A novel ingestible electronic drug delivery and monitoring device

Peter J. van der Schaar, MD,[1,2] J. Frits Dijksman, PhD,[3] Henny Broekhuizen-de Gast, MD, PhD,[4] Jeff Shimizu, PhD,[5] Niels van Lelyveld, MD, PhD,[2] Hans Zou, PhD,[5] Ventzeslav Iordanov, PhD,[3] Christoph Wanke, PhD,[3] Peter D. Siersema, MD, PhD, FASGE[2]

Nieuwegein; Eindhoven; Utrecht, The Netherlands; Briarcliff Manor, New York, USA

Background: We developed an ingestible electronic drug delivery and monitoring system. This system includes an electronic capsule comprising a drug reservoir, a pH and temperature sensor, a microprocessor and wireless transceiver, a stepper motor, and batteries. The location of the capsule in the gut derived from pH data can be monitored in real time. The stepper motor can be remotely actuated to expel the contents of the drug reservoir.

Objectives: First human study.

Design: Two consecutive observational studies.

Setting: University medical center.

Subjects: Twenty healthy volunteers.

Interventions: Study I: Ingestion and passage of the capsule. Study II: Ingestion and passage of the capsule, loaded with ^{99m}technetium-pertechnetate (^{99m}Tc); remotely actuated expulsion of ^{99m}Tc in the gut.

Main Outcome Measurements: Study I: Safety, tolerability, and functionality (wireless pH and temperature recording). Study II: Tracing of the capsule and expulsion and distribution of ^{99m}Tc from the drug reservoir by scintigraphy. Correlating location pH with scintigraphy.

Results: Study I: Ingestion and passage of the capsule was safe and well tolerated. Transmitted pH and temperature data were received by the recorder in 96.5% ± 3%. Study II: pH-determined passage of the esophagogastric, gastroduodenal, and ileocolonic junction correlated well with scintigraphy. Expulsion of ^{99m}Tc from the capsule was successful in 9 of 10 subjects.

Limitations: Subjects with relatively low body mass index.

Conclusions: This electronic drug delivery and monitoring system may be a promising tool for targeted delivery of substances to well-defined areas of the GI tract. (Gastrointest Endosc 2013;78:520-8.)

Since its introduction, wireless capsule endoscopy has rapidly become the procedure of choice for the diagnosis of various small-bowel disorders.[1,2] More recently, a variety of ingestible electronic devices with expanded and new functionalities, such as improved visual imaging, smart power management systems, pH and pressure sensors, biosensors, remotely controlled magnetic manipulation, and therapeutic capabilities, has been developed.[3]

The development of formulations that provide reliable drug absorption, reproducible bioavailability, and/or pharmacokinetic profiles in humans represents a major bottleneck in today's development of orally administered drugs.[4]

Abbreviation: ^{99m}*Tc,* ^{99m}*technetium-pertechnetate.*

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Current affiliations: Department of Gastroenterology, St Antonius Ziekenhuis, Nieuwegein, The Netherlands (1), Department of Gastroenterology and Hepatology (2), Department of Nuclear Medicine (4), University Medical Center, Utrecht, The Netherlands; Medimetrics, Philips Research, Eindhoven, The Netherlands (3), Medimetrics, Philips Research, Briarcliff Manor, New York, USA (5).

Reprint requests: Peter van der Schaar, MD, Department of Gastroenterology, St Antonius Ziekenhuis, PO Box 2500, 3430 EM Nieuwegein, The Netherlands.

Traditionally, the site of enteral absorption of a drug is based on chemical characteristics of the drug dosage form (coating or matrix).[5] However, highly predictable delivery and exact dosing of chemically based drug formulations at specific sites in the GI tract are difficult to accomplish because of unpredictable gastric emptying time and varying physiochemical characteristics of the GI tract.[6,7]

To overcome some of the problems with chemically based drug release systems, an electronically controlled drug delivery and monitoring system was developed (IntelliCap system, Philips Research Eindhoven, the Netherlands, and Briarcliff Manor, NY, USA) that includes an ingestible electronic capsule comprising a drug reservoir, diagnostic sensors (pH, temperature), an electromotor-driven piston, a programmable microprocessor, and a wireless transceiver. Wirelessly transmitted temperature and pH data are monitored in real time. The stepper motor can be remotely actuated to expel the contents of the drug reservoir into the gut lumen. The capsule has comparable dimensions with other commercially available wireless capsule endoscopy devices such as Given Imaging SB (Given Imaging, Yoqneam, Israel), Endocapsule (Olympus, Tokyo, Japan.), and Smart Pill (SmartPill, Buffalo, NY, USA).[8,9]

We performed the first human study with the electronic drug delivery and monitoring system. The goal was to assess safety, tolerability, functionality, and precision of pH-based localization of the capsule.

