

Development of a methodology to enable non-linear *in vitro-in vivo* correlation for complex long-acting injections

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Purpose

- Linear *in vitro in vivo* correlation (IVIVC) methods for both oral and non-oral dosage forms are reported [1-5], however linear IVIVC may be inappropriate for complex parenterals
- Long-acting injections (LAIs), with complex release profiles, likely require a non-linear relationship to correlate accelerated *in vitro* release to real time *in vivo* release

Methods

To demonstrate the steps required for non-linear IVIVC, we simulated datasets for accelerated *in vitro* dissolution and PK profiles for three different formulations that are typical of a parenteral PLGA microsphere product

Steps to perform non-linear IVIVC

- Deconvolution of the absorption profile of each formulation
- Model dissolution profiles and calculate scaled *in vitro* timepoints
- Creating a Levy plot, by plotting *in vivo* timepoints against the scaled *in vitro* timepoints. The IVIVC is said to be non-linear if the Levy plot is best described by a non-linear function
- Generation of a scaled dissolution profile
- Simulation of PK profiles using scaled dissolution. Assessment of the resulting IVIVC against the guideline criteria set by the FDA [1]

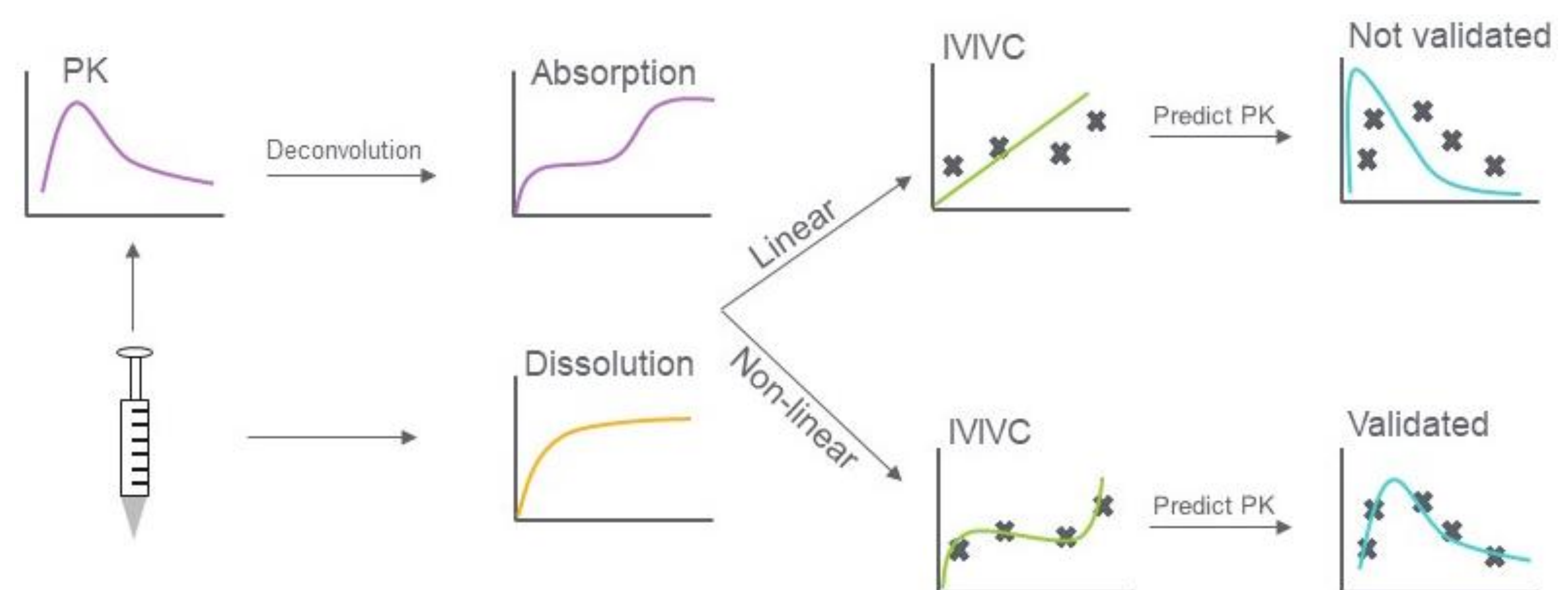


Figure 1 Flow chart of IVIVC methodology

Results

- Linear and non-linear IVIVC performed on 3 formulations. Example of IVIVC steps on one formulation is shown in Figures 2 & 3
- For the non-linear approach, high-order polynomials were used to describe the *in vitro-in vivo* relationship

