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Analysis of small intestinal transit and colon arrival times of non-disintegrating tablets administered in the fasted state

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ABSTRACT

In this study individual data on tablet gastrointestinal transit times (i.e. gastric emptying, small intestinal transit, ileocecal junction residence, and colon arrival times) were obtained from literature in order to present and analyze their distributions and relationships. The influence of the time of food intake after tablet administration in fasted state on gastrointestinal transit times was additionally evaluated.

There were 114 measurements from subjects who received the first meal at 4 h after tablet administration. Approximately 32% of the tablets arrived into the colon before the meal intake at 4 h. An evident increase in the frequency of colon arrival of tablets within 40 min after the meal intake at 4 h post-dose was observed, where approximately 39% of all tablets arrived into the colon. This is in accordance with findings described in literature where a meal ingested several hours post-dose accelerates tablet transit through the terminal ileum and shortens the transit through the small intestine. The median (min, max) of gastric emptying, small intestinal transit, and colon arrival times in the group where the first meal intake was at 4 h post-dose is 35 (0,192), 215 (60,544), and 254 (117,604) minutes, respectively. The dependence of colon arrival times on gastric emptying times was described by the nonparametric regression curve, and compared with the presumed interval of colon arrival times, calculated by summation of observed gastric emptying times and frequently cited small intestinal transit time interval, i.e. 3–4 h. For shorter gastric emptying times the trend of colon arrival times was within the presumed interval. At short gastric emptying times many observation points are also within the presumed interval since this interval coincides with short period after meal intake at 4 h post-dose. Additionally, in numerous occasions relatively long ileocecal junction residence times were obtained, which may be important information from the point of view of drug absorption. The findings of gastrointestinal transit times are important and should be taken into consideration when predicting the *in vivo* performance of dosage forms after oral administration.

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1. Introduction

The stomach, small intestine (SI), and colon are fundamental parts of a human gastrointestinal (GI) tract. They differ in anatomical structure and physiological condition, which leads to different influences of each part of the GI tract on performance of a dosage form after oral administration, and consequently on absorption kinetics of a drug (Yuen, 2010). The SI has an immense absorptive area and it is mainly the primary site of drug absorption, thus, the transit time of a dosage form through the SI is a significant factor influencing drug absorption. (Yuen, 2010).

There are many different methods that are used for evaluation of GI transit, namely X-ray imaging (radiology), magnetic marker monitoring, gamma-scintigraphy, and indirect methods such as the hydrogen breath test. Gamma-scintigraphy is commonly used method and as such represents a gold standard for studying the transit of various dosage forms through the GI tract (Wilding et al., 2001). It is a non-invasive technique with sequential imaging of a gamma-emitting radioisotope with a short half-life, which is incorporated into the dosage form (Digenis et al., 1998). Magnetic Marker Monitoring is a technique which utilizes a magnetic dipole of labeled solid dosage form in order to determine its location. It enables high spatial and temporal resolution in the range of a few millimeters and milliseconds, respectively (Weitschies et al., 2010).

There are numerous factors that may affect the transit along the GI tract. GE is mainly influenced by the size of the dosage form and feeding condition of the stomach, i.e. a fasted or fed state (Adkin et al., 1997). Davis et al. reported that SI transit times were not affected by type and size of the formulation, nor by feeding

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condition where dosage forms were either administered in a fasted or fed state (Davis et al., 1986). Additionally, in special feeding conditions, where a tablet is administered 30 min before a standard breakfast (Ibekwe et al., 2008a) or where subjects remained fasted 1.5, 4, or 9 h after the administration of a multiparticulate dosage form (Mundy et al., 1989), research has shown no statistical evidence that feeding condition influences the SI transit time.

However, Fadda et al. (2009) demonstrated that in feeding conditions where a tablet was administered 45 min before a standard breakfast, the SI transit time was significantly shorter for a tablet that had already emptied the stomach at the time of breakfast intake. Furthermore, Weitschies et al. (2010) suggest that SI transit times are defined by a study protocol of food intake in clinical studies where subjects in a fasting condition are often served the first meal at 4 h after the dosage form administration. The suggestion is supported by another study from the same research group (Schiller et al., 2005), where it was observed that non-disintegrating capsules that were given 7 and 4 h before magnetic imaging were, in a majority of the time (9 out of 12 and 12 out of 12, respectively), still located in the terminal SI at the time of imaging. This was observed for conditions where subjects received capsules in a fasted state and continued fasting until magnetic imaging, which was done 7 h after the first dose. Conversely, in other conditions from the same study when subjects were also given capsules in a fasted state, but had ingested meal 1 h before imaging, all capsules (12 out of 12) and 5 out of 12 capsules that were given at 7 and 4 h before magnetic imaging, respectively, were located in the colon (Schiller et al., 2005).

