**Introduction**

- The in vivo performance of non-dissociating single-unit (tablet/capsule) and multiple-unit (pellets, multi-tablets) dosage forms may sometimes be markedly influenced by their transit through the gastrointestinal (GI) tract.

- Different regions of the GI tract have different drug absorbptive properties, and therefore, the transit time in each GI region and its variability between subjects may contribute to the variability in the rate and/or extent of drug absorption between subjects.

- There have been numerous literature studies that have examined the transit times of non-dissociating single-unit and multiple-unit dosage forms in the stomach, small intestine and colon. However, the experimental design, such as the method of investigation: size and density of the dosage form; fed status; and meal caloric content have varied widely making it difficult to make comparisons and 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 (GI) transit times of non-dissociating single-unit and multiple-unit solid dosage forms under fed and fasted conditions, with respect to documenting factors affecting oral drug absorption.
  - Present quantitative meta-models of the distributions of GI transit times.

**Methods**

- The literature was systematically reviewed for the values of, and the variability in, GI transit times for non-dissociating dosage forms under fed and fasted conditions in healthy subjects.
- GI locations for meta-analysing GI transit times were categorized as stomach, small intestine, colon and whole gut transit.
- Search engines of Web of Science, PubMed and Google Scholar were used to screen for potential articles. The keywords used for search were “gastric emptying”, “small intestinal transit”, “colonic transit”, AND “non-dissociating tablets,” OR “pellets,” AND “healthy subjects.”
- Meta-analyses of the means and SDs of GI pH were conducted using the “metafor” 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.
- Categorical moderators investigated in the analysis included the method used for transit time measurement, meal type (liquid vs. semi-solid meals), nature of the dosage form (multiple unit versus single unit dosage forms) and study protocol.
- Continuous moderators investigated in the analysis included the caloric content of administered food, population average age, population average body weight, the diameter and density of the dosage form, and the time of meal administration (TOM) relative to the time of dosage form administration.
- Publication bias was diagnosed using funnel plots.

**Results**

- The final numbers of studies (k) included in the meta-analysis of GI transit times were k = 29 with a total number of 125 mean and SD values for the GI transit time in the stomach, small intestine and colon.
- Two level meta-analysis models, where correlated random effects were added at the study level, were chosen to conduct the meta-analysis based on the assessment of the likelihood diagnostic plots.

**Small intestinal transit time**

- All tested moderators, including food caloric content, had no significant effect on the meta-mean small intestinal transit time of both single- and multi-unit dosage forms (Figure 2). However, caloric content had significant influence on the variability in the small transit time where between-subjects variability increases with increased food caloric content (Figure 3 & Table 1).

**Colon and whole gut transit time**

- There were only 4 means and SDs sourced from 3 studies that were used in the meta-analysis of colonic transit time (COTT) and whole gastrointestinal transit time (WITT) among which only one observation was for multiple-unit dosage form (pellets).

**Discussion & Applications**

- Unlike the meta-analysis conducted by the Davis et al. study, the current meta-analysis provided a quantitative evaluation and prediction of the values of, and variability in, gastrointestinal transit time under fasted and different fed conditions and all the data included in the analysis were collated from published studies.
- GI transit times are of particular importance for orally administered BCS Class I, II, III and IV enteric coated formulations.
- The rate limiting step for the absorption of BCS Class I drugs is gastric emptying, therefore, factors that delay gastric emptying will delay the absorption. Similarly, a delay in gastric emptying of enteric coated formulations to the more alkaline intestinal environment delay drug absorption and may influence the drugs’ oral bioavailability.
- Gastric emptying may also influence the dissolution and the solubility of poorly water-soluble weakly basic drugs (e.g., tricyclics) where a delay in gastric emptying after food ingestion, associated with increased gastric pH, will diminish drug’s dissolution and, therefore, influence the drug’s bioavailability.
- Many of BCS Class III drugs, such as captopril, show regionally-dependent drug absorption with better absorption in the upper small intestine, giving them a limited window for drug dissolution and absorption.
- The meta-values of GI transit times can be used as part of semi-physiological absorption models to characterize the influence of transit time on the dissolution, absorption and in vivo pharmacokinetic profiles of oral drugs.

**Conclusion**

- A quantitative meta-analysis and meta-models were presented to characterize the GI transit times of non-dissociating single- and multi-unit solid dosage forms in the fed and fasted states.
- GI transit time is an important physiological factor that may influence the dissolution and absorption of oral drugs and thus should be taken into consideration for proper prediction of in vivo formulation performance.

**References**

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