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Research Article

A Quantitative Review and Meta-models of the Variability and Factors Affecting Oral Drug Absorption—Part II: Gastrointestinal Transit Time

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Abstract. This study aimed to conduct a quantitative meta-analysis for the values of, and variability in, gastrointestinal (GI) transit times of non-disintegrating single-unit ("tablet") and multiple-unit ("pellets/multi-unit tablet") solid dosage forms, characterize the effect of food on the values and variability in these parameters and present quantitative meta-models of the distributions of GI transit times in the respective GI regions to help inform models of oral drug absorption. The literature was systemically reviewed for the values of, and the variability in, gastric, small intestinal and colonic transit times under fed and fasted conditions. Meta-analysis used the "metafor" package of the R language. Meta-models of GI transit were assumed to be log-normally distributed between the studied populations. Twenty-nine studies including 125 reported means and standard deviations were used in the meta-analysis. Caloric content of administered food increased variability and delayed the gastric transit of both pellets and tablets. Conversely, food caloric content reduced the variability but had no significant influence on the mean small intestinal transit time (SITT). Food had no significant effect on the transit time through the colon. The transit of pellets through the colon was significantly slower than that of single-unit tablets which is most likely related to their smaller size. GI transit times may influence the dissolution and absorption of oral drugs. The meta-models of GI transit times may 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.

KEYWORDS: colonic transit time; gastric emptying; gastrointestinal transit time; meta-analysis; small intestinal transit time.

INTRODUCTION

Single-unit ("tablet/capsule") and multiple-unit ("pellets, multi-tablets") dosage forms are two widely used formulations administered by the oral route. The performance of such formulations *in vivo* may sometimes be markedly influenced by their transits through the gastrointestinal (GI) tract (1). The different regions of the GI tract exhibit different characteristics in terms of absorptive properties, surface area, enzymes and transporters, pH and luminal content. All these variables may affect the absorption and kinetics of oral drugs.

There have been numerous literature studies that have examined the transit times of non-disintegrating single-unit and multiple-unit dosage forms in the stomach, small intestine and colon (2–30). 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 or choose values for use in models of oral drug absorption.

In this article, we reviewed the literature for the values of, and the variability in, GI transit times of non-disintegrating single-unit and multiple-unit solid dosage forms with respect to documenting factors affecting oral drug absorption. We then conducted a quantitative meta-analysis for the mean values of, and variability in, GI transit times of non-disintegrating solid dosage forms in the different GI regions, including the impact of food and caloric content. The presented meta-analysis fills a gap in the literature in documenting and presenting meta-models of transit times in the respective GI regions. In a companion paper, a similar analysis was conducted for GI pH.

The aims of this article were to:

- Review the literature to document the values of, and the variability in, GI transit times of non-

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disintegrating single-unit and multiple-unit solid dosage forms under fed and fasted conditions, with respect to documenting factors affecting oral drug absorption
- Perform a quantitative meta-analysis on the literature data of the reported means and standard deviations of GI transit times and investigate the influence of food on the values and variability in these parameters
- Present quantitative meta-models of the distributions of GI transit times

METHODS

Inclusion Criteria

The inclusion criteria for studies used in the analysis were the following: (1) studies reporting GI transit times measured in healthy adult human participants; (2) studies reporting GI transit times of pellets and non-disintegrating tablets/capsules; and (3) studies reporting GI transit times in the fasted state or after a meal administered at a defined time. Only English articles were considered.

Search Strategies

Multiple methods were used to obtain relevant research for inclusion in the meta-analysis of the current study. First, the search engines of Web of Science, PubMed and Google Scholar were used to screen for potential articles. The key words used for the search were "gastric emptying", "small intestinal transit", "colonic transit" AND "non-disintegrating tablets" OR "pellets", AND "healthy subjects". Second, gastrointestinal transit time (GITT) studies included in the Culen *et al.* review (31) were reviewed and relevant studies were included in the analysis. Third, references located in primary articles of GI transit times were reviewed and relevant studies were included in the analysis. No restriction was placed on publication dates, and articles available before October 2015 were included in the meta-analysis.

GI Locations

GI locations for meta-analysing GI transit times were categorized as stomach, small intestine, colon and whole gut transit.

Effect Sizes

As per convention, the term "effect sizes" was used generically throughout the manuscript to denote the measures used for meta-analysis and does not necessarily imply an effect size of a clinical treatment (32). The effect sizes of the current analysis were the literature-reported means and standard deviations of GI transit times of single- and multiple-unit solid dosage forms. The mean values for the transit time of multiple-unit dosage forms (i.e. pellets/multi-unit tablets) were recorded as the mean time needed to empty 50% of the pellets/tablets ($T_{50\%}$) from the corresponding GI location. If the standard error of the mean (SEM) was reported in the studies, then the standard deviation (SD) was calculated using a standard formula [SD = SEM * sqrt(n), where n is the number of subjects in the study].

To apply the meta-analytic methods on means and SDs of GI transit times, it was assumed that the sampling distribution of means and SDs across studies was approximately normal. The corresponding sampling variances of the means and SDs (33) were calculated as per Eq. (1).

$$vi.\ mean = \frac{\sigma^2}{n};\ \ vi.\ SD = \frac{\sigma^2}{2 * n} \tag{1}$$

where *vi.mean* and *vi.SD* are the sampling variance of means and standard deviations, respectively; σ^2 is the (unknown) true variance which, for the current analysis, is the observed sample variance (s^2); and n is the number of subjects in the study.

Statistical Analysis

Meta-analyses of the effect sizes (means and SDs of GI transit time) were conducted using the metafor package (34) of the R statistics software (35). Random- and mixed-effects models were implemented in the meta-analysis. Some studies included in the meta-analysis reported data for multiple comparisons (e.g. gastric transit time under fed and fasted conditions); therefore, multi-level random- and mixed-effects models were investigated in the meta-analysis to account for the correlation induced by the multi-level structure of the data.

Several multi-level meta-analysis models were tested. These included two-level models, where random effects were added at the study level, and three-level models, where random effects were added at the study level and prandial status. The models were evaluated for identifiability of random effects using the profile likelihood plots of the variance components of the respective models. The restricted maximum-likelihood (REML) estimation method (36) was used for model fitting. A p value of <0.05 was adopted as the statistical criterion throughout the analysis.

