# 1 Implantable Wireless Medical Devices for Gastroesophageal Applications

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## 1.1 Introduction

Advances in low-power-consumption radiofrequency integrated circuits (RFICs), multi-functional integrated circuits, high-sensitivity sensing electrodes, biocompatible materials, and packaging techniques have made implants with wireless communication functionality and/or wireless charging capability more feasible and practical. However, wireless communication or wireless powering has not been widely used in implants. There are several challenges. The implant applications are typically disease oriented and implementation focused. The designs of implants have to address specific needs in the disease diagnosis or treatment modalities, which are strongly related to both electronic and mechanical parameters. The sensing modalities or therapy methods determine the electrical specifications, while the biological environments often present serious design constrains. The implementation has to suit clinical settings for safe, cost-effective, and relatively easy implantation procedures and, most important, the needs and comfort of patients in daily life.

It is obvious that integration of wireless communication functionality in implants can provide critical and increased capabilities in applications. The outbound communication brings sensor signals and device conditions to the reader outside the body. The sensors can monitor physiologic signals, such as blood pressure, intracranial pressure, core temperature, electrical signals of tissue or motility of organs, and biochemical conditions such as pH and certain protein or factor concentrations, of patients *in vivo* and in real time. In addition, the wireless communication can periodically report device conditions such as battery level, electrical resistance of electrodes, and current/voltage delivered to tissues. The inbound communication can be used for device reconfiguration, dosage setting, and condition probing. Bidirectional communication will be ideal for remote access of the implants, adding capabilities for real-time feedback as an integrated system between body and computer. The wireless closed-loop system also can provide real-time patient condition alerts, patient self-diagnosis using smart phones, and autonomous treatment-efficacy studies over a population of patients.

From the perspectives of patients, wireless communication removes the discomfort and inconvenience of tethered wires coming out of the body. Currently, the wires either go through small surgical openings in the body, such as for the extension wire from the head in deep brain stimulation, or an orifice, such as the nostril for stomach stimulation and multichannel intraluminal impedance tests or the urethra for bladder monitoring.

The tethered wires connecting to the external electronic device, either a reader or a pulse generator, obviously bring some inconvenience to patients and sometimes pain, and they often limit patient mobility, hindering quality of life. Often the discomfort and suffering affect patients' daily regular activities and alter their behavior subconsciously or consciously. This could have an effect on the accuracy of monitored physiologic parameters. Given these limitations, it is difficult to use sensors with tethered extension wires in the long term. Many such sensor systems are for short-term or temporary use, lasting from hours to a few days. This limits the possibility of using them to quantitatively monitor patient progress in therapy or as alert monitors continuously checking critical parameters. Treatment systems such as stimulators, because patients depend on them to restore tissue functions, suffer from these unavoidable nuisances and burdens.

## 1.2 Wireless Communication in Medical Implant Applications

Several electrical implants have been widely used, and more are coming to the market and are being researched in hospitals and laboratories. Cardiac pacemakers for controlling abnormal heart rhythms, implantable cardioverter defibrillators for detecting abnormal ventricular heart rhythms and delivering electrical signals to restore the heart's normal rhythms, and neurostimulators for deep brain stimulation in tremor control for patients with Parkinson's disease and dystonia, as well as in spinal cord stimulation for chronic pain management, have been cleared for wide clinical applications. Research on neurostimulation for obsessive-compulsive disorder, depression, tinnitus, epilepsy, respiratory support, malignant pain, spasticity, amyotrophic lateral sclerosis, Huntington's disease, gastroparesis, irritable bowel syndrome, headaches, traumatic brain injury, angina pain, peripheral vascular disease pain, pelvic pain, incontinence, and sexual dysfunction are on the way to clinical validation.

Most of these devices or systems are still not equipped with wireless communication or wireless powering functionalities. In limited applications, such as neurostimulation, inductive coupling to adjust electrical dosages or wireless rechargeable batteries has been implemented [1,2]. The wireless functions of changing settings or charging are only used for limited time periods instead of continuous communication connection or powering. Nonetheless, it is quite clear that both patients and doctors can greatly benefit from wireless signal transduction and wireless controlling/monitoring of implants; thus manufacturers are working on incorporating these capabilities into the next generation of products.

