# Selecting in Vitro Dissolution Tests Using Population Pharmacokinetic Modelling to Help Bioequivalence Studies

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## Objective

Before conducting bioequivalence (BE) studies or any related pilot studies for in vivo clinical trials, selecting an appropriate in vitro dissolution test is a key analytical test for detecting physical changes in an active pharmaceutical ingredient (API) for any solid oral dosage forms. The main objective of this work is to build population pharmacokinetic (Pop-PK) models with direct in vitro-in vivo correlation (IVIVC) for selecting effective test technology matching the in vivo human absorption of API from the innovator and provide in vitro test bounds (BE 'safe space') and hence to indicate the performance of the test formulation (T) – either success or likely failure mechanisms related to the in vivo human studies.

## Methods

Nifedipine was taken as an example to demonstrate the benefit of Pop-PK model with direct IVIVC. A total of 34 in vitro dissolution experiments were performed using USP1, USP2, USP3, and USP4 methodologies with various combinations of pH, volumes (mL), media type (FaSSGF with or without grapefruit juice), rotation speed (rmp), dipping rate(dpm), flow rate (mL/min), and ethanol content (%v/v) [2] (see Figure 1).

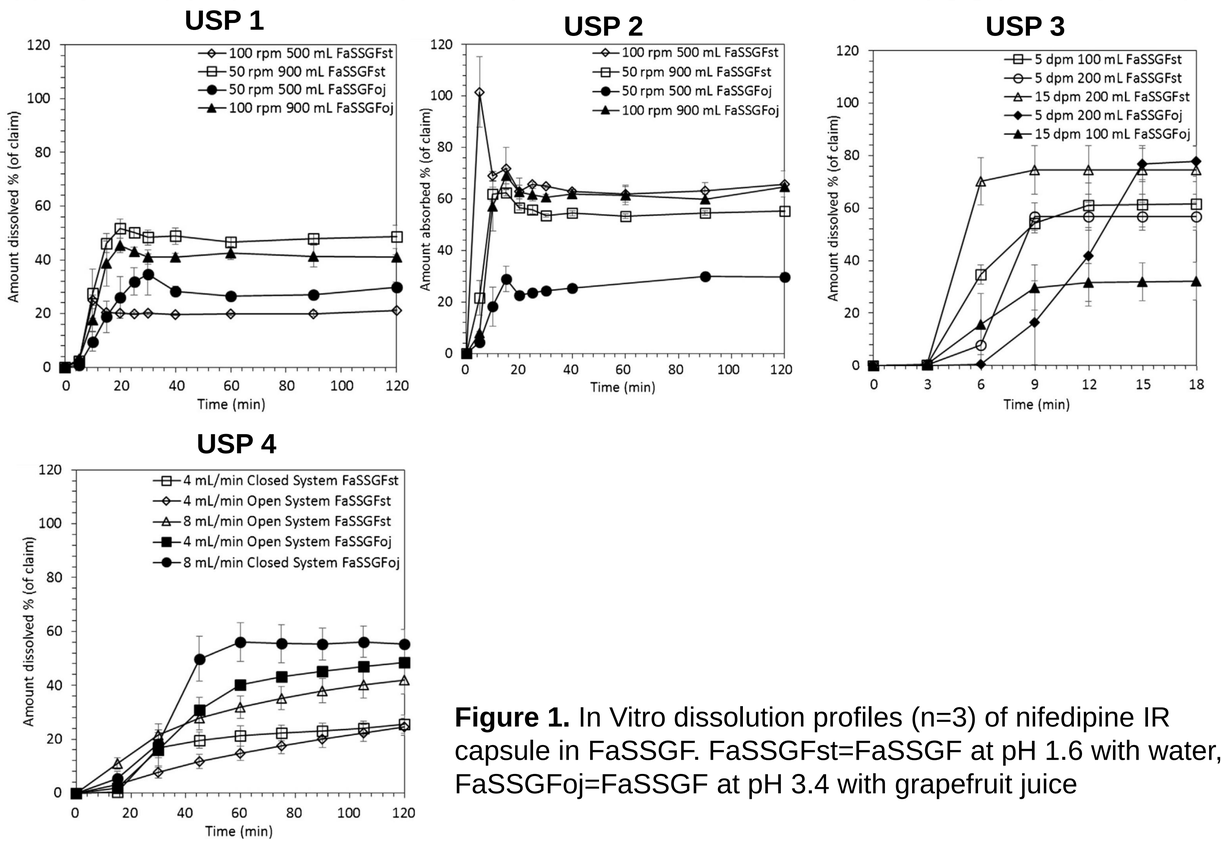


**Figure 1.** In Vitro dissolution profiles (n=3) of nifedipine IR capsule in FaSSGF. FaSSGFst=FaSSGF at pH 1.6 with water, FaSSGFoj=FaSSGF at pH 3.4 with grapefruit juice

The in vitro dissolution profiles were then fitted by using the best selected sigmoidal models such as Hill equation and cumulative Weibull distribution. The Hill equation (Eq 1) together with a $t_{lag}$ parameter showed better fitted with the in vitro dissolution profile.

