

# Characterisation of different absorption rate constants after inhalation of olodaterol

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## Background and Objectives

### Background

- Today, there is a **lack of quantitative mechanistic understanding** about how disposition and dissolution of particles in the lung and physiological aspects of the lung influence the absorption and the plasma concentration-time profiles of inhaled drugs [1, 2].
- Many drugs in literature show the characteristics of **flip-flop kinetics** and different terminal half lives after inhalation compared to intravenous administration of the drug [3, 4].
- The model substance olodaterol, a long acting beta-agonist, has two important characteristics:

- 1) No expected influence of a dissolution process because the drug substance is administered as a solution
- 2) Swallowed drug is virtually not bioavailable, therefore plasma concentrations of the drug reflect lung absorption only (unpublished data).

### Objectives

- **Initiation of a work flow** to mechanistically explain the specific characteristics of plasma concentration-time profiles after inhalation compared to the kinetic behaviour after intravenous administration.
- The absorption characteristics of olodaterol were to be characterised

## Methods

### Data/Study

- Data of three trials in healthy volunteers after intravenous administration and inhalation was available (Table 1).

	Inhalation	Intravenous
Doses administered	Range: 2.5 µg to 70 µg	Range: 0.5 µg to 25 µg
Number of Patients with PK	Total: 65	Total: 48
Plasma samples	N = 1003 (TAD: 0.02h to 48h)	N = 849 (TAD: 0.03h to 48h)
Fraction of BLQ (LLOQ = 2 pg/mL)	All dose groups: 60% Per dose group: 100% to 4%	All dose groups: 60% Per dose group: 100% to 4%

### Absorption rate constant characterisation

- Data analyses were performed with NONMEM<sup>TM</sup>VII, R 2.14.2 and Berkeley Madonna 8.3.14.
- Different population PK models for the intravenous administration were developed. Three methods to account for BLQ values have been applied to these PK models (M1, M3, M6 [6]).
- Model selection was based on several criteria, such as goodness-of-fit plots, precision of parameter estimates and the changes in the NONMEM objective function
- To characterise the absorption processes of olodaterol after inhalation, a **numerical deconvolution method** (area-point method [5]) was applied to a geometric mean plasma concentration-time profile after inhalation. The weight function of the deconvolution method was a typical simulated plasma concentration-time profile after bolus injection.

**References** [1] JL Sporty, L Horáková, C Ehrhardt. Expert Opin Drug Metab Toxicol J4: 333-345 (2008)

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## Discussion and Conclusions

- Results are in **agreement with physiological characteristics** of the lung. Particles deposited in the **conducting airways may be absorbed slowly**, whereas particles deposited in the **alveolar space may be absorbed fast** (Fig.4). This characteristic was explained with differences in the thickness of the absorption barrier.
- An additional **intermediate absorption rate constant** may represent an absorption process for particles deposited in **intermediate airways**.
- Although more than three slopes would physiologically be plausible due to differences in the airway wall thickness, a more complex mathematical model to describe the curve (Fig. 3) is not expected to have additional benefit to mechanistically explain the PK model, because a more complex description of deposition patterns was not substantiated by experimental data.

### Outlook

- The estimation of different fractions of the drug absorbed by the previous identified absorption rate constants will be done with a population modeling approach.
- To establish a physiologically motivated link between the absorption processes occurring after inhalation and deposition patterns of droplets across the lung, the estimated fractions will be compared to deposition patterns across the lung [7].

## Results

### Model development

- Modelling results suggested a **three compartment model with interindividual variability on clearance and the central volume of distribution and a proportional residual variability model** as the model best describing the intravenous data (Fig. 1, Fig. 2, Table 2).
- For BQL-data: M1 method of choice as only minor differences occurred and the M1 method was most robust.

