Investigation of pH and Temperature Profiles in the GI Tract of Fasted Human Subjects Using the Intellicap® System

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ABSTRACT: Gastrointestinal (GI) pH and temperature profiles under fasted-state conditions were investigated in two studies with each 10 healthy human subjects using the IntelliCap® system. This telemetric drug delivery device enabled the determination of gastric emptying time, small bowel transit time, and colon arrival time by significant pH and temperature changes. The study results revealed high variability of GI pH and transit times. The gastric transit of IntelliCap® was characterized by high fluctuations of the pH with mean values ranging from pH 1.7 to pH 4.7. Gastric emptying was observed after 7–202 min (median: 30 min). During small bowel transit, which had a duration of 67–532 min (median: 247 min), pH values increased slightly from pH 5.9–6.3 in proximal parts to pH 7.4–7.8 in distal parts. Colonic pH conditions were characterized by values fluctuating mainly between pH 5 and pH 8. The pH profiles and transit times described in this work are highly relevant for the comprehension of drug delivery of solid oral dosage forms comprising ionizable drugs and excipients with pH-dependent solubility. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2855–2863, 2015
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INTRODUCTION

The drug release and absorption behavior of oral dosage forms is affected by various factors that differ along the gastrointestinal (GI) tract. These include physicochemical (e.g., pH value, buffer capacity, or osmolality), enzymatic, and mechanical (e.g., pressure, movement) parameters.[1–3] The characterization of GI transit conditions is therefore required for a thorough comprehension of *in vivo* drug release and absorption processes of oral dosage forms. In particular, intraluminal pH values are highly relevant owing to pH-dependent solubility of a multitude of drugs as well as of various excipients used in oral dosage forms. Thus, regional pH differences and transit times along the human GI tract are known to alter drug release from solid oral dosage forms. Especially the drug delivery behavior of enteric coated or modified release dosage forms is often affected by the GI pH profile.[4,5]

For the majority of solid oral dosage forms, the transit time through oral cavity and esophagus is rather short. Therefore, the stomach is typically the first section of the GI tract, in which disintegration and dissolution of solids such as drugs and formulations thereof take place. Thus, the characterization of physiological factors acting on the dosage form during the gastric residence helps to gain insight into the drug delivery characteristics of oral formulations. The fasted stomach is characterized by acidic pH values of pH 1–3.[3,6,7] The intake of food or liquid typically results in an increase of the pH value because of the low fasted-state volumes of 10–50 mL and low buffer capacity of the gastric content. Depending on composition and volume of the ingested contents, even pH values of pH 6 and higher are likely.[2,7] Subsequently, the pH value recovers to baseline levels because of the gastric secretion of hydrochloric acid (HCl) and gastric emptying. In case of water ingestion, the pH increase is only of short duration owing to the absence of buffering components such as proteins or fatty acids and fast gastric emptying.[8,9] Interestingly, the effect of the ingested liquid on the temperature of the intragastric milieu has so far been recognized, but not considered as important for the characterization of disintegration and dissolution of solid oral dosage forms. The high variability of intragastric pH conditions can have an impact on the drug delivery behavior of modified release dosage forms. For instance, the onset and kinetics of drug release can be remarkably changed as it was shown for extended release (ER) products such as pH-dependent swellable matrices.[10] In case of enteric coated products, both parameters, the onset of release (lag time prior to the release) as well as the overall release kinetics, may be changed because of the variable gastric transit conditions.[11,12]

The intestines are the main absorption site for nutrients and drugs. Therefore, the investigation of intestinal transit conditions is required to understand drug delivery processes of drugs and their formulations. The entry of solid dosage forms into the small intestine is accompanied by a sharp pH increase because of the duodenal secretion of alkaline bicarbonate.