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

The fitted in vitro dissolution models were then differentiated to provide the input rate added to the IVIVC models (Eq 2) which were directly incorporated in PK models [3].

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

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

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

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

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

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

Nonlinear mixed effect modeling (NLME) was used to estimate PK models with direct IVIVC by fitting 30 subjects blood samples created from [4, 5, 6] for both Caucasian population and south Asian population. The south Asian population shows a lot more fluctuation at the absorption phase than Caucasian population (Figure 2). In the model building and validation step, the Caucasian model built with a constant rate $K_a(t) = K_a$. However the south Asian model had to use double Weibull to capture the double peak phenomenon $K_a(t) = \beta_1 * K_{d1} * (K_{d1} * t)^{(\beta_1 - 1)} e^{-(K_{d1} * t)^{\beta_1}} + \beta_2 * K_{d2} * (K_{d2} * t)^{(\beta_2 - 1)} e^{-(K_{d2} * t)^{\beta_2}}$.

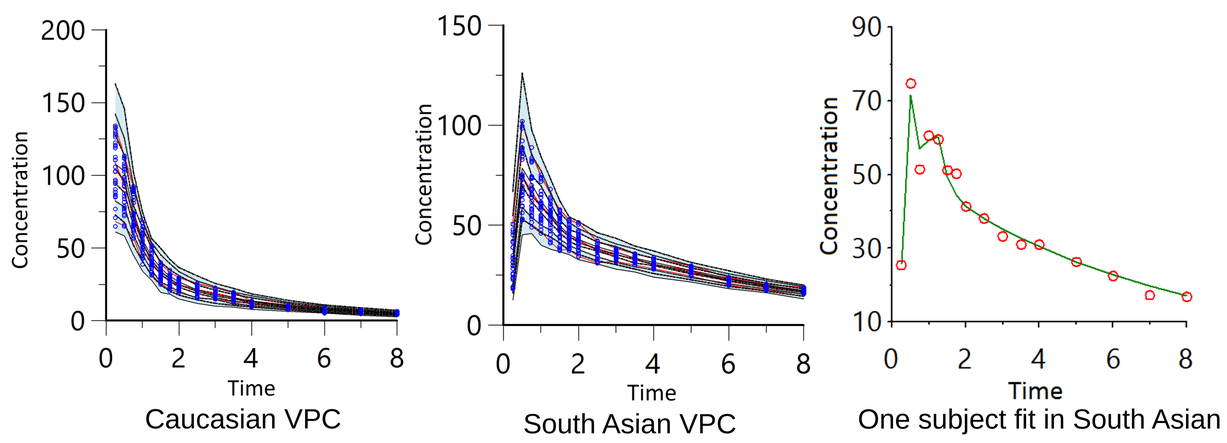


**Figure 2.** Caucasian and South Asian population model selection and validation

The best fitted models with related in vitro dissolution experiments were selected for test formulation dissolution experiments (Table 1). Both test and reference formulation (T&R) in vitro dissolution were used for simulation using parallel design and 2 by 2 crossover design. Simulated PK parameters such as Cmax and AUC calculated by NCA analysis were used to determine the bioequivalence between T&R using fixed effects and analysis of variance (ANOVA) analysis.

## Results

Both Caucasian and south Asian data shows consistent results for the in vitro dissolution test methods that USP2 is the preferred method and in vitro dissolution tests without grapefruit juice match better with the in vivo concentration (Table 1).

| | In Vitro Test | |
|---|---|---|
| Ranking | Caucasian | South Asian |
| 1 | USP2rpm100mL500Fst | USP2rpm500mL900Fst |
| 2 | USP2rpm100mL900Foj | USP3rpm15mL200Fst |
| 3 | USP2rpm500mL900Fst | USP2rpm100mL500Fst |
| 4 | USP3rpm5mL100Fst | USP3rpm5mL200Fst |
| 5 | USP1rpm50mL500Foj | USP1rpm100mL500Fst |
| 6 | USP3rpm15mL100Foj | USP3rpm5mL100Fst |
| 7 | USP1rpm100mL500Fst | USP2rpm100mL900Foj |
| 8 | USP1rpm50mL900Fst | USP3rpm15mL100Foj |
| 9 | USP1rpm100mL900Foj | USP3rpm5mL200Foj |
| 10 | USP3rpm5mL200Foj | USP1rpm50mL900Fst |
| 11 | USP3rpm15mL200Fst | USP1rpm100mL900Foj |
| 12 | USP3rpm5mL200Fst | USP1rpm50mL500Foj |
| 13 | USP4mlmin8CSFoj | USP4mlmin8CSFoj |
| 14 | USP4mlmin4OSFoj | USP4mlmin8OSFst |
| 15 | USP4mlmin8OSFst | USP4mlmin4OSFst |
| 16 | USP4mlmin4OSFst | USP4mlmin4OSFoj |
| 17 | USP2rpm50mL500Foj | USP2rpm50mL500Foj |
| 18 | USP4mlmin4CSFst | USP4mlmin4CSFst |

