

Development of a level A *in vitro*/*in vivo* correlation (IVIVC) using applications of the MonolixSuite

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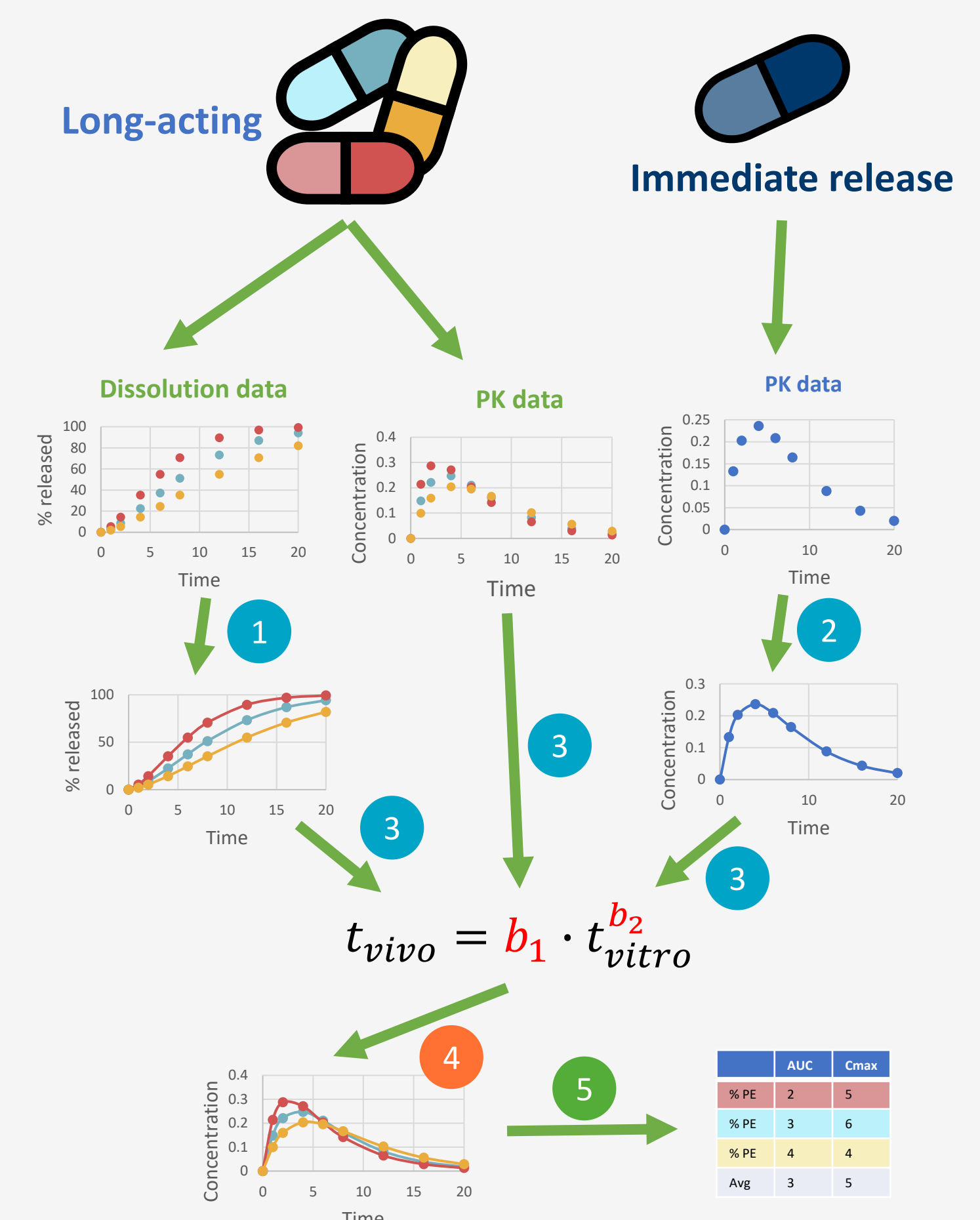
INTRODUCTION

Post-approval changes in manufacturing processes or approval of new strengths of a drug product requires expensive and often long bioequivalence trials. However, in some cases it is possible to predict the results of these studies using an established *in vitro* - *in vivo* correlation and waive a bioequivalence trial.

