In Vitro / In Vivo Correlation (IVIVC) Development for a model compound with release rate specific bioavailability.

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Purpose

To develop insights into the exploration and development of an IVIVC for a model compound and formulation that, upon casual review, would not seem to support an IVIVC.

Formulation

The formulation under study is a capsule containing four different types of delayed release beads.

The beads are characterized by a mean dissolution time (MDT) and a time lag (Tlag).

	Tlag	MDT
Type 1	10	30
Type 2	75	60
Type 3	150	120
Type 4	300	240

Each of the seven formulations under study is comprised of some mass fraction (Xi) of each type of bead.

	X1	X2	X3	X4
CR01	1	0	0	0
CR02	0.5	0.5	0	0
CR03	0.25	0.5	0.25	0
CR04	0.25	0.25	0.5	0
CR05	0.15	0.25	0.3	0.3
CR06	0.1	0.15	0.25	0.5
CR07	0.05	0.05	0.2	0.7

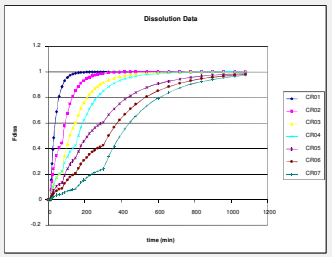
Dissolution / In Vitro Data

In vitro dissolution of the formulations wass modeled according to the following equation:

$$Fdiss(t) = \sum_{i=1}^{4} X_i \left(1 - e^{-\frac{U(t - Tlag_i)}{MDT_i}} \right)$$

$$U(y) = \begin{cases} 0 \text{ for } y <= 0 \\ y \text{ for } y > 0 \end{cases}$$

yielding the dissolution profiles plotted below:



In Vivo Data

Four crossover studies were simulated where CR01 was given in each study as a reference. CR01 was chosen due to its rapid dissolution time.

The data simulation model was complex and contained elements of stomach emptying, intestinal and colon transit, first pass metabolism in the small intestine and multi-compartment pharmacokinetics.

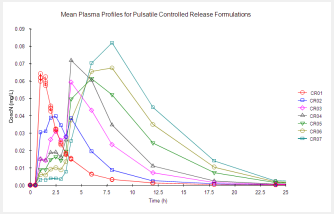
The simulations were done in three stages

1. Simulation of dissolution profiles
2. Generation of subject PK parameters from a multivariate log-normal distribution
3. Simulation of individual plasma profiles using
   - Three kinetic compartments
   - Two absorption compartments with transit times
   - Proportional error on observations

Four studies were simulated, with varying sample sizes. A subset of the formulations were simulated in each study group:

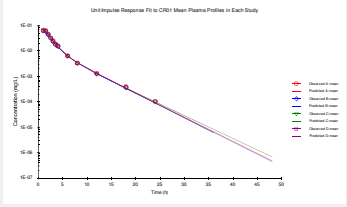
Study	Formulations	Patients
A	CR01 CR02	10
B	CR01 CR03 CR04	10
C	CR01 CR05 CR06	15
D	CR01 CR07	20

The mean responses per formulation were taken and used in this analysis.



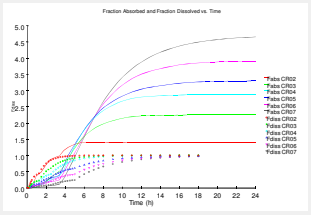
One can see that CR01 is rapidly absorbed. It can be used to generate PK parameters for an IV -bolus unit impulse response function for use in deconvolution.

- Assumes CR01 is absorbed via first order process (single ka)
- Assumes time-lag is not part of the systemic kinetics (is due to absorption processes)



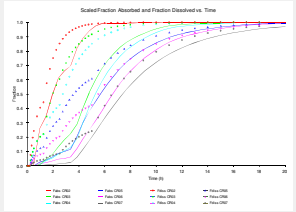
Deconvolution of Fraction Absorbed

The mean plasma profiles were deconvolved using the parameters that would relate to the intra-venous kinetics of the compound. This gives a series of fraction absorbed (Fabs) profiles. These are shown below, overlaid with the dissolution profiles:



The plot indicates that the slower formulations have greater bioavailability than the fast release CR01 reference. Furthermore, the slower the release, the greater the bioavailability becomes.

Scaling the Fabs values to the maximum for each formulation allows one to compare absorption and release rates. Note that each formulation requires a distinct scale factor.