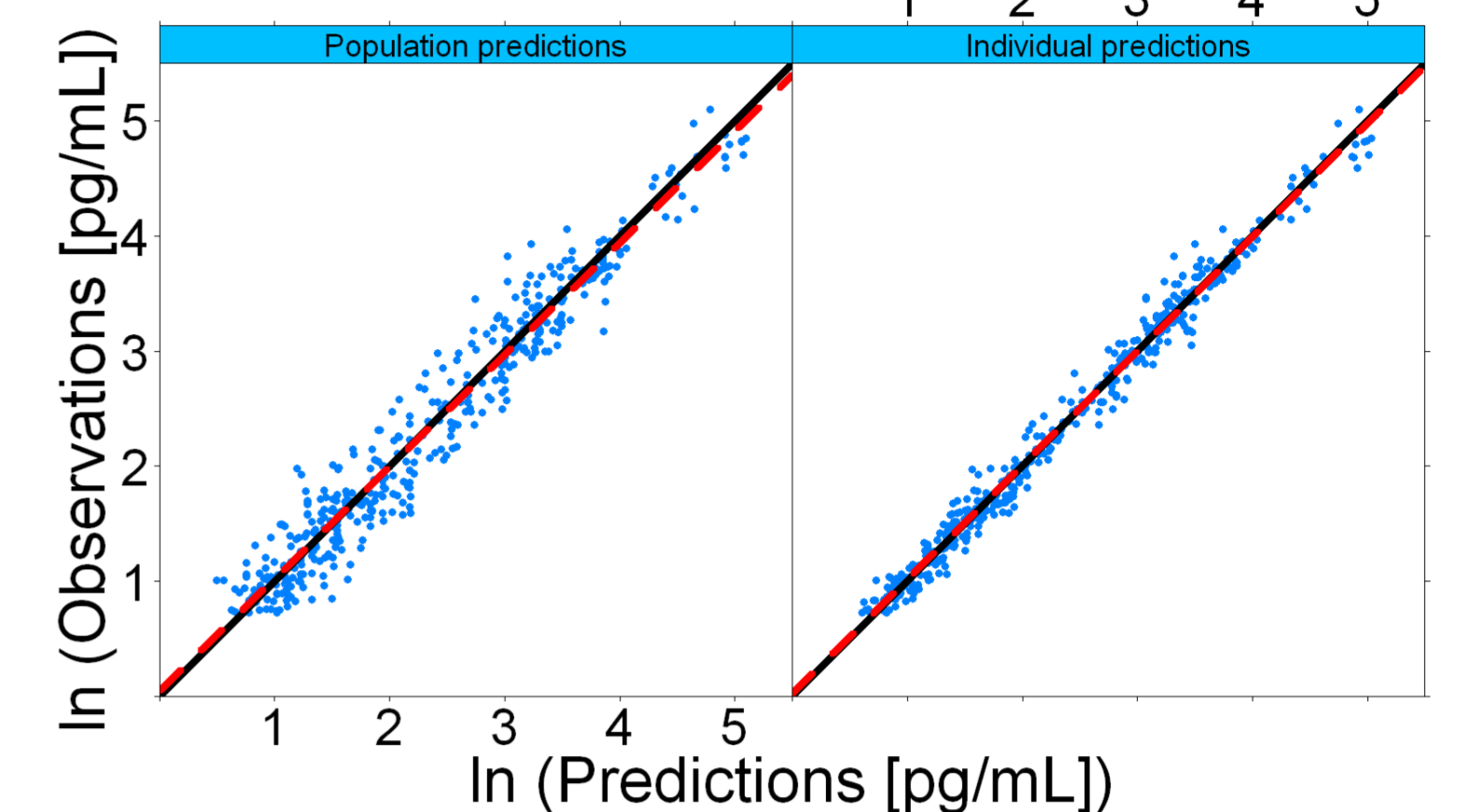


Fig. 1: Log transformed observations plotted versus log transformed population predictions (left plot) and log transformed individual predictions (right plot), red dashed line: Smoothed fit, black line: Line of identity

Table 2: Estimated PK parameters of the final PK model

PK Parameter	Unit	Estimate (RSE, %)
V1	[L]	23.5 (4.51)
V2	[L]	842 (7.51)
V3	[L]	23.7 (12.4)
Q2	[L/h]	80.3 (4.86)
Q3	[L/h]	27.0 (5.70)
CL	[L/h]	88.6 (3.54)
$\omega_{Cl}$	[% CV]	21.7 (23.8)
$\omega_{V1}$	[% CV]	19.5 (30.0)
Residual variability $\sigma_{proportional}$	[% CV]	14.4 (0.9)