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Moreover, literature data suggest a subsequent increase of the pH value from pH 6 in the duodenum to pH 7–8 in the terminal ileum.[4,13,14] The transit time through the small bowel in healthy humans typically amounts to 3–6 h, although higher variations are also reported in literature.[15–17] As was demonstrated in a recent study by Zarate et al.,[18] colon arrival time (CAT) can be identified by a pH drop, which was 1.45 ± 0.20 pH units at ileocaecal valve. Colonic pH values are slightly more acidic compared with the ileal pH values because of the fermentation processes of the colonic microbiota.[19,20] The colon transit time is typically longer than the gastric and small bowel transit times (SBTTs) and can amount up to 72 h.[21]

To date, several techniques are available for the evaluation of GI pH conditions. Besides analysis of human aspirates, endoscopic methods such as nasogastric tubes or telemetric capsules aid to gain insight into intraluminal pH conditions. Recently, Medimetrics Personalized Drug Delivery B.V. (Eindhoven, The Netherlands) introduced the IntelliCap® system, an electronic drug delivery device.[22,23] This ingestible, telemetric capsule is able to deliver a drug at a certain place with a programmable release profile, which is realized by a miniaturized pumping system. The drug release is based on the localization within the GI tract identified in real-time by the typical gut pH profile. Moreover, the IntelliCap® system is a helpful diagnostic tool for the *in vivo* investigation of dosage form transit because of its capability of real-time pH and temperature monitoring.

In the present work, pH and temperature profiles inside the human GI tract from two studies with each ten fasted healthy subjects were investigated using the novel IntelliCap® system. Gastric emptying time (GET), SBTT, and CAT were identified by significant pH changes.

MATERIALS AND METHODS

Two studies with each 10 healthy human subjects were performed at the Department of Gastroenterology and Hepatology and the Department of Radiology and Nuclear Medicine of the University Medical Center Utrecht, The Netherlands. The studies were performed to assess safety and tolerability (study 1) as well as functionality (study 2) of the novel IntelliCap® system. A thorough description of the two studies is given by the publication of van der Schaar and co-workers.[22]

Subjects

Both studies were conducted with 10 healthy human subjects (Table 1). None of the subjects had undergone abdominal surgery, took medication or suffered from diseases affecting GI motility. All subjects gave their written informed consent. The study protocol was approved by the Medical Ethical Committee of the University Medical Center Utrecht.

Table 1. Summary of Subject Characteristics

	Study 1 ($n = 10$)	Study 2 ($n = 10$)
Male/female	3/7	3/7
Age (years)	19–25	19–25
Body weight (kg)	52–84	57–75
BMI	18.1–24.0	18.7–24.2

Study Protocol

After an overnight fast, the subjects ingested the IntelliCap® capsule together with 200 mL of water of room temperature. During the subsequent 4 h, any further oral intake of liquids or food was not allowed. An exception to this rule was made in study II, where 20 mL of ice-cold water were given in order to verify gastric emptying. In case a temperature drop was observed, it could be concluded that the Intellicap® capsule was still inside the stomach. Lunch was served 4 h after capsule ingestion. The subjects were allowed to leave the study unit earliest 10 h after capsule ingestion. Stool was collected by the subjects to recover the capsule. After return of the excreted capsule, its structural integrity was checked.

IntelliCap® System

The IntelliCap® system is composed of a swallowable single-use capsule, a start-up unit for activation and programming of the capsule, a portable unit to record and relay the measured data wirelessly to a computer and to relay commands from a computer to the IntelliCap® capsule inside the body. The capsule has a size of 27 × 11 mm and is built up of a drug reservoir and an electronic body made of biocompatible polymers. The electronic body of the capsule houses a sensor for pH and temperature, an integrated programmable microprocessor, a wireless transceiver, batteries and a motor actuator expelling the payload from the reservoir under the control of the microprocessor.[22] Temperature data (relative accuracy: ±0.1°C) and pH values (relative accuracy: ±0.3 pH units) were recorded via wireless communication every 10 s. The pH sensor was calibrated before administration and after excretion. During the first 10 h, real-time data were transmitted directly to a computer. After leaving the study unit, a data receiver must be worn close to the body to record the data packages. After capsule excretion, the data receiver was returned by the subjects and pH and temperature data were transferred to a computer.

Data Analysis

Data were analyzed by aid of graphical software packages Axum 5.0c (MathSoft, Cambridge, Massachusetts) and Origin 8.5G (OriginLab Corporation, Northampton, Massachusetts). Three independent investigators determined gastric residence time (GRT), SBTT, and colonic arrival time (CAT) by consideration of significant pH changes (>0.9 pH units). GRT was defined as time from capsule ingestion until gastric emptying. Stomach entry was registered by enduring low pH values. Gastric emptying could be identified by a significant and permanent pH change to values of pH 5 and higher. Colonic entry was registered by a sharp pH decrease of not less than 0.5 pH units that occurred at least 30 min after gastric emptying. Capsule excretion could be identified by decreased temperature.

