

A New Parameterisation to Describe Parallel Absorption Processes After Drug Inhalation

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Background and Objectives

- **Pulmonary absorption** of inhaled drugs is a **complex process** possibly influenced by pulmonary deposition patterns [1, 2].
- **Pulmonary absorption has previously been described by using parallel first-order absorption processes** by applying empirical models (see Table 1).

Table 1. Previously applied way of parameterisations to describe pulmonary absorption

Glycopyrronium [3] (“traditional parameterisation”)	Tiotropium [4]
$F_{Lung} = \frac{BIO}{1 + BIO}$ $F(Lung)_{fast} = \frac{1}{FS}$ $F(Lung)_{int} = \frac{R_{int}}{FS}$ $F(Lung)_{slow} = \frac{R_{slow}}{FS}$ $FS = 1 + R_{int} + R_{slow}$	$F_{Lung} = F_{fast} + F_{slow}$ $F_{fast} = \frac{R_{fast}}{FS}$ $F_{slow} = \frac{R_{slow}}{FS}$ $FS = 1 + R_{fast} + R_{slow}$

BIO, R_{int} , and R_{slow} represent estimated proportionality parameters. BIO: proportionality parameter estimated to represent the pulmonary bioavailable fraction of the nominal dose. FS: scaling factor, F_{Lung} : pulmonary bioavailable fraction of the nominal dose, F_{fast} , F_{slow} : fraction of the nominal dose absorbed by the fast and slow absorption rate, respectively. $F(Lung)_{fast}$, $F(Lung)_{int}$, $F(Lung)_{slow}$, parameters need to be multiplied with F_{Lung} to be comparable with F_{fast} and F_{slow} .

- For the traditional way of parameterisation, variability on proportionality factors (R_{fast} , R_{med} , R_{slow}) was assumed to be log-normally distributed before transformation (see Table 1, normalising to FS), which is in contrast to the usually applied logit-transformation, for which variability is assumed to be normally distributed on the logit scale.

Objective

- **To develop an alternative way of parameterisation** that allows modelling proportionality factors directly on a zero to one scale, **by only applying logit transformation**.

Methods

- The new parameterisation to characterise pulmonary absorption was inspired by “Advanced Compartmental Absorption and Transit” (ACAT) models applied to describe gastrointestinal (GI) absorption [5] (see Figure 1).

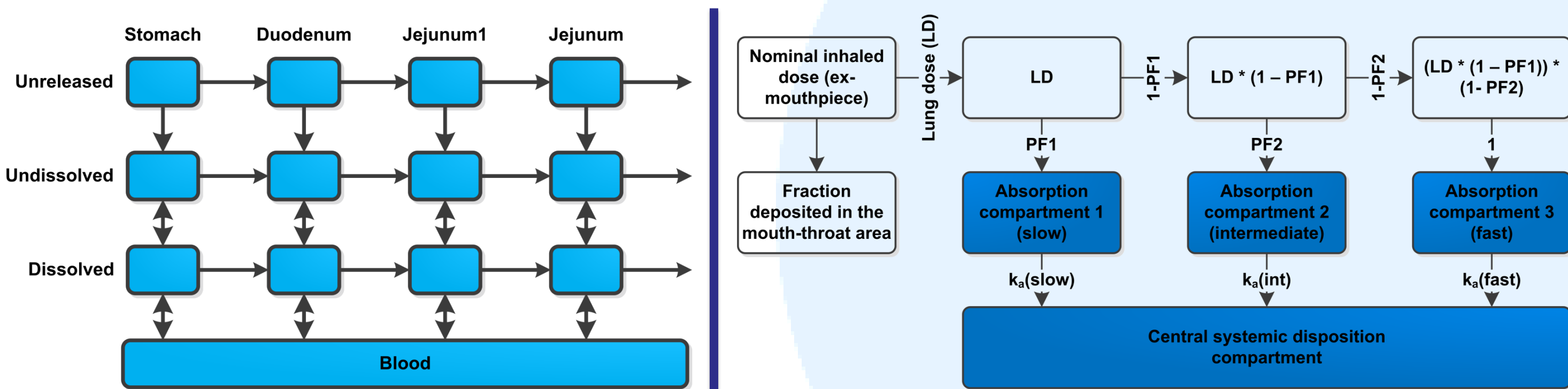


Figure 1. Comparison between an ACAT model (left panel) and the parameterisation applied to characterise pulmonary absorption processes (right panel). Filled compartments represent compartments with mass characterised by ordinary differential equations (ODE), whereas non-filled compartments represent calculations, arrows represent mass flow. LD: lung dose, PF: proportionality factor, k_a : absorption rate constant. Left representation adapted and simplified from [5].

