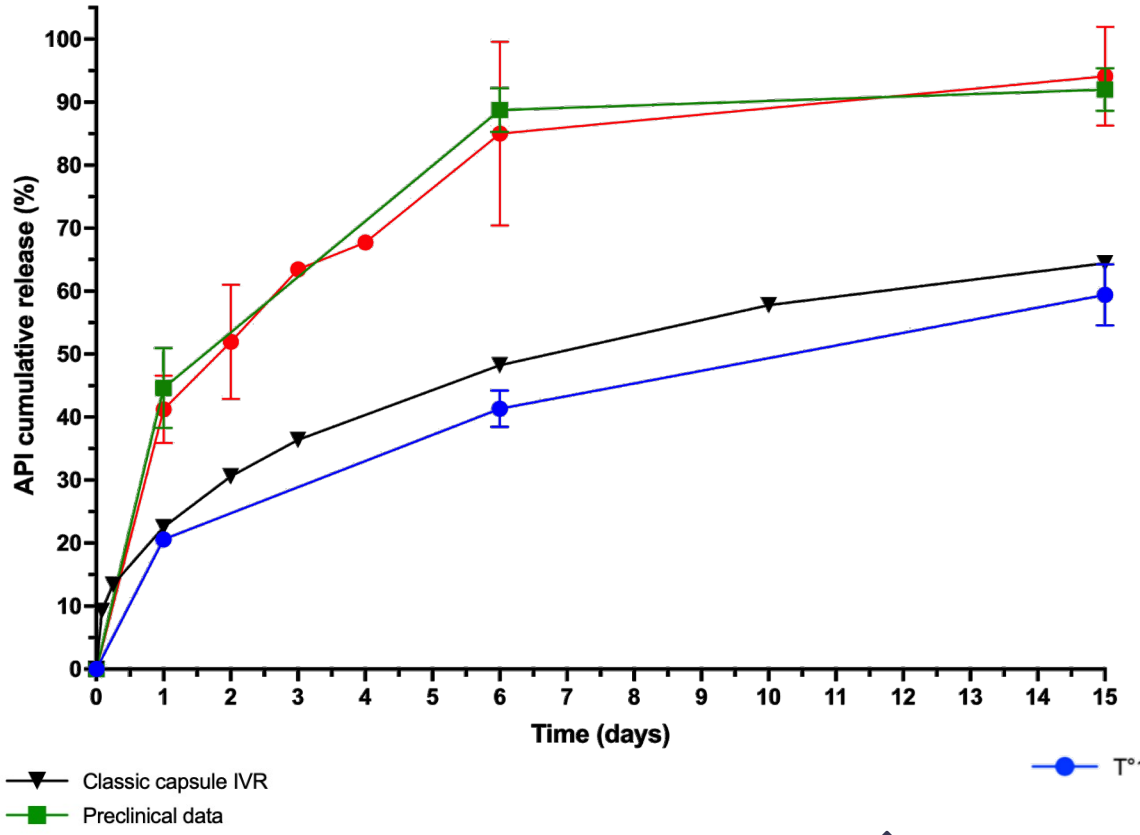


Test:

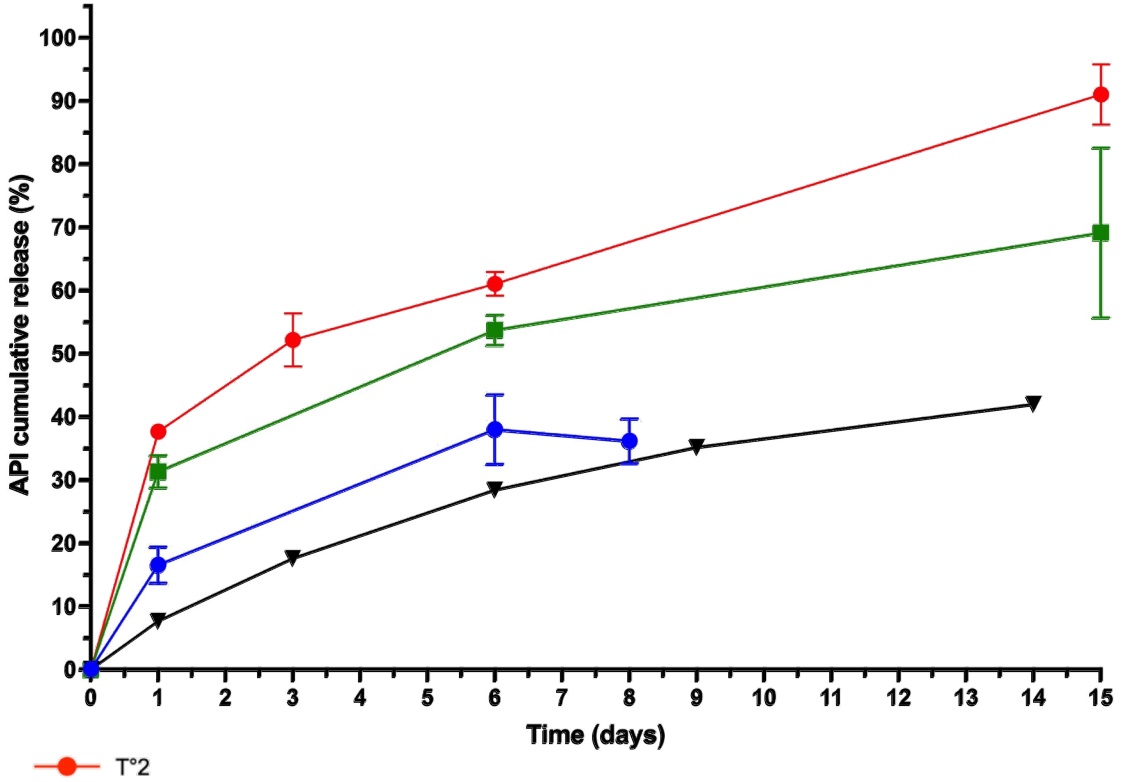
- **2 temperatures: T°1 < T°2**
- **2 flow rates: Flow 1 < Flow 2**