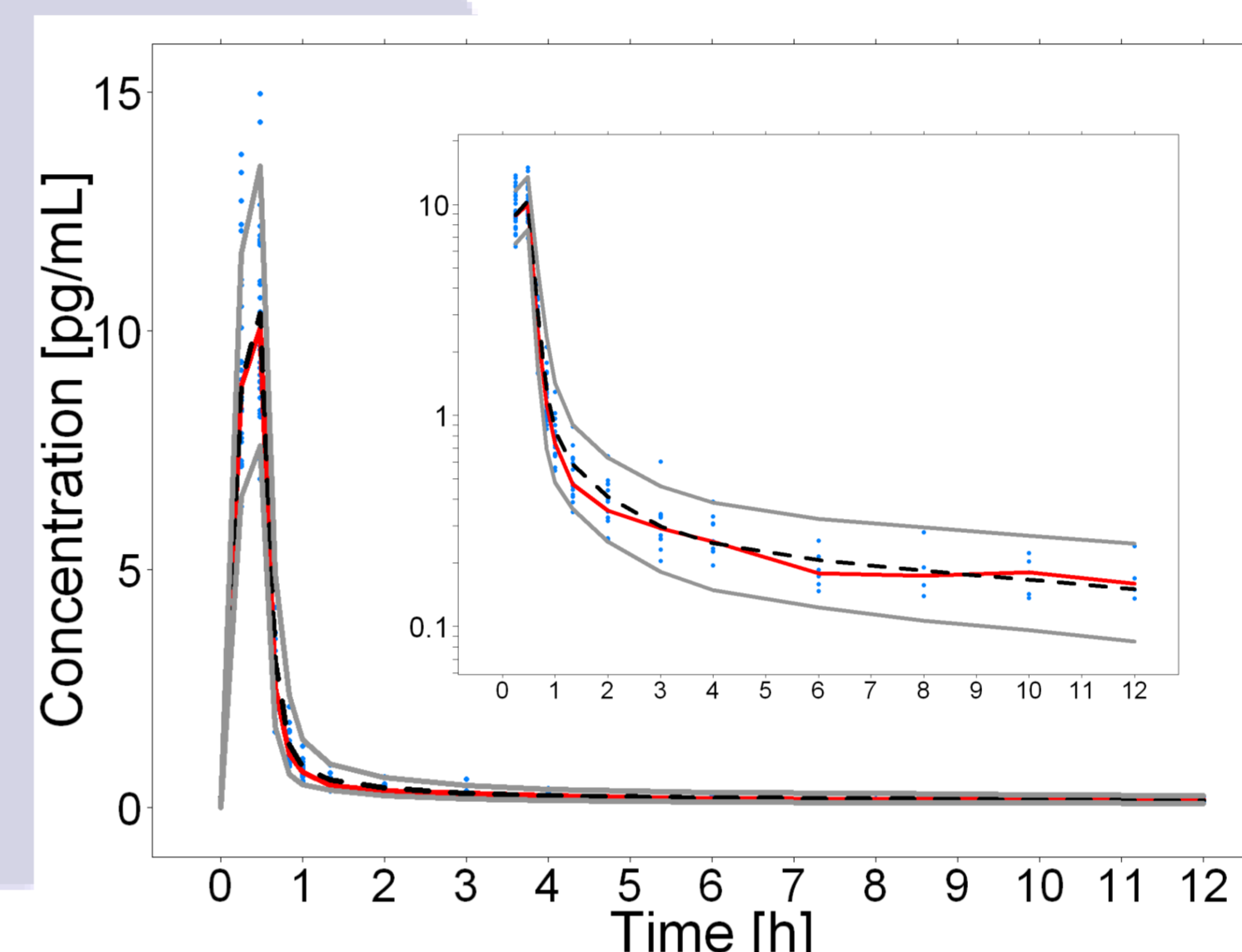


Fig. 2: VPC of the PK model describing intravenous administration, the concentrations are dose normalized, red line: Median of the trial data, black line: Median of the simulated data, grey lines: The 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile of the simulated data, blue dots: Raw data points. The smaller graphic is showing the same VPC as a semi logarithmic plot

### Area-point deconvolution

- The results of the deconvolution underlined the special absorption characteristics of inhaled drugs as it was not possible to describe the unabsorbed fraction/time, plotted on a semi logarithmic scale, with one single first-order absorption rate constant (Fig. 3).
- As a first approach the curve presenting the unabsorbed fraction/time was described in a simplified way using **three different slopes** on a semi logarithmic scale (Fig. 3). Therefore a least square method in R was used to estimate these slopes and the 2 intersection points (Table 3).

