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Navigating the human gastrointestinal tract for oral drug delivery: Uncharted waters and new frontiers☆

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ABSTRACT

Many concepts of oral drug delivery are based on our comprehension of human gastrointestinal physiology. Unfortunately, we tend to oversimplify the complex interplay between the various physiological factors in the human gut and, in particular, the dynamics of these transit conditions to which oral dosage forms are exposed. Recent advances in spatial and temporal resolution of medical instrumentation as well as improved access to these technologies have facilitated clinical trials to characterize the dynamic processes within the human gastrointestinal tract. These studies have shown that highly relevant parameters such as fluid volumes, dosage form movement, and pH values in the lumen of the upper GI tract are very dynamic. As a result of these new insights into the human gastrointestinal environment, some common concepts and ideas of oral drug delivery are no longer valid and have to be reviewed in order to ensure efficacy and safety of oral drug therapy.

Contents

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1. Introduction

The oral administration is the most obvious, the most convenient, and, as a consequence, the prevalent route for drug therapy. Unfortunately, it is not as simple as it seems. The extent and rate of drug absorption from the gastrointestinal (GI) tract depends on different factors that are either related with the drug itself, the formulation or the patient (Table 1) [1–10]. It is typically not known which of the numerous confounding influences effectively affects drug absorption from the GI tract. Despite manifold attempts using animal models, in vitro, tissue or cell culture test systems as well as in silico calculations, reliable predictions of the extent and rate of drug absorption in man – as well as in other species – are extremely difficult and often deficient. Obviously, there are still many "unknowns" that are determining drug absorption from the GI tract. Thus, the determination of oral bioavailability and the identification of parameters that might interfere with drug absorption, e.g., metabolizing enzymes, uptake, and efflux transporters or concomitant food, intake, are still a matter of human drug absorption studies.

In the vast majority, the available absorption characteristics have been obtained in clinical studies on pharmacokinetics or bioequivalence with healthy volunteers under the strongly standardized phase I conditions that do not reflect the real life situation. Unfortunately, only a very few information is available for drug absorption under "real life" conditions or in patients with certain diseases. However, to understand the physiological rationale behind drug absorption from the GI tract, it is essential to characterize the conditions under which pharmacokinetic data are gathered.

The present article was written to point out the often neglected importance of the dynamics of the gastrointestinal conditions for the in vivo performance of orally administered medications in both fasted and fed subjects. We will provide examples for dynamic processes in the human gut as recently explored using modern medical measurement technologies and explain how these processes may influence oral drug absorption. Particular attention is paid to the gastrointestinal conditions arising in clinical trials as they are the background of the pharmacokinetic data published in literature. Moreover, we will discuss adapted dissolution test methods capable of simulating critical dynamic conditions arising during the GI passage of oral dosage forms, as well as possible contributions of gastrointestinal dynamics to the variability in drug absorption of small and large molecules. It must be noted that this article expresses the authors' opinions and that it is specifically focused on selected physiological parameters in stomach and small intestine rather than on comprehensively reviewing the transit conditions in the human GI tract or the biopharmaceutical tools used to predict oral drug absorption. The interested reader is referred to reviews published by the European Innovative Medicines Initiative (IMI) on *Oral Biopharmaceutics Tools* (*OrBiTo*) and others [11–16].

2. Gastrointestinal (hydro)dynamics

The recent progress in non-invasive medical measurement techniques such as magnetic resonance imaging (MRI), magnetic marker monitoring (MMM) or telemetric capsules, and the rapidly advancing capabilities of medical imaging devices provided new fascinating insights into gastrointestinal physiology, but also into the fate of orally administered drugs and drug delivery systems within the human GI tract [17–19]. Furthermore, some groups even re-evaluated old knowledge on gastrointestinal physiology and came up with surprising results. For instance, Helander and Fändriks revealed that the surface of the human gut mucosa is not in the order of a tennis court (250–300 m^2), but approximately half the size of a badminton court (approximately 32 m^2) [20].