Take-home Message

- In this first human study of a remotely controlled ingestible drug delivery device, we showed that pH sensors in the device reliably indicate its location in the gut. Based on real-time pH data, we remotely activated an electronic motor in the device to expel the contents of the drug reservoir into the gut at a predetermined location.
- The device may be used for targeted drug delivery to well-defined areas of the gut.

METHODS

Subjects

Twenty healthy volunteers were recruited by advertisements in the local media. Exclusion criteria were known or suspected GI strictures, including (suspected) Crohn's disease, other GI disorders, pacemakers or other implanted electromedical devices, swallowing disorders, pregnancy, unwilling to institute contraceptive measures until >1 month after study completion, use of acid-reducing medications or nonsteroidal anti-inflammatory drugs, known cardiopulmonary disorder, and an American Society of Anesthesiologist physical status classification > 1. Magnetic resonance imaging studies were not allowed with the capsule in the body.

During a screening visit, subjects were informed about the study. Inclusion and exclusion criteria were evaluated. Written informed consent was obtained.

Electronic drug delivery and monitoring system

The system consists of an ingestible electronic capsule, a start-up unit to program and activate the capsule, and a smartphone-sized portable unit to record and relay data to a control center (personal computer) and vice versa (Figs. 1 and 2). The capsule consists of an electronic compartment and a 300-μL drug medication compartment (Fig. 3). The liquid contents of the drug reservoir can be expelled through the dispensing holes by the motion of a piston driven by the stepper motor via a screw-rod mechanism.

Various release profiles can be programmed, including continuous release profiles with different release speeds (rapid vs sustained release) and intermittent release profiles (single or dual-burst profiles). The minimum release time is 10 minutes, and the maximum time is only limited by battery lifetime (>48 hours). The capsule can be operated by remote commands from an operator or autonomously, based on sensor input (pH, temperature, and clock). The system is approved by the European Union Legislation, and the capsules are approved for 1-time use.

Study objectives

The study consisted of 2 parts. In study I, the primary objective was to assess safety and tolerability of the capsule by recording any signs of capsule retention, GI bleeding, or perforation and by studying the structural integrity of the capsule after GI passage. In study II, the primary objectives were to investigate (1) the functionality of the system in healthy volunteers by real-time measuring of pH and temperature and dispensing a payload upon an externally triggered command and (2) the correlation between anatomic location of the capsule based on 3-dimensional nuclear imaging using both ^{99m}technetium-pertechnetate (^{99m}Tc) within and released from the capsule, based on the recorded temperature and pH.

Secondary objectives were to study the quality of two-way electronic data transmission, to record GI transit times of the capsule, and (in study II) to investigate the spatial and temporal distribution of intraluminally released ^{99m}Tc and the relationship between the position of the capsule and intraluminal ^{99m}Tc.

Study design

The study was performed at the Department of Gastroenterology and Hepatology and the Department of Radiology and Nuclear Medicine of the University Medical Center Utrecht, The Netherlands. Capsules were prepared in advance and the pH sensor calibrated using standard pH

