Population PK Model for Pooled Data of Different Oral Diclofenac Formulations

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Background – Oral Diclofenac

- Available in different formulations.
- Absorption of some diclofenac formulations is known to be highly variable[1,4] up to the point that fitting a population PK model was deemed impossible in some cases[2].
- Significant differences in absorption parameters in function of formulation.
- No comprehensive PK analysis available across formulations.

Objective

- Develop a population PK model based on pooled data from multiple studies in healthy subjects.
- Develop a common PK framework for the description of existing oral formulations.

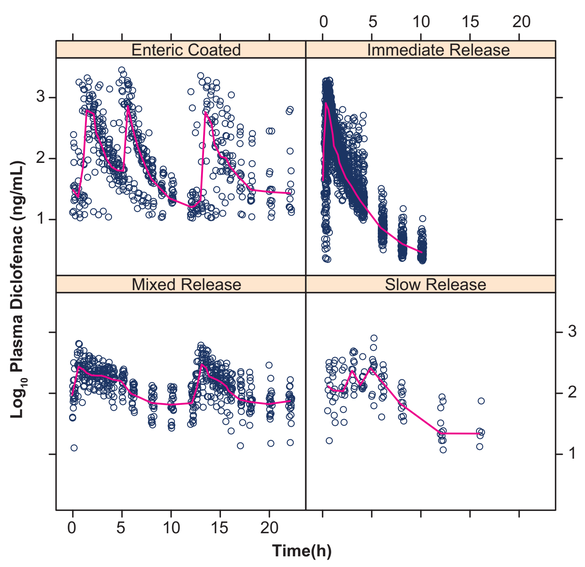
Data

- Pooled data set: immediate release, mixed release, slow release, enteric coated.
- Healthy subjects, rich sampling.
- Data below the limit of quantification (LOQ) was excluded from the analysis and plots.

Table 1. *Summary of Pooled PK Data Set*

Formulation	Dosing	Number of Subjects	Number of Observations above LOQ	Number of Samples below LOQ
Immediate Release	Single Dose	117	2042	298
Mixed Release	5 Days, b.i.d. at 0h and 12h	21	650	43
Slow Release	Single Dose	21	109	47
Enteric Coated	5 Days, t.i.d., at 0h, 4h and 12h.	12	598	221

Figure 1. *Observed Plasma Diclofenac Concentrations Over Time*



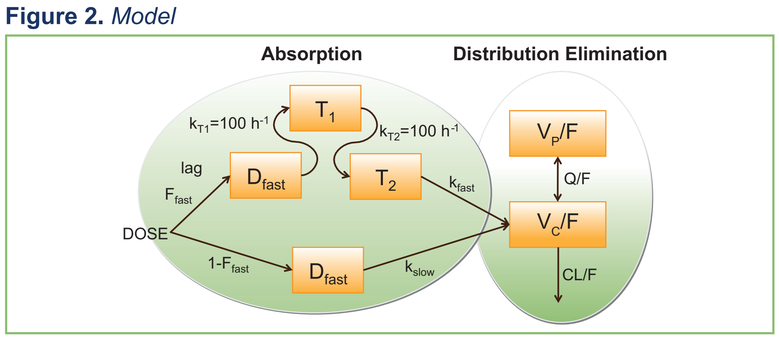
Data is plotted for the day with rich sampling. Samples below limit of quantification are not shown or included in the analysis. The line goes through the median values at each time point.

- As designed – pronounced differences between formulations:
  - Immediate release: rapid onset after about 10 minutes (with accompanying rich data).
  - Slow release: slow persistent release.
  - Mixed release: rapid onset and persistent release.
  - Enteric coated: delayed release.
- To note:
  - Relatively higher variability with enteric coated formulation.
  - Presence of multiple peaks in some of the profiles (not shown).

Methods

- Non-linear mixed effect model using NONMEM® (version VI 2.0) with first-order conditional estimation (FOCE) of log-transformed PK data.
- Formulation related differences were assessed on absorption and relative bioavailability.
- No additional covariate analysis was performed.
- Structural PK model:
  - Distribution and elimination: two-compartment PK model.
  - Absorption: two parallel first order compartments.
    - Fast release compartment with lag time. Coupled to two sequential first order processes (transition compartments) to ensure that first order partial derivatives of observed amounts with respect to model parameters are defined for all times.
    - Slow release compartment. To describe mixed release formulation with fast and slow phase, and to improve fit of slow release formulation.