In vitro - *in vivo* correlation (IVIVC) corresponds to a mathematical correlation between *in vitro*, most often dissolution testing, and *in vivo*, pharmacokinetic profile, data. Dissolution testing experiments are done in a laboratory and measure the rate and extent of active pharmaceutical ingredient solution formation from a drug product.

The strongest possible correlation between *in vivo* and *in vitro* data is called level A correlation and it is a point-to-point relationship between dissolution and pharmacokinetic profiles, which means that an equation exists that can be used to predict an entire pharmacokinetic profile of a drug by using the drug product's dissolution profile.

Here we show how to develop a one-stage level A IVIVC model using the MonolixSuite software. The analysis uses methylphenidate hydrochloride (MPH) data from the study which enrolled 17 participants in a four-treatment, four-period, single-dose, randomized crossover design study, but only 16 subjects were retained for the final PK analysis. The subjects received four treatments, three Ritalin long-acting capsule formulations (40 mg) and Ritalin immediate release (IR) tablets (two 20 mg given 4 hours apart) as the reference. The three Ritalin LA formulations were selected to provide slow-release, medium-release, and fast-release *in vitro* dissolution rates, respectively.



1. MODELING DISSOLUTION DATA

Dissolution data can be represented with a double Weibull function, written here:

$$r_{vitro}(t) = 100 - \left(ff \cdot e^{-\left(\frac{t}{\tau D}\right)^{SS}} + (100 - ff) \cdot e^{-\left(\frac{t}{\tau D1}\right)^{SS1}} \right)$$

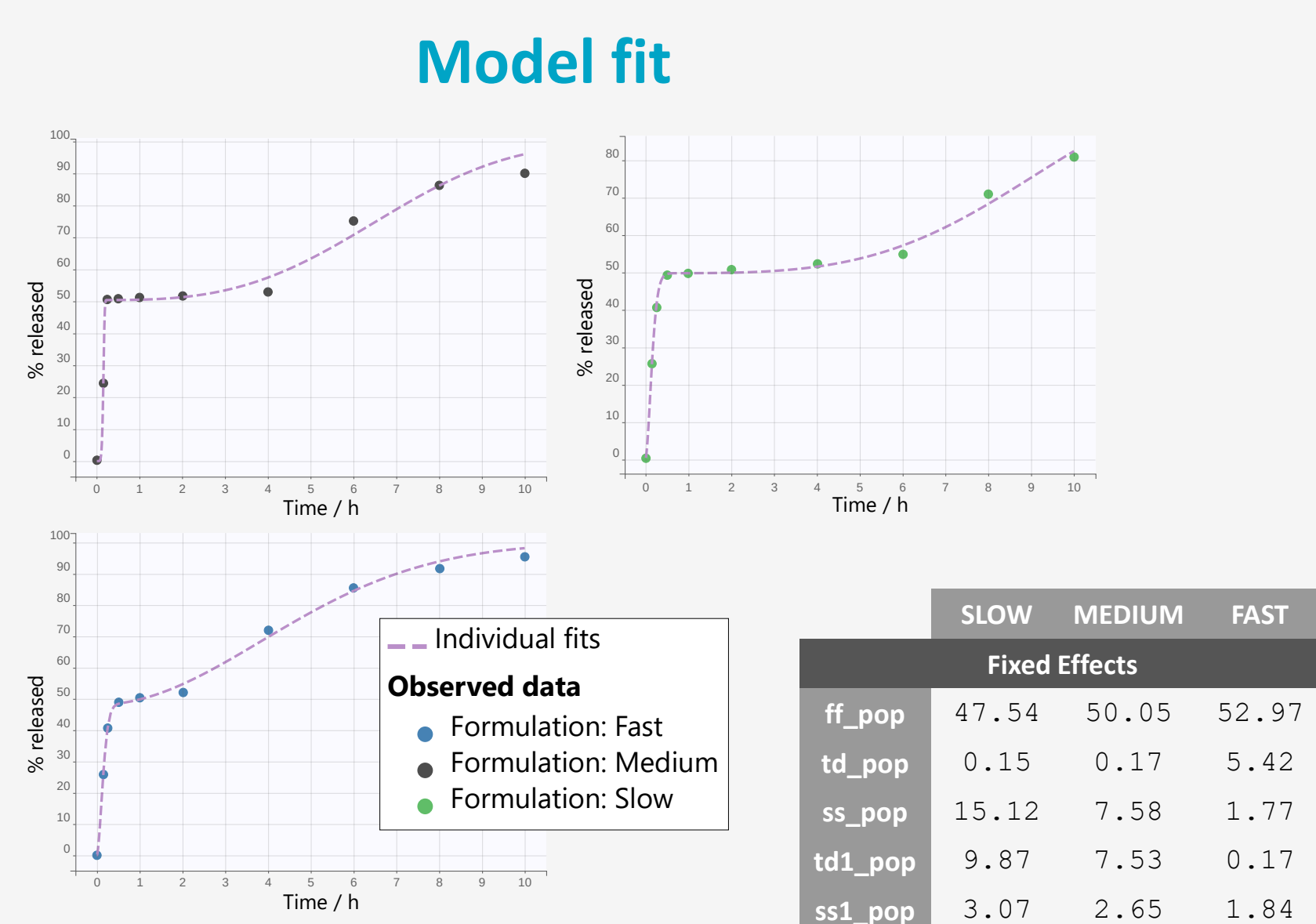
To model dissolution profiles in Monolix, custom models can be written in mlxtran language. Estimated parameters for each formulation are then used in the correlation model as regressors.

