Research Platform Tool: Miniaturized Screening and Tailoring of Preclinical XR-Formulations for NCEs

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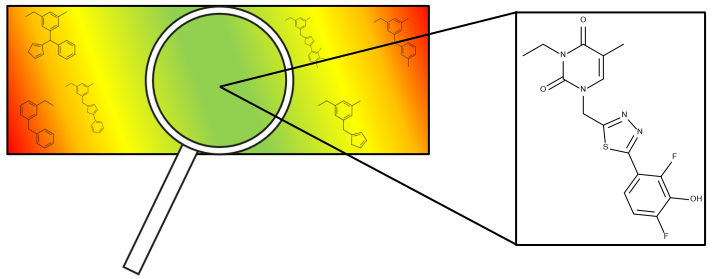
Life forward

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

INTEGRATING
Delivery Science
ACROSS DISCIPLINES

API-candidate-screening:
Potential new
BLOCKBUSTER…



…but

- ☐ rapid clearance or
- ☐ c_{sol} > 25x IC_{50}

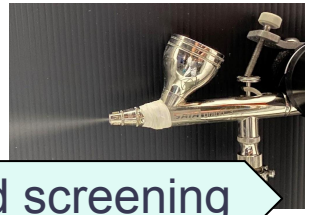
require **tailored** XR-formulation for Pharmacological Proof-of-Concept (PPoC)

How to enable a certain c_{ss} with

- only **<< 1,000 mg of API** and
- **least** number of **animal** experiments

?

(1) Miniaturized formulation-tailoring



need for XR-formulation

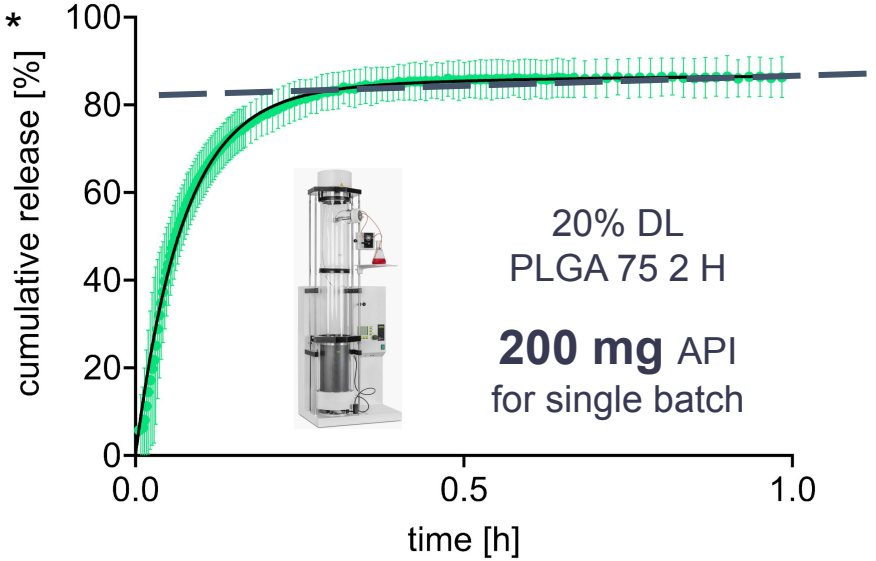
cpd A

solubility (tissue medium)	0.043 µg/mL = 42 nM
IC_{50}	0.24 nM
required RR in rat for 10-fold IC_{50}	0.887 **n**g/d

☐ rapid clearance

☑ ☐ c_{sol} > 25x IC_{50}

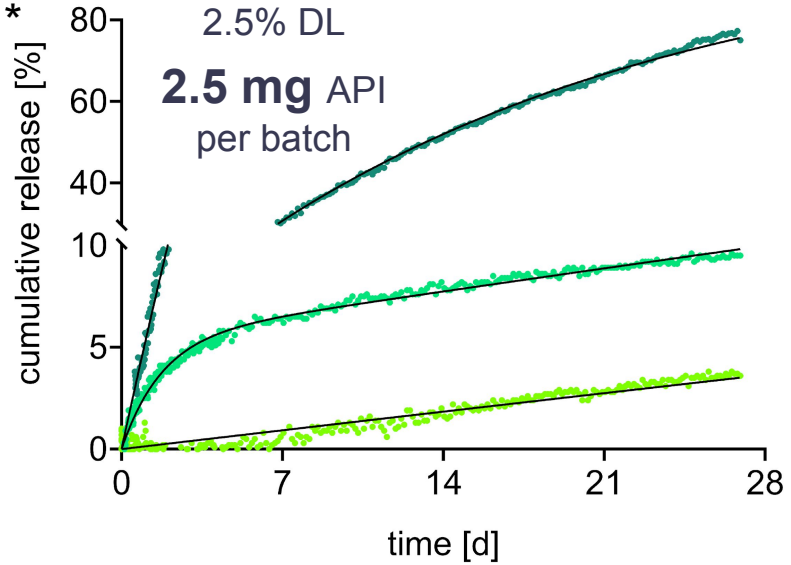
„traditional“ approach



terminal RR at standard dose = 5.3 µg/d

☐ **6,000-fold >> required RR**

miniaturized screening



● PLGA	low M_W	☐ **0.65**	**ng/d**
● PLA	low M_W	☐ 0.022	ng/d
● PLA	high M_W	☐ 0.017	ng/d