Table 3: Estimated absorption rate constants and intersection points

	Unit	Estimate
Ka <sub>1</sub> : fast	[1/h]	<b>0.574</b>
Ka <sub>2</sub> : intermediate	[1/h]	<b>0.063</b>
Ka <sub>3</sub> : slow	[1/h]	<b>0.017</b>
Intersection point time 1	[h]	1.43
Intersection point time 2	[h]	10.7

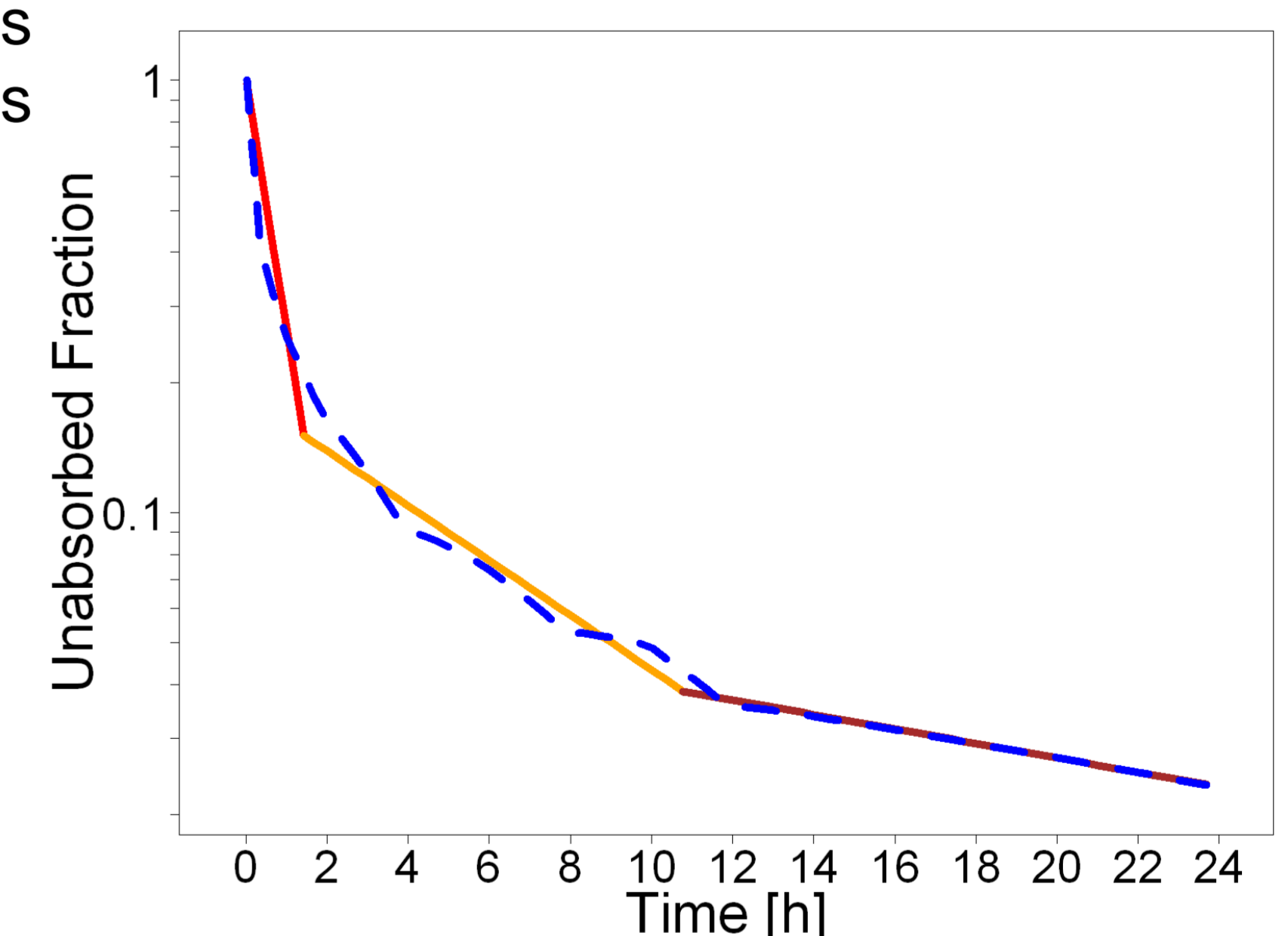


Fig. 3: Unabsorbed fraction versus time, blue dashed line: Unabsorbed fraction (result of the deconvolution), red, orange and brown line: Estimated slopes

