A comprehensive and systematic review of gastric pH and factors affecting gastric fluid volume dynamics under fasted and fed conditions in healthy adults.

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Abstract

In order to enhance modelling of oral drug absorption processes in physiologically-based pharmacokinetics (PBPK) models, in-depth understanding of gastro-intestinal (GI) physiology and its related variability is required. Currently, interindividual variability and the impact of food on gastric parameters are insufficiently explored. Hence, an extensive review of literature and meta-analysis was carried out on reported values of salivary flow rates, gastric pH, fluid volumes, gastric secretion rates and bile salt concentrations in the stomach of healthy human subjects under fasted and fed conditions. The results indicate high inter-subject variability in these key GI parameters in both conditions. Also, food significantly influenced these parameters, with a 2-17 fold increase in the mean values in the presence of food.

Background

The extent and rate of drug absorption from the gastrointestinal tract depends on different factors which include the active pharmaceutical ingredient properties, the formulation characteristics and physiological and anatomical parameters (Zhang *et al.,* 2014). An in-depth understanding of GI physiology and its related variability is essential for mechanistic modelling of oral drug absorption using PBPK models. Among other factors, the stomach fluid volumes, transit times, pH and pressure can significantly affect release/disintegration, dissolution and precipitation of drugs (Hens *et al.,* 2016). In this study, a systematic review of the literature was carried out to collate and analyse gastric pH and factors affecting gastric fluid volume dynamics under fasted and fed conditions in healthy humans.

Methods

Measured data from the literature (using the PubMed, Google and Google Scholar search engines) were collated, systematically reviewed and meta-analysis conducted. About 105 articles published between 1943 and 2018 were collated reporting the measured values for salivary flow rates, gastric pH, fluid volumes, gastric secretion rates and bile salt concentrations in the stomach of healthy human subjects under fasted and fed conditions. Studies were included/excluded based on strict criteria. Statistical analysis of these physiological parameters was carried out and the parameters, weighted mean (*n* = number of subjects), standard deviation (SD) and variability [*i.e.*, individual range, CV% (Coefficient of Variation)] were calculated.

Results

Under fasted conditions, the weighted mean ± SD values (ranges) of salivary secretion rate, initial gastric fluid volume, gastric secretion rates, bile salt concentrations in the stomach and gastric pH were 22.7 ± 21.4 (3-249) mL/h (n=1161), 31.4 ± 25.1 (1-96) mL (n=335), 69.9 ± 38.8 (18-234) mL/h (n=217), 0.41 ± 0.50 (0.002-1.8) mM (n=196) and 2.1 ± 1.5 (0.07-7.7) (n=716), respectively.