☐ ● **slightly higher dosed (x1.36) will enable 10-fold IC_{50} for 28 d**

*all *in vitro* release data measured in triplicate and under sink conditions

(2) Prediction of pseudo c_{ss}

need for XR-formulation

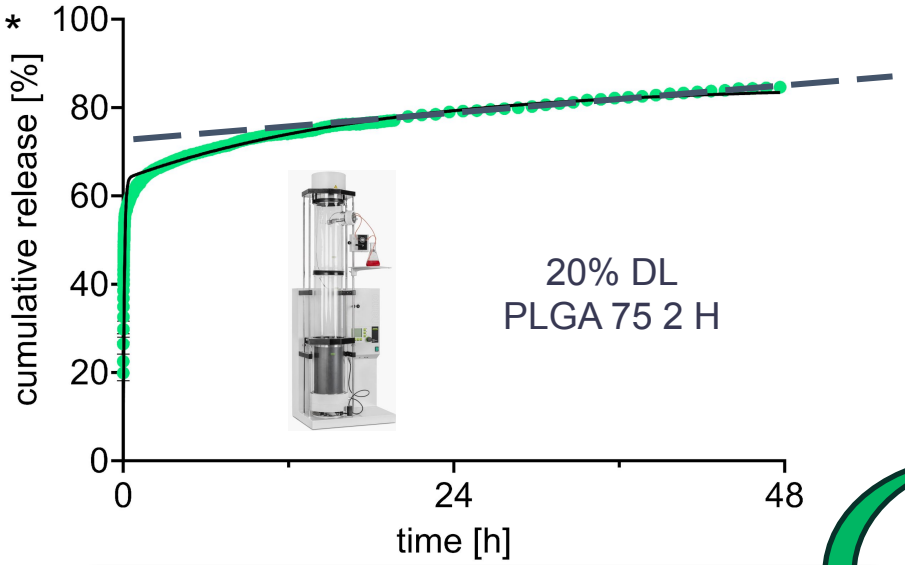
cpd B

solubility (tissue medium)	36 µg/mL = 87 µM
IC_{50}	60 nM
s.c. t_{max} / MRT	1 h / 3.6 h
required $_pc_{ss}$ for PPoC	1 µM for 24 h

☑ rapid clearance

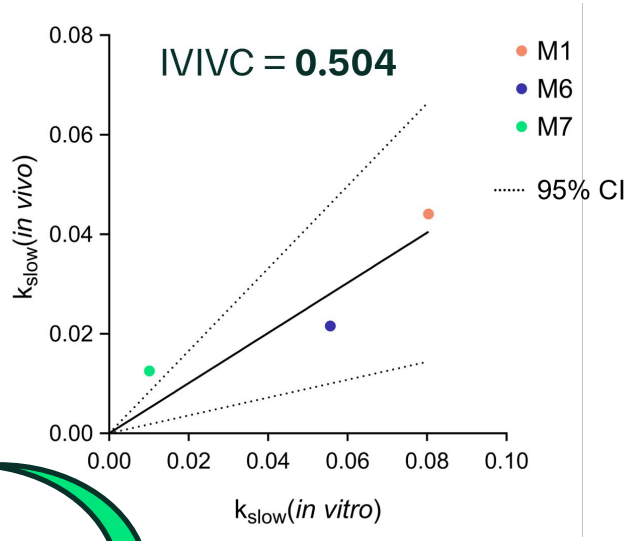
☑ c_{sol} > 25x IC_{50}

„traditional“ approach



terminal RR = k_{slow}(*in vitro*) = 0.1115 h^{-1}

IVIVC + $_pc_{ss}$



k_{slow}(***in vivo***) = **0.05620 h^{-1}**

☐ **28.6 mg/kg particles (20% DL) 1x/d will enable 1 µM**

*all *in vitro* release data measured in triplicate and under sink conditions

- [x] Explore how limitations of downscaled spray drying can be surmounted
- [x] Engage the use of established tool sequence to reduce animal experiments
- [ ] How exactly does the miniaturized spray dryer work?
- [ ] Are the miniaturized formulations stable and comparable?
- [ ] What if t_{rel} from initial screening is not sufficient?
- [ ] How to calculate ${}_{p}c_{ss}$ / how does it translate *in vivo*?