Forest plots were generated to show the effect sizes for each of the relevant studies with the estimated meta-mean and meta-standard deviation (meta-SD) generated from the meta-analysis along with their corresponding 95% confidence intervals. The presence of heterogeneity and publication bias was diagnosed for each meta-analysis using funnel plots (37) with the effect size (for random-effects models) or residual value (for multi-level mixed-effects models) on the horizontal axis plotted against the corresponding standard error (SE) on the vertical axis. Funnel plot asymmetry was tested using Egger's regression test (38) using the sampling variance as the measure of the precision of the studies.

Moderator Analysis

Various categorical and continuous moderators were investigated in the meta-analysis of GI transit time. Categorical moderators included the method used for transit time measurement, meal type (liquid versus non-liquid meals), nature of the dosage form (multiple-unit versus single-unit

dosage forms) and study protocol. The latter categorizes the time of dosage form administration relative to the time of meal administration (0, fasted; 1, immediately after meal; 2, immediately before meal; 3, after at least 15 min of administering the meal; and 4, at least 30 min before administering the meal).

Continuous moderators 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; for example, if the meal was administered just before or after the dosage form, then TOM = 0, and if the meal was administered 0.5 h before the dosage form, TOM = −0.5 and so on.

RESULTS

Result of the Systematic Review

The final numbers of studies (k) included in the meta-analysis of GI transit time 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. A summary of the effect sizes and moderators used in the analysis is provided in Table SI of the supplementary material.

Some studies reported the range (minimum and maximum), rather than the mean/median values, of the continuous moderators of density [1 study; (2)], diameter of the dosage form [7 studies; (2, 5, 9, 10, 15, 19, 28)], population age [17 studies; (2–6, 9–12, 15, 16, 20, 21, 24, 26, 28, 30)] and population weight [13 studies; (2, 5, 9–12, 15, 16, 20, 24–26, 28)]. For such studies, the average of the minimum and maximum of the corresponding moderator was used in the moderators' analysis.

Caloric content of administered food was an important aspect of the current analysis. Some studies provided no direct information about the caloric content of the administered meal. Whenever possible, the caloric content of such studies was imputed based on inferences from other studies that reported the caloric content of the administered meal and used a similar study design. The caloric content of the light breakfast used in the Coupe *et al.* (5) and Christensen *et al.* (28) studies was assumed to be similar to the light breakfast (358.5 Cal) used in the Khosla *et al.* (12) study. The standard breakfast administered in the Ibekwe *et al.* (21) and Weitschies *et al.* (26) studies was assumed to be similar to the standard breakfast (669.2 Cal) used in the Abrahamsson *et al.* (2) study.

Remaining missing continuous moderators of density [18 studies; (2–8, 10–12, 14, 17, 21, 23, 24, 26, 29, 30)], diameter [2 studies; (3, 12)], age [2 studies; (19, 27)] and weight [12 studies; (3, 4, 6, 8, 13, 17–19, 21, 23, 27, 30)], where no inferences were possible about their actual values, were imputed by the corresponding median.

Gastrointestinal Transit Time Distribution

The distribution of GITT was assumed to be log-normally distributed between subjects as this prevented negative values for the GI transit time.

The meta-model GITT distribution plots were constructed by randomly generating 100,000 meta-mean GITT values, in the respective GI region, from a log-normal distribution with a mean of log(meta-mean) and standard deviation of (meta-SD/meta-mean) using the *rlnorm* functionality in R (35).

Statistical Analysis

In the three-level models, large parts of the likelihood profile diagnostic plots of the variance components were flat (figures not shown) indicating that the variance (and correlation) components of the model were unidentifiable, thus suggesting an over-parametrized model. Conversely, the likelihood profiles of the two-level meta-analysis models, where correlated random effects are added at the study level, indicated that variance components were identifiable, and therefore, this was chosen to conduct the meta-analysis.

Gastrointestinal Transit Time

Gastric Transit

A total of 70 means and SDs sourced from 28 studies were used in the meta-analysis of gastric transit time (GTT) of single- and multiple-unit dosage forms. The mean GTT data used in the analysis are visualized in Fig. S1 of the supplementary material. The caloric content of the administered meal was a significant moderator affecting the estimated meta-mean and meta-SD (p value < 0.001) of the gastric transit time. Increased caloric content resulted in increased gastric transit time and increased between-subject variability in gastric transit of single- and multi-unit dosage forms. Additionally, administering snacks 2.5 h after the main meal significantly delayed gastric transit by ~1.5–2 h.

The predicted meta-mean and meta-SD of gastric transit time, as a function of caloric content, with the 95% credibility interval are presented in Figs. 1 and 2, respectively. Based on the fitted model, the predicted meta-mean (with/without snacks) and meta-SD of GTT under the fasted state and after 100-, 300-, 700- or 1000-Cal meals are summarized in Table I; a graphical overview of the meta-mean and meta-SD results is presented in Fig. 3 and Fig. S2 of the supplementary material, respectively. Assuming a log-normal distribution of transit times among individuals in a population, the distribution density plots of GTT under fasted and selected fed conditions are presented in Fig. 4a.

Small Intestinal Transit

A total of 51 means and SDs sourced from 22 studies were used in the meta-analysis of small intestinal transit time (SITT) of single- and multiple-unit dosage forms. The mean SITT data used in the analysis are visualized in Fig. S3 of the supplementary material. All tested moderators, including food caloric content, had no significant effect on the meta-mean small intestinal transit time. However, caloric content had significant influence on the variability in the small transit time between subjects. Unlike the gastric transit time, where the variability in gastric transit time increased with increased caloric content, the variability in SITT decreased with