Apart from major improvements in image quality and spatial resolution, modern medical measurement techniques provide essentially higher temporal resolution. The reduction of measurement duration and movement artifacts led to a turn of the acquired information from rather static to dynamic. As a result, a number of studies were conducted in recent years, which aimed at the characterization of the dynamics of the gastrointestinal transit conditions. These studies showed that the common idea of a more or less continuous transport of drug delivery systems and drug substances through the GI tract was a misconception. Indeed, the opposite holds true as the gastrointestinal transport of solid oral dosage forms was found to be extremely discontinuous. In all major segments of the GI tract, i.e., stomach, small intestine, and colon, gastrointestinal transport is characterized by phases of rest, slow propagation, and events of rapid transport of variable duration and range.

In the following chapters, we will present the results of recent studies, in which the dynamics in the upper GI tract were investigated with the aid of modern medical measurement technologies in both fasted and fed state. We will focus on luminal fluid volumes, pH values, and GI motility, and we will discuss how these parameters may affect the gastrointestinal transit behavior of solid oral dosage forms.

2.1. Luminal fluid volumes

2.1.1. Fasted state

In the current guidelines for the determination of oral bioavailability or bioequivalence, investigations in fasted state are recommended after a fasting period of at least 8 h (EMA) or 10 h (FDA) prior to drug administration together with at least 150 mL (EMA) or 240 mL of water (FDA) [21–23]. After such long overnight fasting period, the stomach is regarded as almost empty. However, a small volume of gastric content is always present in the gastric lumen. Recent MRI investigations that considered the conditions of the guidelines revealed that the fasted state volume of the stomach is typically below 50 mL but can vary considerably (Table 2). These data are in good accordance with published data for fasted state gastric content volumes determined with other tools under varying conditions [24,25].

The (hydro)dynamic conditions in the fasted human upper GI tract mainly result from the distinct cyclic pattern of propagating myoelectric activation that typically starts in the stomach and ends in the distal small intestine, the so-called interdigestive migrating motor complex (IMMC) [32]. As can be seen in Fig. 1, the IMMC consists of three phases of different duration. Phase I is a longer phase of rest, whereas phases II and III are characterized by strong motility. In particular, during phase

Table 1
Different factors known to influence drug absorption from the gastrointestinal tract [1–10].

Drug-related factors	Formulation-related factors	Patient-related factors
Molecular weight	Drug release profile	Intake condition
Water solubility	Excipients	Disease
Partition coefficient		Age
Stability toward gastrointestinal conditions, including digestive enzymes and pH values in the physiological range of pH 1–8		Ethnic group
		Genetic polymorphisms
		Gender
		Lifestyle and eating habit
		Co-medications

Table 2
Gastric content volumes after a fasting period of at least 8 h as determined by MRI (n/a—unreported data).

MRI study	No. of subjects	Gastric content volumes (mL)			
		Min	Max	Median	Mean ± SD
Schiller et al. [26]	$n = 12$	13	72	47	45 ± 18
Goetze et al. [27]	$n = 12$	n/a	n/a	n/a	65 ± 22
Goetze et al. [28]	$n = 12$	n/a	n/a	n/a	40 ± 27
Babaei et al. [29]	$n = 10$	n/a	n/a	n/a	85 ± 29
Koziolek et al. [30]	$n = 12$	4	64	28	31 ± 19
Mudie et al. [31]	$n = 12$	n/a	n/a	n/a	35 ± 7
Data on file	$n = 72$	1	95	17	31 ± 17

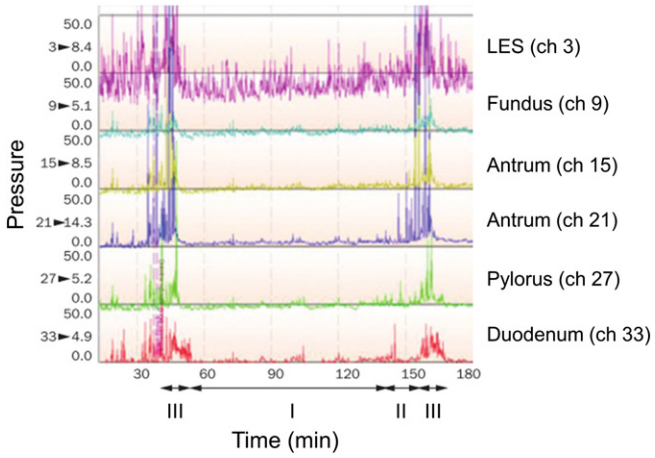

Fig. 1. Pressure–time profiles obtained by high-resolution manometry (36 pressure channels) illustrating the different phases (I–III) of the interdigestive migrating motor complex. LES—lower esophageal sphincter. Adapted by permission from Macmillan Publishers Ltd: Nat. Rev. Gastroenterol. Hepatol. (Deloose et al.), copyright (2012) [32].