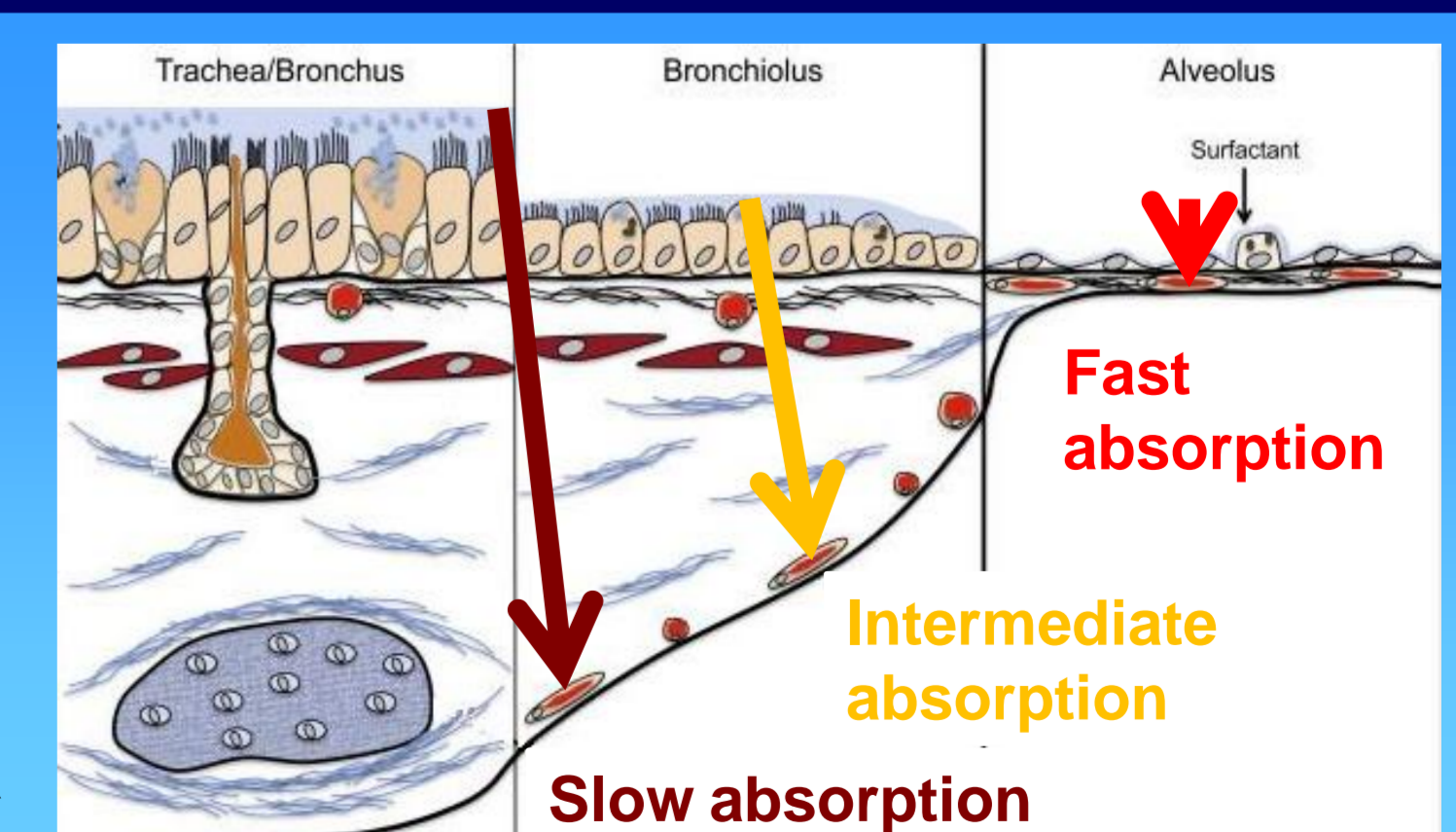


Fig. 4: Simplified structure of the airway wall at the three principal levels; The trachea and the bronchus, the bronchioles and the alveolar space. Adapted and modified from Ochs and Weibel [8]