Clinical trial simulation for a new rapidly absorbed paracetamol formulation development from the conventional Paracetamol tablet

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Abstract

A new rapidly absorbed paracetamol tablet (NP) containing sodium bicarbonate was developed [1, 2, 3]. Researches [1, 3] did the comparison of the clinical trial results between the new and conventional paracetamol (CP) formulation. In vitro-in vivo correlation (IVIVC) analysis [2] was also used for explanation of the observed in vivo variability of NP and CP. However, how to integrate these low-cost in vitro dissolution data to inform the clinical trial is still a mystery [4]. The aim of this work is to take the in vitro dissolution data and use the existing in vivo data from CP to build a population IVIVC-PK model. The best in vitro test method (from USP monograph at pH5.8 at stirrer speeds between 10 and 50 rpm) was identified. The identified test method was used for in vitro model building and clinical trial simulation. The bioequivalence (BE) statistical analysis is used to guide the clinical trial design and validate the predicted in vivo results from observation data

Background

Clinical trial costs increase rapidly. However, modeling and simulation (M&S) hasn't been adopted well to the BE decision making before the costly clinical trial. M&S may reduce the number of clinical trials and get useful insight by using low-cost experimental data such as in vitro experiments. The aim of this work is to build the population PK models together with the in vitro dissolution data and hence the validated population PK models which can then be used for the clinical trial simulation and BE statistical analysis.

Methods

Twenty eight Caucasian volunteers were recruited for a four way crossover study for both CP and NP at fed and fasted treatment groups [1]. In vitro dissolution profile from both CP and NP was obtained with the USP paddle apparatus with 900 mL of 0.05 M HCL at paddle speeds in the range of 10-50 rpm [2] (see Figure 1).

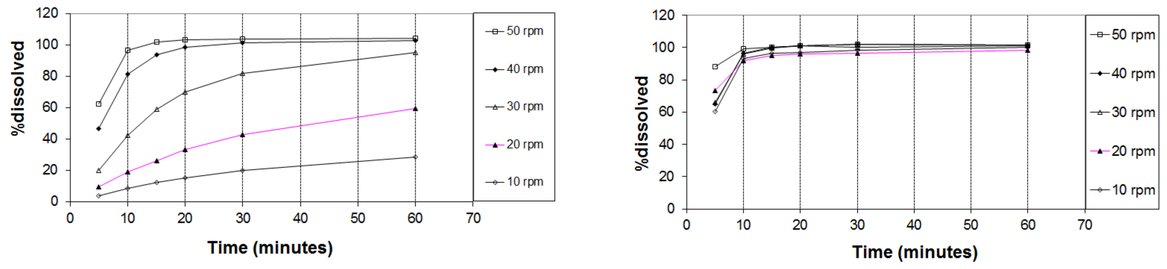


Figure 1. In Vitro Dissolution Profile for CP (left) and NP (right)

The in vitro dissolution profiles was fitted by using the best selected models such as Hill equation (Eq1), accumulative Weibull distribution. The fitted in vitro dissolution models were differential as the input rate convolved to the IVIVC-PK two compartmental models [5] (Eq2).

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

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

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

$$\frac{\boldsymbol{dA_{solid}}}{dt} = -r(t) * A_{solid} \quad \textbf{Eq 2}$$

$$\frac{\boldsymbol{dA_{solution}}}{dt} = r(t) * A_{solid} - K_a * A_{solution}$$

$$\frac{\boldsymbol{dA_c}}{dt} = K_a * A_{solution} - \frac{CL}{V_c} * A_c - CL_{12} * (\frac{A_c}{V_C} - \frac{A_p}{V_p})$$

$$\frac{\boldsymbol{dA_p}}{dt} = CL_{12} * (\frac{A_c}{V_C} - \frac{A_p}{V_p})$$

Nonlinear mixed effect modeling (NLME) was used to build and validate the population IVIVC-PK models with inter-subject and intra-subject variability. The best in vitro dissolution test experiment were identified using in vitro and in vivo data from CP. In vitro model build from NP with this identified test method was incorporated into the validated IVIVC-PK model for the clinical trial simulation (CTS). Simulated PK parameters using NCA analysis such as Cmax and AUCs were used to determine the bioequivalence between CP & NP and between observed & predicted data using ANOVA analysis.

Results

The higher paddle speed in the in vitro test methods tended to build and validate a better IVIVC-PK model (see Table 1). In vitro model is in Eq1 and In Vivo IVIVC model is in Eq2.