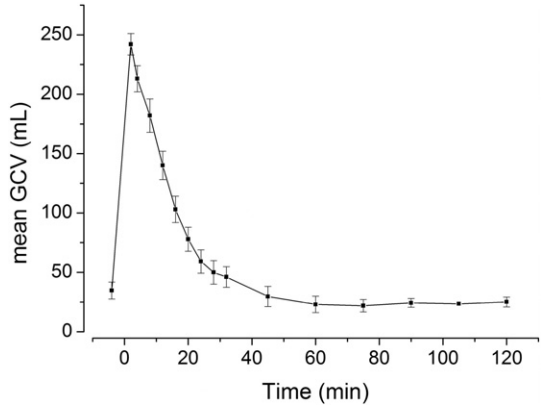

Fig. 2. Mean gastric content volumes after administration of 240 mL of water in fasted state investigated by MRI over a period of 120 min, $n = 12$. Reprinted from Mudie et al. [31]. Copyright (2014) American Chemical Society.

III, strong peristaltic waves of variable amplitudes are generated in the stomach and propagate toward the terminal ileum (Fig. 1).

It is very likely that the stomach is completely empty immediately after the occurrence of the strong peristaltic contractions of IMMC phase III (housekeeping waves). Therefore, to our understanding, the observed variability in residual gastric content volumes reflects the time that has passed since the last housekeeping wave. During the subsequent quiescent phase I of the IMMC, oral and gastric secretions are gathered within the lumen of the stomach, but not emptied into the small intestine. Assuming a typical basal gastric secretion rate of about 1 mL/min and a saliva flow rate of 0.1–1 mL/min, about 75 mL of gastric juice may accumulate within 1 h after the last IMMC phase III [33].

Under fasting conditions, the 240 mL of water co-ingested with the medication according to the guidelines is emptied from the stomach typically within 15–30 min, as shown by Mudie and co-workers (Fig. 2) [31]. It is believed that non-caloric liquids such as water are emptied from the stomach mainly by contractions of the distended stomach wall. Even though the volunteers are in supine position during the MRI investigations, gastric water emptying in fasted state is almost complete. Fig. 3 illustrates nicely how MRI can be used to visualize the process of gastric emptying of water.

The small intestine is mostly empty in fasted subjects and, unlike the gas filled colon, the small intestinal walls are collapsed. Non-absorbed small intestinal fluid is segregated in a few "fluid pockets" of variable volume [26]. After overnight fasting, a mean total volume of about 50 to 100 mL of fluid is present in the small intestine (Table 3).

The largest pocket is typically found in the terminal ileum (see Fig. 4), where also non-absorbable material gathers. By contrast, free water is rarely observed in the colon [26], although the typical filling volumes of the colon are high [35].

The 240 mL of water swallowed for drug administration obviously undergo rapid absorption from the small intestine. Thus, the total fluid volume in the small intestine remains nearly unchanged [31]. Water reaching the small intestine is immediately scattered over the jejunum and absorbed as illustrated in Fig. 5. The common idea of a water front traveling rather slowly down the small intestine is not supported by MRI data undertaken with high sampling rates.

2.1.2. Fed state

Food intake leads to numerous physiological changes in the upper GI tract and, therefore, can exert significant effects on drug absorption [33,36]. A classification of how food intake can influence drug absorption from the human GI tract is given in Fig. 6.

In order to investigate the impact of food on drug absorption, most food effect studies are performed according to the guidelines of FDA and EMA [21–23] . These studies follow a study protocol, which is equivalent to the one used for fasted state investigations, with the only difference that the subjects receive a high-caloric (800–1000 kcal), high-fat (50% of the calories derived from fat) breakfast 30 min prior to drug intake with 240 mL of water. This meal shall provoke a drastic effect on gastrointestinal physiology and, thus, on drug absorption. In a footnote of the FDA guideline, an example for a typical test meal is given,