It was observed that when five tablets were administered concomitantly in a fasted state (Khosla and Davis, 1989) as well as in fed state (Khosla et al., 1989), their passage into the cecum often occurred as a bolus, which indicates tablets gathering and stagnating at the ileocecal junction (ICJ). This is supported by Adkin et al. (1997), who have stated similar findings. The ICJ is a segment of the GI tract which joins the terminal ileum and the cecum (Quigley et al., 1984; Shafik et al., 2002). It includes the ileocecal sphincter that displays a persistent high-pressure region with a sustained tone, where episodes of prominent phasic and propagating pressure waves occur (Dinning et al., 1999; Guyton and Hall, 2000). Motility of the ICJ is one of the main factors that regulate the flow of intestinal content, i.e. chyme, from SI into the colon (Dinning et al., 1999; Malbert, 2005; Shafik et al., 2002). Researchers have reported that after a meal the phasic activity of the sphincter at the ICJ increases, and the ileal propagating sequences are associated with episodic cecal filling (Dinning et al., 2008; Malbert, 2005). Additionally, it is reported that meal intake may prompt the transition of the chyme from the ileum into the colon, a mechanism known as gastro-ileocecal reflex (Schiller et al., 2005; Varum et al., 2013a; Weitschies et al., 2010), which may also determine the transit of a dosage form from the ileum through the ICJ into the colon.

Consequently, since the residence time in a particular part of the GI tract is one of the main factors defining the extent of drug absorption in that part (Parr et al., 1987), it is important to explore the effect of the time of the meal intake and its composition after the dosage form administration on dosage form transit through the SI and colon in more depth. Additionally, as the highest pH values are present in the distal small intestine (Basit, 2005; Ibekwe et al., 2008b), the residence time at the ICJ is expected to be an important factor for drug delivery systems that utilize pH as a control factor in drug release.

The present study was designed to evaluate the individual GI transit data of tablets obtained from a systematic literature review, where specific attention was given to the tablet transit through the SI, since it represents the main absorption region in the GI tract. Tablet residence times at the ICJ were also assessed. Additionally, *in vivo* study protocols were inspected with the aim to assess the potential influence of the ingestion time of a post-dose meal on tablet transit through the GI tract.

2. Methods

A systematic literature review of the intestinal transit time of a tablet was performed in the databases MEDLINE, Web of Science, and ScienceDirect in January 2015. The basic general query that was used for each database consisted of the following research terms and operators: "(tablet *OR* solid formulation) *AND* (gamma scintigraphy *OR* X ray imaging *OR* Magnetic Marker Imaging *OR* Magnetic Marker Monitoring) *AND* (gastrointestinal transit *OR* intestinal transit *OR* bowel transit) *AND* (human *OR* volunteer *OR* adult *OR* subject)." Although there were some syntactic differences between the queries in different databases due to dissimilarities in the specific searching rules of the database, the queries were semantically equivalent.

Duplicated records gained from the search of the three databases were excluded, and the articles of the remaining records were fully retrieved. The articles were examined for eligibility; the article had to contain individual data of SI transit times of the tablets in humans and tablets had to be given to the subjects in a fasted state at the time of administration. Measurements of SI transit times were included in the evaluation given that the tablets had not disintegrated until their passage to the colon.

2.1. Data collection and grouping

The retrieved data was gathered and evaluated by Microsoft excel. Additional data analysis and distribution plots were performed using statistical software R (R Core Team, 2014). In all subjects tablet was administered after overnight fast with no concomitantly taken food. Due to large differences in food intake regimens after tablet administration across the obtained studies, two main groups were defined where occasions with the same or similar food intake regimens were gathered together: subjects who had fasted up to 4 h after tablet administration when the meal was given were assigned to the first group. Subjects who had eaten either refreshments, orange juice and biscuits, or breakfast earlier than at 4 h post-dose, which in all observations occurred in the range from 30 min to 2 h post-dose, were assigned to the second group. In addition to the first meal, which was between 30 min and 2 h post-dose, subjects in the second group also received lunch at 4 h post-dose in most cases. Location of tablets at time of meal intake may be an important factor, so the first and the second group were further divided into 2 sets as described in Sections 2.2 and 2.4, respectively.

2.2. Comparisons of distributions of GI transit times

Comparisons of distributions of GI transit times were only made for subjects who had the first meal intake at 4 h post-dose (the first group). Thus food intake regimen was the same for all subjects in this group. The distribution of GI transit times, i.e. gastric emptying (GE), SI transit time, and colon arrival (CA) times, were compared for two "theoretical" sets that were defined on the basis of results given in the articles; i.e. whether the meal intake at 4 h post-dose was before or after the CA time. The CA time of a tablet represents the time it takes the tablet to arrive into the colon since the tablet administration. The SI transit time is determined as the time difference between CA and GE time. Histograms are plotted for graphical comparison.

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