Modeling double peak phenomenon and in vitro-in vivo correlation (IVIVC) in pharmacokinetics (PK) for Clinical trial simulation (CTS) of virtual bioequivalence (BE) studies

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Abstract

Models have been proposed to resolve the double-peak phenomenon [1,2,3,4] in population PK modeling. IVIVC was a separate topic [6] and not used in pop-PK analysis. This work is to build the IVIVC model using nifedipine in vitro dissolution profile [7] for the double-peak phenomenon in south Asian population-PK modeling. It is a tricky exercise to model the variability of complex absorptions and link to IVIVC models. Three absorption models are used to capture the double-peak phenomenon and compare the advantages between them. After the absorption models were built using the same two compartmental PK models under the same initial conditions, CTS was used for BE studies to inform the clinical trial design and decision-making.

Background

Modeling and simulation (M&S) is an emerging approach for abbreviated new drug applications (ANDA). However, no tools are available to conduct the BE strategy decision-making by M&S approaches. One of the reasons is due to few researches and little M&S expertise in generic drug development. Complex absorption is also hard to model for the correct inter-subject and intra-subject variability with distinction between reference (R) and test formulation (T), which are essential for BE crossover studies. Double-peak phenomenon is one of complications in the absorption phase after administrated with oral doses. The aim of this work is to resolve the double-peak phenomenon together with IVIVC models and hence produce correct inter-subject and intra-subject variability for BE decisions.

Methods

Multiple peaks in PK has seen considerable interest recently [1,2,4]. Three absorption modeling approaches were used here to capture the complex absorption, including 1) **double-Weibull distribution (DWD)**, 2) **two-parallel pathways (TPP)** and 3) **enterohepatic recirculation (ER)**. A two compartmental PK model was used for the nifedipine double-peak concentration data (see Figure 1), with a direct IVIVC model [5] using the in vitro dissolution data [7].

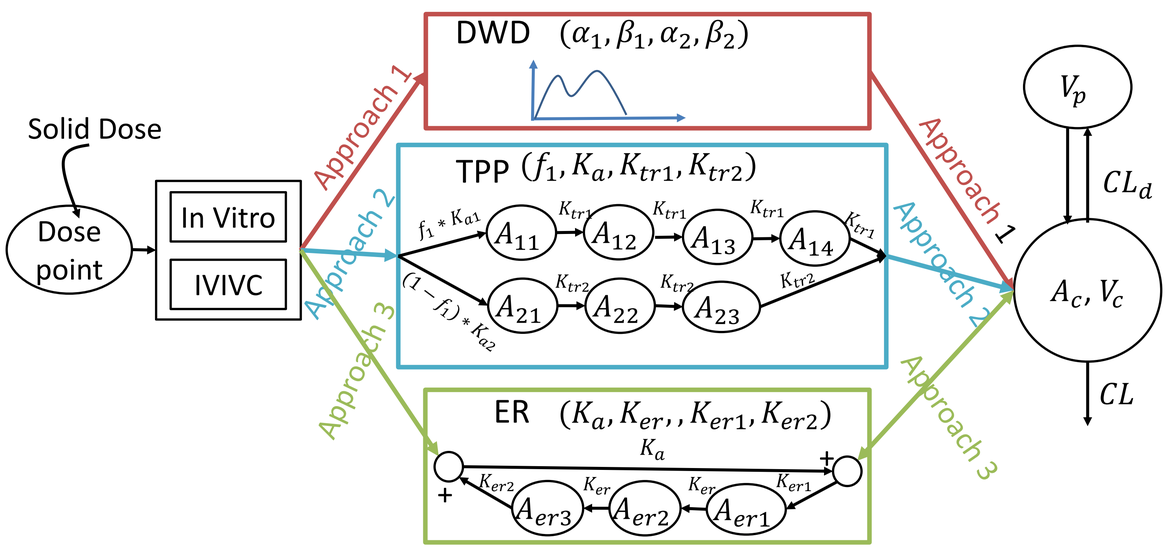

Figure 1 Three absorption approaches with 2-compartmental PK models

Where the In Vitro model is Hill equation defined in Eq1 and IVIVC defined in Eq2

$$f_{dis}(t) = \frac{F_{max} * (t)^H}{(f_{50})^H + (t)^H} \quad \textbf{Eq 1}$$

$$r_{dis}(t) = \frac{df_{dis}}{dt}$$

$$r(t) = \varphi_{abs}(t) S_r r_{dis}(t_0 + S_1 t) \qquad \begin{cases} \varphi_{abs}(t) = 1; if\ t \le t_{cut} \\ \varphi_{abs}(t) = 0\ ; t > t_{cut} \end{cases} \quad \textbf{Eq 2}$$

CTS and BE statistical analysis was used to compare these methods using different BE study protocols such as parallel, crossover and replicated design. Single dose and multiple doses was considered during the CTS. Dose superimposition in multiple doses was handled and demonstrated [3,4].

Results

For consistency, the same number of parameters (in Figure 1) are used for the model building and the results are shown in Table 1.

Methods	LogLik	-2LL	AIC	BIC
DWD	-1271	2542	2584	2672
TPP	-1295	2591	2633	2720
ER	-1429	2857	2899	2987

Table 1 Three absorption approaches for model building comparison

Results (Con't)

The VPCs of the comparison are demonstrated in Figure 2.