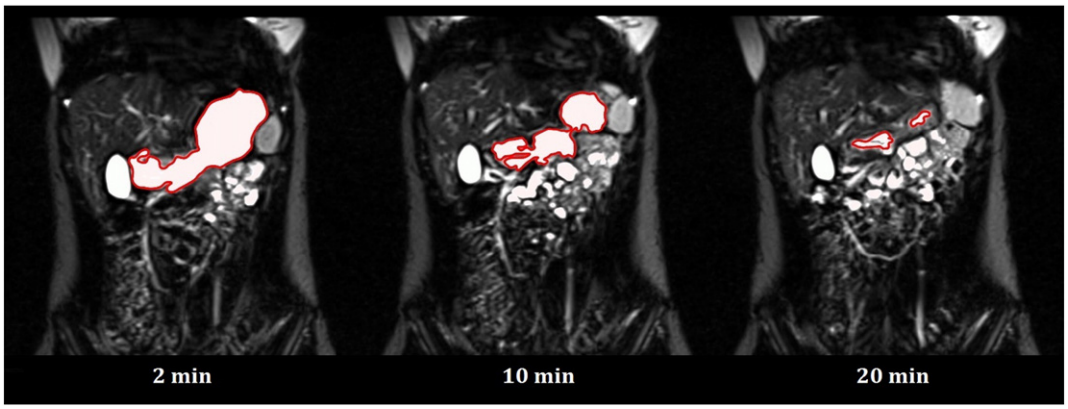

Fig. 3. MRI sequences demonstrating rapid gastric emptying of 240 mL water administered in the fasted state. Water inside the stomach is delineated by the red line. *Left*: 2 min—177 mL;

Table 3
Comparison of total small intestinal water volumes observed by MRI in healthy volunteers after an overnight fast.

MRI study	No. of subjects	Small intestinal fluid volume (mL)			
		Min	Max	Median	Mean ± SD
Schiller et al. [26]	$n = 12$	45	319	83	105 ± 72
Marciani et al. [34] (calculations based on digitized data)	$n = 16$	12	253	81	91 ± 68
Mudie et al. [31]	$n = 12$	5	159	–	43 ± 14
Data on file	$n = 48$	7	230	52	65 ± 51

consisting of two toasts with butter, two eggs fried in butter, two strips of bacon, hash brown potatoes, and 240 mL milk. Thirty minutes after start of meal intake, i.e., typically 10–20 min after finishing the meal, the medication to be tested is administered together with 240 mL of water. After drug administration, water intake is prohibited for 1 h and food intake for at least 4 h, respectively.

Food intake has a marked effect on the motility of the GI tract as the ingestion of caloric food or liquids causes an interruption of the IMMC and induces the digestive myoelectric motor activity [37,38]. The motility pattern of the fed stomach is completely different from fasted state and characterized by constantly propagating antral contraction waves with a frequency of three waves per minute that are continued in the small intestine with an increased frequency of 12 waves per minute [37]. The gastric emptying rate is reduced in fed state. Thus, large volumes can gather in the gastric lumen, which serve as the dissolution medium of solid oral dosage forms administered after food intake. In Fig. 7, individual gastric content volumes over time are provided as measured in a recent MRI study that was performed considering the above mentioned FDA recommendations for fed state bioavailability/bioequivalence studies [30].

After eating the fat-rich FDA meal and ingestion of 240 mL water, the mean gastric content amounted to about 580 mL. This volume was higher than the volume of the eaten meal, suggesting that there is additional oral and/or gastric secretion. The initial peak in volume was followed by a plateau phase, during which secretion and gastric emptying seemed to be more or less equally. Just 60–90 min after swallowing 240 mL water, gastric volume decreased with a rate of ~1.7 mL/min. Even after more than 6 h, the gastric content exceeded the volumes assessed in fasting healthy subjects. These observations are in good accordance with emptying rates of 2–4 kcal/min reported in literature [39–41].