IVR optimization – Flow 1 _ T°1 & T°2

API 1



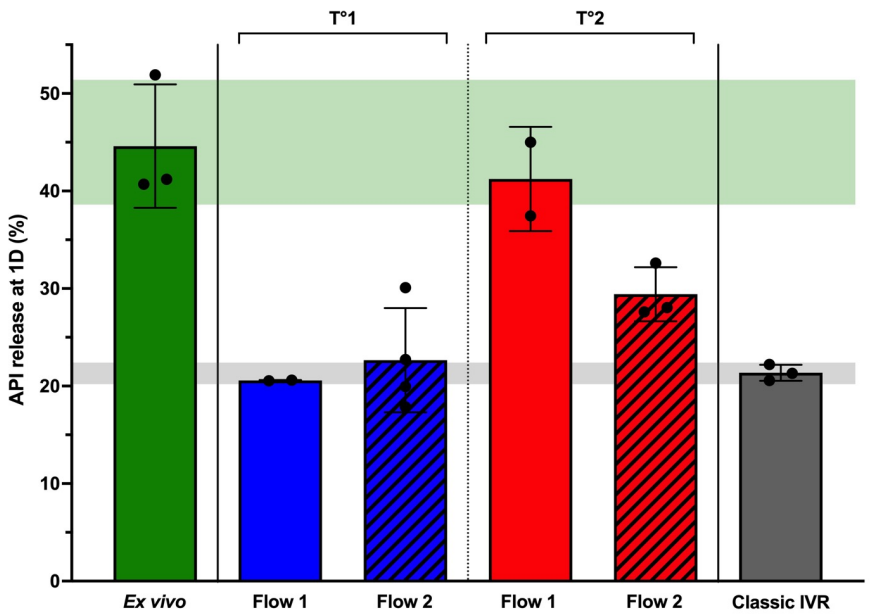
API 2



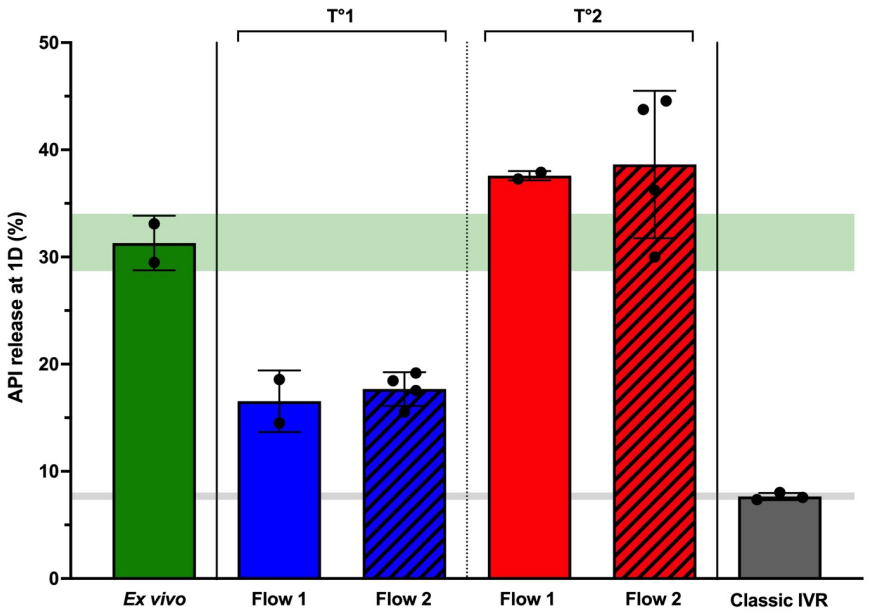
↑ temperature = ↑ drug release

IVR optimization – Flow 1 vs Flow 2

API 1



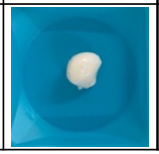
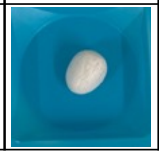
API 2

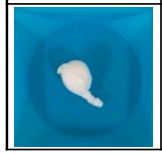
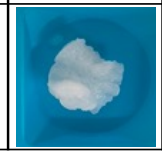


No improvement when ↑ flow

- Temperature is critical parameter

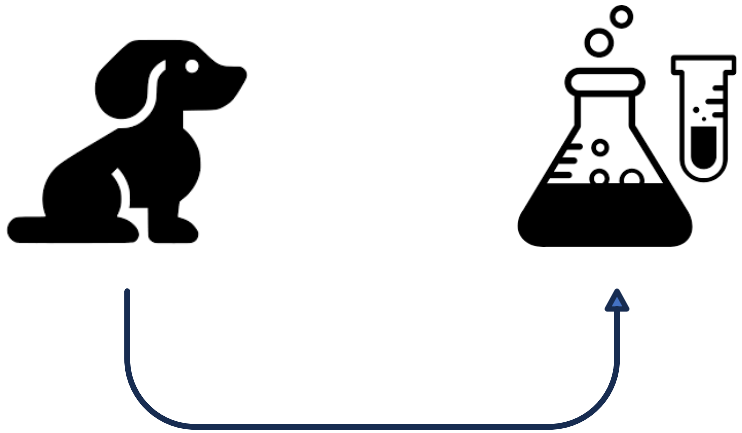
- Morphology at T°1 closer to *vivo*, but not drug release

T°1 (4D)		T°2 (4D)		Classic *in vitro* (4D)	*Ex vivo* rat (6D)
Flow 1	Flow 2	Flow 1	Flow 2		
					

T°1 (4D)		T°2 (4D)		Classic *in vitro* (4D)	*Ex vivo* rat (6D)
Flow 1	Flow 2	Flow 1	Flow 2		
					

From *vivo* to *vitro*

Optimizing IVR results



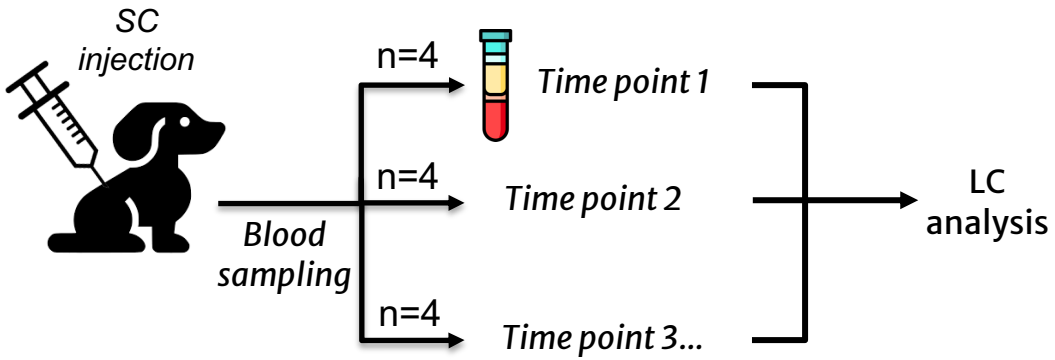
Test 2: formulations tested in Beagle dogs