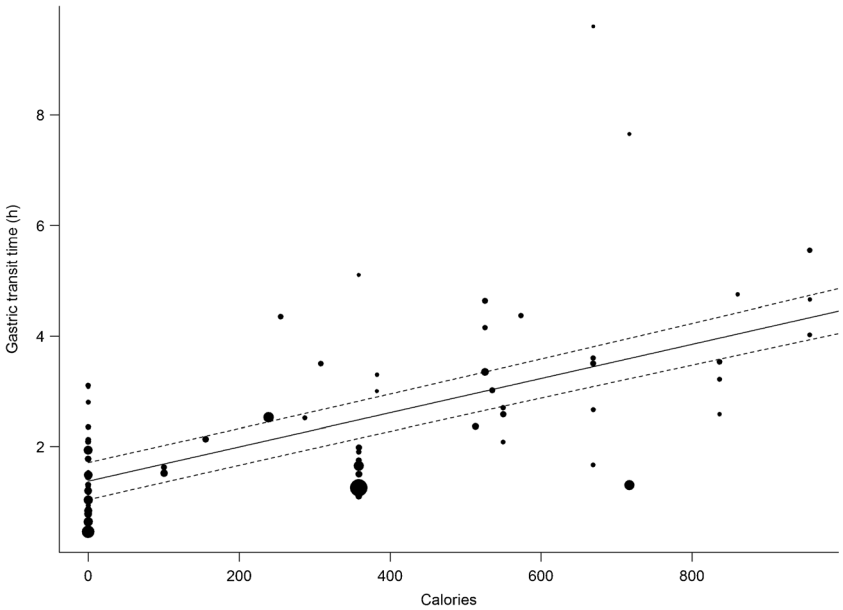

Fig. 1. The predicted meta-mean gastric transit time (GTT) as a function of food caloric content. *Black circles* are the observed mean GTT in individual studies drawn with size proportional to the inverse of the corresponding standard errors. The *solid black line* is the predicted meta-mean GTT. The *two dashed lines* constitute the interval estimates where 95% of the true GTT would fall in the hypothetical population of studies

increased meal caloric content. The predicted between-subject variability (i.e. meta-SD) in SITT as a function of caloric content, with the 95% credibility interval, is presented in Fig. 5. A summary of the estimated meta-mean and meta-SD of SITT is presented in Table I, and a graphical overview of the results of the meta-mean and meta-SD SITT is presented in Fig. 6 and Fig. S4 of the supplementary material, respectively. The distribution density plots of SITT are presented in Fig. 4b.

Colonic and Whole Gut Transit

There were only 4 means and SDs sourced from 3 studies that were used in the meta-analysis of colonic transit time

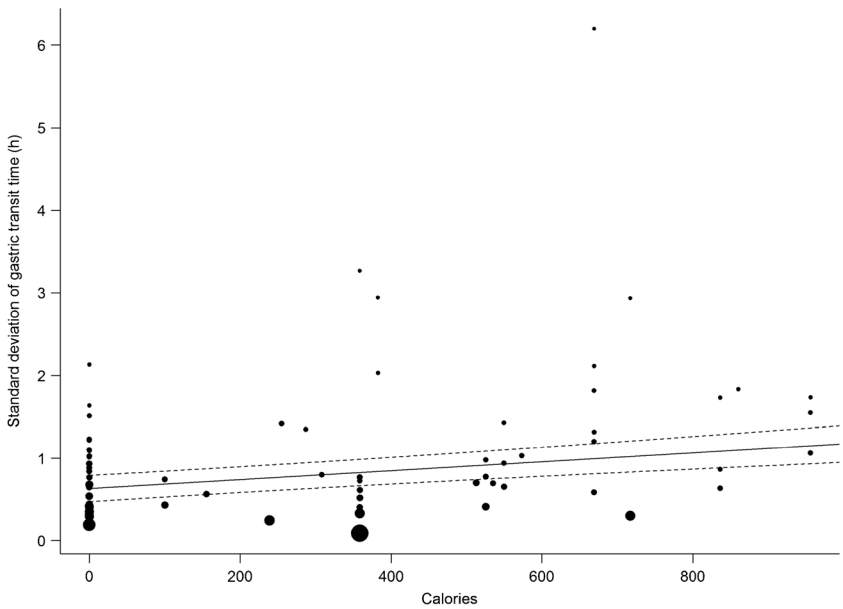

Fig. 2. The predicted variability in gastric transit time as a function of food caloric content. *Black circles* are the observed standard deviations in individual studies drawn with size proportional to the inverse of the corresponding standard errors. The *solid black line* is the predicted meta-SD. The *two dashed lines* constitute the interval estimates where 95% of the true SD would fall in the hypothetical population of studies

Table I. Estimated Meta-mean and Meta-standard Deviation of Gastrointestinal Transit Time

GI location	Meta-mean	SE mean	95% CI	Meta-SD	SE-SD	95% CI
Gastric transit time						
Fasted	1.37	0.17	1.04–1.71	0.63	0.08	0.47–0.79
100 Cal	1.68	0.17	1.35–2.02	0.67	0.08	0.53–0.84
300 Cal	2.30	0.17	1.97–2.64	0.79	0.08	0.64–0.95
700 Cal	3.54	0.19	3.18–3.91	1.01	0.09	0.83–1.20
1000 Cal	4.47	0.21	4.06–4.88	1.17	0.11	0.95–1.40
100 Cal + snacks[a]	3.15	0.32	2.52–3.78	–	–	–
300 Cal + snacks[a]	3.77	0.32	3.15–4.39	–	–	–
700 Cal + snacks[a]	5.00	0.31	4.39–5.62	–	–	–
1000 Cal + snacks[a]	5.94	0.32	5.31–6.55	–	–	–
Small intestine transit time						
Regardless of food[c]	3.49	0.16	3.17–3.80	1.02[b]	0.10	0.83–1.20
100 Cal	–	–	–	1.11	0.09	0.92–1.29
300 Cal	–	–	–	1.00	0.09	0.83–1.19
700 Cal	–	–	–	0.81	0.10	0.61–1.01
1000 Cal	–	–	–	0.66	0.13	0.41–0.91
Colon transit time						
Single-unit	20.28	3.5	13.42–27.15	13.09	2.02	9.12–17.06
Multi-unit	31.95	6.23	19.73–44.16	13.09	2.02	9.12–17.06
Whole gut transit time	29.81	2.26	25.38–34.24	14.52	1.60	11.39–17.65