- In ACAT models, transport through transit GI absorption compartments is described by transit rate constants, which describe the time-dependent drug transfer between different GI tract compartments (see Figure 1).
- In contrast to GI tract absorption, inhaled particles are deposited during one breath cycle in the **different airways** (typically in the range of 10-30 seconds), **possibly represented by multiple absorption compartments**.
→ Drug distribution across pulmonary absorption compartments was assumed to be instantaneous.

References:

- [1] JS Patton, JD Brain, et al. J Aerosol Med Pulm Drug Deliv J 23 Suppl 2: S71-87 (2010).
- [2] JS Patton, PR Byron. Nat. Rev. Drug Discovery J 6: 67-74 (2007)
- [3] C Bartels, M Looby, et al. Br. J. Clin. Pharmacol. J 76: 868-79 (2013)
- [4] Z Parra-Guillen, B Weber, et al. J Pharmacokinet Pharmacodyn J 41: S54. (2014)
- [5] W Huang, SL Lee, LX Yu. The AAPS journal J 11: 217-24 (2009)
- [6] JM Borghardt, B Weber, et al. PAGE 23 Abstr 3245 (2014)

Methods (cont.)

New parameterisation:

$$F_{Lung} = Lung\ dose \quad (Equation\ 1)$$

$$F(Lung)_{slow} = PF1 \quad (Equation\ 2)$$

$$F(Lung)_{int} = (1 - PF1) * PF2 \quad (Equation\ 3)$$

$$F(Lung)_{fast} = 1 - PF1 - ((1 - PF1) * PF2) \quad (Equation\ 4)$$

Both the *lung dose* and the *proportionality factors* (PF) are estimated on a logit-scale. $F(Lung)_x$ represents **fractions of the lung dose absorbed by specific absorption rate constants**. Interindividual variability (IIV) is assumed normally distributed on the untransformed parameter on the logit scale (Lung dose, PF1, PF2, equation 5). As a last step, retransformation from the logit to the normal scale is performed (equation 6).

$$PHI = \theta + \eta \quad (Equation\ 5)$$

$$Parameter\ (e.g.,\ lung\ dose,\ PF) = \frac{e^{PHI}}{1 + e^{PHI}} \quad (Equation\ 6)$$

- After transformation to the normal scale, **each fraction absorbed and the sum of all fractions absorbed (lung dose) are between 0 and 1** for both the population and the individual level.
- Comparison of the performance (objective function value (OFV), results of estimation and covariance step) of the new parameterisation (NP) with the traditional parameterisation (TP) was performed for PK data of inhaled olodaterol [6], for which both parameterisations were applied in NONMEM with and without IIV. IIV was accounted for either by a reduced omega matrix with no off-diagonal elements (no covariances, runs named TP1 and NP1) or as a full omega matrix (runs named TP2 and NP2).

Results

- As expected, without allowing for IIV, both parameterisations provided numerically identical description of the data (see Table 2).
- **Accounting for IIV resulted in a better data description by the new parameterisation.**
- The new parameterisation without covariances (NP1, OFV: 9723.78) provided a comparable data description to the traditional parameterisation with covariances (TP2, ΔOFV : -0.23 for three additional degrees of freedom (df)), whereas the traditional parameterisation without covariances provided a worse data description (TP1, ΔOFV : 52.6, same number of df as NP1).
- Additional covariance inclusion to the new parameterisation did not provide a significantly better data description (NP2, ΔOFV : -1.17).
- The probability density distributions of the $F(Lung)_x$ parameters were identical between TP2 and NP1, however, deviated for the TP1 (see Figure 2).
- Correlations between model-derived individual parameters (parameters not directly estimated, e.g., between $F(Lung)_{slow}$ and $F(Lung)_{int}$ given in brackets) were in agreement between TP2 (-92.4%) and NP1 (-92.3%), but slightly deviated for TP1 (-98.0%).