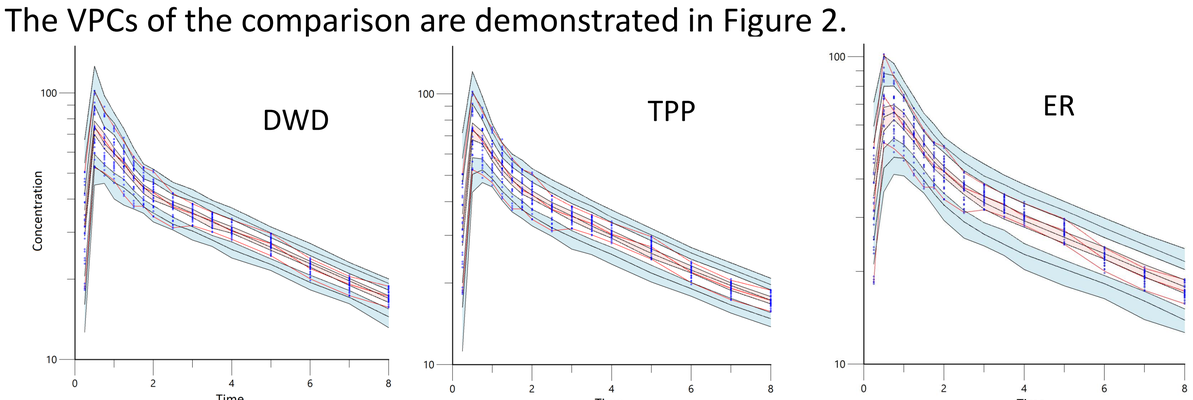

Figure 2. VPC for the models building

By looking into more details on the individual fit, the same subject concentration profiles are shown in Figure 3 across the three approaches.

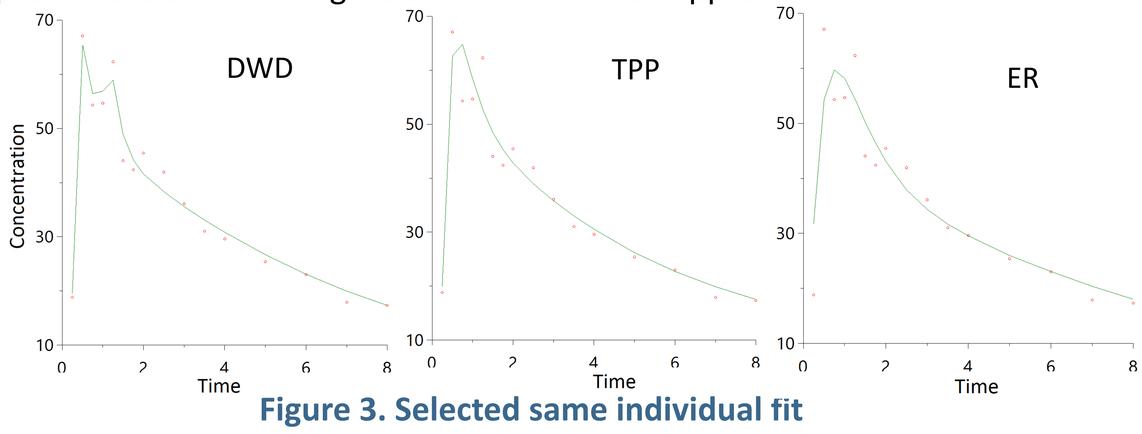

Figure 3. Selected same individual fit

The second bump is too small to pick up by TPP and ER methods with rich samples. Both DV vs IPRED and DV vs PRED shows better results using DWD method.

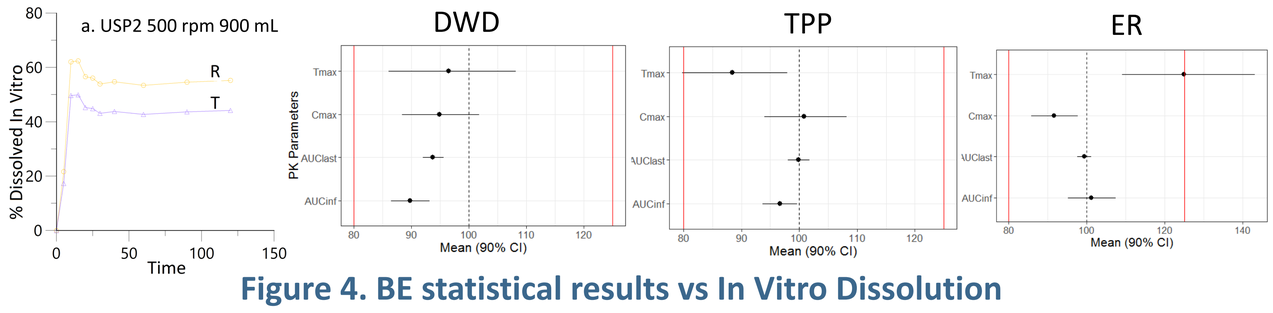

Figure 4. BE statistical results vs In Vitro Dissolution

The same in vitro R and T dissolution profile (Figure 4 a.) is used for CTS. Three different models gives different BE suggestion (Figure 4, both DWD and TPP are OK but not for ER model. DWD produces best results and flexible during modeling.

Conclusions

DWD method got better fit with the double-peak rich concentration data in single dose scenarios. TPP method obtained good results after manually tuning the number of transit compartments in each of the pathways. ER method with a continue feedback is less robust. DWD method is more difficult for dose superimposition at multiple doses if any carryover effect occured, while two-parallel pathway method handled it naturally from ODEs at each transit-compartment. CTS and BE statistical analysis further affirms the above findings and produces informative BE decisions for these complex absorption phenomena.

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