Values are in hours. For multiple-unit dosage forms, the values represent the $T_{50\%}$
CI confidence interval, *SE* standard error, *SD* standard deviation
[a] Additional snacks administered after 2.5 h of the main meal. Snacks consisted of an apple or yogurt or a piece of cake/cookie with a cup of tea or coffee
[b] Meta-SD value regardless of caloric content
[c] Food caloric content had no significant effects on the meta-mean estimate of small intestinal transit time

(COTT) and whole gastrointestinal transit time (WGITT) among which only one observation was for multiple-unit dosage form (pellets). The data used in the analysis are visualized in Fig. S5 of the supplementary material. Due to the small number of observations, full moderator analysis was not possible and only formulation type (tablet versus pellets), diameter and caloric content were assessed as potential moderators on colonic transit time and a random-effects model was used to estimate the meta-mean and meta-SD WGITT. The meta-model of COTT revealed a statistically significant difference between the transit of a single-unit tablet and multi-unit pellets. A summary of the estimated meta-mean COTT and WGITT and the associated meta-SD is presented in Table I, and a graphical overview of the meta-mean results of COTT and WGITT is presented in Figs. 7 and 8, respectively. A graphical overview of the meta-SD results is presented in Figs. S6 and S7 of the supplementary material. The distribution density plots of COTT and WGTT are presented in panels c and d of Fig. 4, respectively.

Publication Bias

Funnel plots of the meta-mean and meta-SD models of gastric, small intestinal and colonic transit times are presented in Fig. 9. Eggers' regression test indicated no significant asymmetry in the funnel plots of the meta-mean models for small intestine and colon transit time; however, it indicated significant asymmetry in the gastric meta-mean transit time models (p value < 0.05). The latter may be an indication of publication bias in the published gastric transit time data; however, visual inspection of funnel plots shows that the asymmetry in the funnel plots was not substantial and the two studies on the extreme right-hand side of the gastric meta-mean funnel plot may have had excessive influence on the regression test results. We believe that a potential publication bias of this extent would not greatly impact the conclusions from the meta-analysis models. Funnel plots of meta-SD models of the stomach and small intestinal are left censored due to the fact that the standard deviation of GITT cannot be less than zero.

DISCUSSION

The article herein presents a systematic review and meta-analysis of the literature for the values of, and the variability in, the gastrointestinal transit time of non-disintegrating single- and multiple-unit dosage forms in the fed and fasted states. Several literature studies aimed to characterize GI transit times for pellets and/or single-unit tablets (39, 40). Unlike the meta-analysis conducted by the Davis *et al.* study (39), 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. Furthermore, all the data included in the current analysis were collated from published studies. A more recent meta-analysis study has been reported by Henin *et al.* (40) where individual GI transit time data were collated across five magnetic marker monitoring studies to characterize the transit of non-disintegrating and slowly eroding tablets under fasted and fed conditions. The latter study has the advantage of using subject-specific data of GI transit times rather than mean aggregate data; however, it did not investigate the

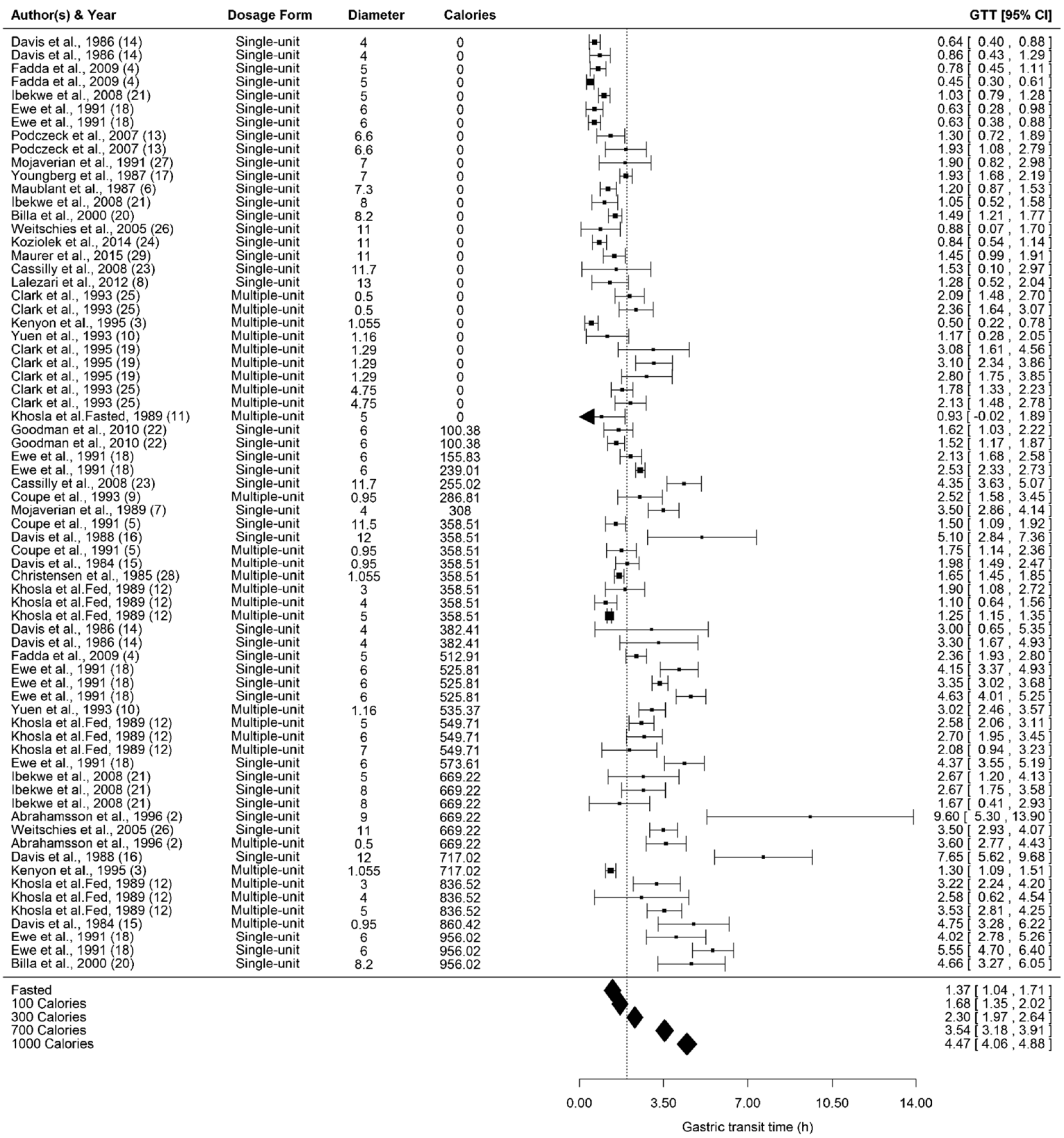

Fig. 3. Forest plot of the estimated meta-mean gastric transit time of single- and multiple-unit dosage forms. The figure shows mean gastric transit time (GTT) with the corresponding 95% confidence intervals in the individual studies and based on a two-level mixed-effects model. The *dotted vertical line* is the meta-mean regardless of food. References: (2–29)

