

A Population-based PBPK Model for the Prediction of Time-varying Bile Salt Disposition within GI Luminal Fluids – Toward a Mechanistic Model

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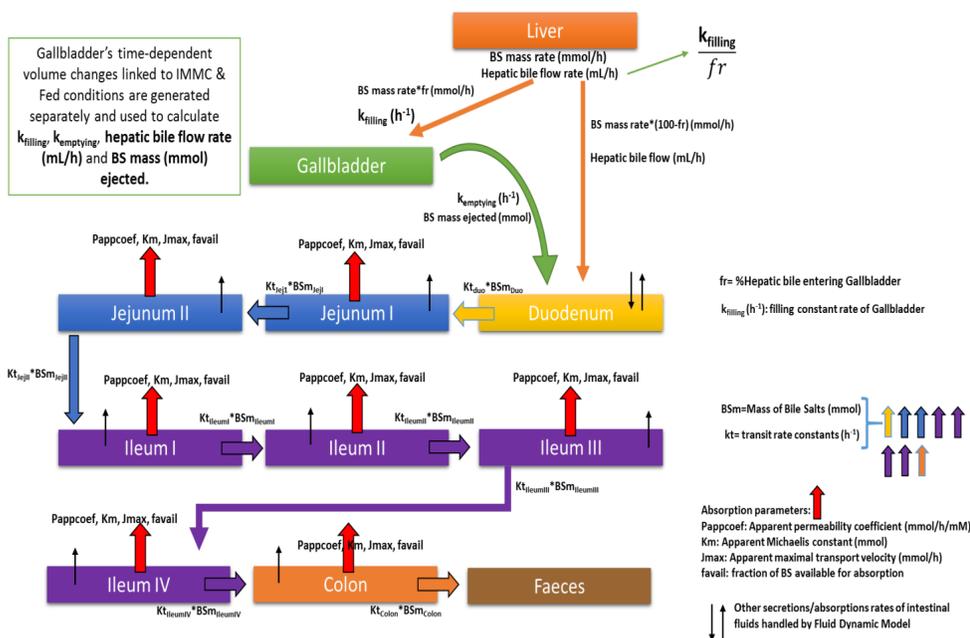
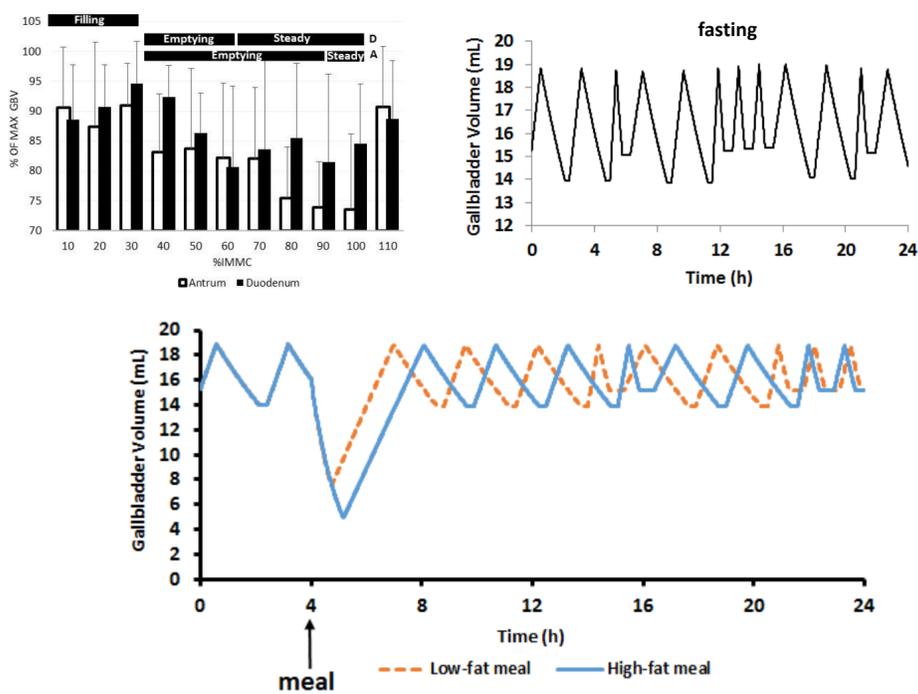
Background

Bile salts (BS) play a crucial role in the solubilisation and absorption of lipophilic and poorly soluble drug compounds. The concentration of BS, however, varies significantly within the GI tract due to factors such as the cyclic motility patterns of the gall bladder (GB) linked to the interdigestive migrating motor complex (IMMC) [1,2], dynamic changes of the GI luminal fluid volumes and most importantly the prandial state. As opposed to the fasted state, strong GB contractions empty a significant amount of BS in response to feeding events. Thus, a novel mechanistic BS model (the Advanced Dynamic Bile Salt Model – ADBSM) was developed and coupled with a previously developed dynamic GI fluid volumes model [3]. The model can be used to predict the mean and population variability of intestinal BS concentrations [BS] as a function of time and prandial status.

