Introduction

The oral bioavailability of drugs is influenced by a variety of factors, including the regional gastrointestinal (GI) pH. Small changes in the GI pH profile may have a great influence on the dissolution and absorption of drugs that exhibit pH-dependent dissolution and absorption.

Therefore, a precise knowledge of GI pH levels and their variability under different dosing conditions is of particular importance for formulation scientists and modellers to help them properly design and target drug release correctly and to further characterize the impact of GI pH on a drug’s in vivo plasma pharmacokinetic profile.

There have been numerous literature studies that have examined the pH in different regions of the GI tract. However, the experimental design, such as the method of measurement, fed status, meal caloric content, and number of subjects included in the studies, have varied widely, making it difficult to make comparisons or choose values for use in models of oral drug absorption.

Study Objectives

The aims of this study were to:

- Review the literature and conduct a quantitative meta-analysis for the values of, and variability in, gastrointestinal pH throughout the different GI segments and characterize the effect of food on the values and variability in these parameters.
- Present quantitative meta-models of the distributions of GI pH throughout the GI segments.
- Model the time course of postprandial gastric pH after administration of food of different caloric content.

Methods

The literature was systematically reviewed for the values of, and variability in, GI pH under fed and fasted conditions in healthy subjects.

The GI tract was categorised into 10 distinct regions: stomach (proximal, mid-distal), duodenum (bulb, mid-distal), jejunum, ileum, transverse, descending, and ascending colon.

Search engines of Web of Science, PubMed, and Google Scholar were used to screen for potential articles. The key words used in the search were “gastric pH,” “small intestinal pH,” “gastrointestinal pH,” “transit pH,” AND “healthy subjects.”

Meta-analyses of the means and SDs of GI pH were conducted using the “metfor” package of the R language. Multi-level random-effects and mixed-effects models were investigated in the meta-analysis to account for any correlations induced by the multi-level structure of the data.

Publication bias was diagnosed using funnel plots.

Modelling the time course of postprandial stomach pH and other GI pH measurements.

The effect of various categorical and continuous moderators on GI pH were investigated including method of pH measurement, study origin, food caloric content, age, and time since last meal.

Results

The final number of studies (K) included in the meta-analysis of GI pH was k = 23 with a total number of 89 mean and SD values for the pH in the different GI locations/sub-locations.

Table 1: Transient meta-mean and meta-standard deviation of postprandial pH

<table>
<thead>
<tr>
<th>GI Segment</th>
<th>Meta-mean</th>
<th>Meta-SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>6.98</td>
<td>0.51</td>
</tr>
<tr>
<td>Duodenum</td>
<td>7.02</td>
<td>0.68</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>6.55</td>
<td>0.73</td>
</tr>
<tr>
<td>Colon</td>
<td>6.38</td>
<td>0.88</td>
</tr>
<tr>
<td>Rectum</td>
<td>6.33</td>
<td>0.86</td>
</tr>
</tbody>
</table>

The mean gastric pH was more variable in the fasted state than in the fasted state (Table 1).

Small Intestinal pH

The duodenal pH was significantly different from the other intestinal segments, as the data were significantly different from each other in the postprandial state (Table 1). The pH in the duodenum was significantly lower than in the jejunum and ileum, while the pH in the jejunum and ileum were not significantly different from each other.

The pH in the distal small intestine was significantly different from the proximal and mid small intestine (Table 1).

Colon pH

The meta-mean pH for the descending colon was significantly different from the ascending and transverse colon (Table 1). None of the tested moderators had significant effects on the meta-SD estimate of pH in the different parts of the colon.

Time course of postprandial gastric pH

Overall, 213 mean gastric pH data points were extracted from 4 studies and were used in the fitting postprandial gastric pH profile.

The time course of postprandial pH was described using an exponential model. Caloric content, stomach sub-location and meal type (liquid vs. solid meal) were significant covariates retained in the final model. Increased caloric content increased the extent and duration of postprandial gastric pH buffering (Figure 2).

Discussion & Applications

The study presents a list of gaps in the literature and, to our knowledge, is the first systematic review and quantitative meta-analysis for the values of, and variability in, the GI pH in the fed and fasted states.

The presented analysis has important implications for both formulation scientists and modellers. For example, gastrointestinal pH is an important aspect to consider in the development of pH-sensitive formulations, such as enteric-coated dosage forms. Polymers used in enteric coated dosage forms have pH-dependent dissolution, and therefore, it becomes important to know the pH levels along the GI tract and their variability between people for the proper formulation design. The knowledge of pH levels is important for modellers to perform mechanistic in silico predictions of product performance.

The presented meta-models of GI pH can be used as part of semi-physiologically based absorption models to represent the effects of GI pH in the different GI compartments on the in vivo drug release and dissolution. For example, establishing IVIVC and predicting the impact of GI pH on the in vivo pharmacokinetics of BCS class II low pH weakly acidic/weakly basic drugs that exhibit pH-dependent dissolution.

The current analysis of postprandial gastric pH in this study accounted for the effect of the magnitude of caloric content on gastric pH but we were not able to include the form of the meal administered (e.g. high protein vs high carbohydrate meals). In the latter case, different effects on gastric pH may be observed depending on the content of the meal administered.

Conclusion

A quantitative meta-analysis and meta-models were presented to characterize the pH throughout the GI tract in the fed and fasted states.

The fed status significantly influenced the estimated mean gastric pH and duodenal pH but had no significant influence on intestinal segments distal to duodenum.

The knowledge of GI pH levels and their variability between subjects is important for optimizing pharmaceutics dosage forms, and for in silico and in vivo prediction of formulation performance.

References


Acknowledgments

Richard N Upton and David J.R. Foster were supported by an Australian Postgraduate Research Scholarship.