Poster Position **100**

Background Article: Block et al. 2024

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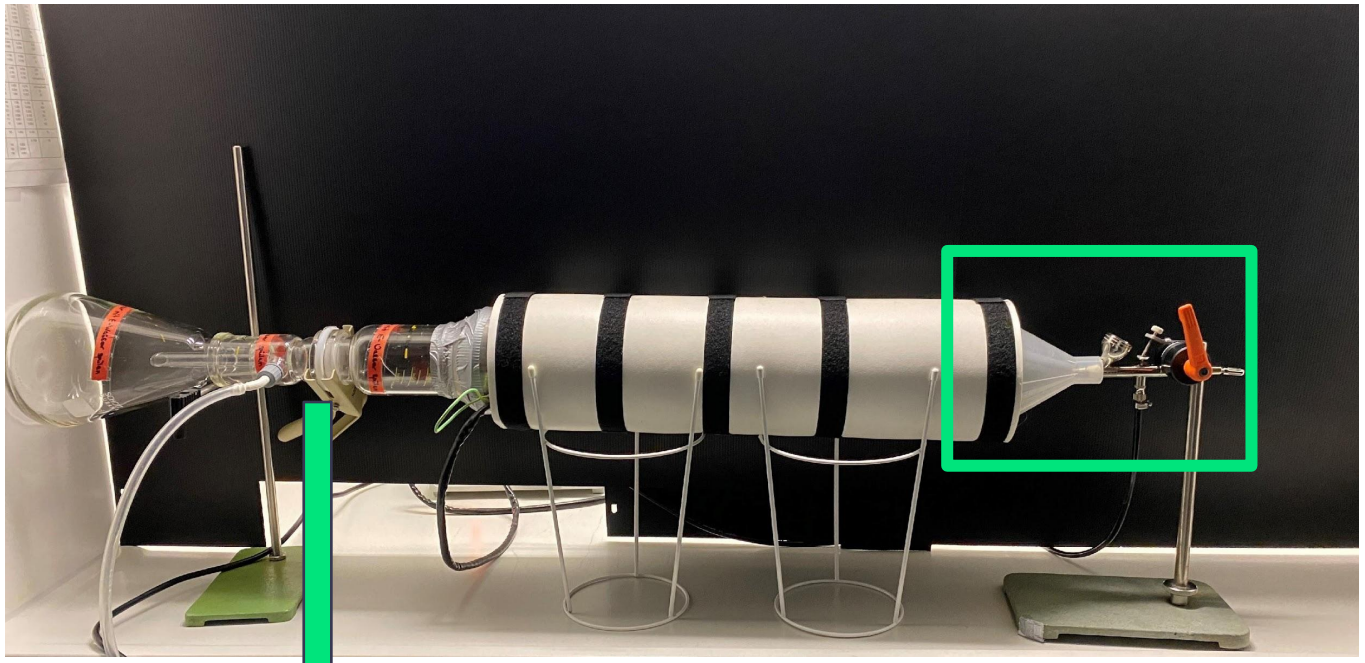
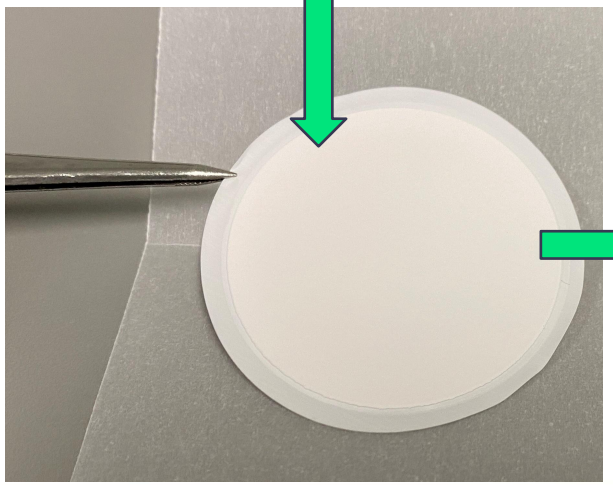