effect of various factors, such as caloric content, on the values of, and variability in, gastric and/or small intestinal transit time. The study herein fills a gap in the literature in documenting and presenting quantitative meta-analysis models of transit times of non-disintegrating single- and multiple-unit solid dosage forms in the respective regions of the GI tract under fasted and different fed conditions.

Multi-level meta-analysis models were investigated in the current analysis. The two-level random- and mixed-effects models with study as the level of grouping variable were selected for the final analysis. Three-level models resulted in over-parametrized models and, therefore, were avoided as they may result in misleading conclusions. For the two-level models, the effect sizes within the same study received the same random effects while effects from different studies were assumed to be independent and thus accounted for the correlation induced by the multi-level structure of the data as, for example, effect sizes reported within the same study may be more similar to each other than effects reported from a different study. The multi-level meta-analysis models assumed that the sampling error of the effect sizes was independent. This assumption may be violated when several effect sizes are obtained from the same subjects in cross-over design studies.

The analysis used the REML method for estimating between-study heterogeneity. Based on the Viechtbauer 2005 simulation study (36), the REML method is the preferred method as it is approximately unbiased and efficient in estimating the amount of heterogeneity in the population effect sizes as compared to the other methods (36).

The meta-SD estimates in the current analysis may be interpreted as between-subject variability; however, the reported SD from primary studies may also have incorporated other sources of residual unexplained variability such as measurement error. Unfortunately, it is not possible in the

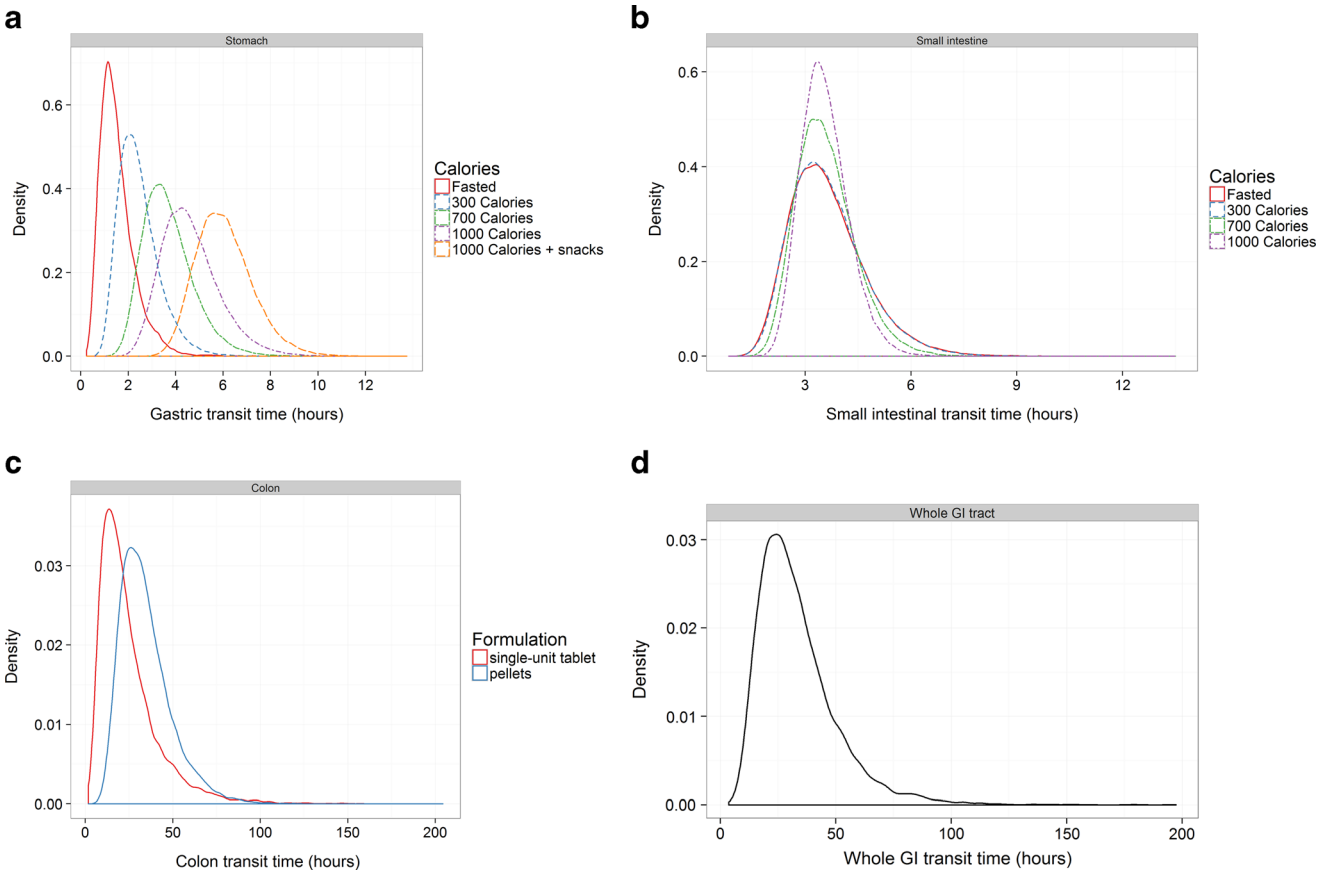

Fig. 4. Meta-distribution density plots of gastrointestinal transit times. **a** Gastric transit time of 1.37 ± 0.63 (*Fasted*), 2.30 ± 0.79 (*300 Calories*), 3.54 ± 1.01 (*700 Calories*), 4.47 ± 1.17 (*1000 Calories*) and 5.94 ± 1.17 (*1000 Calories + snacks*). **b** Small intestinal transit of 3.49 ± 1.02 (*Fasted*), 3.49 ± 1.00 (*300 Calories*), 3.49 ± 0.81 (*700 Calories*) and 3.49 ± 0.66 (*1000 Calories*). **c** Colonic transit of 20.28 ± 13.09 and 31.95 13.09 for *single-unit tablet* and *pellets*, respectively. **d** Whole GI transit time of 29.81 ± 14.52