Study design: formulations tested in dogs

675 mg depot

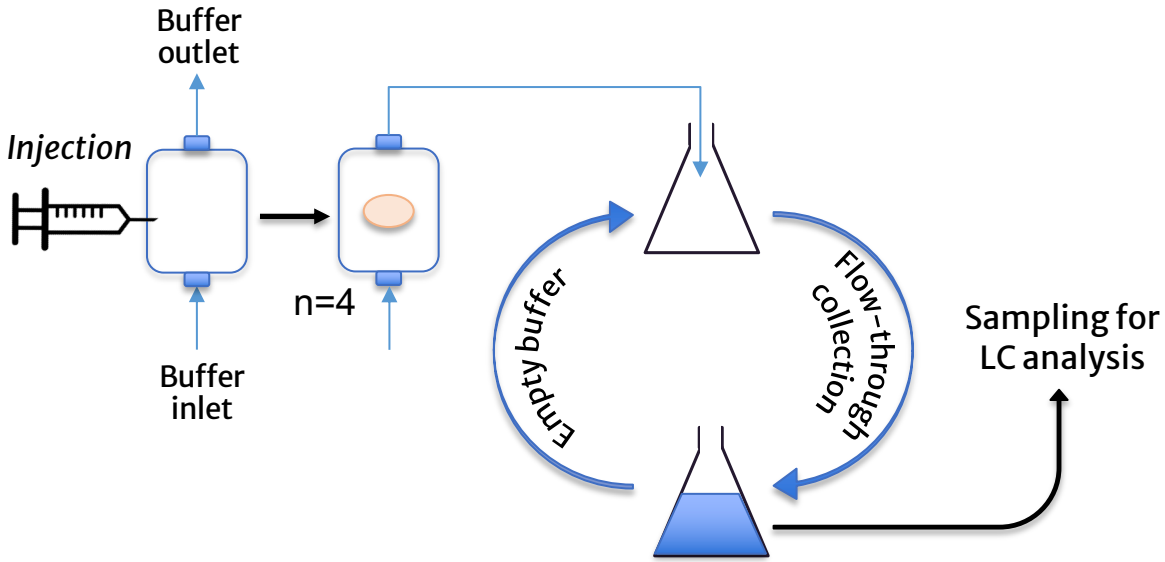
In vivo design

Classic PK study



Dosage of released API in the blood

In vitro design

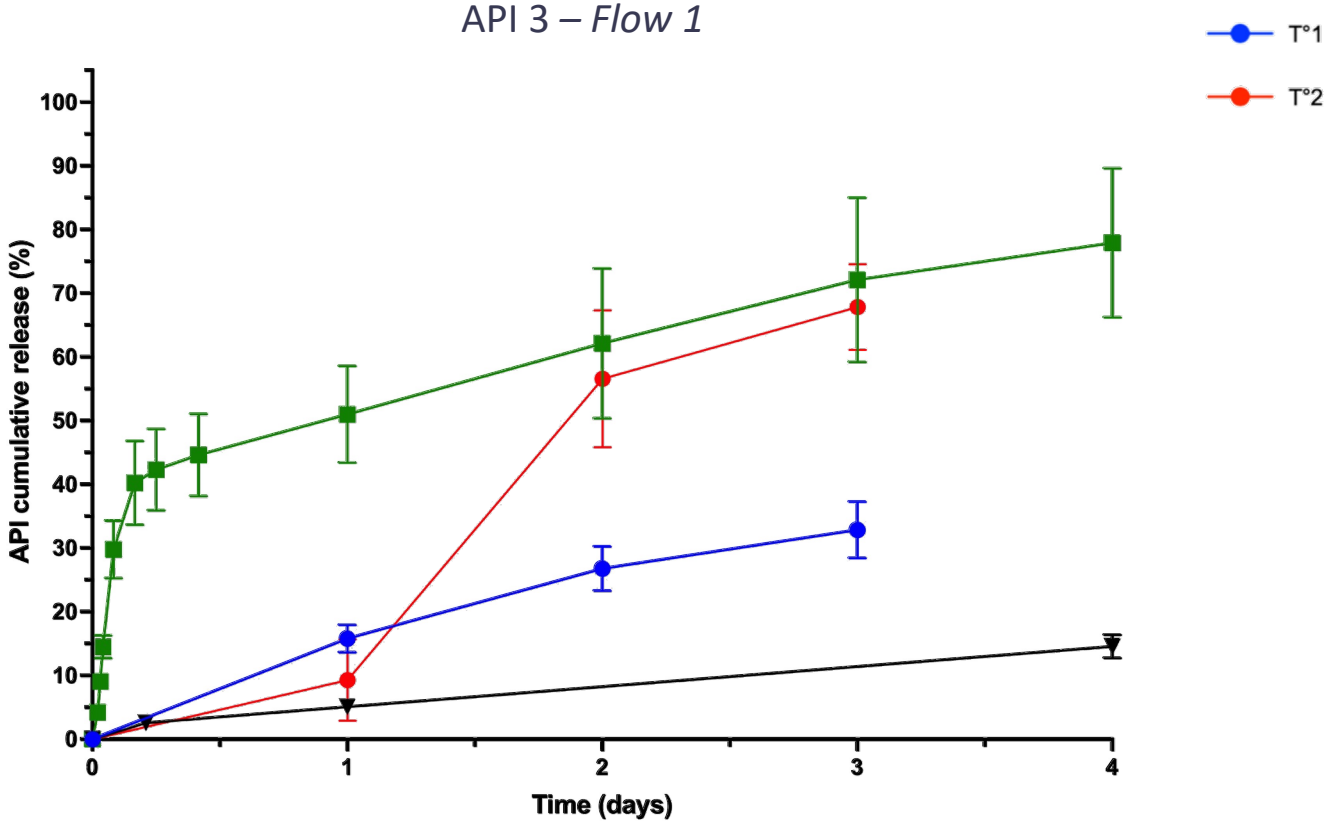


Test:

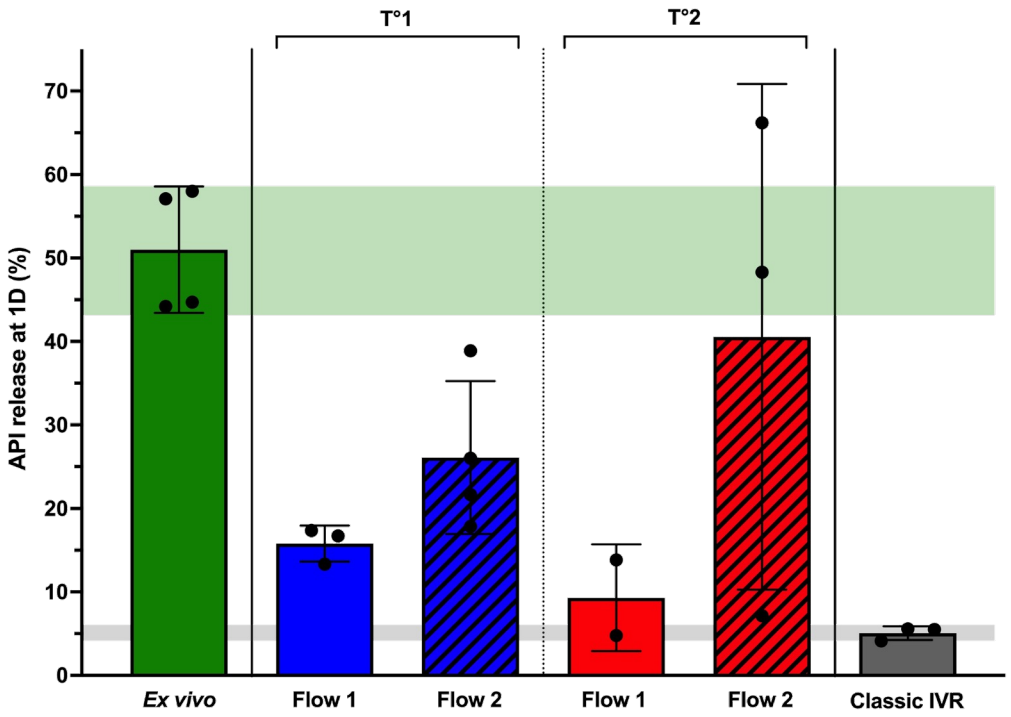
- **2 temperatures: T°1 < T°2**
- **2 flow rates: Flow 1 < Flow 2**

IVR optimization – 2 Flows _ 2 T°

API 3 – *Flow 1*



Flow 1 vs Flow 2 – T°1 vs T°2



- Same conclusions as formulations tested in rats

And now… what's next?

- Relevance of using Flow-through IVR apparatus
- Start identifying optimal conditions
- Tool for preclinical candidate selection

Optimization work:

- Reduce variability
- Additional inputs/outputs:
  - Addition pressure sensor
  - Work on matrix
  - Real-time API dosage by UV-Vis

Power of the group

Thank you to the team
And thank you for your attention

Marc SALIOT

Romain DELAMARE

Etienne YVORRA

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