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

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PURPOSE

The rate and extent 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). 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).

An in-depth understanding of gastrointestinal physiology and its related variability is essential for mechanistic modelling of oral drug absorption using physiologically-based pharmacokinetic (PBPK) models.

Currently, interindividual variability and the impact of food on gastric parameters are insufficiently explored.

OBJECTIVES

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 adult 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

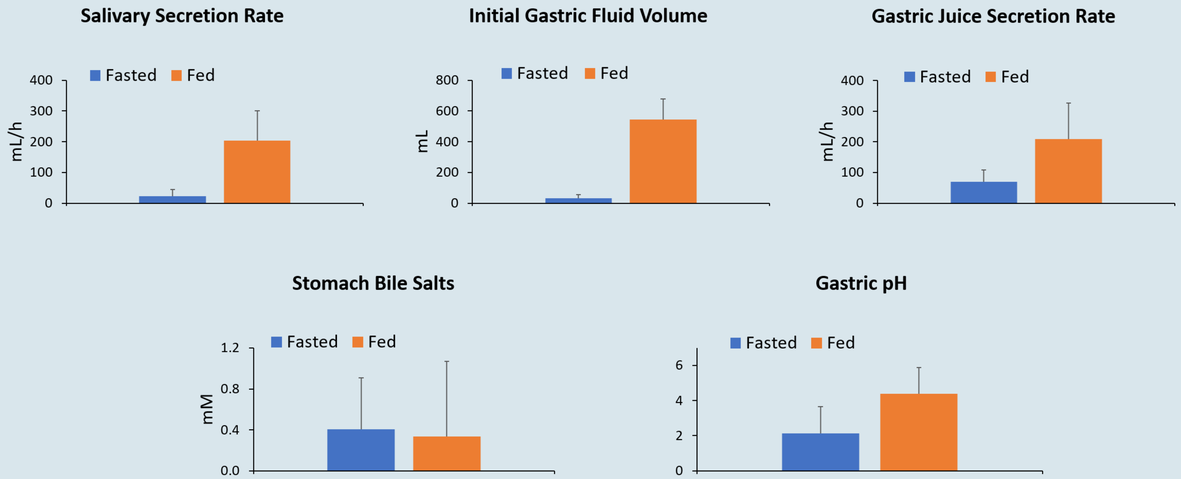

Figure 1 : Measured (weighted mean ± SD) gastric secretions, fluid volumes, bile salt concentrations and gastric pH under fasted and fed conditions in healthy humans

- 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.

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

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