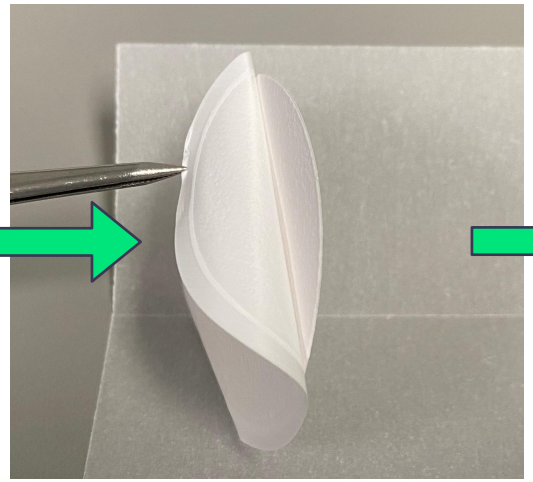
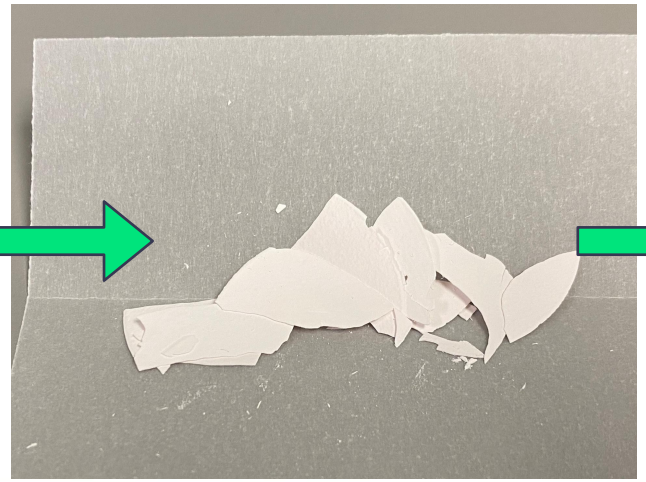
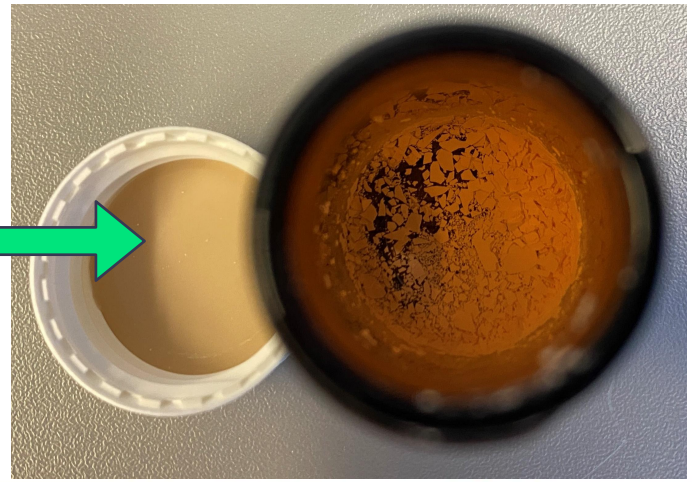
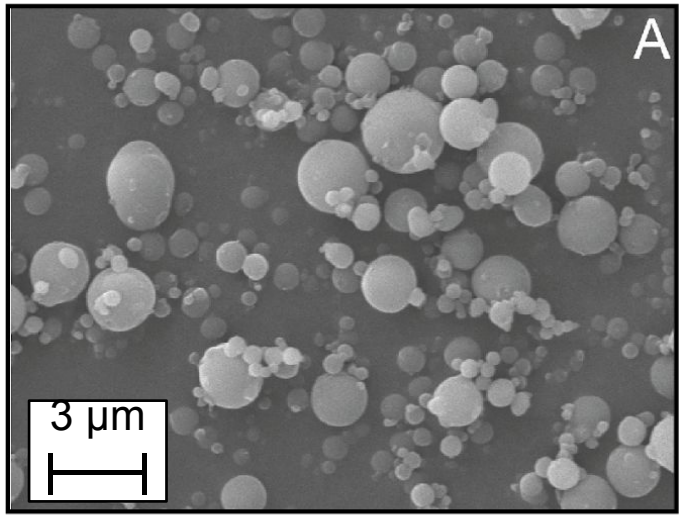