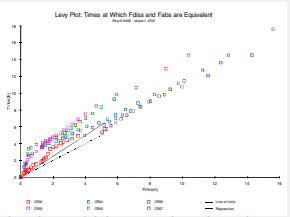


From these two plots it is apparent that a corrrelation must be developed that will allow the Fdiss values to map to Fabs > 1 AND yield different values of MAX(Fabs), depending upon the release rate.

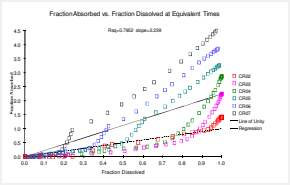
Another relevant observation from the plots above is the appearance of a time lag for absorption - different from the lag for dissolution. This is most evident on the scaled version of the plot.

IVIVC Analysis

Two specialized plots are routinely used to aid in selecting a correlation model for IVIVC. The Levy Plot, shown here, indicates if time-scaling (indicated by slope) of the dissolution data may allow for a correlation.



The other useful diagnostic chart plots Fabs vs. Fdiss at equivalent times.



Together these plots can help identify parameters in a simple linear correlation of the form:

$$Fabs(Time_{new}) = AbsScale * Fdiss(TimeScale * Time_{new} - TimeShift) + FabsShift$$

This is the first model attempted, but the results are very poor because time scaling cannot be used effectively to differentiate Fabs for each formulation.

The Levy plot indicates that there are two time scales. The steep slope at the early time points is indicative of in vitro dissolution occurring faster than in vivo dissolution / absorption. The slope of the points changes at 3 to 4 hours in vivo. This motivates one to attempt a bi-linear model. To increase the generality of the model, one can use different absorption and time scale factors, and lags, before and after the critical time (where the model switches). The new empirical model is:

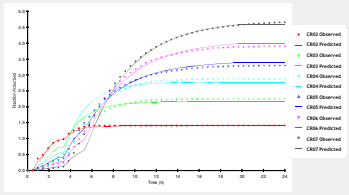
$$Fabs(Time_{new}) = \begin{cases} (AS1 * Fdiss(TS1 * Time_{new} - TL1)) \\ Fabs(Time) + AS2 * (Fdiss(TS2 * Time_{new} - TL2) - Fdiss(T_{cut})) \end{cases} \quad \begin{matrix} Time_{new} < T_{cut} \\ Time_{new} \geq T_{cut} \end{matrix}$$

Where the parameters have been abbreviated:

- TimeShift – TS1 and TS2
- AbsScale – AS1 and AS2
- TimeLag – TL1 and TL2

IVIVC Modeling

The empirical model was fitted and demonstrates the appropriate properties.



The parameter values, however, indicate TS1 and TS2 are both close to 1, are highly correlated with the other parameters, and TL2 is insignificant. In addition, the mean prediction errors are quite large for CR03 and CR04. Removing the extraneous parameters preserves the correlation while improving the prediction errors.

Formulation	Parameter	Predicted	Observed	PE (%)
CR02-mean	AUC	0.230	0.232	-0.6
	C_{max}	0.037	0.040	-7.6
CR03-mean	AUC	0.334	0.349	-4.2
	C_{max}	0.057	0.059	-3.1
CR04-mean	AUC	0.429	0.445	-3.4
	C_{max}	0.074	0.072	2.9
CR05-mean	AUC	0.573	0.559	2.5
	C_{max}	0.057	0.061	-6.7
CR06-mean	AUC	0.677	0.662	2.2
	C_{max}	0.072	0.067	7.5
CR07-mean	AUC	0.799	0.763	4.7
	C_{max}	0.090	0.082	10.2
Avg	AUC	0.466	0.465	3
	C_{max}	0.062	0.060	6.3

Parameter	Estimate	CV%
Tcut	0.145092	0.63
TL1	0.550266	6.82
AS1	0.199592	1.36
AS2	0.336732	0.38

The presence of the lag (TL1) was noted during data exploration, and could be consistent with a stomach emptying effect. The difference in bioavailability seems to be due to time dependent first pass metabolism. If this occurs in the small intestine only,then Tcut may represent the intestinal transit time. In fact the parameters identified are consistent with the 80% first pass and 3.3 hour transit time used to simulate the data.

Conclusions

The development of an *In Vitro - In Vivo* Correlation can be guided by inferences drawn from data exploration. In this case an initial model can be proposed after analyzing two exploratory plots. Refinement of the model is motivated by consideration of physiological mechanisms and leads to a suitable IVIVC.

References

Extensive references are available on request.

All analysis was performed with the IVIVC Toolkit for WinNonlin, available from Pharsight.

Pharsight