Rotation Speed	LogLik	-2(LL)	AIC	BIC
10 rpm	-955.0785	1910.157	1938.157	1997.5209
20 rpm	-830.35797	1660.7159	1704.7159	1798.002
30 rpm	-790.94661	1581.8932	1625.8932	1719.1793
40 rpm	-773.47033	1546.9407	1590.9407	1684.2267
50 rpm	-768.46898	1536.938	1580.938	1674.224

Table 1. Ranking of In Vitro Dissolution model

Results (Con't)

Thus the rotation 50 rpm is used to build the PK model (Figure 2) for the simulation for the trial simulation between NP and CP. The same validated PK IVIVC model was used for the simulation using different CP and NP in vitro dissolution .

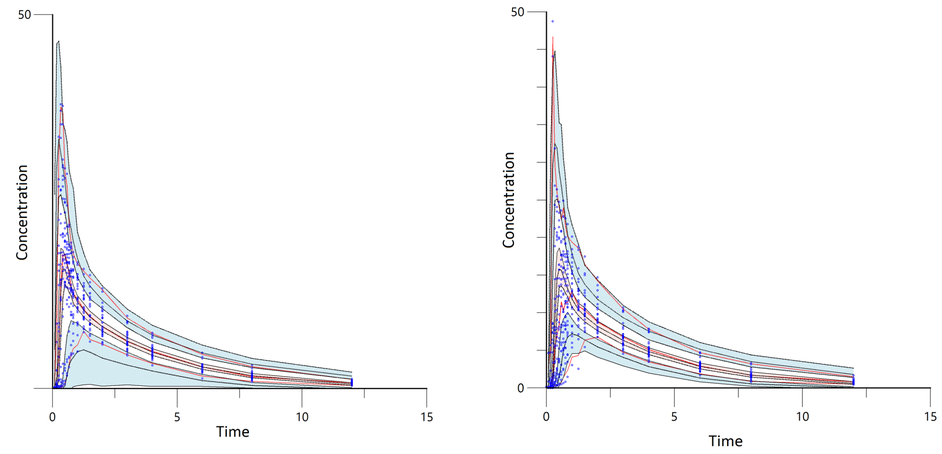
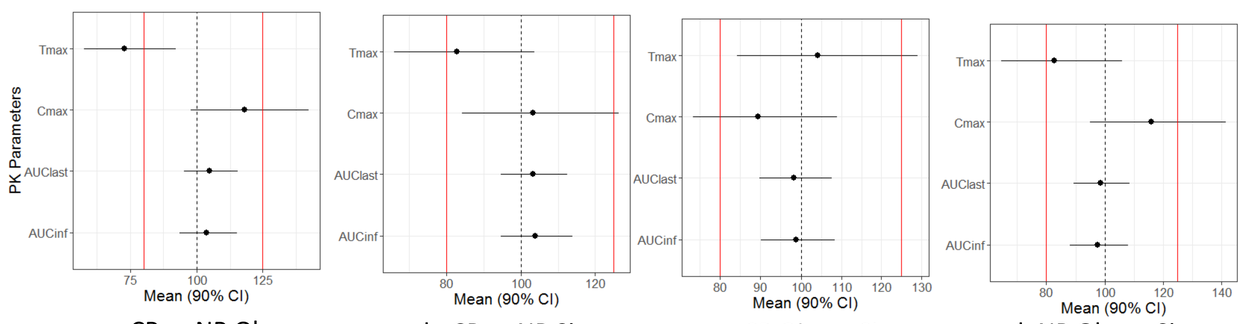


Figure 2. VPCs for CP (left) on 50 rpm and NP(right)

By using the CTS simulation data incorporating inter-subject and intra subject variability, the BE statistical test gives combination of design scenarios as in Figure 3.



a. CP vs NP Obs b. CP vs NP Sim c. CP Obs vs Sim d. NP Obs vs Sim

Figure 3. BE statistical test for validation

	Tmax(Obs)	Tmax(Sim)	Cmax(Obs)	Cmax(Sim)	AUClast(Obs)	AUClast(Sim)	AUCinf(Obs)	AUCinf(Sim)
Sample Size	122	110	82	90	24	18	24	22
Achieved Power	80.62%	80.29%	80.26%	80.43%	81.45%	81.37%	81.15%	80%

Table 2. Power and sample size comparison (TOST method)

Conclusions

The NP simulation data was produced from the validated population PK model from CP using NP's in vitro dissolution profile. Without even conducting the clinical BE trial, the simulation gives informative results (Figure 3 b.) which predicts well with the real clinical trial (Figure 3 a.). Figure 3c & 3d gives additional validation between the observation and simulation for CP and NP respectively.

The low-cost in vitro dissolution data was successfully used to build the population IVIVC-PK models. The CTS and statistic BE analysis help to predict the NP before conducting any clinical trial and propose sample size and power (Table 2). The method helps to identify the correct in vitro dissolution test and create optimal CTS and hence increases the successful rate of any new formulation and may reduce the number of clinical studies performed during the initial approval process or certain scale-up and post approval changes [1].

References

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