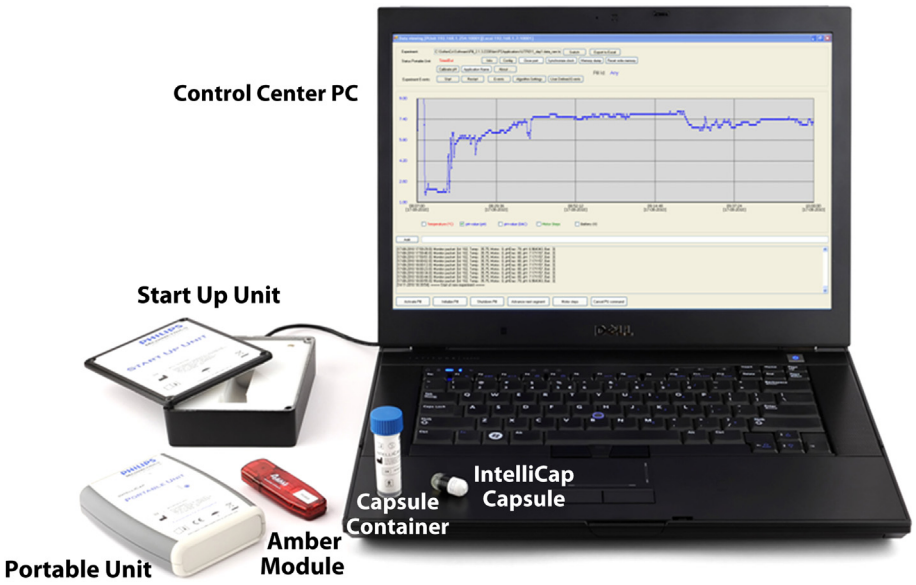

Figure 1. Components of the electronic drug delivery and monitoring system.

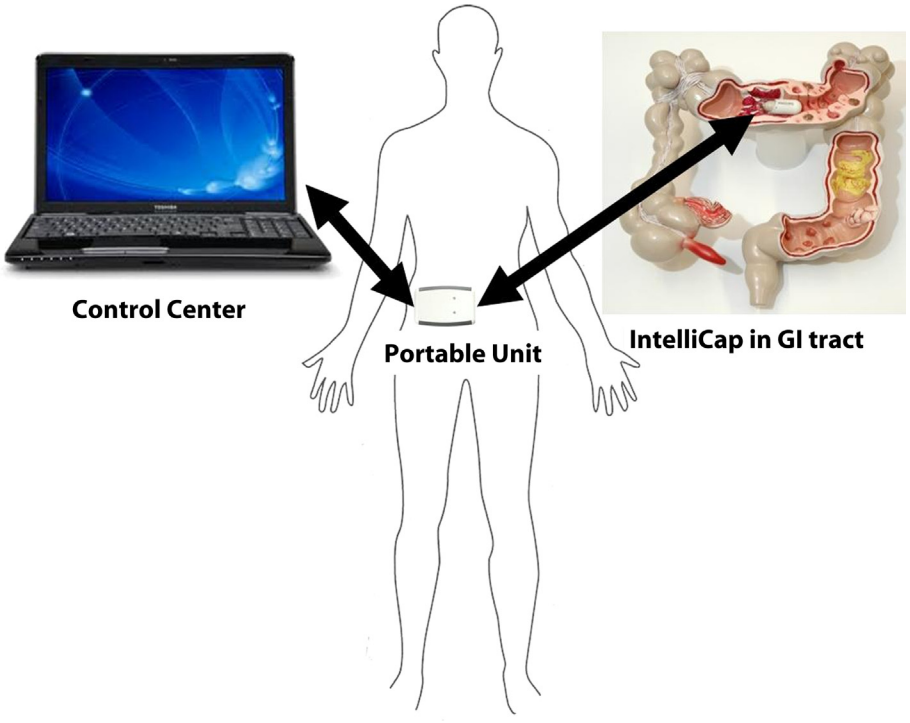

Figure 2. Schematic diagram of the system's mode of operation with 2-way wireless communication.

buffers. The capsules were programmed to monitor pH and temperature every 10 seconds. In study I the drug reservoir was filled with normal saline solution; in study II the drug reservoir was filled with normal saline solution containing 200 MBq ^{99m}Tc.

After an overnight fast, the subjects reported to the research unit. They were instructed to report any signs of capsule retention, GI bleeding, or perforation until the capsule had left the body. The capsule was administered with a glass of water. Oral intake was not allowed during the first 4 hours. Thereafter, a lunch was given. After 10 hours, the subjects left the research unit, keeping the portable unit close to the body to enable further data collection. They collected their stool in a container to retrieve the capsule.

