M1022

Physiologically Based IVIVC at a Population Level - Deconvoluting *in vivo* Dissolution and Identifying Sources of Variability

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LOGO

PURPOSE

Conventionally, *in vivo/in vitro* correlations (IVIVCs) are developed by numerical and model-based deconvolution procedures. Recently, mechanistic [physiologically based pharmacokinetic (PBPK)] approaches were explored as a method for developing predictive models that can be used to identify both the critical physiological variables and drug product physicochemical attributes influencing drug absorption characteristics. This was achieved by deconvoluting *in vivo* dissolution ($Diss_{vivo}$) rather than *in vivo* absorption (Abs_{vivo})[1]. With the goal of models that can predict product performance within the population and provides ability to develop tolerance limits, this necessitated the use of individual data for identification of between-subject (BS) and within-subject (WS) variability, rather than the use of mean data. Here we provide an example of the use of *in silico* models for developing physiologically-based deconvolution and corresponding population predictions for *in vivo* product performance. Our aim was to develop a mechanistic -based IVIVC that can be used for exploring the impact of formulation and physiological variables and the corresponding population variability that influence the relationship between *in vitro* and *in vivo* product performance.

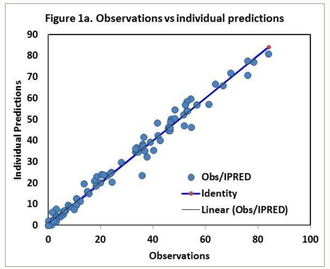
METHODS

Metoprolol tartrate PK profiles were generated using an oral solution (50 mg) and three modified release (100 mg) tablets (Fast, Medium and Slow) in a four way crossover design, n=7 [3F,4M][2]. The in vitro dissolution data was also obtained from the same study. All subjects included in study were extensive metabolizers phenotype of CYP2D6 enzyme. Exploratory analysis of the PK data indicated significant BS and WS variability. Given small duration of clinical study, we considered only BS variability and assumed the WS variability in disposition parameters to be negligible. Disposition parameters were estimated using solution PK data of individual subjects. The model performance was assessed using typical model diagnostics and the parameter values were compared with independent clinical data obtained with IV dosing. Each individual was analyzed separately to obtain *in vivo* dissolution predictions. With sensitivity analysis, we found that the Gastric emptying time (GET) could be potentially critical physiological factor influencing *in vivo* product performance of the studied formulations and is known to have considerable BS and WS variability[3,4]. Accordingly, the individual *in vivo* dissolution predictions were generated using either fixed GET (Simcyp simulator V13.1 default value) or individually variable (estimated) values of GET (WS and BS variability) in each study period. Regression analysis of the individual data (n=210 observations) was generated using the Proc Reg procedure (SAS v9.3), constraining the intercept to 0/0. The 90% confidence and prediction limits were estimated at α=0.05/tail.

RESULTS

The fitted model parameters based upon the oral solution are provided in Table 1. The resulting relationship between the observed vs predicted values and the corresponding individual residual errors (IRES) across all seven study subjects are provided in Figure 1b. As seen in Figure 1a an Figure 1b, the cross-correlation between estimated parameters and objective function trend indicates good and low bias in the model fit.

Characterising disposition using oral solution PK data:



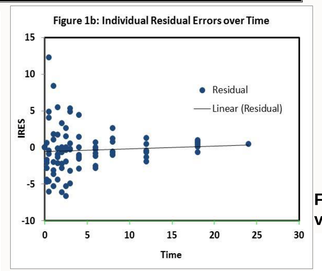


Figure 1. Model diagnostics (oral solution): (a) Observed vs predicted values; (b) Residual error for across all subjects as a function of time.

Sub#	Peff	CLh (L/h)	CLr (L/h)	Vss (L/kg)
Sub1	5.10	45.23	3.35	2.98
Sub2	1.21	48.88	3.81	4.51
Sub3	4.80	58.29	6.39	3.11
Sub5	2.63	55.42	11.94	5.60
Sub6	5.19	56.65	8.64	2.55
Sub7	4.94	63.46	7.48	2.96
Sub9	5.71	53.91	3.56	3.91
Mean	4.23	54.55	6.45	3.66
SD	1.65	6.03	3.19	1.08
%CV	39.05	11.05	49.35	29.61

Table 1: Individual fitted parameter values (solution)

GET	Sub1	Sub2	Sub3	Sub5	Sub6	Sub7	Sub9	Mean	%CV
Fast	0.32	0.30	0.39	0.35	0.28	0.28	0.39	0.33	13.36
Med	0.49	0.25	0.27	0.26	0.28	0.25	0.48	0.33	31.09
Slow	0.37	0.21	0.30	0.43	0.28	0.23	0.36	0.31	23.62
Mean	0.39	0.25	0.32	0.35	0.28	0.25	0.41		
%CV	18.14	14.53	15.93	20.03	0.00	8.11	12.44		