Used model file

```
[LONGITUDINAL]
input={ff, td, ss, td1, ss1}

EQUATION:
r = 100 - (ff * exp(-(t/td)^ss) + (100 - ff) * exp(-(t/td1)^ss1))

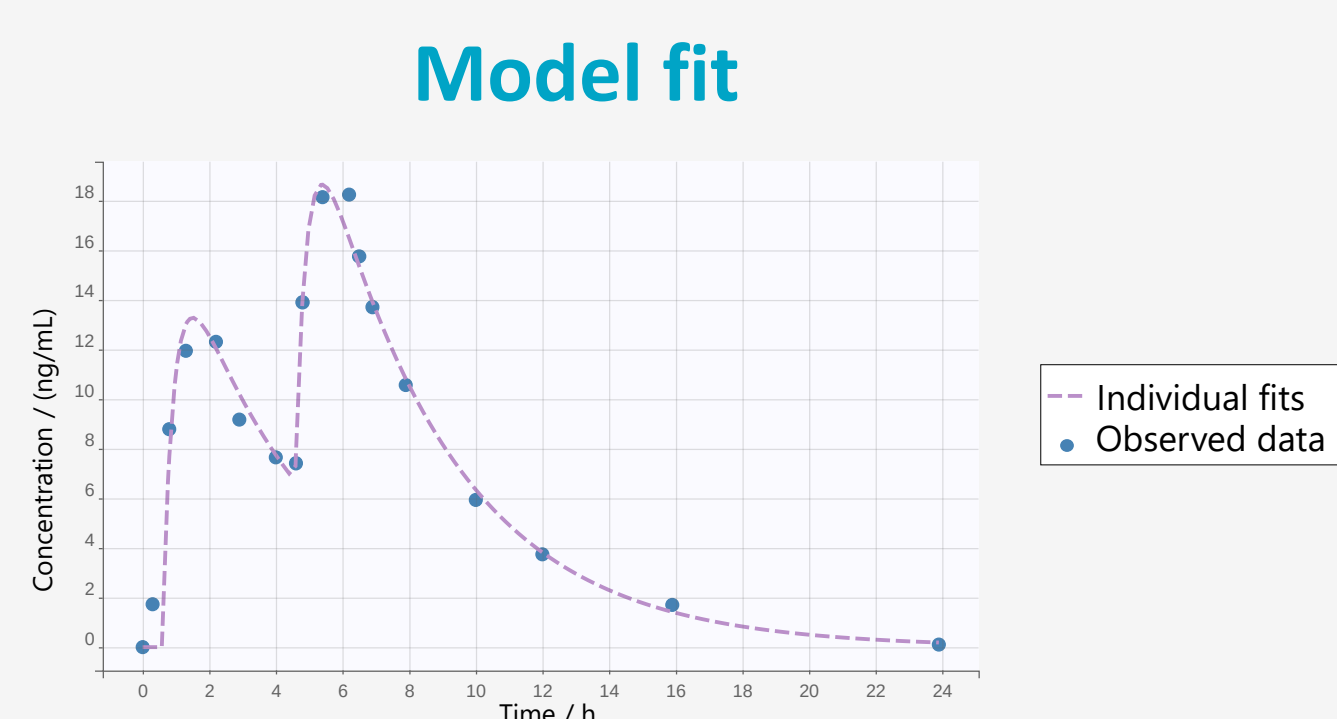
OUTPUT:
output = {r}
```