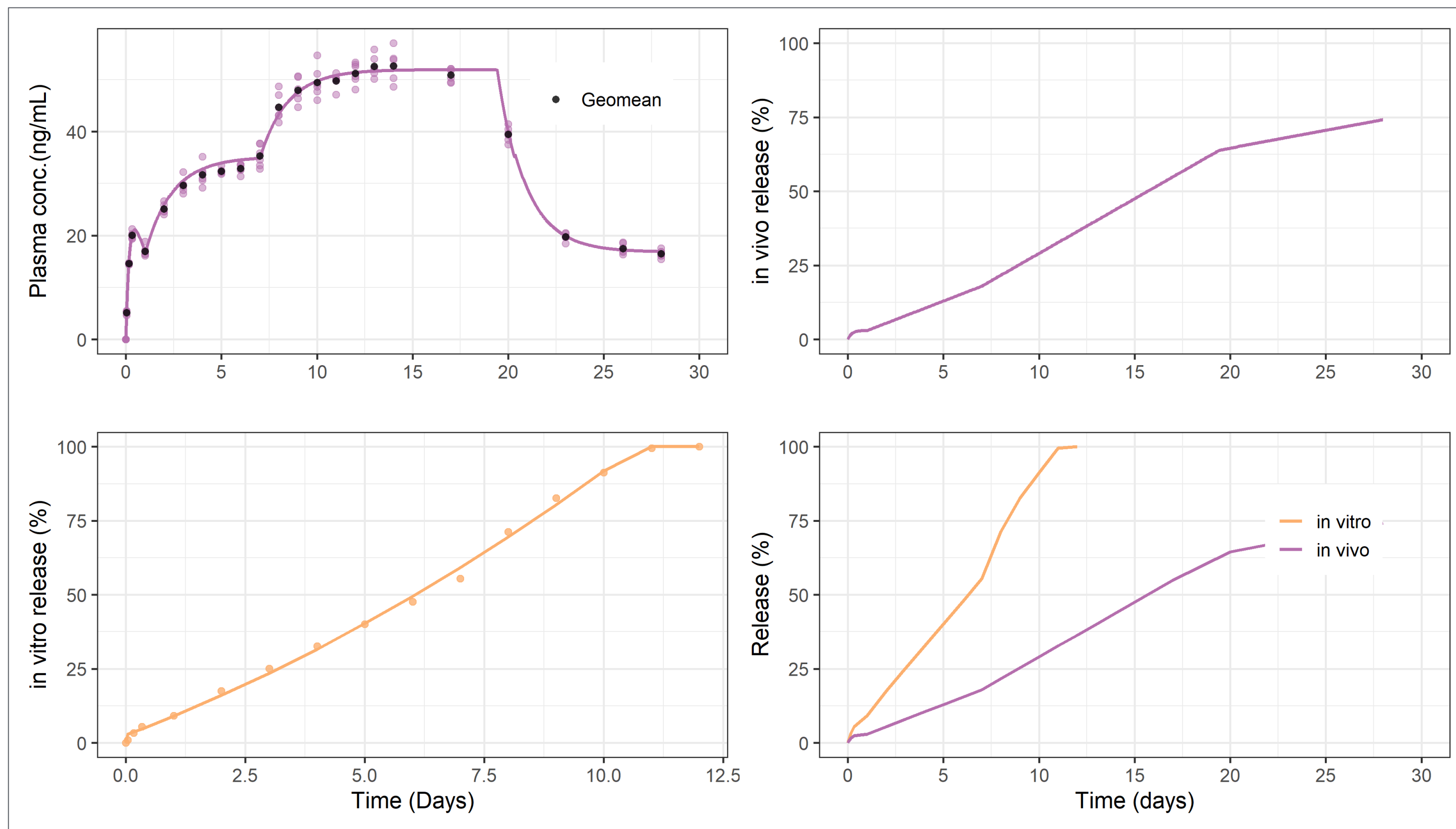


Figure 2 Deconvolution of *in vivo* release profile (points and line correspond to raw and fitted data, respectively) and modelling of dissolution data (yellow points and line correspond to raw and fitted data, respectively)

Validation

- Only the non-linear approach met FDA validation criteria
- The % PE's of the non-linear approach are summarised in Table 1

Formulation	Obs C_{max} (ng/mL)	Pred C_{max} (ng/mL)	C_{max} % PE	Obs AUC (ng*h/mL)	Pred AUC (ng*h/mL)	AUC % PE
1	59.7	56.8	4.73	26500	26400	0.200
2	54.2	52.0	4.08	24100	24200	0.400
3	64.5	59.5	7.75	29200	27700	5.24
MAPPE			5.52			1.95

Table 1 Observed (Obs) and predicted (Pred) C_{max} and AUC following non-linear IVIVC and the associated percent error for each formulation.