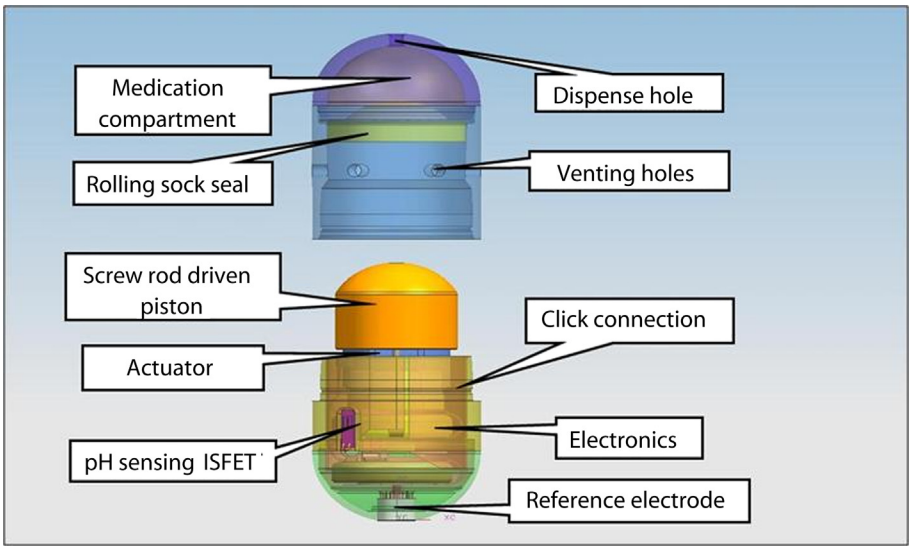

Figure 3. Schematic diagram of the capsule showing mechanical layout and the main components. The electronic compartment houses pH and temperature sensors, a programmable microprocessor with a real-time clock, a wireless transceiver, an antenna, a stepper motor, and batteries for powering all functionalities. The medication compartment contains a 300-μL drug reservoir. The medication compartment can be separately filled with drugs and later clicked onto the electronic compartment. *ISFET*, ion sensitive field effect transistor.

TABLE 1. Subject demographics

	Average	Range
Study I		
Weight (kg)	62.1	52-84
Body mass index, kg/m^2	20.4	18.1-24.0
Age, y	21.6	19-25
Study II		
Weight (kg)	65.6	57-75
Body mass index, kg/m^2	21.5	18.7-24.2
Age, y	20.6	19-25

The next morning the subjects returned to the research unit to check for any adverse events and to return (if applicable) the excreted capsule together with the portable unit. If at that time the capsule had not been retrieved and transmitted data suggested it was still in the body, subjects continued wearing the portable unit until the capsule was excreted. All data received by the portable unit were downloaded into a computer after return of the portable unit. In addition, real-time data were simultaneously sent to the control center (relayed by the portable unit) during the first 10 hours while the subjects were in the research unit. Retrieved capsules were checked for structural integrity.

In study I, no additional interventions were performed. In study II, when pH readings suggested pyloric passage, subjects ingested 20 mL of ice-cold water. Nuclear scintigraphy was performed using a dual-headed gamma camera fitted with a Vertex high resolution collimator (Philips FORTE, Philips Healthcare, Eindhoven, The Netherlands). Imaging reference points at the xyphoid and left iliac crest were marked with Cobalt-57 (^{57}Co). Perpendicular static nuclear images were obtained every hour during the first day, after ileocecal valve passage (based on pH readings) and after 24 hours . When pH and temperature readings indicated pyloric passage, the capsule was remotely actuated to expel 75% of ^{99m}Tc from the reservoir. Thus, both the position of the capsule (with 25% of ^{99m}Tc still in the capsule) and the distribution of intraluminally released ^{99m}Tc could be studied. Two 30-minute dynamic nuclear imaging sequences with a 15-minute break were recorded starting immediately before expulsion of ^{99m}Tc.

Data analysis

Received data fidelity was expressed as the number of data packages received by the data recorder divided by the number of data packages the capsule was programmed to transmit. Temperature tracings and pH tracings were analyzed by five gastroenterologists with experience in capsule endoscopy (CE) and/or GI motility. An expert-based definition of passage of anatomic landmarks was agreed on after reviewing all tracings:

- Esophagogastric passage: a rapid and sustained decrease of pH, briefly after ingestion of the capsule
- Pyloric passage: a rapid increase of pH to >6, lasting more than 6 minutes
- Ileocecal valve passage: a sustained decrease of pH of 0.5 to 2 units occurring within 2 to 5 minutes and at least 30 minutes after pyloric passage.[10]
- Anal passage: a marked and sustained decrease in temperature