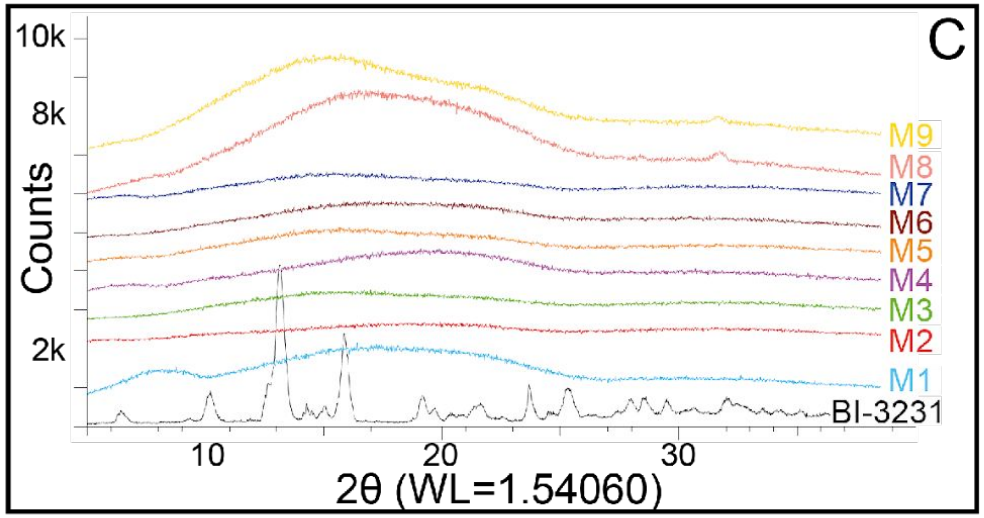


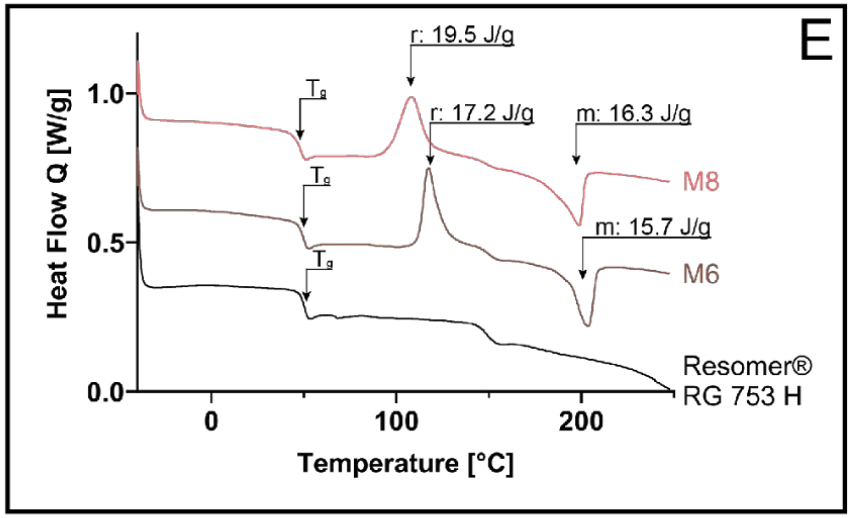


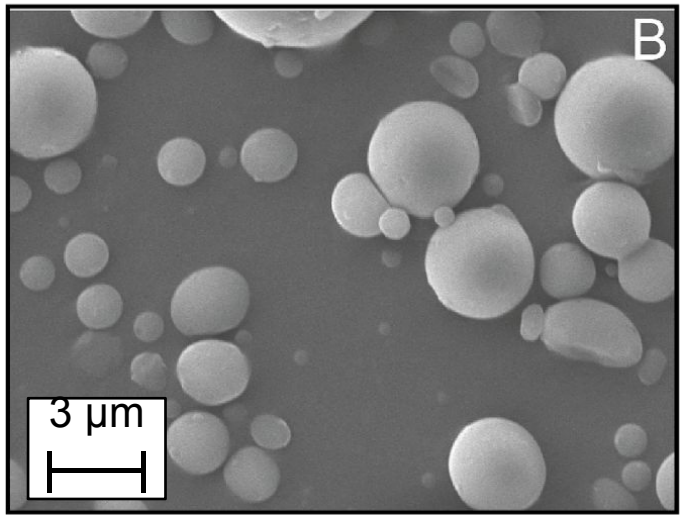


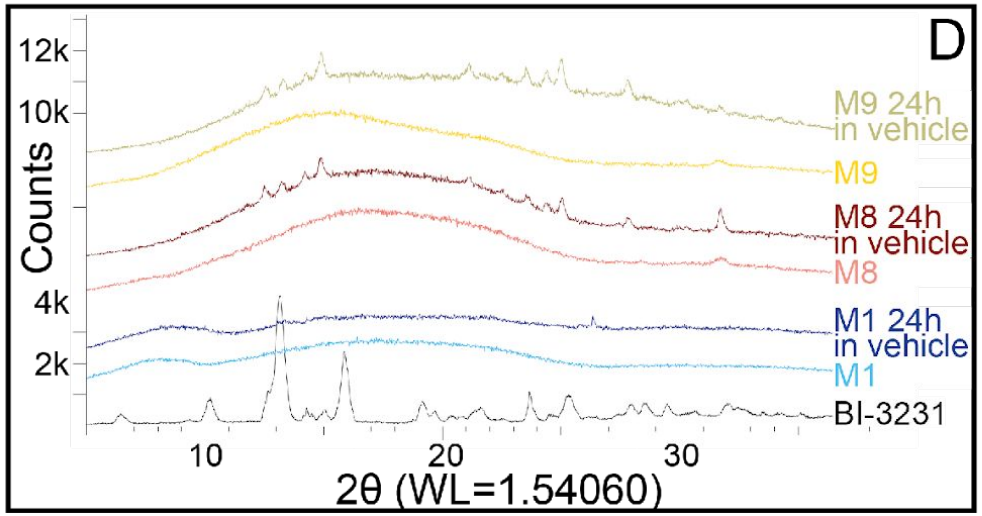


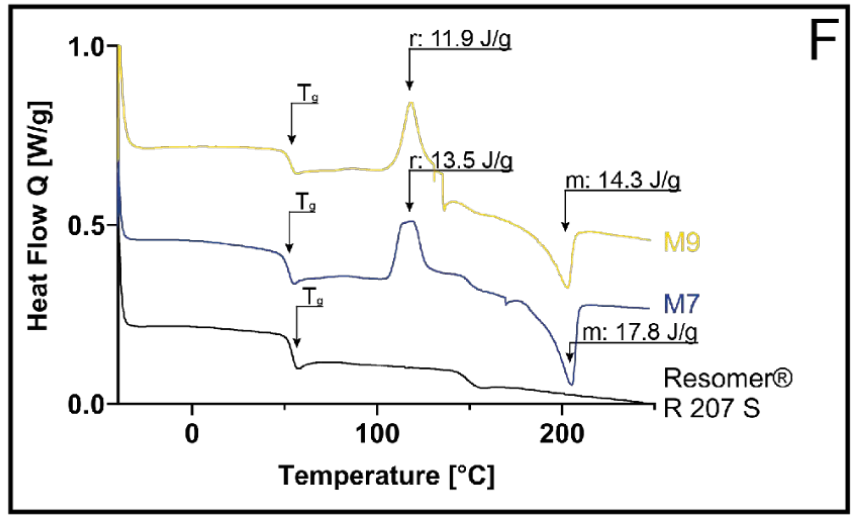