The SBTT was normalized by the following equation to enable the comparison of individual pH profiles despite different transit velocities:

$$\mathrm{SBTT_{norm}} = \frac{t - \mathrm{GET}}{\mathrm{CAT} - \mathrm{GET}} \quad (1)$$

where $\mathrm{SBTT_{norm}}$ is the normalized SBTT, t is the time frame in minutes passed after Intellicap® ingestion (the time of capsule ingestion was defined as 0 min), GET is the gastric emptying time, and CAT is the colon arrival time.

Table 2. Gastrointestinal Transit Times Obtained by Use of IntelliCap® System ($n = 20$)

	GET (min)	SBTT (min)	CAT (min)
Median	30	247	272
Interquartile range	15–52	210–352	254–439
Min	7	67	74
Max	202	533	578

Statistics

Data were characterized by minimum, maximum, interquartile range, median, and arithmetic mean ± SD where appropriate. Statistical calculations (Kruskal–Wallis one-way ANOVA with post-hoc Dunn's test) were performed by using GraphPad Prism 5 (GraphPad Software Inc., La Jolla, California).

RESULTS

GI Transit Times

Gastrointestinal transit times were calculated successfully by consideration of significant pH changes. The transit times in stomach and small intestine as well as the CAT are given in Table 2. High interindividual variations were observed. Colon transit time could be precisely determined only in 13 out of 20 subjects because of technical reasons and amounted to 1503 ± 470 min.[22] Under consideration of the whole gut transit time, which was 1834 ± 459 min, IntelliCap® was located 82% of its total GI transit time inside the colon.

pH and Temperature Profiles

All individual pH and temperature profiles obtained after ingestion of IntelliCap® in fasted state are given in Figures 1 and 2.

Gastric pH Profiles

During gastric residence of IntelliCap® in fasted-state highly variable pH values from pH 1 to pH 8 were observed (Fig. 3). The median pH values differed from pH 1.4 to pH 4.6. The mean pH value calculated from the individual means of all 20 subjects was pH 2.7 ± 0.8.

Small Bowel pH Profiles

During small intestinal transit, slightly increasing pH values from pH 6 to pH 7–8 were registered. These results are in accordance with literature data.[14,19,24,25] By normalizing the pH profiles of the small bowel, regional characteristics could be investigated (Fig. 4).

By calculating the normalized SBTT according to Eq. 1, proximal ($SBTT_{norm}$: 0–0.1) and distal ($SBTT_{norm}$: 0.9–1) sections of the small intestine could be compared (Fig. 5). In all 20 subjects, pH values were significantly different in the two segments (Kruskal–Wallis one-way ANOVA with post-hoc Dunn´s test, two-tailed, $p < 0.05$). In proximal parts, pH values were about pH 5.9–6.3 (mean 6.0 ± 0.2) with temporary fluctuations, whereas in distal parts, pH values amounted to pH 7.4–7.8 (mean 7.7 ± 0.15) and showed only minor fluctuations.

Colonic pH Profiles

As can be seen from Figures 1 and 2, colonic transit was characterized by highly variable pH conditions. The values fluctuated between pH 5 and pH 8. A tendency for a pH shift within the colon could not be identified. The pH ranges for colonic transit are given in Figure 6. The mean pH value in the colon was pH 6.5 ± 0.3.

DISCUSSION

Besides its potential use as a programmable universal drug delivery tool, the novel IntelliCap® system offers the opportunity to study GI conditions in terms of pH and temperature in real-time. By the identification of characteristic temperature and pH changes, it was possible to determine transit times in different sections of the GI tract. The temperature drop that resulted from the intake of 20 mL of ice-cold water (study II) was used for the confirmation of the gastric residence of the Intellicap® capsule.

It was shown in a recent publication by Garbacz et al.[26] that temperature effects can be relevant for the disintegration and dissolution behavior of capsules and tablets. Based on literature data, an initial intragastric temperature of 25°C–30°C after intake of 240 mL of water at 20°C, which are requested for dosage form administration under clinical trial conditions, was estimated.[26] In the present study, after the intake of Intellicap® together with a glass of water, an exponential increase of the temperature inside the human stomach from roughly 23°C directly up to 36°C within approximately 10 min was observed. However, in the two studies fluid intake conditions were not standardized in terms of volume and temperature. Therefore, it was not possible to reproduce the initial temperature as well as the dynamics of the temperature gradients, which may be observed under application of the standardized study protocol used in bioequivalence studies.