TABLE 2. GI transit times determined from capsule data

Subject ID	Gastric transit time	Small bowel transit time	Colon transit time	Whole gut transit time
UTR001	00:35	06:40	22:30	29:45
UTR002	02:12	05:51	29:47	37:50
UTR003	00:41	05:46	16:59	25:26
UTR005	00:17	08:24	(ca. 63 h)*	(ca. 72h)*
UTR006	00:04	03:43	29:51	33:38
UTR007	00:13	05:21	(ca. 26 h)*	(ca. 32 h)*
UTR008	00:48	03:42	46:38	51:08
UTR009	00:23	04:00	(ca. 20 h)*	(ca. 25 h)*
UTR010	00:27	03:41	15:54	20:02
UTR011	00:13	01:00	24:00	25:13
1001	0:17	4:15	19:00	23:33
1002	1:00	3:45	(ca. 40 h)*	(ca. 45 h)*
1003	0:33	3:54	23:04	27:32
1004	0:27	4:24	(ca. 20 h)*	(ca. 25h)*
1005	0:19	3:26	32:37	36:24
1006	0:47	8:50	23:41	33:20
1007	1:18	2:14	(ca. 56 h)*	(ca. 60 h)*
1008	2:22	5:51	16:20	24:33
1009	0:31	7:24	(ca. 52 h)*	(ca. 60 h)*
1010	3:22	3:16	23:58	30:38
Average (SD)	0:50 (00:51)	4:46 (01:59)	24:56 (08:23)	30:41 (08:06)
Minimum	0:04	1:00	15:54	20:02
Maximum	3:22	8:50	46:38	51:08

Values are in hours:minutes. The first 10 subjects participated in study I; the last 10 subjects participated in study II.
*Estimated times based on subject-reported excretion (not used for statistics). Excretion not recorded by portable unit due to battery drainage (UTR007 29 hours, UTR 009 13 hours, 1002 45 hours, 1007 59 hours, 1009 61 hours), due to return of the portable unit before capsule excretion (UTR005) and due to temporary loss of data transmission (1004).

Ethics

The studies were approved by the Medical Ethical Committee of the University Medical Center, Utrecht.

RESULTS

Twenty subjects (Study I: 3 men, 7 women; Study II: 3 men, 7 women) were included in the 2 studies (Table 1). All subjects completed the studies. All subjects returned the capsule to the study unit.

Safety/tolerability

All subjects swallowed the capsule without any problems and excreted the capsule without symptoms. All capsules were structurally intact upon return. No signs or symptoms suggesting capsule retention, GI bleeding, or perforation were reported. No adverse events were observed.

Data reception

Temperature and pH data from all subjects were recorded during the period in the research unit. In all 10 subjects (study I) and 9 of 10 subjects (study II), data were recorded for >24 hours or throughout GI passage of the capsule (Table 2). In study II, in subject 1009, the capsule temporarily displayed irregular data transmission upon the dispense command trigger, leading to lower data reception values. After some time the reporting frequency returned to the programmed 10-second interval.

In all subjects, during the first 10 hours in the research unit, a high percentage of data transmission and reception was observed. The percentage of data reception decreased slightly after the subjects had left the research unit (Table 3). During the time the capsule was in the body and an operable portable unit was worn, data packets sent by the capsules were recorded with an average success rate of 96.5% ± 3%.

TABLE 3. Received data package success rate

Subject ID	Received data packets (%)	
	Day 1, inpatient period	Administration to excretion
UTR001	100	98.7
UTR002	99.7	93.7
UTR003	98.4	96.5
UTR005	98.1	97.4
UTR006	99.8	96.5
UTR007	99.4	95.7
UTR008	99.9	98.7
UTR009	99.9	99.3
UTR010	99.9	98.0
UTR011	99.9	98.4
1001	99.6	92.9
1002	99.3	94.9
1003	99.5	99.1
1004	99.6	99.2
1005	98.6	98.0
1006	96.4	95.6
1007	98.8	94.6
1008	99.1	97.5
1009	66.1*	87*
1010	99.5	99.2
Average (SD)	97.6% (7.5%)	96.5% (3%)

The first 10 subjects participated in study I; the last 10 subjects participated in study II.
*Capsule temporarily displayed irregular reporting periods.