Methods

Twenty-four hour fasting-fed-fasting motility profiles of the GB were generated together with a meal ingested at a random time during this period. The distinctive characteristics of the model (Fig. 1) include: the generation of individualised IMMC cycle patterns; IMMC-associated GB filling and emptying phases; hepatic bile acid secretions rates and regional bile acid absorption kinetic parameters. The total bile mass within in the GB as well as that within the gut lumen fluids is assumed to be well mixed. The performance of the proposed model was assessed by comparing the predicted regional [BS] with those reported from *in vivo* studies [4 -5]. The current simulation results were obtained using Simcyp v18.

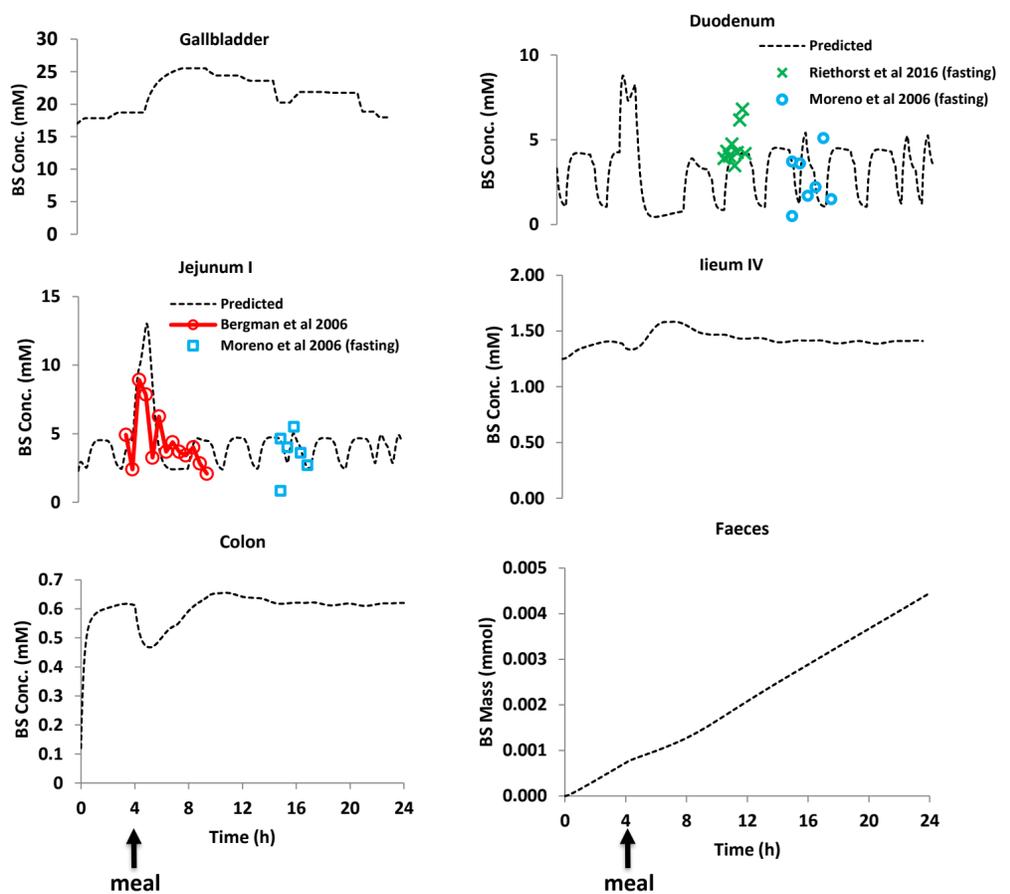
Fig. 1 Some features of the Advanced Dynamic Bile Salt Model (ADBSM).



Results

Fig. 2 shows the results of the simulations of an average individual showed the cyclic fluctuations of BS concentration in the GB, duodenum, proximal jejunum, terminal ileum and colon. The predicted Bile Salt concentrations [BS] in the duodenum ranged between 0.25-14 mM (fasted) and 0.45-48 mM (fed) which is within the reported *in vivo* ranges (fasted: 0.03-36.18 mM; fed: 0.74-86.14 mM, [4]). [BS] within proximal Jejunum (i.e. within the first jejunal compartment) ranged 2.5 – 5 (fasting) and 8.9 – 12.9 (fed) which is fairly similar to observed data 4.45 ±2.05 mM and ~9 mM for fasting and fed conditions, respectively [5].

Fig. 2 Simulated bile salt concentration (or mass) vs time profiles.



Conclusions

Quantitative estimation of time-varying [BS] and its population variability within the GI tract may be critical for the accurate prediction of oral drug absorption of certain drugs. *In vivo* measurements of BS duodenal concentrations have shown multiple BS peaks [1] which can be linked to coordinated GB and GI tract motility. The developed ADBSM, coupled with GI fluid volume dynamics, can describe the *in vivo* observations for the GB and also predict reasonably well the duodenal and jejunal [BS] within known physiological ranges [4 - 6]. Further work is underway to introduce time-dependent hepatic secretions according to the feedback mechanism from the lumen of GI tract. The ADBSM has been integrated into the Simcyp Simulator v18. It can also be used for enterohepatic re-circulation of drug and/or metabolite(s).

References

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