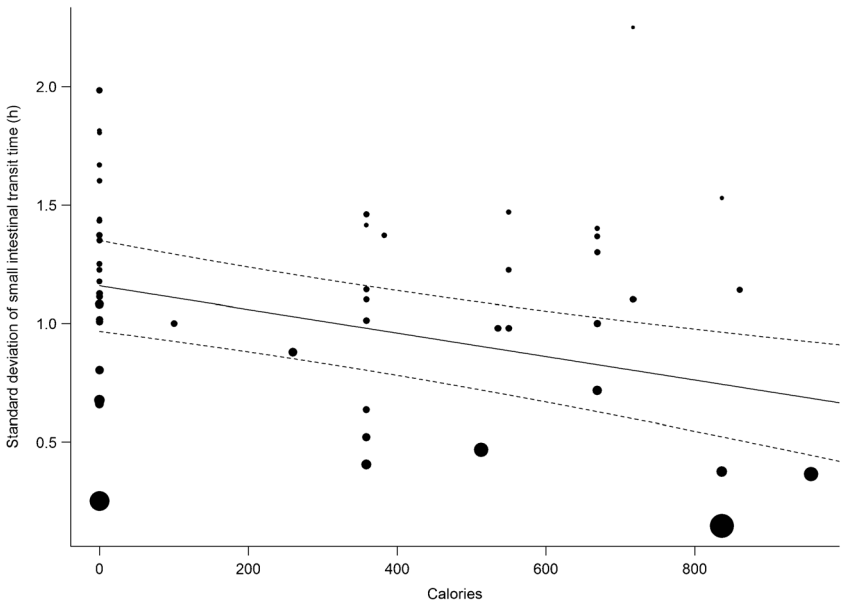

Fig. 5. The predicted variability in small intestinal transit time (SITT) as a function of food caloric content. *Black circles* are the observed standard deviations (SD) of SITT in individual studies drawn with size proportional to the inverse of the corresponding standard errors. The *solid black line* is the predicted meta-SD of SITT. The *two dashed lines* constitute the interval estimates where 95% of the true SD would fall in the hypothetical population of studies

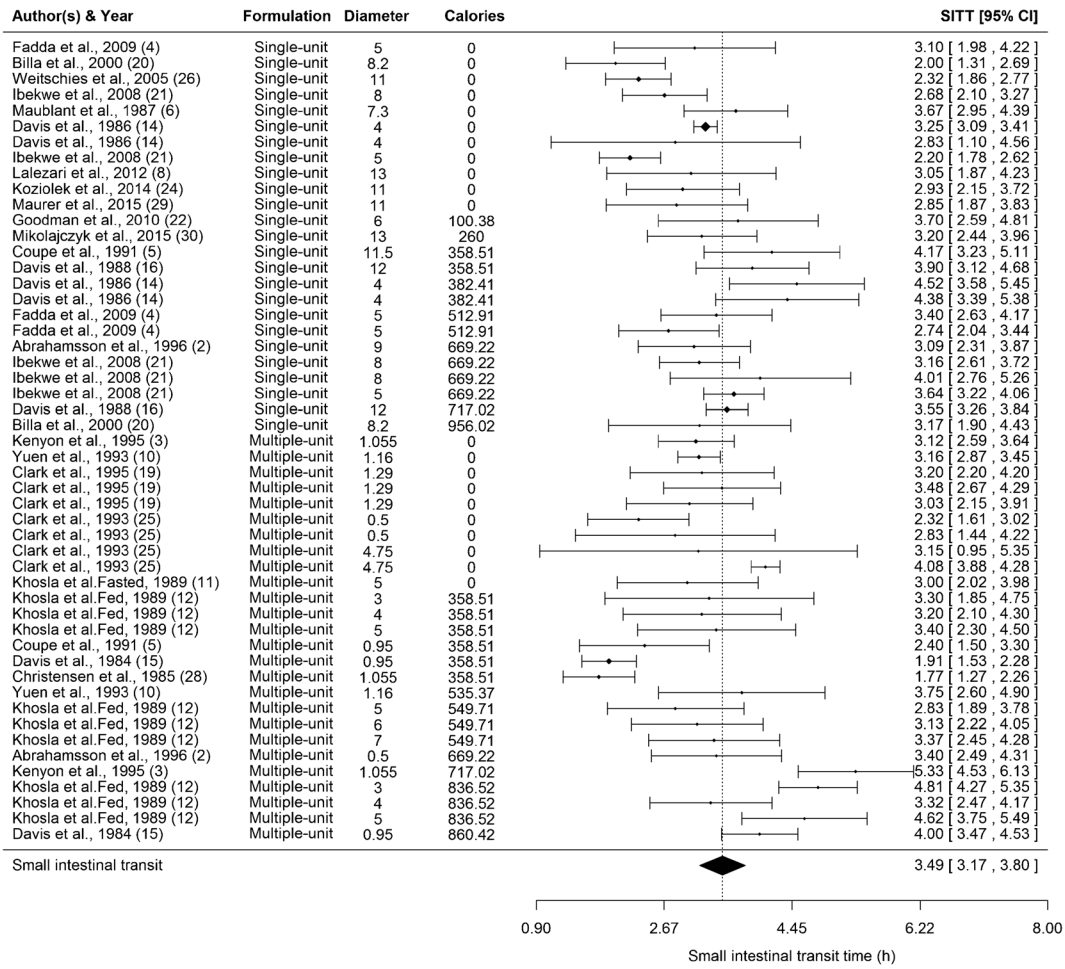

Fig. 6. Forest plot of the estimated meta-mean small intestinal transit time (SITT). The figure shows mean SITT with the corresponding 95% confidence intervals in the individual studies and based on a two-level random-effects model. References: (2–6, 8, 10–12, 14–16, 19–22, 24–26, 28–30)

current analysis to distinguish between inter-subject and intra-subject variability.