GI landmark identification based on pH and temperature recordings

In both studies, esophagogastric and pyloric passage were identified in all subjects. In study II, after presumed pyloric passage, ice-cold water was ingested. A significant temperature drop indicated the capsule was still in the stomach, and a small temperature drop indicated the capsule had passed the pylorus (Fig. 4). The ileocecal valve could be identified in all subjects. After the capsule passed the ileocecal valve, variability in pH markedly increased in all subjects (Fig. 5). Anal passage was identified in all subjects from whom data were obtained at this time point. Computed transit times are shown in Table 3.

Scintigraphy (study II)

Capsule localization based on pH profile correlated well with scintigraphically determined position in all 10 subjects (Fig. 6). Approximately 5 minutes after ingestion the first static images were taken. In all subjects scintigraphy indicated the capsule was in the stomach, coinciding with a low pH reading.

When pyloric passage was suspected (based on pH rise and no significant temperature drop after ingestion of ice-cold water), the capsule was triggered to release 75% of its contents. During dynamic imaging the release and distribution of ^{99m}Tc in the small bowel was observed. In addition, the locale of the capsule could be identified (Fig. 7). In the earlier scintigraphic images after release of ^{99m}Tc, the small bowel was visualized better than in the later images. This is related to dispersion of ^{99m}Tc in the small bowel and rapid transfer and distribution into the interstitial space. A steady and continuous aboral distribution pattern of intraluminal ^{99m}Tc was observed. In contrast, the capsule showed antegrade and retrograde movements alternated by stationary periods. These 2 different movement patterns resulted in the capsule being ahead of the intraluminal ^{99m}Tc at some times, whereas it followed the intraluminal ^{99m}Tc at other times.

One capsule failed to accept the release command. After issuing the release command, this capsule displayed temporarily irregular data reporting intervals (see above).

DISCUSSION

This is the first study in humans with a newly developed electronically controlled drug delivery and monitoring system. We demonstrated that the capsule, which is the part of the system inside the body, was well tolerated in healthy volunteers. The capsule passed the GI tract without any adverse effects. All capsules were retrieved structurally intact. In addition, received data fidelity was high. The average body mass index of the study population was relatively low, and the data capture rate in subjects with higher body mass indices remains to be determined. Remotely controlled payload release was successful in 9 of 10 capsules. One capsule did not accept the release command and displayed a temporary, irregular data reporting frequency, indicating an electronic malfunction. Using scintigraphy as the criterion standard, the capsule's pH and temperature data reliably identified passage of anatomic landmarks in the GI tract. Recorded pH profiles corresponded well with previously published profiles.[10]

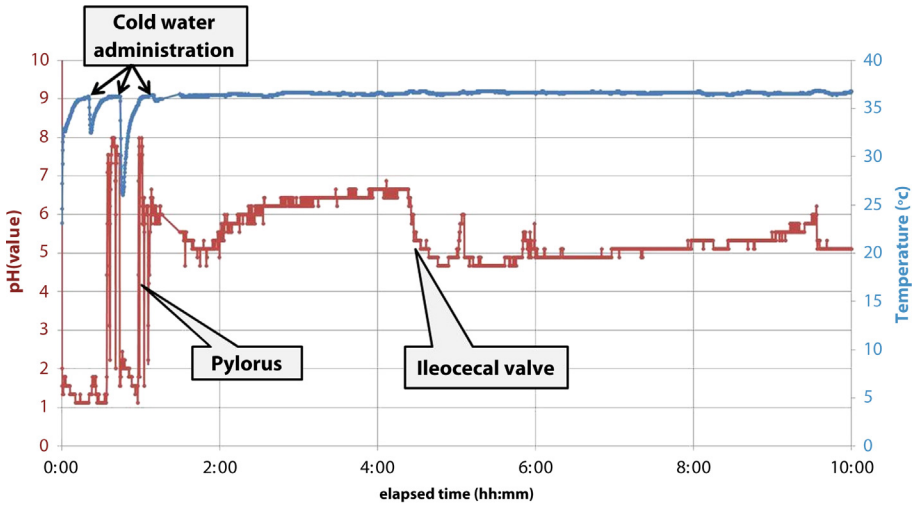

Figure 4. Representative pH and temperature profile of GI transit of the capsule during the first 10 hours after administration (subject ID 1002). Pyloric passage and ileocecal passage as well as cold water administration are indicated.