In case of non-disintegrating monolithic formulations with modified release such as enteric coated tablets or extended release products, the GRT can be expressed as the time point of gastric emptying.[27] However, several factors can affect the event of gastric emptying and in consequence, the GRT is highly variable and can range between a few minutes and several hours.[2,28,29] The transit times revealed by use of the IntelliCap® system were in accordance with literature data generated by use of other telemetric capsules.[30] The GRT of the IntelliCap® capsule was highly variable between 7 and 202 min. Such variable GRTs are typical for monolithic dosage forms under fasting conditions.[15] Accordingly, the GRTs corresponded nicely to the results of a recent Magnetic Marker Monitoring study.[31] Large, non-disintegrating objects such as the IntelliCap® capsule are typically emptied by strong peristalsis that most likely occurs during MMC phase III contractions. Therefore, the GRT was probably determined by the recurrence of the MMC phase III motility. Typically, every 60–120 min a new MMC cycle begins in the proximal stomach and moves toward the ileum.[32,33] In the three subjects (1–2, 2–8, and 2–10) that showed GRT longer than 120 min, it was likely that the IntelliCap® capsule was not emptied by the first MMC III activity or that the MMC cycle started after the stomach.

The SBTT observed in the two studies reported here were in the range of 67–553 min. This is in contrast to the assumption that the SBTT is relatively consistent with values of