The meta-analysis of gastric transit time showed that the meal caloric content prolonged gastric residence and resulted in higher variability in gastric emptying for both single- and multi-unit dosage forms. This significant correlation between caloric content and gastric emptying is most likely due to the differences in the initiation of the phase III housekeeping wave of the migrating motor complex (MMC). Administering snacks 2.5 h after the main meal had a significant influence in delaying the gastric transit of ingested tablets. The latter finding agrees with the observation made by Ewe *et al.* (18), who showed that administering snacks after breakfast, lunch or dinner caused further delay of gastric emptying of an indigestible tablet by approximately 1.5 h. The snacks in the latter study consisted of a cup of yogurt or an apple or a piece of cake/cookie with a cup of tea/coffee.

Analysis of SITT revealed that food caloric content had no significant influence on the meta-mean estimate of small intestinal transit time of both single- and multi-unit dosage

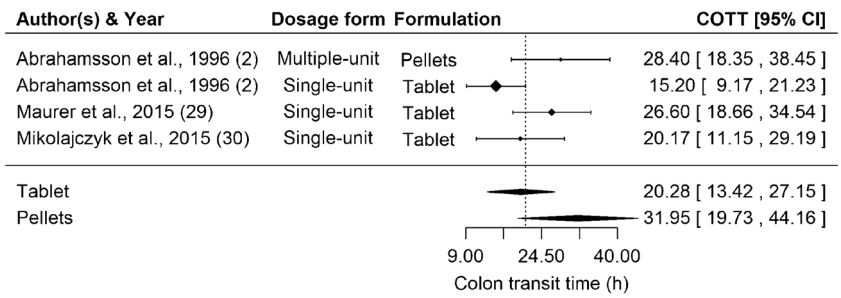

Fig. 7. Forest plot of the estimated meta-mean colonic transit time (COTT). The figure shows COTT with the corresponding 95% confidence intervals in the individual studies and based on a two-level random-effects model. References: (2, 29, 30)

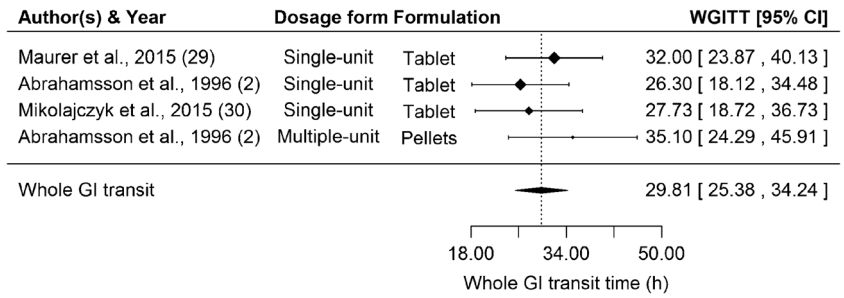

Fig. 8. Forest plot of the estimated meta-mean whole gastrointestinal transit time (WGITT). The figure shows mean WGITT with the corresponding 95% confidence intervals in the individual studies and based on a two-level random-effects model. References: (2, 29, 30)

forms. This finding agrees with several literature studies which reported no significant influence of food on small intestine transit time (3, 4, 10, 14, 20). However, caloric content had a significant influence on the variability in SITT. Higher variability in SITT was observed in the fasted state while the predicted variability was lower in the fed state and when the caloric content of food was increased. The higher variability in SITT in the fasted state may pertain to the likely increase in variability that may occur when measuring small intestinal transit times based upon certainties associated with the time of dosing versus the occurrence of the MMC under fasted conditions. The values of SITT arising from the meta-analysis are in agreement with the SITT values reported by Davis *et al* (39), for pellets (~3.21 ± 1.59 h) and a single-unit tablet (3.22 ± 1.22 h).

There were few studies reporting colonic and whole intestinal transit times of pellets and tablets. Colonic and whole transit times were characterized by high variability as can be seen from Figs. 7 and 8. Pellets had significantly longer colonic transit than the large single-unit tablets (p value < 0.05). The latter finding is in line with the Abrahamsson *et al*. study (2) who observed that the transit of metoprolol pellets through the colon was significantly slower than that of the larger-size single non-disintegrating tablet. The longer residence time of pellets has been suggested to be a result of the motility patterns of the colon that cause retention of the smaller pellets within the haustra of the colon whereas larger-size tablets are able to move rapidly through the colon (2). However, there was a non-significant trend for diameter as a moderator of colonic transit (p value = 0.1). More studies may be needed to confirm the effect of particle size on colonic transit time.

There are other factors that may potentially affect GI transit time of non-disintegrating tablets and pellets but have not been included in the current analysis. These factors may