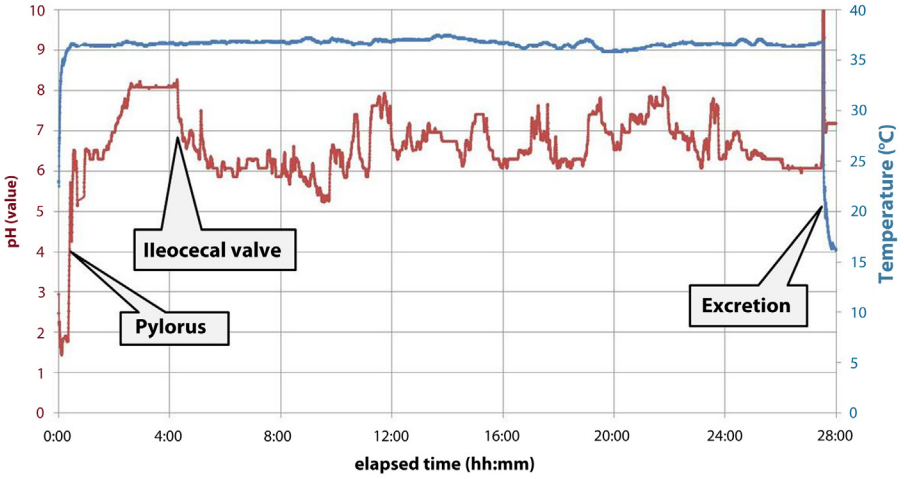

Figure 5. Representative pH and temperature profile of GI transit of the capsule from administration to excretion (subject ID 1003). Pyloric passage, ileocecal passage, and excretion are indicated.

Several electromechanical devices have been developed to deliver medication to specific parts of the GI tract. The Enterion capsule has a 1-mL drug reservoir and a sealed compartment that can be filled with a radioactive marker for scintigraphic location of the capsule. Drugs are expelled by applying an external oscillating magnetic field actuating a spring-controlled piston.[11] Liu et al[12] reported the use of a remotely controlled capsule containing a drug reservoir, a magnet for localization of the device, and a piston and actuation system to empty the drug reservoir by an external command. Another electronic ingestible electronic device, the SmartPill, was not developed as a drug delivery device. However, it shares some functionality because it also samples intraluminal pH and, additionally, intraluminal pressure. Applications of the device include assessment of gastric emptying and colonic and whole gut transit time.[13,14] Other ingestible devices are being developed for a variety of applications, including advanced imaging techniques, remotely controlled steering and locomotion, performance of mucosal biopsies, and neurostimulation.[3]

The system is designed for use as an individualized, highly accurate drug delivery system. In this study, the exact position of the capsule could be determined when it was in the stomach and during passage of the pylorus and ileocecal valve. When localized drug release in the stomach, in the duodenum/proximal jejunum, or in the cecum is required, an easily programmable drug-release algorithm using pH and temperature data may be used. Further down the small bowel or further down the colon, localization of drug release may be less accurate. If it is possible to predict segmental transit times of the capsule, the capsule might be programmed to deliver its payload at even more specific locations in the GI tract. Simply using segmental