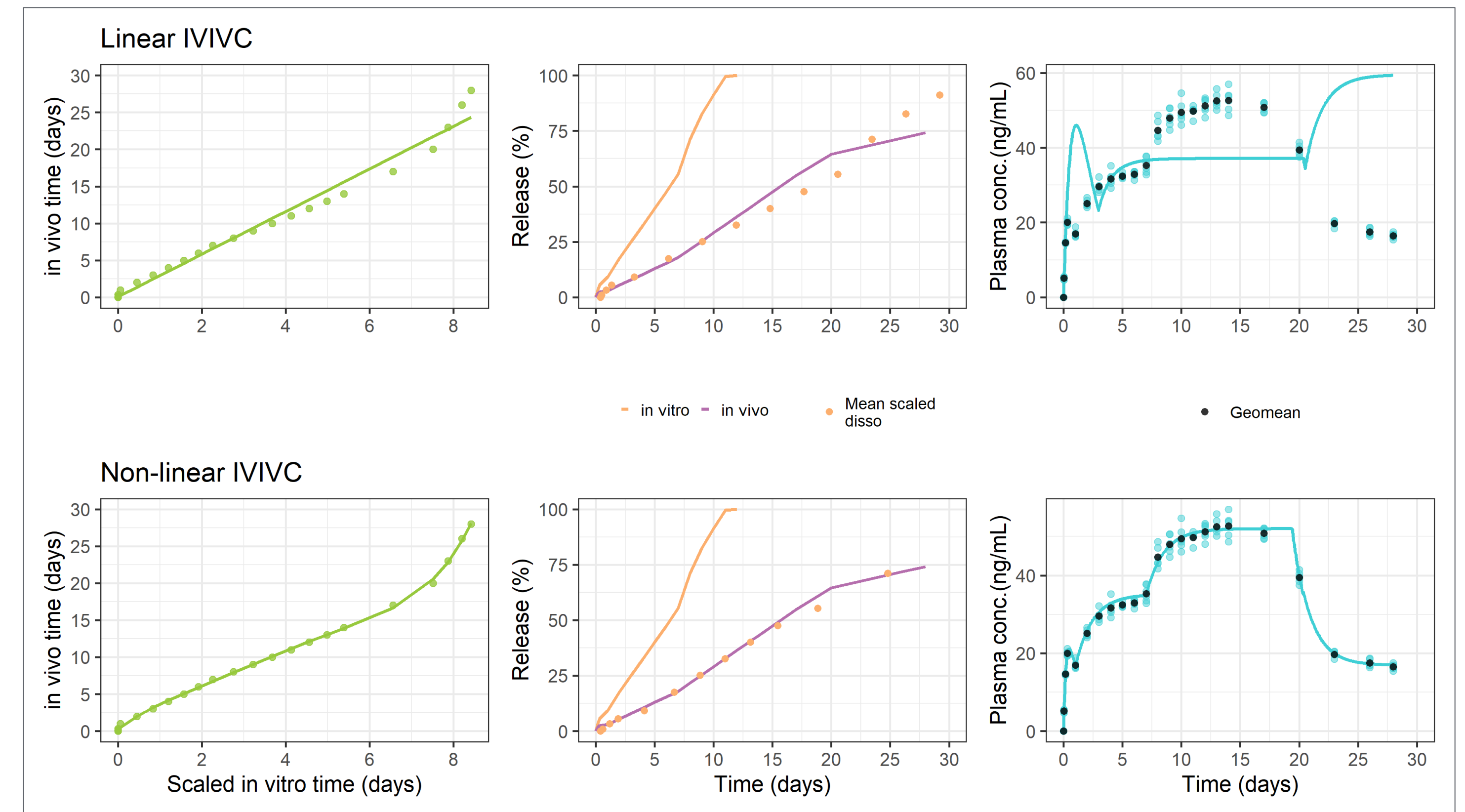


Figure 3 Comparison of linear (top) and non-linear (bottom) IVIVC approaches. From left to right: fitted Levy plots, mean scaled *in vitro* profile (yellow points), predicted PK from established IVIVC

Conclusions

In this work, we have demonstrated a step-by-step approach for non-linear IVIVC using higher order polynomials.

The results showed that in this instance, when dissolution was much faster than absorption and the complexity of the release profile was high, a linear IVIVC was invalid and said to be inconclusive whereas a non-linear approach led to a valid IVIVC.

References

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