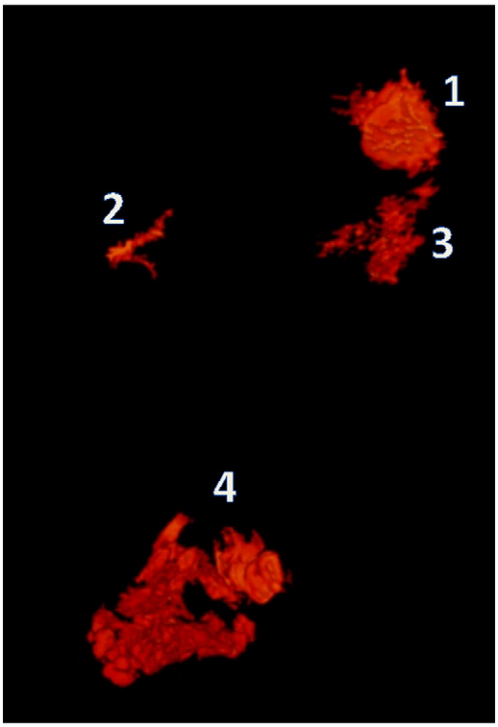

Fig. 4. Distribution of water (red) in the gastrointestinal tract of a healthy volunteer after overnight fasting as observed by MRI (frontal view). In this example, water is present in the stomach (1: 27 mL) as well as in three "fluid pockets" located in duodenum (2:

In that study, moreover, it was also seen that swallowing of 240 ml water for virtual drug administration was not the reason behind persistent increase in gastric volume. Actually, water was rapidly emptied within 15–35 min (Fig. 8). This finding confirms old experience that there is a gastric route for rapid emptying of liquids from the postprandial stomach known as *Magenstrasse* (stomach road) or *canalis gastricus* [42,43]. In the original concept of the *Magenstrasse*, it was assumed that the pathway follows the lower curvature of the stomach. However, the present MRI data suggest that the water flows around the chyme in the lumen along the entire stomach wall. Similar observations were made in dogs by Scheunert and co-workers already in 1912 [44]. The authors demonstrated that fluids ingested after a meal can flow around the stomach contents and thereby, reach the small intestine rapidly. It was also observed in these dog experiments that, depending on the texture of the food mass, certain amounts of the fluid can even flow through the matrix. In our understanding, it seems likely that the volume-induced relaxation of the fundus of the stomach creates a small gap between the viscous food mass and the fundus wall. Fluid that goes this way around the food mass gathers in the antrum of the stomach and is emptied from there into the duodenum within a few minutes (Fig. 8).

Similar observations were made by Malagelada and co-workers [45,46]. In their studies, the water taken together with solid meals is emptied rapidly from the stomach. By contrast, the solid food is retained in the stomach, which enables sufficient time for digestive processes. As opposed to the rapid flow of water around the food mass in the fundus, the mass itself is astonishingly static. As already described in 1923 by Groedel, food is segmented in different layers inside the stomach [47,48]. This has been confirmed for different meals by MRI [28,49]. For instance, Wilson and co-workers demonstrated the formation of a dough ball in the stomach, which was surrounded by fluids [50]. These data show that the mixing properties of the stomach for drugs taken after a solid meal are rather marginal. In a study by Faas and colleagues, this has been strikingly demonstrated for a liposomal preparation of an MRI contrast agent (Fig. 9) [51].

Due to the poor mixing properties of the fundus, non-disintegrating solid dosage forms like extended release (ER) tablets can stay for several hours on top or within the gastric content [52,53]. In case of ER tablets, the static residence of the tablets in the food bolus may result in a local accumulation of the released drug substance. If such a bolus of accumulated drug is suddenly emptied into the small intestine, e.g., by postural changes, this may create a sharp rise in the drug plasma concentration. Notably, these plasma peaks can also be misinterpreted as *dose dumping* caused by failure of the drug delivery system [52].

In the small intestine, food intake triggers the gastro-ileocecal reflex and, thus, causes the emptying of contents from the terminal ileum into the caecum [54,55]. Thereby, the small intestinal fluid volume decreases initially. Schiller et al. showed that the fluid volume decreases from 105 ± 72 mL in fasted state to 54 ± 41 mL in fed state (1 h after a