Figure 2. *Model*



Results

Parameter Estimates

Table 2. *Distribution and Elimination*

Label	Estimate	RSE%
CL/F (L/h)	40.3	2.05
V_C/F (L)	23.5	6.26
V_P/F (L)	21.3	4.16
Q/F (L/h)	10.6	7.42

Table 3. *Absorption*

Label	Formulation	Estimate	RSE%
$F_{relative}$ (relative to IR)	Immediate	1	FIX
	Slow	1	FIX
	Enteric	0.784	9.27
	Mixed	0.856	6
K_{fast} (1/h)	Immediate	4.84	16.3
	Slow	0.204	22.5
	Enteric	0.503	43.3
	Mixed	0.994	19.7
K_{slow} (1/h)	Slow	0.0148	37.3
	Mixed	0.0546	10.7
F_{fast}[1]	Immediate	1	FIX
	Slow	0.76	31.1
	Enteric	1	FIX
	Mixed	0.22	15.3
Lag time (h)	Immediate	0.15	FIX
	Slow	0.15	FIX
	Enteric	0.932	4.62
	Mixed	0.15	FIX

[1]Fraction going into fast absorption compartment; estimated as odds ratio.

Table 4. *Inter-individual (IIV) and Inter-occasion Variability (IOV):*

Label	CV%	RSE%
IIV on CL	14.9	18.4
IOV on K_{fast} and K_{slow}	143	23.1

Exponential error model.

Table 5. *Residual Errors*

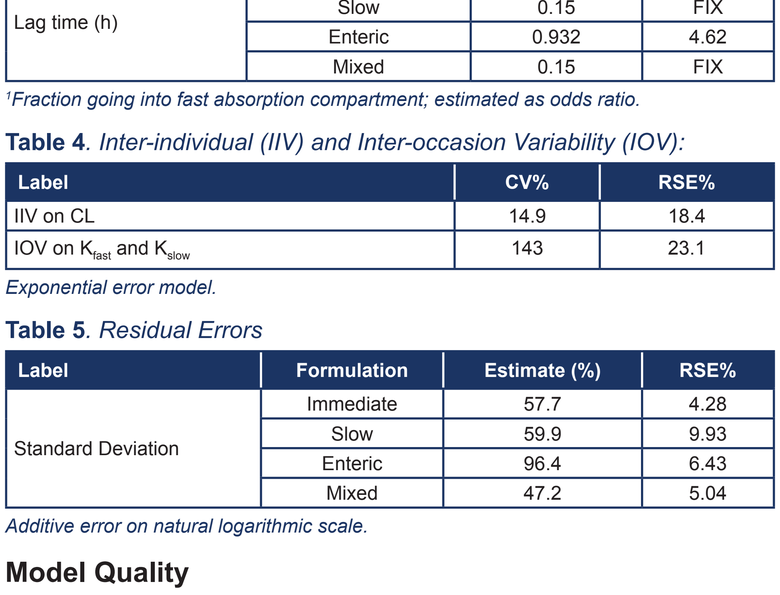
Label	Formulation	Estimate (%)	RSE%
Standard Deviation	Immediate	57.7	4.28
	Slow	59.9	9.93
	Enteric	96.4	6.43
	Mixed	47.2	5.04

Additive error on natural logarithmic scale.

Model Quality

- The integrated PK model describes the different formulations reasonably well.
- Inter-individual and inter-occasion variability is critical for quality of fit.
- Good description of average and variability of immediate release formulation.
- Good description of average profile of mixed release formulation.
- Reasonable description of enteric coated formulation.
- Some limitations: slow release at intermediate times, overestimation of variability of mixed release formulation.

Figure 3. *Visual Predictive Check – 80% Prediction Interval*



Possible improvements and future directions

- Improved candidate model:
  - Inclusion of inter-occasion variability on lag time.
  - Inclusion of formulation as covariate on variability (IIV/IOV) of absorption parameters.
  - Improved fit as judged by model diagnostics, e.g.,