**Table 1.** The ranking of in vitro test method – highlighted one was selected

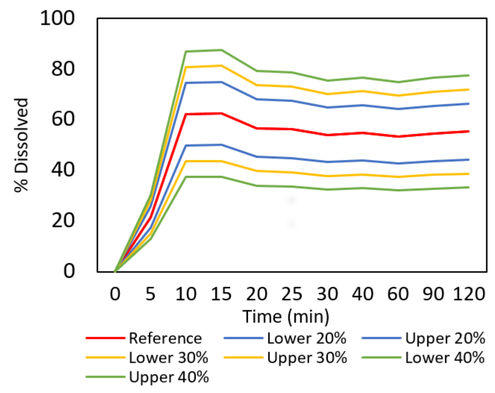


**Figure 3.** In vitro safe space ± 20%, ± 30% and ± 40%

A low bound and upper bound dissolution (safe space ± 20%, ± 30%, ± 40%) profiles for T are created to test the BE with R (Figure 3). The BE test results showed that the T is bioequivalence with the R if the variation of in vitro dissolution of the T is within the range of ± 30% of variation for both Caucasian population and south Asian population (Figure 4). The results indicated that the T is more likely to be successful if the in vitro dissolution is within the safe space and only if the in vitro dissolution experiments were done using the selected test technology (USP 2, 500rmp, 900mL, pH 1.6, with water).

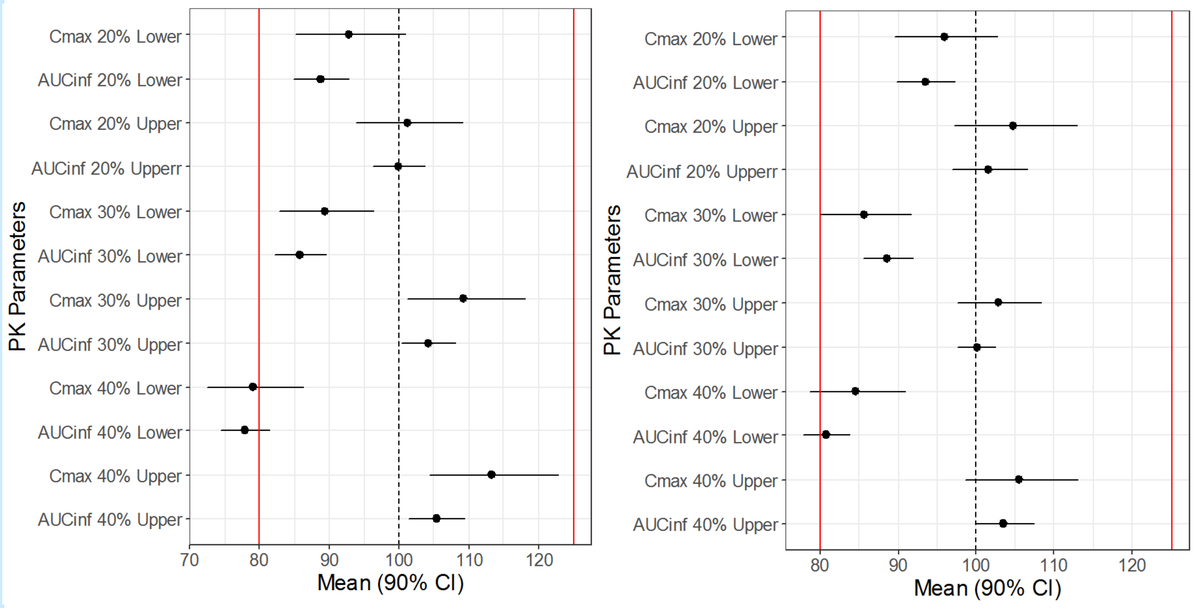


**Figure 4.** BE statistical test (80%~125% criteria for Cmax and AUCinf) results – left (Caucasian), right (South Asian)

## Conclusions

The direct IVIVC method using pop-PK analysis is a novel approach for bioequivalence studies. The method helps to identify in vitro dissolution tests and test bounds, to propose design space of dissolution profiles and hence to increase the successful rate of the test formulation and may reduce the number of BE studies performed during the initial approval process or certain scale-up and post approval changes [1].

## References

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