2. MODELING IMMEDIATE RELEASE DATA

In order to model pharmacokinetic data of the immediate release formulation, the following library model was used: extravascular absorption model with one compartment, first order absorption, absorption lag time, linear elimination and constant residual error. Estimated parameters are used in the correlation model as regressors.

	VALUE	R.S.E.(%)
Fixed Effects		
Tlag_pop	0.575	3.31
ka_pop	2.849	15.7
V_pop	1.189	5.08
k_pop	0.254	7.63
Error Model Parameters		
a	0.764	16.7



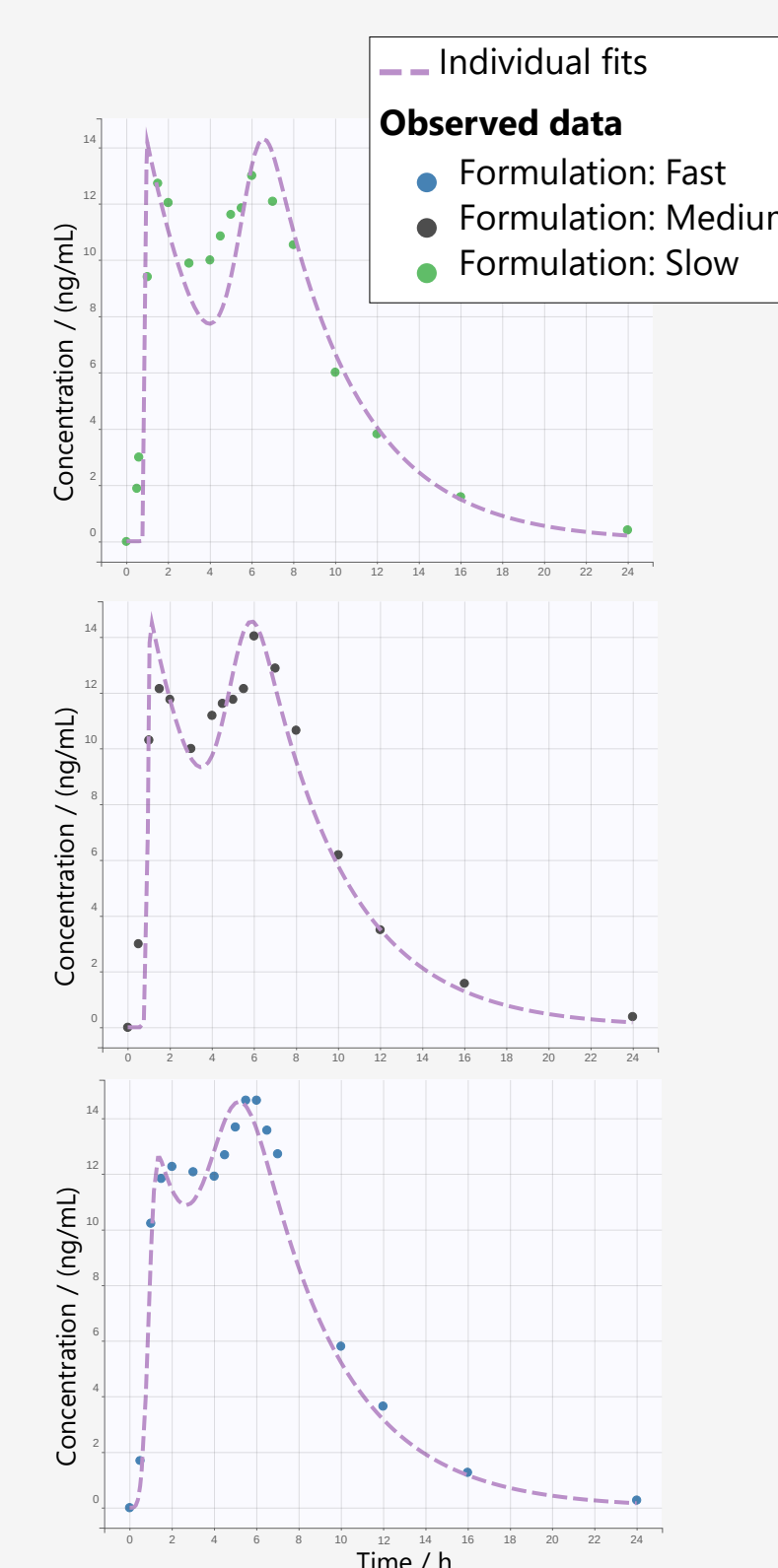
3. CORRELATION MODEL

There is a difference in release rates of Ritalin LA form. *in vitro* and *in vivo*, so, in order to establish an IVIVC model, the dissolution and *in vivo* input curves should be made superimposable by usage of a scaling function:

$$r_{vivo}(t) = r_{vitro}(b_1 \cdot t^{b_2})$$

Derivative of the double Weibull function was obtained and the complete model containing time scaling, dissolution and PK parameters was written in mlxtran language and used to estimate parameters b_1 and b_2 .

