Modelling non-linear dose-dependent absorption profiles after oral prolonged release formulations

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Background

- After oral administration of prolonged release tablets of a new candidate drug compound, complex absorption profiles with high inter-individual variability and multiple peaks were found (Figure 1).
- The PK showed dose dependency, since C_{max} increased more than proportional with increasing dose (Figure 2). No dose dependency in AUC was observed.
- Exploratory analysis showed that intake of food prior to administration of the study drug might affect its PK.

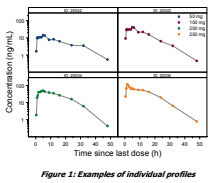


Figure 1: Examples of individual profiles

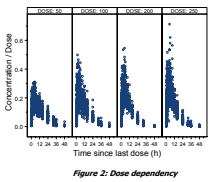


Figure 2: Dose dependency

Objectives

- Development of a population PK model that was able to adequately describe the complex absorption.
- Investigation of possible food effect.

Data available

- PK data from five richly sampled phase 1 studies.
- 140 subj's were dosed (SD) with 50-250 mg of a prolonged release formulation.
  - 26 subj's took the study drug after a high-fat, high-calorie breakfast.
  - 84 subj's took the study drug under fasting conditions.
  - 30 subj's took the study drug under fasting and non-fasting conditions in a crossover design.
- Under fasted conditions all doses were tested; under non-fasted conditions only a 250 mg dose was tested.

Deconvolution

- The absorption process was explored using deconvolution of the raw data.
- Rate of absorption was estimated for small time frames:
  - 0-0.75; 0.75-1.25; 1.25-1.75; 1.75-2.5; 2.5-3.5; 3.5-5.5; 5.5-7.5; 7.5-10.5; 10.5-14; 14-20; 20-28; >28 h.
- All disposition parameters were fixed to the values obtained from data analysis after administration of an immediate release formulation of the compound and bioavailability was set to 1.

Visual Predictive Check

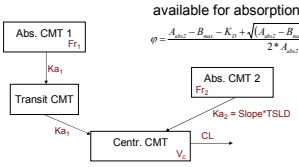
- 1000 PK curves were simulated for each group (doses 50, 100, 200, and 250 mg under fasted conditions, and dose 250 mg under non-fasted conditions).
- 90% confidence interval and observed data were plotted.

PK model

Route 1:
- First-order absorption
- Delay via buffer CMT

Route 2:
- Time varying first-order absorption rate constant
- Saturable "binding" in absorption compartment → free fraction (φ), available for absorption:

$$\varphi = \frac{A_{abs2} - B_{max} - K_D + \sqrt{(A_{abs2} - B_{max} - K_D)^2 + 4 * K_D * A_{abs2}}}{2 * A_{abs2}}$$



Abbreviations:
Fr_1&Fr_2: fraction of dose via input function 1 or 2; F_a: apparent bioavailability, set to 1; Ka_1: absorption rate constant for input function 1; Ka_2: time dependent absorption rate constant for input function 2; *TSLD*: time since last dose; V_c: distribution volume of central compartment; *CL*: clearance; B_{max}: max. capacity; K_D: conc. at which 50% is "bound".

Results

- **Deconvolution of the raw data displayed two absorption peaks (~0 h and ~4 h post dose), of which the latter one was non-proportional with dose (Figure 3).**
- **The absorption process is adequately described when using 2 input functions (see PK model), resulting in concentration-time profiles that differ between doses (Figure 4):**
  - **The first input function (~39% of total dose) comprises a first-order absorption with a buffer compartment.**
  - **The second input function (~61% of total dose) has saturable "binding" in the absorption compartment, and a time varying first-order absorption rate constant.**
- **Non-proportionality in other processes (Michaelis-Menten clearance, saturation in central compartment) was tested, but resulted in less adequate descriptions.**
- **A food effect on the PK of the study drug was found (Figure 5):**
  - **The slope of the absorption rate constant of the second input function (*slope* ka_2) was 1.7 times as high under non-fasted compared to fasted conditions.**
  - **This resulted in 20% higher peak concentrations under non-fasting conditions (Figure 6).**
- **The visual predictive check showed adequate prediction of the concentration-time profiles for all doses and under fasted and non-fasted conditions by the model (Figure 7).**

