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.