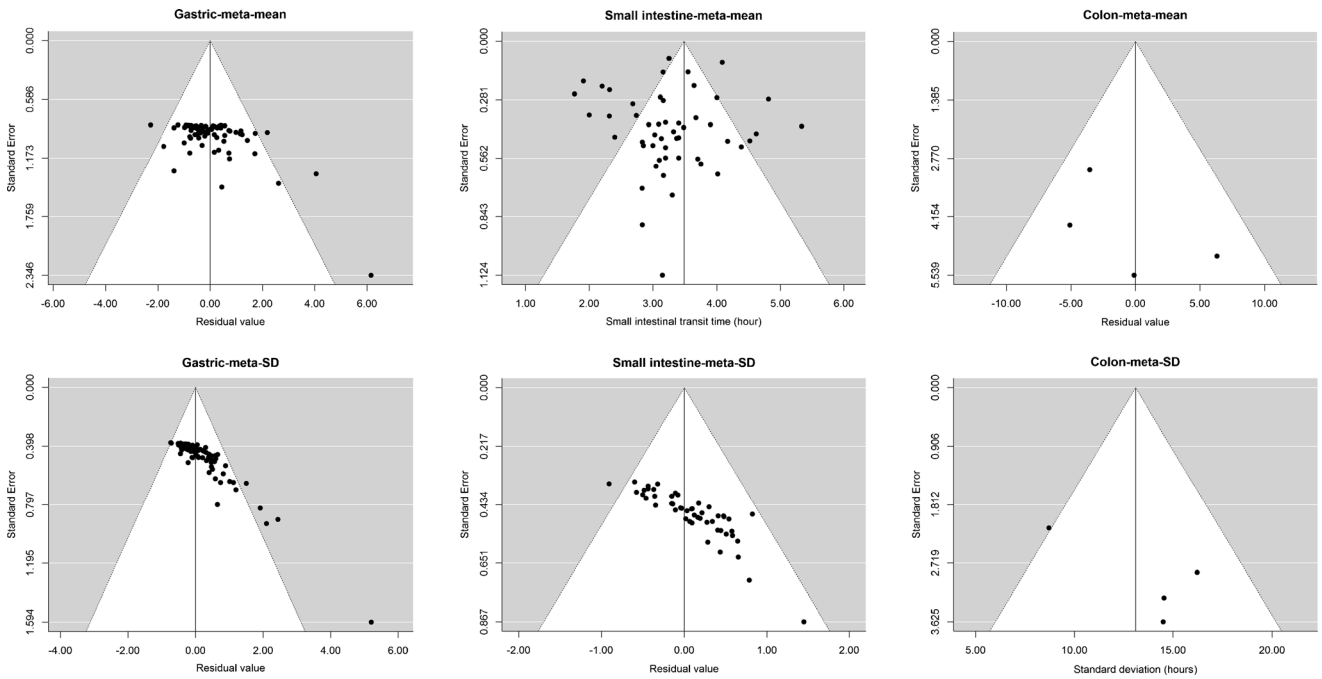

Fig. 9. Funnel plots to assess possible publication bias in the meta-analysis of gastrointestinal transit time (GITT). *Top panel*: funnel plots of meta-mean models of GITT. *Bottom panel*: funnel plots of the meta-SD models of GITT. The figures show the residuals (for mixed-effects models) or transit time and SD (for random-effects models) plotted against the corresponding standard error (i.e. the square root of sampling variances of the corresponding mean GI pH) of GI transit times. A pseudo-confidence interval region drawn around the vertical identity line with bounds equal to ±1.96 * SE

include (1) formulation factors such as the shape and surface properties of the administered solid dosage forms; (2) food-related factors such as osmolarity (41), viscosity (42) and the content of the administered meal (43, 44); and (3) physiological factors such as pregnancy and menstrual cycle (45, 46), gender, exercise (47), body position (48), circadian rhythm (49) and stress (50).

An unavoidable limitation of the current analysis was that the data used in the meta-analysis were mean transit time data rather than subject-specific data. The use of subject-specific data is more advantageous than the use of aggregate mean data (51, 52); however, such data were not available for the current analysis.

The results of the current analysis were based on GI transit time data from healthy subjects and may not be equally valid in patients with certain diseases such as motility disorders (53, 54) and obese patients (55). For the latter, significant differences in the GI transit time for obese patients versus normal healthy subjects have been observed in the literature (55). However, in the data of healthy subjects collected for the current analysis, weight was not a significant moderator on gastric or small intestinal transit time. Body mass index data were not available in the collated data herein and therefore were not investigated as a moderator on GI transit time.

Gastrointestinal transit time is among the physiological variables that may markedly influence the absorption of orally administered drugs (1). Different regions of the GI tract have different drug absorptive 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. For example, the rate of drug absorption of Biopharmaceutics Classification System (BCS) class I (highly soluble, highly permeable) drugs is mainly controlled by gastric emptying; therefore, factors that delay gastric emptying may delay absorption (56). The meta-analysis showed that frequent use of food (e.g. eating snacks after the main meal) may significantly influence gastric emptying of the administered formulation. The latter may have implications on enteric-coated formulations, where a delay in gastric emptying to the more alkaline intestinal environment may delay drug absorption and influence the drugs' bioavailability. Food caloric, as shown in this article, and its impact on gastric transit time will also modulate these effects.

Gastric emptying may also influence the dissolution and the solubility of poorly water-soluble weakly basic drugs. For example, the delayed gastric emptying after food ingestion, associated with increased gastric pH (see companion paper), diminishes drug dissolution and may cause precipitation of the dissolved low-p*K*a weakly basic drugs leading to reduced bioavailability (57). In comparison, a slow gastric emptying without an increase in gastric pH will decrease the extent of absorption of acid-labile drugs such as ampicillin (58).

Many drugs are absorbed from the upper part of the small intestine (duodenum and mid jejunum) which results in a limited window for drug dissolution and absorption. This is of particular importance for solid dosage forms containing BCS class III drugs (high solubility/low permeability). Many drugs in this class show regionally dependent drug absorption with better absorption in the upper small intestine (59). For example, captopril, a BCS class III orally active angiotensin-converting enzyme (ACE) inhibitor, is mainly absorbed from the upper part of the small intestine (duodenum, mid jejunum) and is significantly less bioavailable from the lower small intestine and colon (60).

Further, the presented meta-models of dosage form transit through the GI tract may be connected to *in vivo* disposition models to characterize the regional absorption properties and to predict the impact of GI transit time on the *in vivo* pharmacokinetics of orally administered drugs (61, 62).

CONCLUSION

A quantitative meta-analysis and meta-models were presented to characterize the GI transit time of non-disintegrating single-unit and multiple-unit solid dosage forms in the fed and fasted states. Food caloric content had a significant effect on delaying and increasing the variability of gastric emptying. Conversely, increased caloric content had no significant influence on the mean small intestinal transit time but it has a significant influence in reducing the variability in intestinal transit of single- and multiple-unit dosage forms. Colonic transit time is highly variable and less well characterized in the literature with a tendency for smaller particles to be transported through the colon at a slower rate than large particles. GI transit times can be of great importance for the dissolution and absorption of oral drugs due to the differences in the physiological conditions and absorptive properties in the different GI regions.

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