



Objectives

To investigate the possibility of using prior information on tablet movement through Gastro-Intestinal (GI) tract for a semi-mechanistic modeling of absorption processes.

Methods

Magnetic Marker Monitoring (MMM) technique:

- Visualize the transit of labeled tablet through GI tract
- Monitor tablet disintegration and drug release

Felodipine data: 6 healthy volunteers in MMM study [1]

- administered magnetically labeled extended release tablets containing felodipine
- under fed and fasting conditions

3 types of observations:

- Plasma concentrations of felodipine
- Tablet GI position
- In vivo* drug release

Previously proposed Models [2]: GI tablet transit model

Markov chain model for tablet position, where the probability of observing tablet in different GI position is dependent on the last observed position and time since last observation.

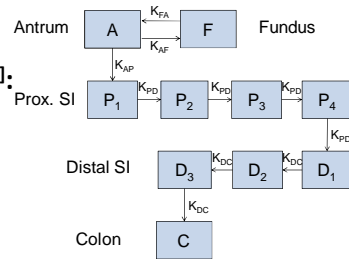
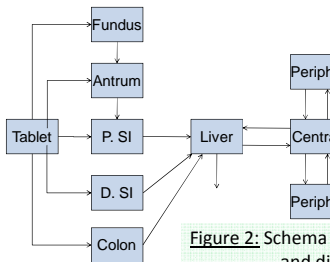


Figure 1: Schema of GI transit model
K: first-order rate constant for tablet movement
SI: Small Intestine

Drug release and disposition model



- Disposition fitted separately on IV data (3 compartments)
- Different drug release rates for each GI region
- Tablet position as measured by MMM used as a covariate

Figure 2: Schema of drug release, absorption and disposition model

Mean Residence Time Approach

- Both models were coupled and estimated simultaneously
- Using prior population estimates for tablet GI transit
- Without using tablet position as covariate
- Mixture modeling for patients with 0, 1 or 2 return from antrum to fundus

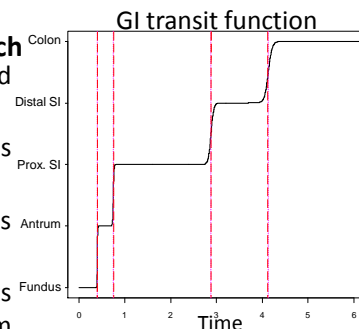


Figure 3: GI transit function
Red lines: MRT at each GI position before movement

Results and Discussion

Empirical Bayes Estimates for each parameter obtained using NONMEM VI

Comparison of tablet movement profiles

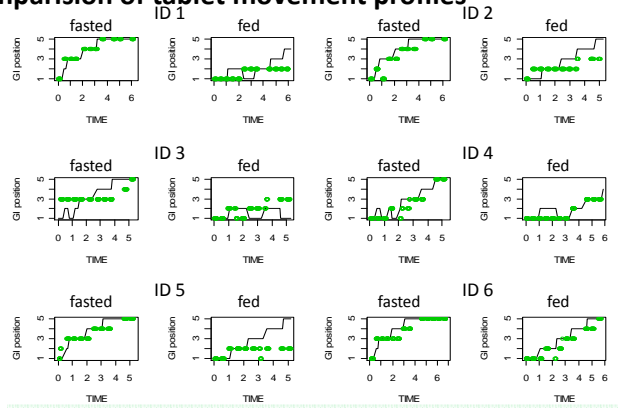


Figure 4: Prediction of individual tablet movement profile in GI tract
Black line: predicted profile
Green points: MMM measured positions

Comparison of Felodipine plasma concentration profiles

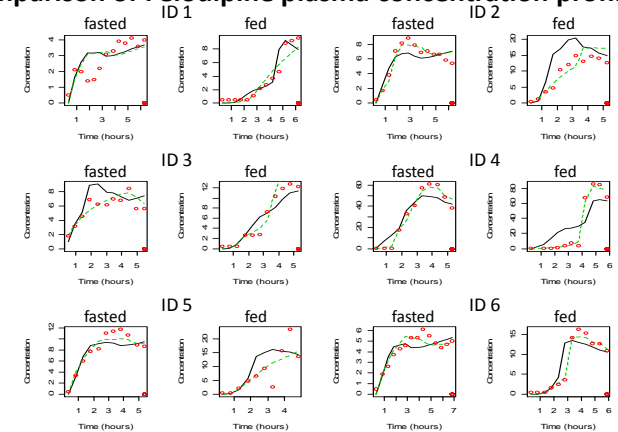


Figure 5: Individual plasma concentration profiles
Observed concentrations (red)
Predicted concentrations, with MRT approach (black) and using GI tablet position (green)

MRT approach can predict correctly in several individuals GI tablet position and concentration profiles.

Similar results were obtained when only plasma concentration data were used.

Conclusions and Perspectives

This work represents a first step in the use of prior information on GI tablet movement in absorption modeling.

This approach will be applied to other substances and formulations in order to investigate the possibility of better characterising erratic concentration profiles.

References

- Weitschies W et al, *J Control Release*, 2005
- Bergstrand M et al, *Clin Pharmacol Ther*, 2009