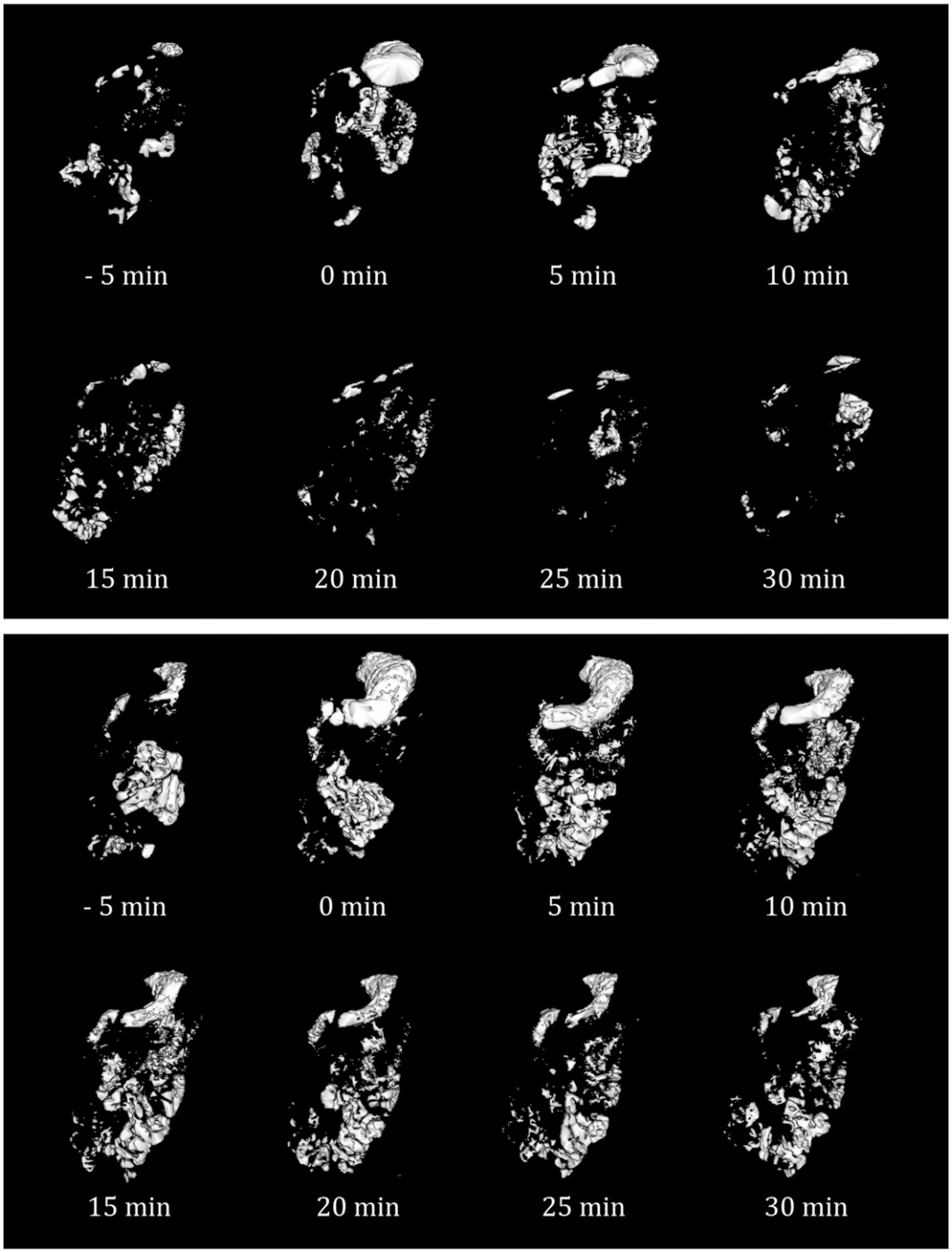

Fig. 5. Two examples of gastrointestinal water distribution directly before (−5 min) and after ingestion of 240 mL under fasting conditions. In these T2-weighted MR images only water is shown.

increased. In a recent study, Marciani and colleagues investigated the dynamics of the small intestinal fluid volume after ingestion of low-caloric test meals over a period of more than 8 h [34]. They showed that the initial decrease of the small intestinal fluid volume is followed by a short plateau phase. Around 90 min after meal intake, the fluid volume begins to rise again but reaches the original level not before 2–3 h post-meal. These data demonstrate that even after higher volumes of food, which typically cause considerable volumes of gastrointestinal secretions, the small intestine is not filled with large amounts of fluid and, thus, does not provide particularly favorable conditions for drug dissolution. fluid dynamics after the FDA standard breakfast were not investigated so far.

2.2. Transit of dosage forms through the GI tract

2.2.1. Fasted state

The physiological phenomenon of the IMMC is essential for the cleansing of the stomach from non-digestible material, but it has also particular importance for the gastric emptying of non-disintegrating dosage forms like enteric coated tablets or certain extended release

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