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Development of a methodology to enable nonlinear in vitro-in vivo correlation for complex longacting injections

Alderley Edge, SK10 4TG

Email: jake.dickinson@sedapds.com Telephone: +44(0)7518528830

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

- 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]

Jake Dickinson, Claire Patterson, Parmesh Gajjar and Paul A Dickinson Seda Pharmaceutical Development Services Ltd, Alderley Park,



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)	P
1	59.65	56.83	4.73	26457	26404	0
2	54.18	51.97	4.08	24091	24188	0
3	64.51	59.51	7.75	29203	27673	5
MAPPE			5.52			1

AUC %

5.24 L.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.

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