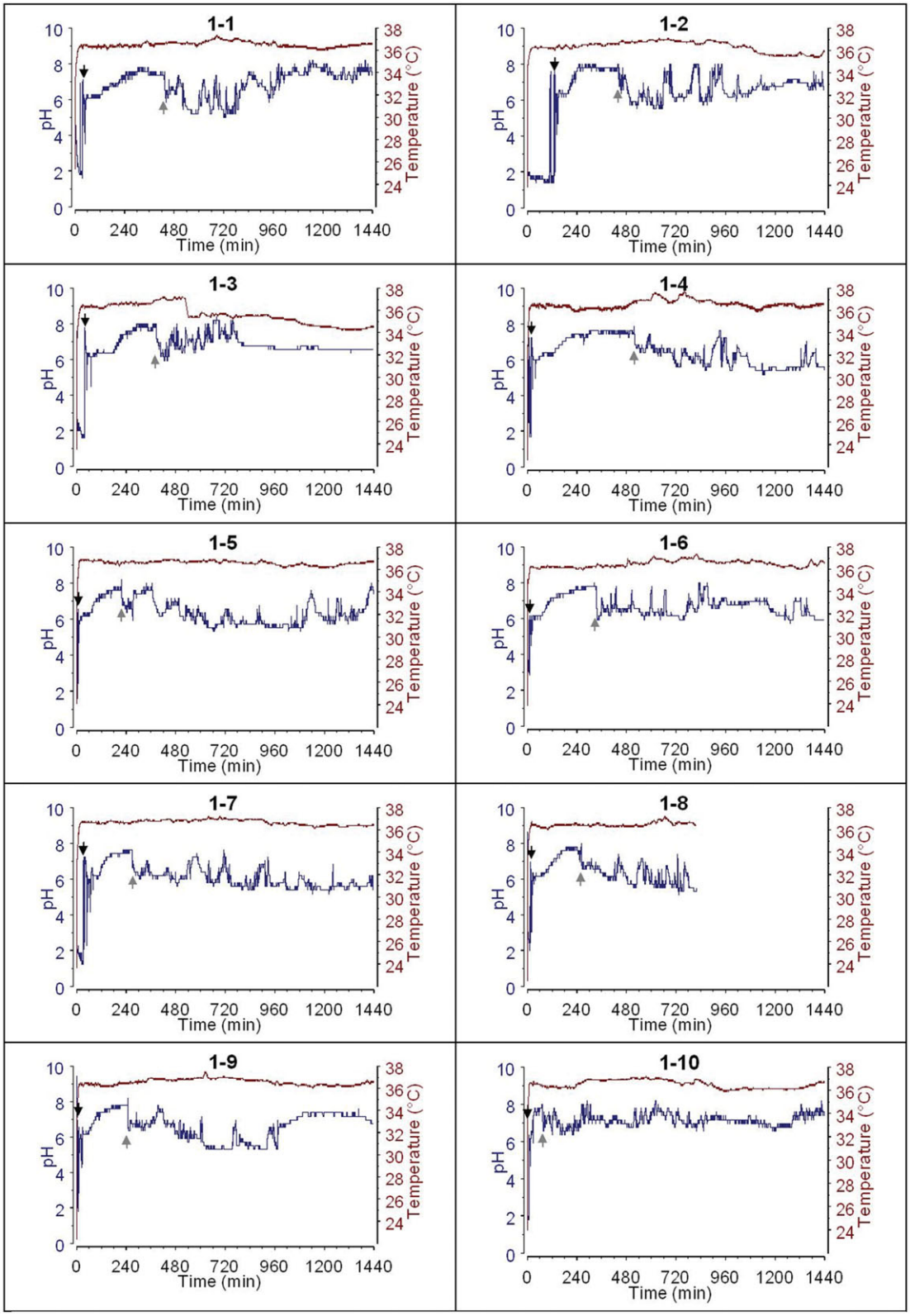

Figure 1. Temperature (red) and pH profiles (blue) during the first 24 h (1440 min) obtained after IntelliCap® ingestion in study 1. Gastric emptying is indicated by black downward arrow and colon arrival by gray upward arrow. In subject 1–8, the battery of data receiver was discharged after about 13 h.

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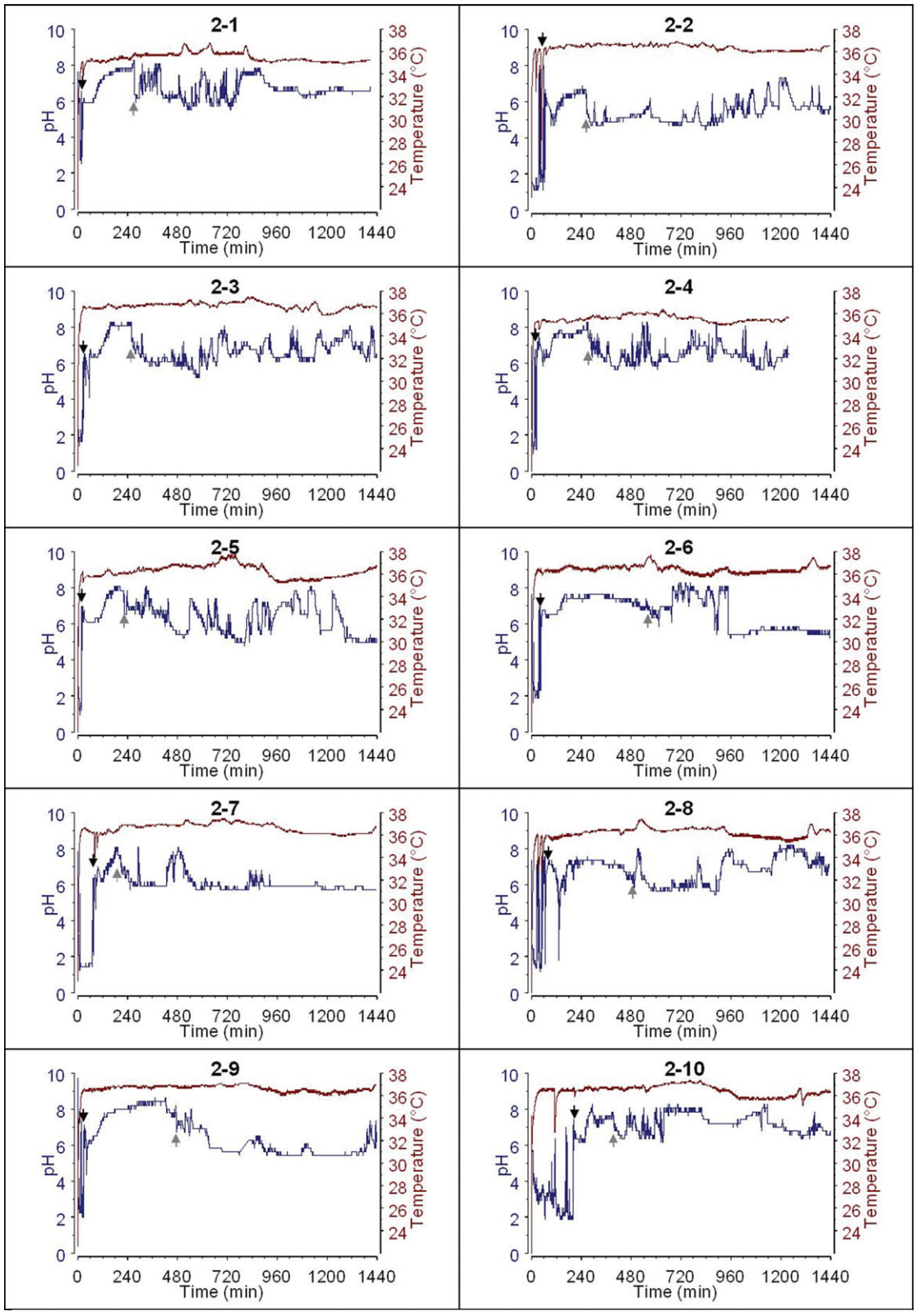