Model fit



Used model file

```
[LONGITUDINAL]
input={F, b1, b2, td, td1, ss, ss1, ff, ke, V_d}
td = {use=regressor}
td1 = {use=regressor}
ss = {use=regressor}
ss1 = {use=regressor}
ff = {use=regressor}
ke = {use=regressor}
V_d = {use=regressor}

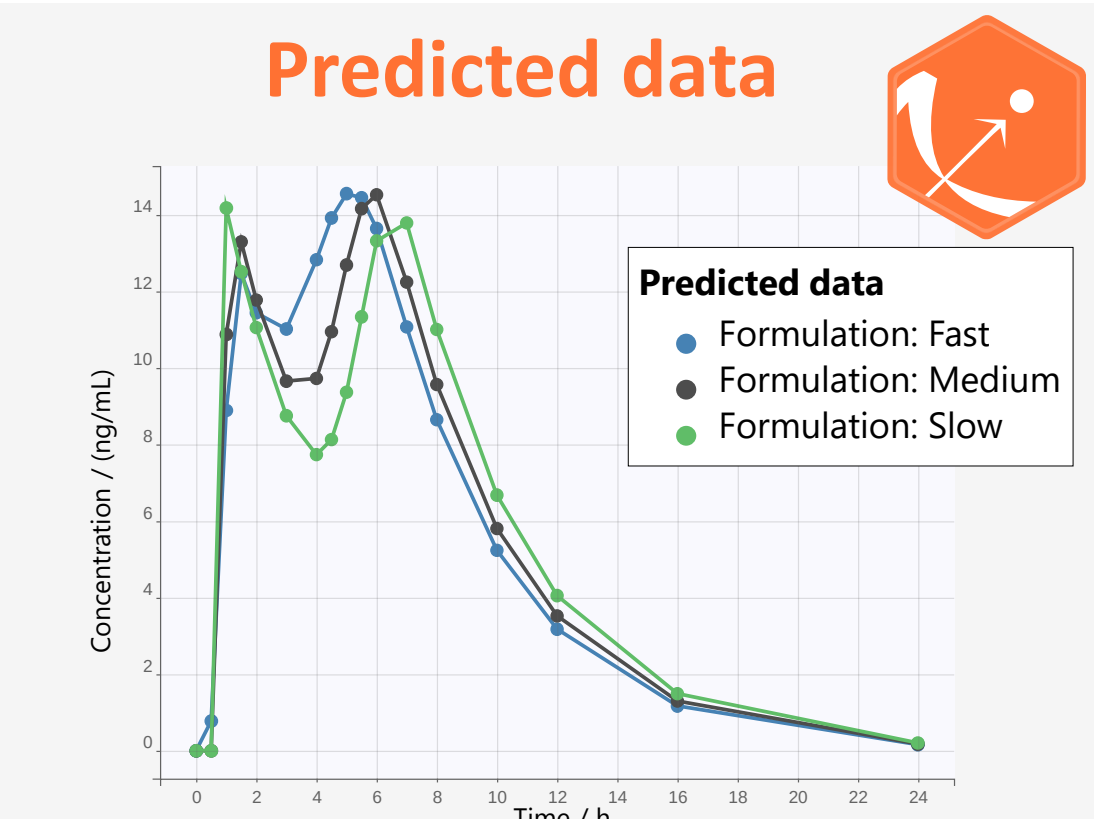
EQUATION:
t_0 = 0
A_0 = 0
t_vitro = b1 * t^b2
t_vitro_d = b1 * b2 * t^(b2-1)
f = t_vitro_d * (ff * exp(-(t_vitro/td)^ss) * (ss / td * (t_vitro/td)^(ss-1)) + (100 - ff) * exp(-(t_vitro/td1)^ss1) * (ss1 / td1 * (t_vitro/td1)^(ss1-1))) / 100

ddt_A = amtDose * f - ke * A
Cc = A / (V_d / F)

OUTPUT:
output = {Cc}
```

4. PREDICTED DATA

Monolix project containing correlation model was imported to Simulx to obtain predictions at the same timepoints that were present in the observed data.



5. NCA AND PREDICTION ERROR CALCULATION

Datasets containing predicted and observed PK data were imported into PKanalix and NCA analysis was performed twice. Relevant NCA metrics (AUCinf, Cmax and partial AUCs between 0 and 3, 3 and 7, 7 and 12 hours) were calculated for both predicted and observed data. Prediction errors were calculated using MS Excel.

Prediction errors conform to the FDA criteria presented in the IVIVC guidance. Successful level A *in vitro* - *in vivo* correlation was established.

Formulation		AUC _∞	AUC ₀₋₃	AUC ₃₋₇	AUC ₇₋₁₂	C _{max}
Slow	Predicted	123.79	25.95	41.43	40.18	14.18
	Observed	127.67	25.89	45.4	37.1	13.01
	PE%	3.0	0.2	8.7	8.3	9.0
Medium	Predicted	122.92	25.75	48.01	35.06	14.52
	Observed	130.81	26.56	48.13	37.62	14.04
	PE%	6.0	3.0	0.2	6.8	3.4
Fast	Predicted	121.85	25.16	52.31	31.65	14.55
	Observed	131.04	27.13	52.79	35.76	14.65
	PE%	7.0	7.3	0.9	11.5	0.7
Average	PE%	5.4	3.5	3.3	8.9	4.4