Table 2: WS and BS GET estimates

GET	Fast	Med	Slow
Fixed	62%	81%	13%
Variable	36%	47%	46%

Table 3: BS Variability in in vivo dissolution at 30 minutes

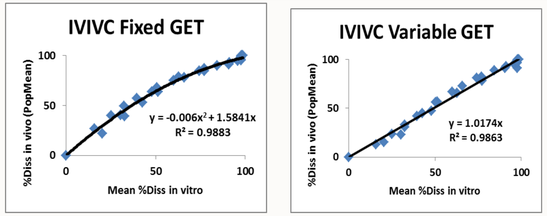


Figure 2: : IVIVC based upon data averaged within a formulation: (a) with variable GET; (b) With fixed GET

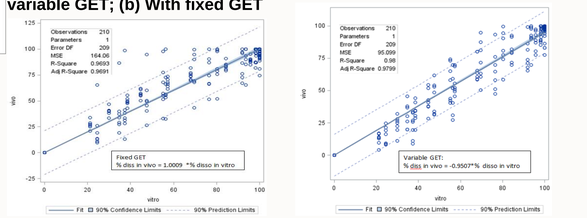


Figure 3: : Individual subject IVIVC with 90% confidence and prediction intervals (α=0.05 per tail): (a) with fixed GET; (b) with variable (fitted) GET.

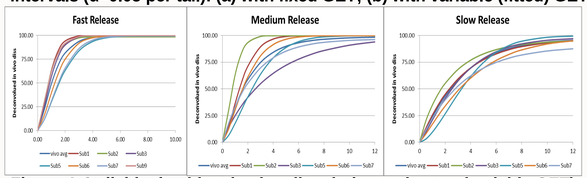


Figure 4: Individual subject in vivo dissolution estimates (variable GET)

Estimation of in vivo dissolution for MR formulations

We compared the *in vivo* correlation with the in vitro dissolution obtained across the four methods[2,5] and observed that the data generated with basket 150 rpm acetate pH 6.8 provided the best correlation with the *in vivo* results. Accordingly, this method was used for all further IVIVC estimation procedures. Using the Population mean (PopMean) of the deconvoluted *in vivo* dissolution (Figure 2) results in a far better fit as compared to the plots using the actual subject data (Figure 3). Furthermore, consistent with the physicochemical characteristics of metoprolol, the linearity of the regression describing the %mean *in vitro* dissolution versus mean *in vivo* dissolution was markedly improved when the GET was included as a fitted (Figure 2b and 3b) rather than fixed (Figure 2a and 3a) model parameter. Thus correlation with previously established bio-relevant *in vitro* dissolution data[2] of three ER products which indicated that accounting for BS and WS variability in GET leads to less biased estimation of *in vivo* dissolution leading to better IVIVCs.

In vivo dissolution estimates exhibited greater BS variability for the medium release as compared to that of the fast and slow release formulations (e.g., 62%, 81% and 13% for the fast, medium and slow percent released *in vivo* at 30 minutes after drug administration). Factoring WS and BS variability in gastric emptying time (GET) reduced the %CV for the fast and medium tablets but increased that of the slow release tablets (corresponding %CV = 36%, 47% and 46% CV). In addition, modeling of the individual subjects allowed for an identification of subjects (Subj 5) whose luminal environment appeared to differ from that of other subjects.

DISCUSSION

Mechanistic models provide an opportunity to refine IVIVC by reducing sources of BS and WS variability that is typically confounded into the deconvoluted profiles from conventional methods. Furthermore, based upon *in vivo* dissolution rather than absorption, there is an opportunity to segregate dissolution from permeability and other presystemic factors. Although one may argue that by incorporating an oral solution into the dataset, numerical deconvolution methods account for these other factors, we found that identification of physiological variables such as GET rely upon models where each in vivo component can be segregated and examined. Such a separation is not possible when generating an IVIVC using numerical deconvolution procedures (which is generally based upon *in vivo* absorption and therefore incorporates the influence of pre-absorption GI processes). Mechanistic model also position the investigator to explore shifts in *in vivo* product performance due to individual patient attributes. For metoprolol, we observed that GET is a rate-limiting factor in drug absorption, and the ability to remove bias introduced by GET improved the overall regression. The use of fitted GET values transformed the mean *in vivo vs in vitro* dissolution from a curvilinear to a linear relationship. However, the prediction limits (i.e., a 50% chance of future values falling within this interval in more than 90% of the samples) showed only a small narrowing using fitted GET values. This outcome likely reflects a formulation-dependent impact of GET (i.e., its role as a rate-limiting parameter), resulting in a decrease in WS and BS for the fast and medium release formulations but an increase for that of the slow formulation.

CONCLUSIONS

Individual subject deconvolution using a PBPK approach provides an opportunity to identify and quantify sources of variability that helps establish critical attributes in assessment of product bioperformance. Therefore, similar to numerical deconvolution, in vivo prediction of formulation behavior relies upon an in vitro method that captures the rate limiting factors controlling drug release. However, unlike numerical deconvolution approaches, it can be used for exploring the in vivo rate limiting factors influencing drug bioavailability and therefore can be used to explore product performance across a range of potential patient populations.

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