Absorption Profile

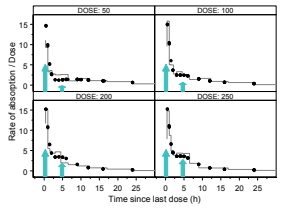


Figure 3: Dose normalised absorption profile from deconvolution and predicted by the PK model
Grey lines: absorption profile from deconvolution; black dots: absorption profile predicted by PK model; arrows indicate absorption peaks

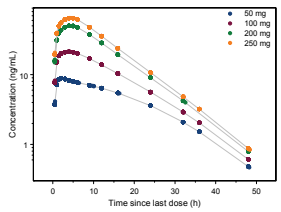


Figure 4: Simulated PK for different dose levels under fasted conditions

Food Effect

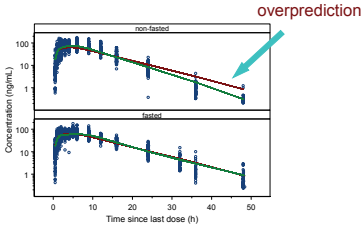


Figure 5: PK after administration of 250 mg study drug in fasted and non-fasted subjects
Blue circles: individual observed concentrations; red line: population prediction without taking into account food effect; green line: population prediction of final model (taking into account food effect)

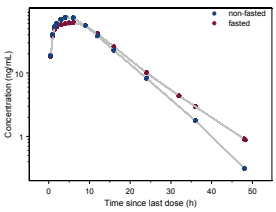


Figure 6: Simulated PK after dosing of 250 mg study drug under fasted and non-fasted conditions
Blue symbols: PK under non-fasted conditions; red symbols: PK under fasted conditions

Visual Predictive Check

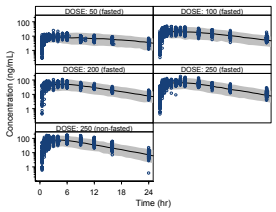


Figure 7: Visual predictive check of PK model with all data
Black line: median of simulation; shaded area: 90% prediction interval; blue symbols: observed concentrations

Parameter Table

Table 1: Parameter estimates of PK model
SE: Standard error of parameter estimate; %SE: relative SE; %CV: coefficient of variation (interindividual variability)

Parameter	Value	SE	%SE	%CV
CL/F (L/h)	259	6.23	2.41	-
V_c/F (L)	1490	137	9.19	20.7
Ka_1 (h^{-1})	2.54	0.211	8.31	-
slope Ka_2 (h^{-2})	0.0889	0.0255	28.7	-
F_a	1 (fixed)	-	-	26.5
$logit(Fr_1)$	-0.719	0.0834	-11.6	-
Fr_1	0.328	-	-	-
Fr_2	0.672	-	-	-
prop. diff. slope Ka_2 under fed conditions	0.695	0.203	29.2	-
slope Ka_2 (h^{-2}) under fed conditions	0.151	-	-	-
B_{max} (ng/mL)	41.5	4.80	11.6	-
K_D (ng/mL)	2.89	0.528	18.3	-

Conclusions

- Deconvolution of the initial raw data is a valuable tool in assessing the components of the absorption process, including detection of dose-dependent (sub)processes.
- The dose-dependency in the PK of the study drug (more than proportional increase in C_{max} with increasing dose) is adequately described by the absorption model.
  - Since the non-proportionality was described with saturation in the absorption processes, the population PK model predicts dose proportional AUCs, substantiating that the dose-dependency is not reflected in AUC, but rather in C_{max}.
- The complex absorption and the food effect on the PK of the study drug was adequately described by the PK model.