# Inter- and intra-individual variability in physiological parameters of gastro-intestinal tract has significant effects on the predicted fraction of dose absorbed

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## Introduction

Oral drug administration is the most convenient and common route for many classes of drugs because of its ease and patient compliance. Therefore, obtaining reliable estimate of oral bioavailability for the selection of the best candidates in drug discovery is of high interest to the pharmaceutical industry.

The most important factors that influence drug absorption include gastric and intestinal motility, physicochemical properties of the drug, the environment in the small intestine and surface area available for absorption (Dressman *et al*., 2000). Many biological and physiological parameters relevant to drug absorption show significant inter- and intra-subject variability and covariates such as sex and age are shown to contribute to some of the inter-subject variation (Argenyi *et al*., 1995; Brogna *et al*., 1999 ; Graff *et al*., 2001).

Recently, different physiologically-based (PB) predictive models are developed to give better estimate of the oral drug absorption. The PB approaches have become particularly significant in *in vitro–in vivo* predictions. Nevertheless, developing such models without considering the inherent inter- and intra-individual variability of the physiological parameters in the target population may lead to flawed conclusions; especially knowing that the early clinical data during drug development are only obtained from small study populations.

Thus, using the available literature reports, we have collected measures of variability for each of the physiological parameters pertinent to the Compartmental Transit and Absorption (CAT) model (Yu et al., 1999) and have assessed impact of these on the outcome of the modelling.

## Methods

Taguchi method (Roy, 1990) was used to assess sensitivity of the estimated fraction of dose absorbed, $f_a$, to the effects of changes in different parameters. The investigated parameters included the small intestinal transit time, $T_{si}$, the radius of the small intestine, R and the drug permeability $P_{eff}$ . This study was carried out for drugs with a wide range of permeability characteristics; for instance Enalaprilat as a low permeable compound ($P_{eff}$= 0.079 cm/h (Lennernas *et al.*, 1994)) and Antipyrine as a high permeable compound ($P_{eff}$= 2.02 cm/h ).



**$f_a$ vs $P_{eff}$ and $T_{si}$ (R=1.7 cm)**



**$f_a$ vs R and $T_{si}$ ($P_{eff}$=0.5 cm/h)**



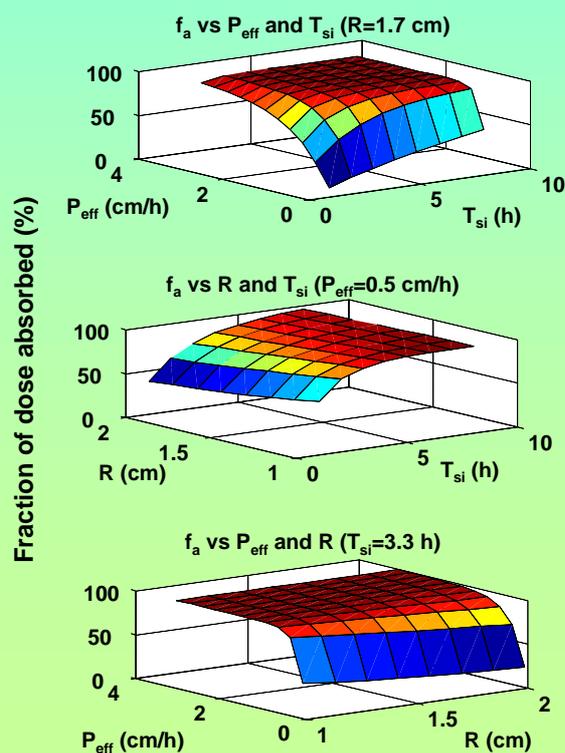**$f_a$ vs $P_{eff}$ and R ($T_{si}$=3.3 h)**

**Figure 2 – The effects of systematic changes to different biological/physiological parameters on $f_a$**

## Results and Discussion

Table 1 shows the range of values used for each parameter and Figure 1 presents the overall sensitivity of $f_a$ to each set of parameter values. Although permeability, a drug dependent parameter, was the most influential factor determining fa, individual parameters, $T_{si}$ and R, were also important.

The results of a detailed sensitivity analysis of $f_a$ for a continuous change of the different parameters are shown in Figure 2.

**Table 1 – Parameter ranges used for simulations**

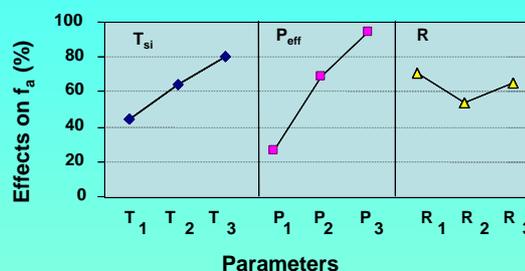|  | $T_{si}$ (h) | $P_{eff}$ (cm/h) | R (cm) |
|---|---|---|---|
| Level 1 | 1.00 | 0.07 | 1.00 |
| Level 2 | 3.30 | 0.40 | 1.70 |
| Level 3 | 8.00 | 2.02 | 2.00 |



**Figure 1 – The effects of factors changes on $f_a$**

Using Taguchi method to assess overall sensitivity and assuming the parameter space given in Table 1, the contribution of $T_{si}$, $P_{eff}$, R to the changes of $f_a$ were 19%, 72% and 3.4%, respectively.

More detailed analysis according to Figure 2 showed that sensitivity to inter-individual differences would be more significant when permeability is low. The effect diminishes as permeability approximates to 1 cm/h.

## Conclusions

The results confirmed the assertion that inter- and intra-variability of the parameters should be considered in any predictive PB modelling studies particularly when less permeable drugs are investigated.

Incorporating such effects not only can increase the power of predictions but also it may help with study design of clinical studies to provide reliable estimates of "$f_a$" which are representative of population values.

## References

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