Table 2. Estimation results for different ways of parameterisation without accounting for IIV

	“Traditional parameterisation”	“New parameterisation”
Parameters	Value	Value
F_{Lung}	48.0% ND	48.0% ND
$R_{med} / PF1$	8.42	62.2%
$R_{slow} / PF2$	15.5	89.4%
$F(Lung)_{slow}$	62.2% LD	62.2% LD
$F(Lung)_{int}$	33.8% LD	33.8% LD
$F(Lung)_{fast}$	4.01% LD	4.01% LD
OFV	10227.5	10227.5

F_{Lung} : Pulmonary bioavailable fraction, ND: nominal dose, R_{med} , R_{slow} , $PF1$, and $PF2$: proportionality factors, $F(Lung)_x$: fraction of the lung dose absorbed via a specific absorption kinetics, OFV: objective function value

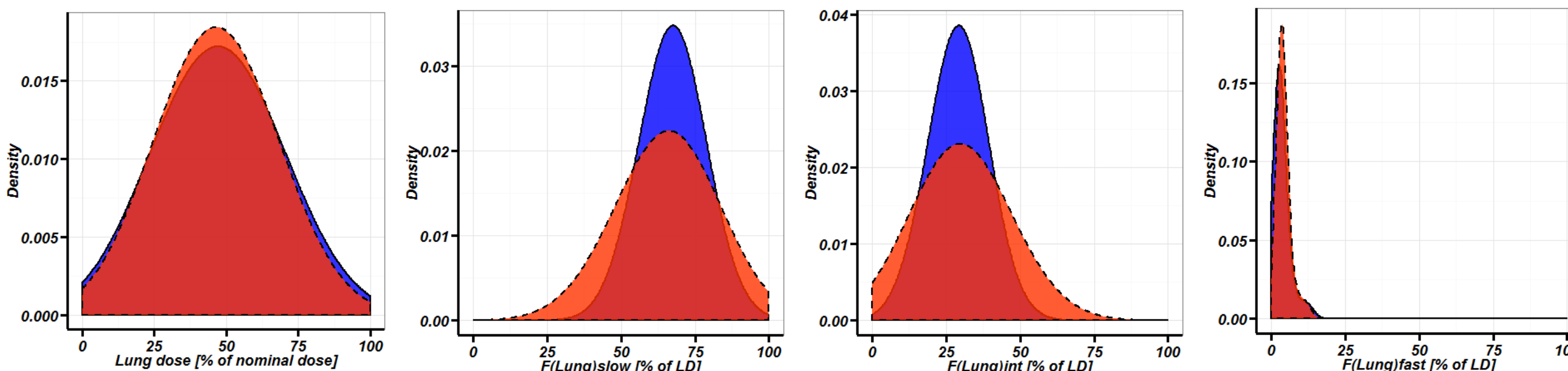


Figure 2. Probability density distributions of pulmonary absorption parameters (LD , $F(Lung)_{slow}$, $F(Lung)_{int}$, $F(Lung)_{fast}$) describing the input to absorption compartments from where drug is being absorbed to the systemic disposition. Red area: traditional parameterisation without covariances (TP1), blue area represents both the traditional parameterisation with covariances (TP2) and the new parameterisation without covariances (NP1) (both distributions completely overlap).

Discussion and Conclusions

- A new parameterisation applying logit transformations to describe parallel pulmonary absorption processes was successfully developed.
- The new parameterisation allowed to adequately describe PK data, and hence, also pulmonary absorption kinetics after olodaterol inhalation.
- For inhaled olodaterol, the new parameterisation was demonstrated to provide a better data description compared to the traditional parameterisation after accounting for interindividual variability in absorption PK parameters.

- However, the new parameterisation requires further evaluation based on additional clinical PK data to perform a more systematic comparison between the different parameterisation.
- The semi-mechanistic nature of the new parameterisation might facilitate interpretation of the parameter estimates.

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