Figure 2. Temperature (red) and pH profiles (blue) during the first 24 h (1440 min) obtained after IntelliCap® ingestion in study 2. Gastric emptying is indicated by black downward arrow and colon arrival by gray upward arrow. In subject 2–4, missing data were caused by temporary loss of data transmission.

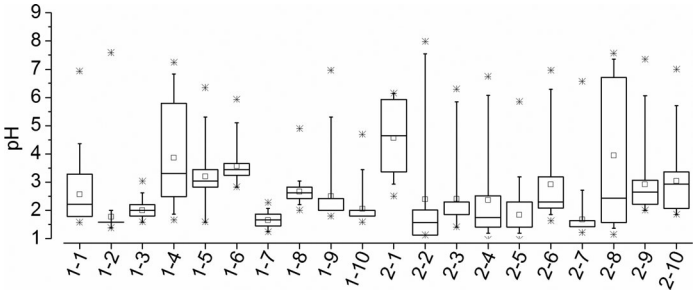

Figure 3. Box plots (box: 50%, whisker: 5%–95%, square: mean, asterisks max/min) of gastric pH values for both studies.

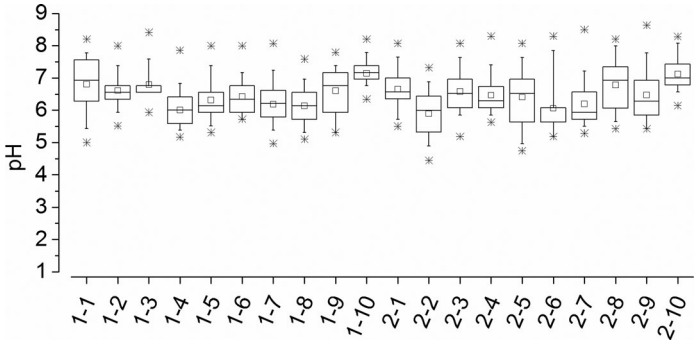

Figure 6. Box plots (box: 50%, whisker: 5%–95%, square: mean, asterisks max/min) of colonic pH values for both studies.

180–240 min, as it was the basis for the development of time-dependent release systems such as Pulsincap™ which was developed for colon targeting.[34] With regard to colon targeted dosage forms based solely on time-dependent release, a reliable delivery of the drug in the colon cannot be guaranteed as it was also shown in recent studies.[35,36]

The broad range of gastric pH values of pH 1–8 measured in this study was in accordance with data from a review recently published by Bergström et al.[24] The observed short episodes of higher intragastric pH values were most likely caused by the coadministered water and oral secretions. Kalantzi et al.[7] obtained similar results for fasted-state pH values in human aspirates. In the majority of cases, acidic pH values of pH 1–4 were investigated within the first hour. However, the coadministered water volume of 240 mL is emptied quickly from the fasted stomach.[37] Therefore, later pH peaks are probably the result of reflux of duodenal contents containing alkaline bicarbonate. The retropulsion of duodenal contents back into the stomach under fasting conditions has been reported by Hausken et al.[38] Considering the low residual volume and buffer capacity of the gastric juice it is likely that the retropulsion of small amounts of duodenal contents may come along with high