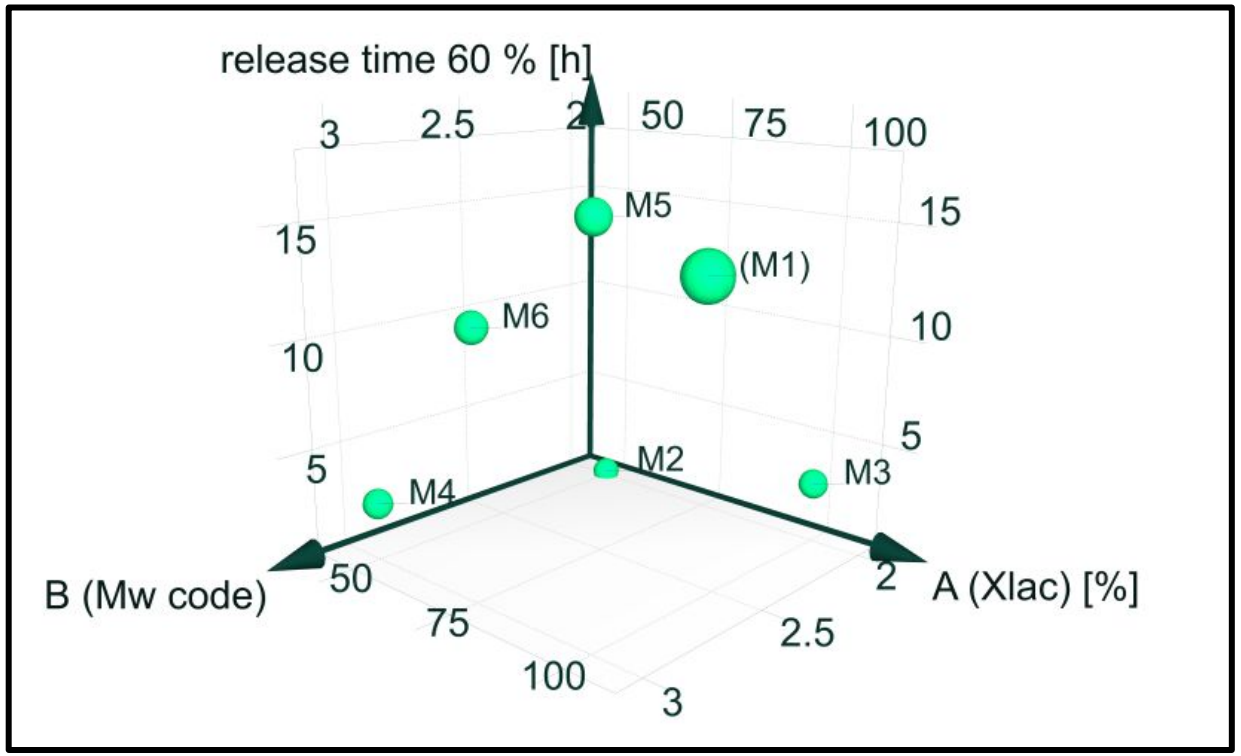


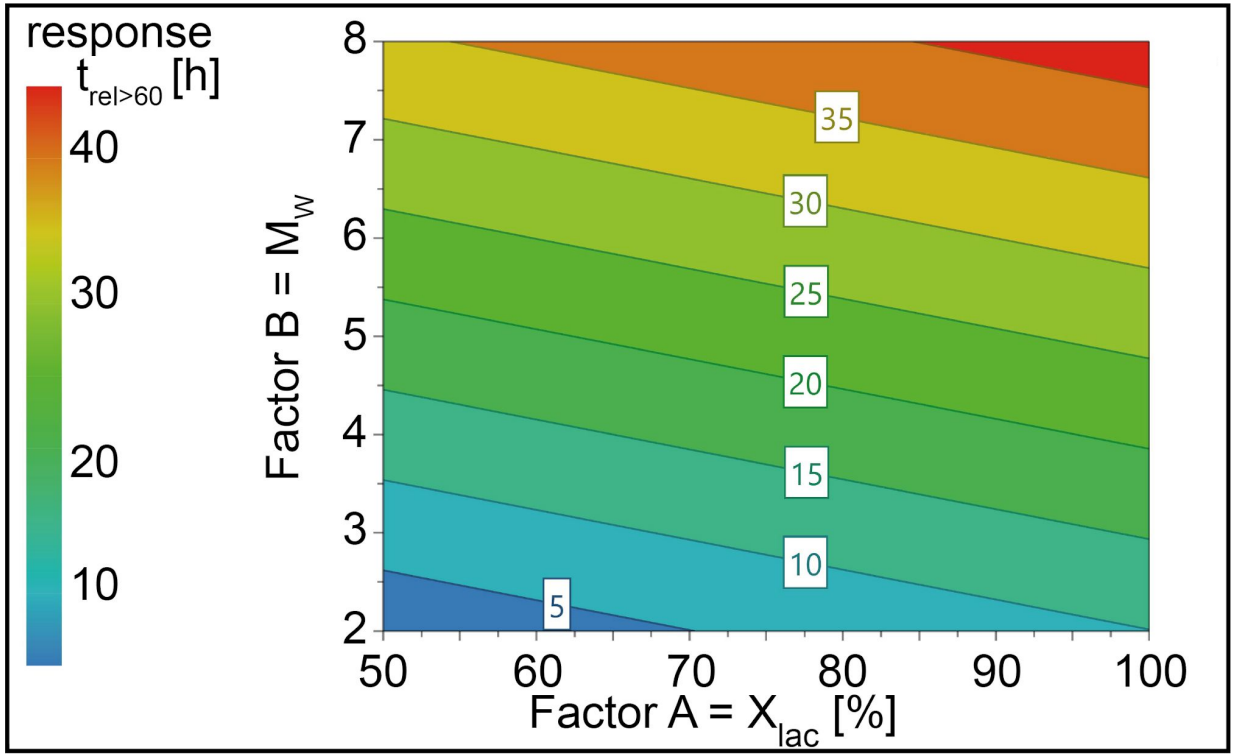


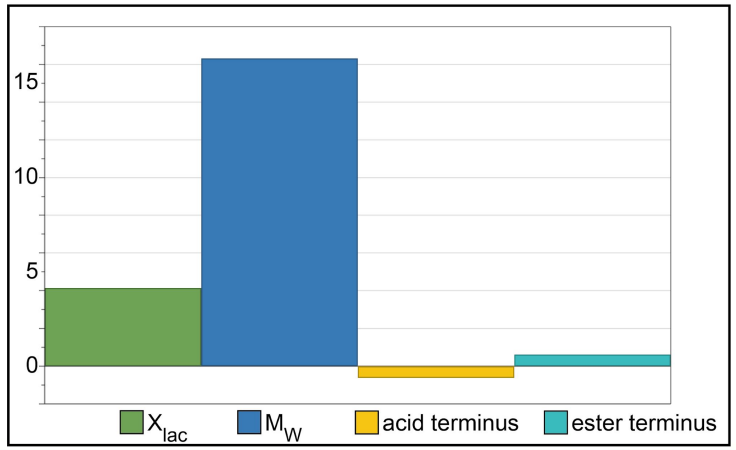












(1) Miniaturized formulation-tailoring

need for XR-formulation