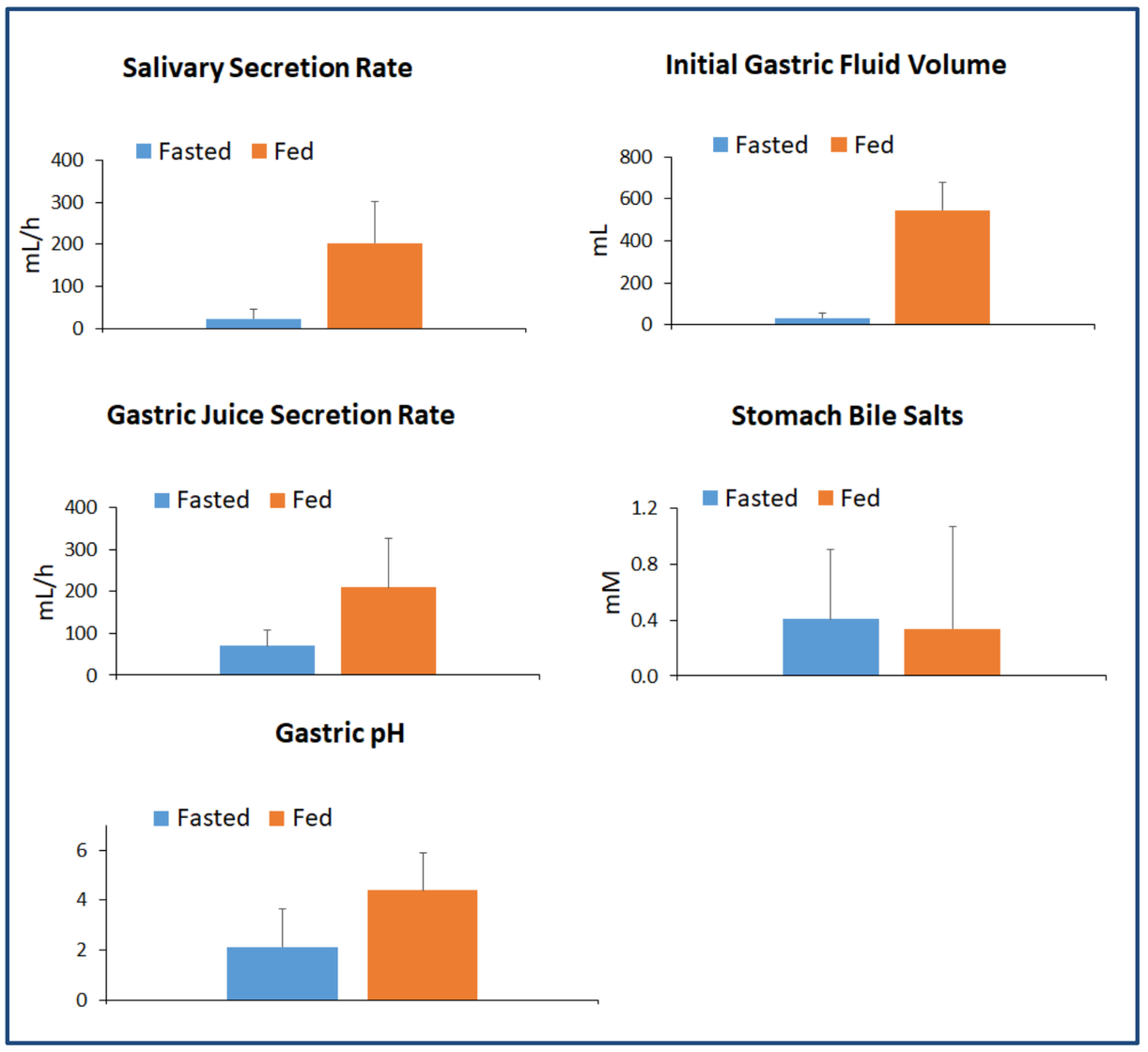
Under fed conditions, the weighted mean ± SD values (ranges) of salivary secretion rate, initial gastric fluid volume, gastric secretion rates, bile salt concentrations in the stomach and gastric pH were 202.8 ± 98.0 (48-379) mL/h (n=184), 545.3 ± 131.5 (310-628) mL (n=40), 209.2 ± 118.2 (104-434) mL/h (n=62), 0.34 ± 0.73 (0.007-4.2) mM (n=119) and 4.4 ± 1.5 (0.1-7.5) (n=323), respectively.

There was high inter-subject variability in these measured parameters with CV ranging from 55-123% and 57-217% in fasted and fed conditions respectively.

In addition to higher inter-subject variability, with the exception of bile salt concentrations in the stomach, the intake of food significantly influenced these key parameters (Fig 1), with a 2-17 fold increase in the mean values in the presence of food.

Results

Fig 1 : Measured (weighted mean ± SD) gastric secretions, fluid volumes, bile salt concentrations and gastric pH under fasted and fed conditions in healthy humans.



Conclusions

- There was very high inter-subject variability in the fluid volumes/ secretion rates, bile salt levels and pH in the stomach.
- The intake of food significantly altered these parameters, when compared to measured values in the fasted state.
- Although the information available is limited, the type of food (*i.e.*, composition, fat/protein content, *etc*.) can also markedly influence these key parameters.
- These physiological parameters are being incorporated into the Simcyp Simulator whereby the inter-subject variability of these and other physiological parameters are integrated to anticipate population variability in fraction absorbed and other PK parameters.
- Such knowledge facilitates more realistic modelling of oral drug absorption and, when coupled with greater knowledge of intra-subject variability of such parameters, paves the way to conduct virtual bioequivalence studies.

References

- Zhang et al., (2014) Clin Pharmacol Ther. 95(5):480-2.
- Hens et al., (2017) Int J Pharm. 519(1-2):79-97.

19th Simcyp Consortium Meeting, September 2018, Sheffield, UK