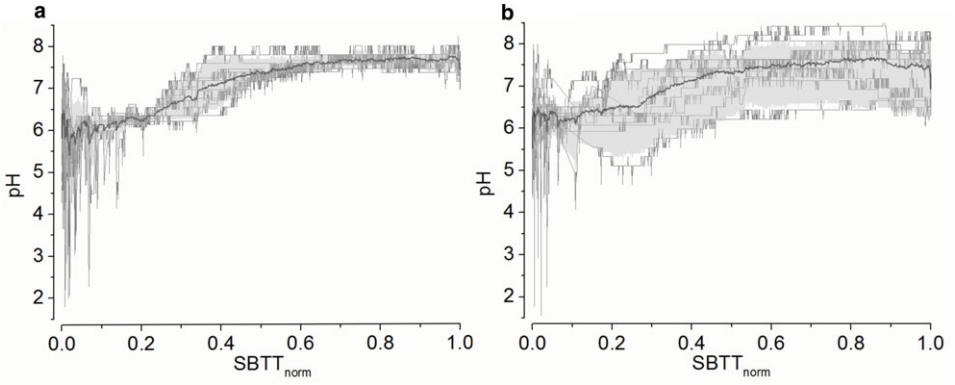

Figure 4. Individual pH profiles (gray) of IntelliCap® in the small intestine over normalized small bowel transit time ($SBTT_{norm}$). (a) Study 1, (b) study 2; each study with $n = 10$ subjects. The black line indicates the mean curve calculated by linear data interpolation. The shaded area represents the 10–90 percentile range.

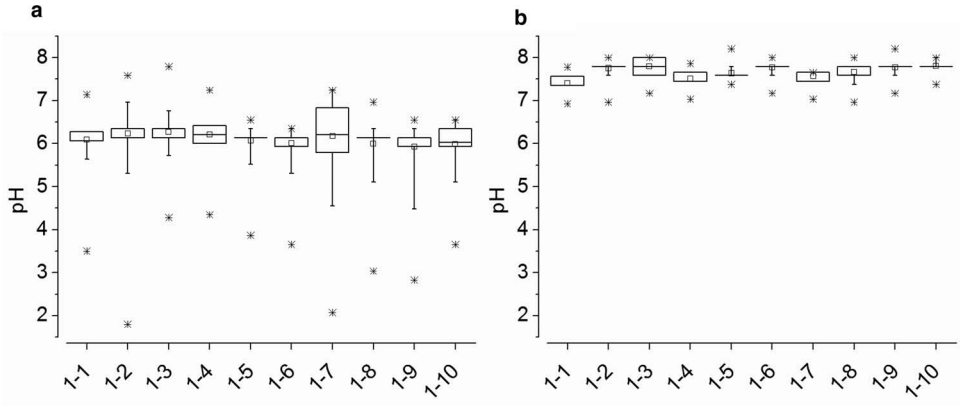

Figure 5. Comparison of pH ranges in proximal (a) and distal (b) small intestine (box: 50%, whisker: 5%–95%, square: mean, asterisks max/min) for study 1 ($n = 10$).

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fluctuations of the intragastric pH value. This hypothesis is at least partly supported by our experience from Magnetic Marker Monitoring studies, where we observed retrograde movements even of large monolithic dosage forms within the duodenum. However, retropulsion of such large solid objects back through the pylorus into the stomach seems quite seldom as we have seen this so far only once.[15]

The results of the present studies demonstrated that the current state of the art for the biorelevant simulation of fasted-state conditions does not reflect human GI physiology. This deficiency can be explained by taking the example of the acidic media that are used for the simulation of gastric conditions. These media are often used at a constant pH in the range from pH 1.0 up to pH 1.8, at a constant temperature of 37.5 ± 0.5 °C and in high volumes of 900–1000 mL. It should be realized that the fasted stomach is in fact characterized by high dynamics and highly variable pH conditions. The physiological situation is clearly not represented by the static conditions generated in many dissolution tests, which may often lead to misleading dissolution results. The acidity of the gastric content under fasting conditions is also overestimated if dissolution media such as 0.1 M HCL or simulated gastric fluid pH 1.2 are applied as the coswallowed water dilutes the gastric content. Furthermore, fluid volumes in the fasted stomach are significantly lower than 1000 mL, even after intake of the drug together with 240 mL of water. In particular for immediate release (IR) products, gastric transit conditions are highly relevant, as these are intended to disintegrate into small particles and to dissolve within a few minutes after intake. However, the precise determination of GRT is rather difficult, because the intragastric milieu, the gastric emptying pattern as well as the disintegration behavior of the dosage form contribute to the overall GRT of (un)dissolved or dispersed material. An approach to simulate the gastric conditions after intake of an IR dosage forms under fasting conditions with respect to fluid volume, pH, temperature, dynamics of water flow as well as gastric motility has been recently presented.[26]