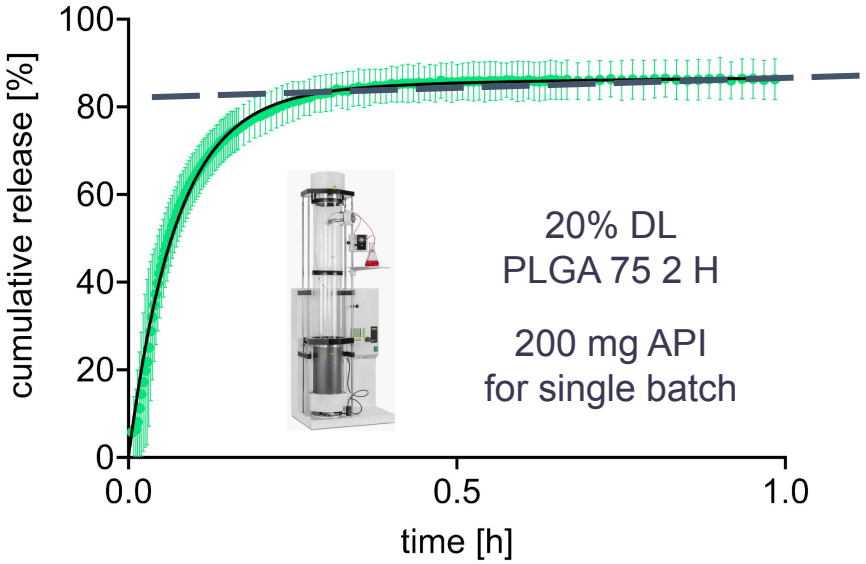
cpd A

M_W	1028 g/mol
logD pH 2 / 11	4.1 / 4.2
solubility (tissue medium)	0.043 µg/mL = 42 nM
IC_{50}	0.24 nM
required RR in rat for 10-fold IC_{50}	0.887 **n**g/d

