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

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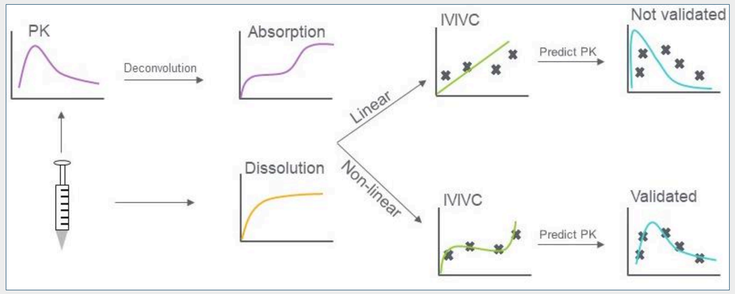
PURPOSE

- **Linear** in vitro in vivo correlation (IVIVC) methods of both oral and non-oral dosage forms are reported [1-5], however linear IVIVC may be inappropriate for complex parenterals.
- For long-acting injections (LAIs), with complex release profiles, it is likely that a non-linear relationship is required to correlate accelerated in vitro release to real time in vivo release.
- Figure 1 is a flow chat of the proposed methodology to perform **non-linear** IVIVC of a LAI

Figure 1 Flow chart of IVIVC methodology



OBJECTIVE

Establish methodology for non-linear level A IVIVC.

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

1. Deconvolution of the absorption profile of each formulation
2. Model dissolution profiles and calculate scaled in vitro timepoints
3. 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
4. Generation of a scaled dissolution profile
5. Simulation of PK profiles using scaled dissolution. Assessment of the resulting IVIVC against the guideline criteria set by the FDA [1]

RESULTS

Establishing an IVIVC

- IVIVC was established on 3 different formulations. To highlight the steps taken for IVIVC we present one formulation in detail:
- Simulated PK data was modelled using compartmental PK analysis (Figure 2a) resulting in the deconvolution of the absorption profiles (Figure 2b) .
- A second order polynomial gave a satisfactory fit of the dissolution data (Figure 2c) . Thus, scaled in vitro timepoints were calculated.
- Figure 2d shows in vivo absorption is slower than in vitro dissolution
- A levy plot was generated of the scaled in vitro timepoints and the measured in vivo timepoints and regressed against using linear and non-linear models, as shown in Figure 3a and 3b
- The established model was used to calculate scaled dissolution profiles
- Figure 3c and 3d illustrates, scaled dissolution profiles compared to the dissolution profile and absorption profile
- Figure 3e and 3f shows the predicted PK profile convoluted form the scaled dissolution profile
- Non-linear IVIVC predicted the PK well, however linear IVIVC gave an unsatisfactory prediction

Validation

- Criteria for a valid IVIVC is specified by the FDA[1]
- To validate the established non-linear IVIVC the mean scaled in vitro time at each associated absorption time point was calculated and used to convolute the PK profiles of each formulation
- A valid IVIVC was established:
  - Mean absolute percent prediction error (MAPPE) was less than 10% for C_{max} and AUC
  - Percent prediction error (%PE) of Cmax and AUC for each formulation was less than 15%
- The %PE's are summarised in Table 1

Figure 2 Deconvolution of absorption profile and modelling of dissolution data

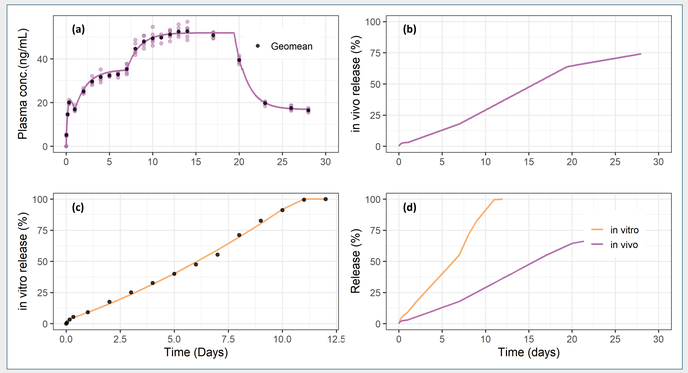


Figure 3 Comparison of linear (top) and non-linear (bottom) IVIVC approaches. From left to right: fitted Levy plots, mean scaled in vitro profile, predicted PK from established IVIVC

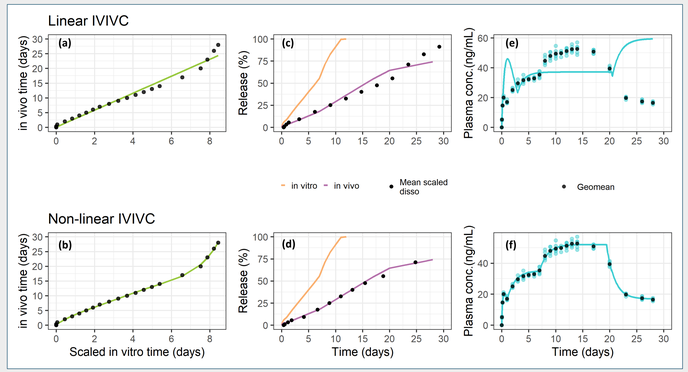


Table 1 Observed (Obs) and predicted (Pred) Cmax and AUC following non-linear IVIVC and the associated percent error for each formulation.

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	59.65	56.83	4.73	26457	26404	0.2
2	54.18	51.97	4.08	24091	24188	0.4
3	64.51	59.51	7.75	29203	27673	5.24
MAPPE			5.52			1.95

CONCLUSIONS

- As the release from LAIs can be prolonged over weeks or months, accelerated in vitro dissolution testing is very desirable.
- However, due to the complexity of LAI formulation, this acceleration can affect the different phases of drug release in different ways meaning that a linear IVIVC model may/will not be appropriate.
- 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, where 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.
- We believe that this an important first step in establishing IVIVC for complex dosage forms.
- We hope this encourages development scientists to attempt to establish an IVIVC regardless of the complexity of a dosage form. Thus, more time can be spent on formulation work and less time and money spent testing in animals and humans.

REFERENCES

1. FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations (1997)

2. Mauger DT & Chinchilli VM (1997) J Biopharm Stat. 1997;7:565–78. https://doi.org/10.1080/10543409708835207

3. Bhalan G, Timmins P, Greene DS, Marathe PH J Pharm Sci. 2001; 90:1176–85. https://doi.org/10.1002/jps.1071

4. Mohamed MEF., Trueman S, Othman AA et al (2019) AAPS J 21: 108. https://doi.org/10.1208/s12248-019-0378-y

5. Shen J, Burgess DJ (2015) J. Control. Release 219 644–651. https://doi.org/10.1016/j.jconrel.2015.09.052

6. Dickinson J, Patterson CM, Gajjar P, Dickinson H and Dickinson PA Development of a methodology to enable non-linear in vitro-in vivo correlation for complex long-acting injections *In preparation*

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