The pH profiles in the small intestine were characterized by pH values of around pH 6 in proximal regions and slightly higher pH values of pH 7–8 in distal areas. The pH increase within the small bowel was also shown in a review by Bergström et al.[24] with data that were mainly generated by intestinal sampling. The duodenal increase to neutral pH values caused by pancreatic bicarbonate secretion is known to affect the intraluminal solubility of certain drugs such as furosemide or indomethacin.[5] It is likely that acidic drugs will experience higher solubility at intestinal pH values, whereas basic drugs might form oversaturated solutions or drug precipitates.[6,39] However, the duodenal transit of non-disintegrating, monolithic objects is typically short within a range from some seconds to several minutes.[27] Despite the short duodenal transit times, some drugs such as levodopa or furosemide have an absorption window in the duodenum.[40,41] In proximal parts stronger pH fluctuations could be observed because of the emptying of acidic contents from the stomach into the duodenum that decreased the intestinal pH value for short time. These dynamic conditions are also not considered by use of simple buffer systems such as United States Pharmacopeia phosphate buffer pH 6.8 or FaSSIF.

Colonic pH values were also highly variable with values between pH 5 and pH 8. These fluctuations are most likely caused by differences regarding the regional distribution of the colonic microbiota leading to different metabolic pathways and rates as well as by the complex movement and mixing conditions of the colon.[2,42,43] The pH drop at the ileocaecal junction is attributed to the production of short-chain fatty acids by bacterial fermentation.[18] It was shown recently that the pH drop between ileum and caecum is variable between subjects and in addition, depends on diet.[44] Therefore, the pH drop upon ileocaecal valve passage was less pronounced in some subjects. Moreover, Evans et al.[13] observed a slight pH increase from pH 6.4 ± 0.6 in the ascending colon towards pH 7.04 ± 0.7 in the descending colon. However, it must be kept in mind that the pH-sensitive radiopill, which was used in that study, showed a strong pH shift. This could have contributed to the described pH increase within the colon. In our study, we could not confirm such a clear tendency. The variation of the pH values measured in our studies was within the buffering pH range of hydrogen carbonate buffers and can be achieved using dynamic pH adjustment devices.[45]

From a biopharmaceutical point of view, the pH value is not the only factor that should be considered in biorelevant dissolution testing. The drug release from solid oral dosage forms also depends on fluid volume and composition along the GI tract. Schiller et al.[46] demonstrated that fluid volumes in the small intestine are low in fasted state and distributed in several pockets. Thus, the small intestine should not be regarded as a simple tube filled with high fluid volume and a static pH value. Indeed, the pH values inside the gut are the result of a dynamic interplay between secretion, motion, and metabolism. The observed pH fluctuations come about in media which volumes and buffer capacities are relatively low and therefore may be very dynamic such as during gastric emptying or colonic passage. Therefore, a deeper comprehension of human GI physiology is highly needed for predictive in vitro testing of oral dosage forms. The novel IntelliCap® system contributes to the understanding of the GI environment with respect to pH value, temperature and transit times to which solid oral dosage forms are exposed within the GI tract. In addition, the effect of the drug on intraluminal pH value and GI transit times can also be investigated in future studies with the aid of the drug delivery unit.

CONCLUSIONS

By use of the telemetric IntelliCap® system, pH and temperature profiles as well as transit times in the GI tract of healthy human subjects were investigated. Owing to the pH-dependent solubility of a variety of pharmaceutical compounds and excipients, the obtained pH profiles and transit times are highly relevant for the comprehension of drug release from solid oral dosage forms in the fasted state. The results revealed high variability in all parts of the GI tract, which is not reflected by the current pharmaceutical dissolution test methods. Therefore, individual pH and temperature profiles generated with high temporal resolution are presented. These can be applied as input functions for pH gradients used for physiologically relevant dissolution testing.

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Conflict of interest: Ventzeslav Iordanov, Jeff Shimizu, Hans Zou, and Chistoff Wanke are employees of Medimetrics. D. Becker acts as consultant for Medimetrics. All other authors declare no conflict of interest.

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