Figure 4. *Observation vs Individual Prediction – Default Model*

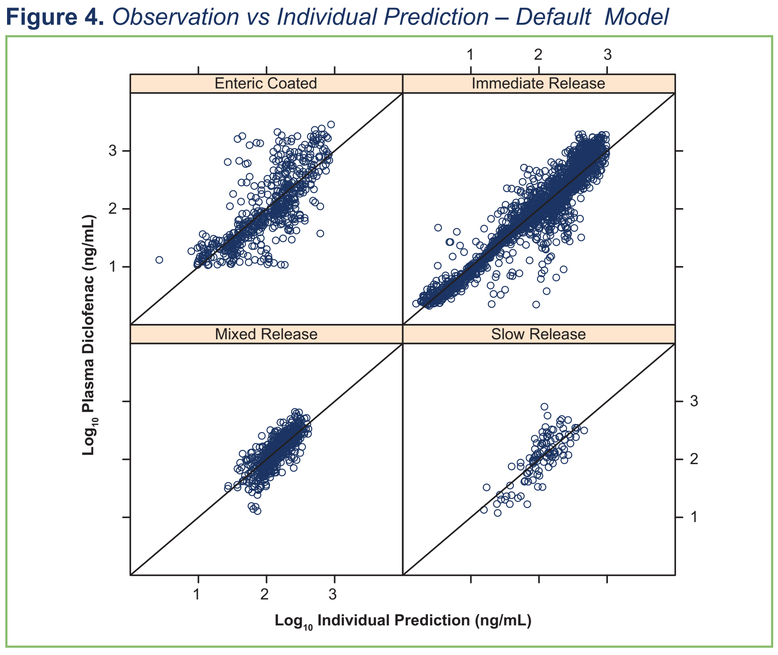
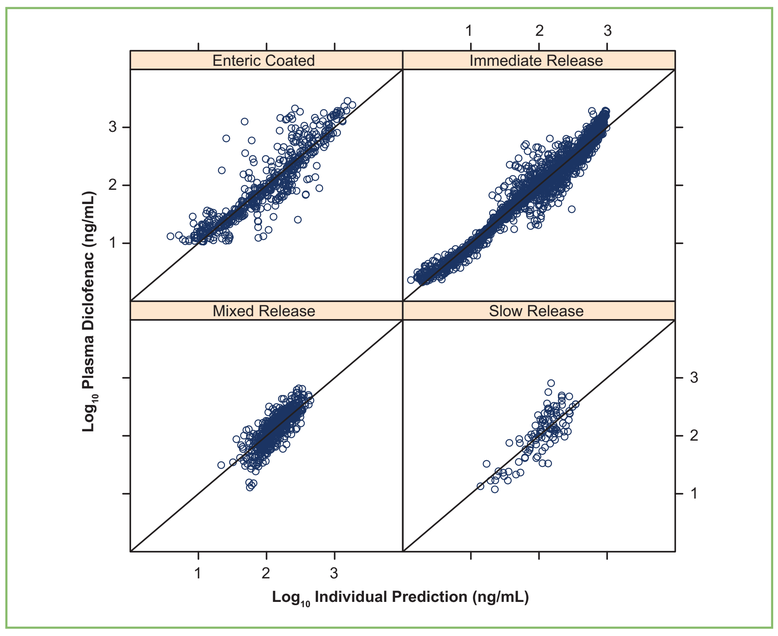


Figure 5. *Observation vs Individual Prediction – Improved Candidate Model*



  - However, minimization of model fails to converge according to NONMEM® standards (ROUNDING ERROR), although significant drop of objective function (from 853 to -240) and improved GOF (**Figure 5**).
  - It may be worth exploring additional improvements/options (e.g., SAEM, Monolix, changes in parameterization).
- Note on transition compartments:
  - Model without transition compartments are non-continuous, if the lag time is equal to an observation time.
  - Increased difficulty without transition compartments to fit model e.g.
    - FOCE fails to provide estimates (NUMERICAL HESSIAN OF OBJ. FUNC. FOR COMPUTING CONDITIONAL ESTIMATE IS NON POSITIVE DEFINITE).
    - Estimates provided by FO are of limited quality as judged by model diagnostics (not shown).

Conclusions

- Integrated population PK analysis allowed reasonable description of selected diclofenac oral formulations.
- Clearance (CL/F) is consistent with previously reported analyses[3,4].
- Significant absorption differences observed between formulations, including differences in variability.
- Further improvements to the PK model are possible.
- PK model is based on linear first order differential equations (ADVAN5) and uses a lag time. As a consequence the PK model is fast to evaluate on a computer. Coupling to transition compartments was introduced to improve convergence (compare to Ref[5]).

Relevance

- May serve as reference to anticipate the impact of the development of potential new formulations.
- Transition compartments may be used, in general, to handle non-continuous partial derivatives due to lag times.

This study was supported by Novartis Pharma AG, Basel, Switzerland.

References

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Poster presented at the Population Approach Group Europe (PAGE), June 7–10, 2010, Athens, Greece.