

# Physiologically-based simulation model for the prediction of oral drug absorption



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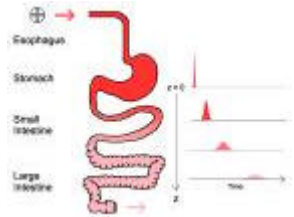


## Introduction

The development of a physiologically-based pharmacokinetic simulation model for orally administered drugs is described. The model is able to calculate the temporal and spatial absorption profile for passively absorbed compounds administered as liquid solutions or suspensions to humans or rats under fasted conditions.

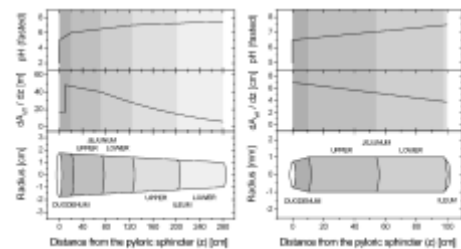
Unlike other models that use a multi-compartmental approach, the gastro-intestinal (GI)-tract is modeled as a continuous tube with spatially varying properties. The mass transport through the intestinal lumen is described via an intestinal transit function.

The only substance specific input parameters of the model are the intestinal permeability coefficient  $P_{int}$  and the solubility in the intestinal fluids  $S_{int}$ .



## Model Development

### • GI-Physiology of Humans and Rats



The physiological parameters affecting oral absorption from the mammalian GI-tract such as length, diameter, effective surface area per unit length, and pH-profile along the intestine have been collected from various literature sources.

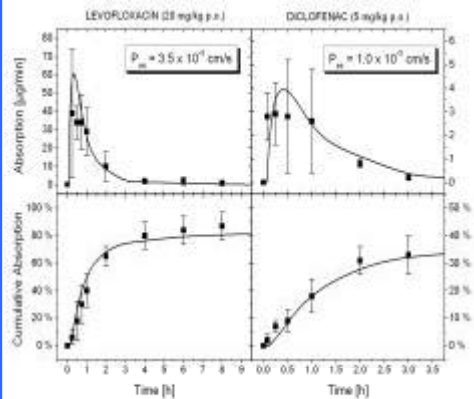
### • Intestinal Transit Function

The emptying of an orally administered liquid from the stomach into the duodenum and the transport through the intestinal lumen are described with the help of an intestinal transit function, that is defined as the fraction of the administered dose found within the various intestinal segments as a function of time after administration. The function is based on experimental data by SAWAMOTO et al. [1] of on a non-absorbable compound (phenol red) after oral administration to rats

## Results

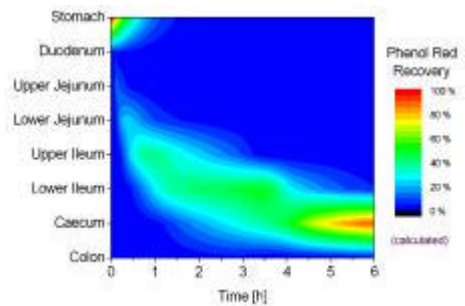
### • Temporal Absorption Profiles in Rats

Simulated concentration vs. time curves in the rat portal vein of Levofloxacin and Diclofenac (lines) were compared to experimental data from the literature obtained using the portal-venous concentration difference method [2,3] (symbols). The intestinal permeability coefficient was varied in these calculations in order to achieve the best agreement between the measured and the calculated data:



The model describes the time dependencies of the absorption rate and the cumulated fraction dose absorbed in the rat portal vein very well.

### • Transit Function: Graphical Representation

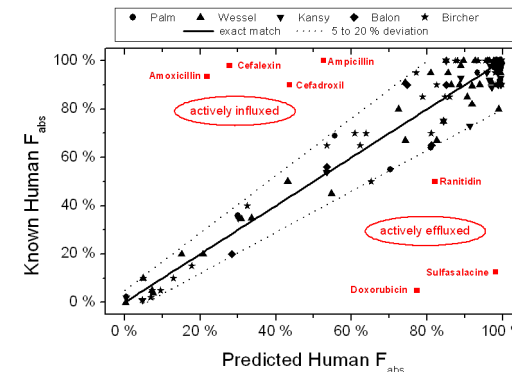


## Permeability-limited Absorption: Comparison to Literature-Data

Human fraction dose absorbed ( $F_{abs}$ ) data were collected from various literature sources [4-8]. A data set of 131 compounds without solubility-limited absorption was used to assess the ability to predict fraction absorbed in humans. Seven of these compounds were known to be at least partly actively transported (influx or efflux, depicted in red in the figure).

$P_{int}$  was calculated from the compound's membrane affinity, which was determined experimentally in house, and molecular weight on the basis of an equation published by LEAHY et al. [9] and CAMENISH et al. [10] after optimization of the parameters therein.

An excellent agreement was found between the known and predicted human  $F_{abs}$ . For the passively absorbed compounds ( $N = 124$ ), a mean absolute difference of  $\langle \Delta F_{abs} \rangle = 5.25\%$  and a linear correlation coefficient of  $R = 0.970$  was obtained.

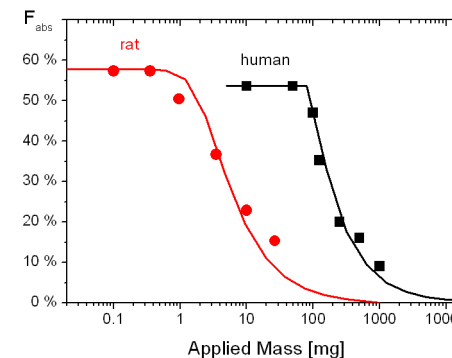


## Solubility-limited Absorption: Comparison to Literature-Data

Chlorothiazide is a drug exhibiting non-linear absorption that has been attributed to a low solubility of the compound. The respective dose-dependent absorption data for humans and rats is available from the literature [11].

The dose-dependency of  $F_{abs}$  found experimentally can be described by the model assuming the following set of input-parameters:

- Human: Intestinal Permeability:  $P_{int} = 6.5 \times 10^{-7}$  cm/s  
Intestinal Solubility:  $S_{int} = 5$  µg/ml
- Rat: Intestinal Permeability:  $P_{int} = 3.4 \times 10^{-6}$  cm/s  
Intestinal Solubility:  $S_{int} = 35$  µg/ml



## References

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