☐ rapid clearance

☑ c_{sol} > 25x IC_{50}

„traditional“ approach

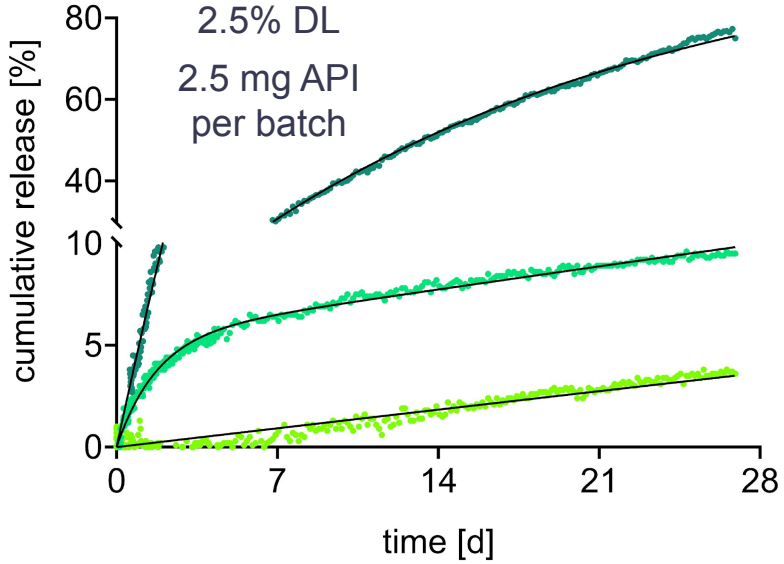


terminal RR = k_{slow} = 0.02210 h^{-1}

terminal RR at standard dose = 5.3 µg/d

☐ **6,000-fold >> required RR**

miniaturized screening



- PLGA low M_W ☐ **0.65 ng/d**
- PLA low M_W ☐ 0.022 ng/d
- PLA high M_W ☐ 0.017 ng/d

☐ **slightly higher dosed (x1.36) will enable 10-fold IC_{50} for 28 d**

(2) Prediction of pseudo c_{ss}

need for XR-formulation

cpd B

M_W	412 g/mol
logD pH 2 / 11	1.2 / 1.8
solubility (tissue medium)	36 µg/mL = 87 µM
IC_{50}	60 nM
s.c. t_{max} / MRT	1 h / 3.6 h

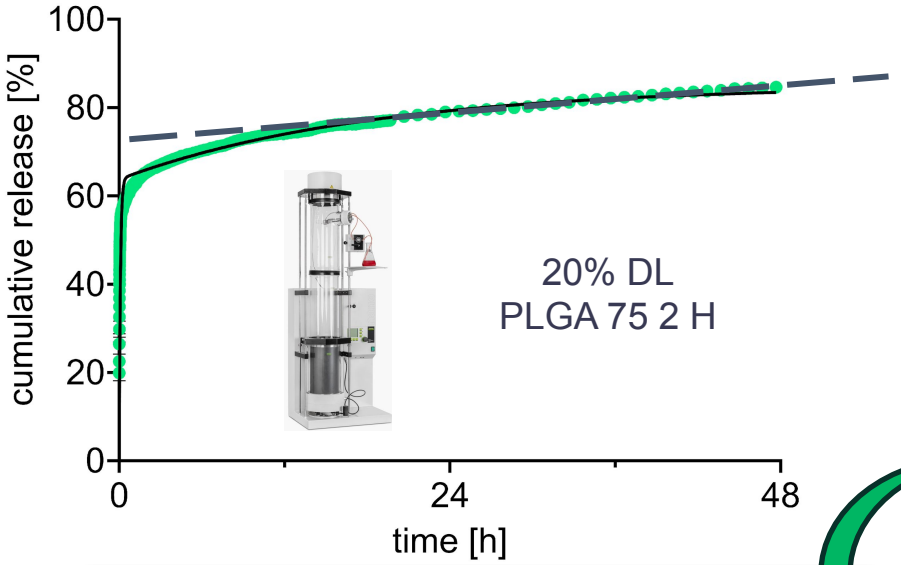
☑ rapid clearance

☑ $c_{ss,ext} > 25x\ IC_{50}$

Required $_pc_{ss}$ for PoC:

1 µM for 24 h

„traditional“ approach



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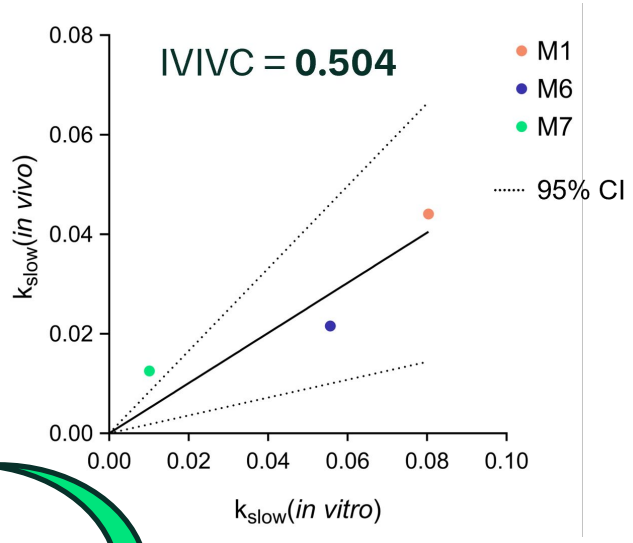

k_{slow}(***in vivo***) = **0.05620 h^{-1}**

$$ {}_pc_{ss} = \frac{k_0}{CL} = \frac{k_{slow} * \frac{D}{M_W}}{CL} \Leftrightarrow D = \left(\frac{{}_pc_{ss} * CL}{k_{slow}}\right) * M_W = \left(\frac{0.001\ \frac{mmol}{L} * 0.78 \frac{L}{h*kg}}{0.05620\ h^{-1}}\right) * 412\ \frac{mg}{mmol} = 5.72\ \frac{mg}{kg} $$

☐ **28.6 mg/kg particles (20% DL) 1x/d will enable 1 µM**