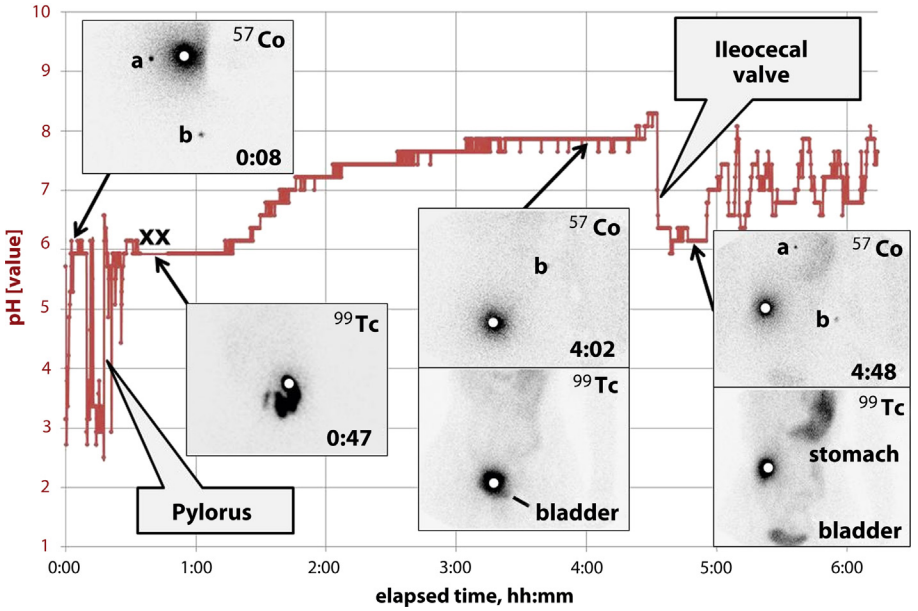

Figure 6. Correlation of capsule localization based on pH and imaging (subject ID 1001). a, xyphoid; b, left iliac crest; xx, payload dispense; ○, capsule.

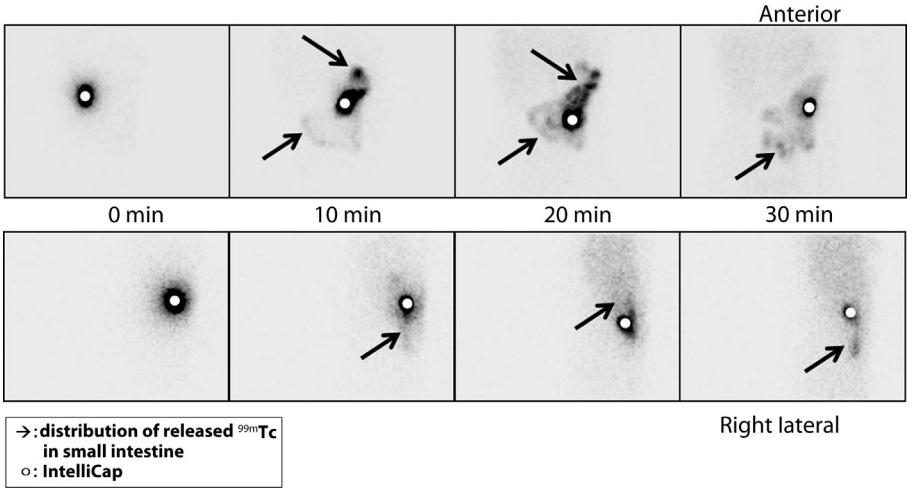

Figure 7. Representative snapshots of dynamic imaging during the release of the payload in the proximal small bowel (subject ID 1004).

transit times on groups of individuals is insufficient for this because there is a large *inter*individual variability in transit times. One study showed that *intra*individual small intestinal transit times are much smaller than inter-individual transit times[15] (D. K. Christodoulou, personal communication). Nonetheless, more data are needed to confirm whether drug-release profiles based on segmental transit times can be used to accurately predict the site of drug delivery.

Future applications of the system include drug absorption or nonabsorption window mapping to guide modified release formulation development. In addition, therapeutic applications such as controlled intraluminal drug delivery in patients with inflammatory bowel disease may have several advantages. The device may reduce toxicity associated with systemic administration of drugs and reduce or even prevent the formation of antibodies to drugs. In inflammatory bowel disease, topical administration of drugs is a well-known concept (eg, rectal suppositories and enemas are effective in patients with inflammatory bowel disease confined to the rectosigmoid region).[16] The efficacy of slow-release budesonide capsules in proximally located inflammatory bowel disease is also attributed to its local effect.[17] Studies on the local effect of more recently developed drugs are limited to rectal administration[18,19] or the use of complicated drug delivery systems (eg, living, genetically modified bacteria carrying synthetically produced interleukin-10).[20]

Nanomedicine is a rapidly evolving field with many potential applications in the GI tract. To further develop nanomedicines, strategies to bypass the hostile environment of various parts of the GI tract for targeted nanoparticle delivery are urgently needed.[21] Our system using a capsule to bypass the hostile gastric and proximal small bowel environment may contribute to the further development of these types of drugs.[22]

In conclusion, our study shows that the capsule is safe and well tolerated in healthy subjects. Using scintigraphy as the criterion standard, both the payload release functionality and landmark identification in the GI tract based on pH profile were successfully demonstrated. Possible applications of this electronic drug delivery and monitoring system include its use in preclinical and clinical studies to investigate regional bioavailability of drugs as well as a therapeutic drug delivery device in diseases requiring high intraluminal drug concentrations in well-defined regions of the GI tract.

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