Two types of implantable systems emerging in recent years require continuous wireless communication between external modules and the implants: cochlear implants and implantable visual prosthetics. Cochlear implants are designed to produce hearing sensations with electrical stimulation of nerves inside the inner ear for patients with severe to profound nerve deafness. The wireless communication carries the signals that are converted from sounds to stimulating electrical pulses from a small module near the ear to the implant. The electrical pulses activate the auditory nerves and create hearing recognition in the brain. Several cochlear implants have been approved by Food and

Drug Administration (FDA) already. Implantable visual prosthetics, such as the Argus II retinal prosthesis system (Second Sight Medical Products, Inc.), have been approved for use as a humanitarian device and are currently being tested clinically for patients with retinal damage (retinitis pigmentosa) [3]. The patient wears a pair of glasses with an attached video camera that captures images. A signal-processing module converts the image signals to electrical stimulation pulse commands for an electrode array, and the commands are wirelessly transmitted into the eye. The electrical pulses then spatially stimulate the retinal cells to induce cellular responses that propagate through optic nerves to the central visual system, resulting in visual percepts. In both cases, the wireless communication carrying the audio signals or visual image data is continuous and conducted within a close distance through tissues around the ear or eye.

## 1.3 Implementation Methods

Wireless communication and energy transfer enable remote control and signal transduction for devices that are surgically implanted inside the body. Conventional systems require major open surgical procedures or laparotomy with a large incision because the devices are bulky, mostly due to the battery. However, the advances in battery technology and integration of multifunctional chips continue reducing implant sizes. Soon these devices will be sufficiently small to be implanted with minimally invasive surgery that involves a smaller incision to access a body cavity. The advantages of minimally invasive surgery include limited to no trauma on nerves and tissues, less bleeding and scarring, and less pain. In return, these mean a shorter hospital stay, a quicker recovery, less risk, and therefore lower costs. It is clear that miniaturization of wireless implants can enable the advantages of minimally invasive surgical implantation procedures in addition to the advantages of the absence of tethered wires.

Furthermore, endoscopic procedures have also advanced in recent years. Modern endoscopes consist of a long and flexible tube with lighting LEDs and a miniature video camera in the probing end. Real-time images inside the body can be seen on a display screen for visualization and orientation. Operating endoscopes are also equipped with irrigation, suction, and additional working channels that are used for inserting special instruments such as biopsy forceps, scissors, clamps, dissectors, graspers, suturing devices, and other surgical tools. These endoscopic imaging and surgical procedures have been used for the gastrointestinal (GI) tract, including esophagus, stomach and duodenum, bile duct, small intestine, large intestine, colon, rectum, and anus; the respiratory tract inside nose and lower respiratory tract; the ear; the urinary tract; and the female reproductive system, including the cervix, uterus, and fallopian tubes. These procedures are generally outpatient or at least simpler, reducing anesthesia time and/or hospital stays, without significant risk to patients.

Endoscopic procedures have also been researched to access normally closed body cavities through a small internal incision, which is generally called *natural orifice translumenal endoscopic surgery* (NOTES) [4–10]. NOTES is still in the research stage as a new surgical technique. It does not produce external scars when abdominal operations are performed with an endoscope passed through a natural orifice such as the mouth, nose, urethra, or anus. Recognized advantages include the ones for endoscopic procedures and, additionally, with decreased neurohumoral stress responses, decreased immune suppression, less pain, faster recovery, and decreased wound-related and pulmonary complications, especially a lower incidence of wound infection and incisional hernia [11]. Endoscopic and NOTES procedures open a wide window for wireless implants because they provide an implantation method with more comfort, easier implementation, less pain, fewer risk factors, faster recovery, and thus more affordable cost for patients.

## 1.4 Endoluminal Capsule Applications

Through endoscopic procedures and NOTES, stomach, liver, pancreas, vagina, bladder, and colon can be accessed with a small internal incision. These organs and nearby cavities thus are good candidates for implanting wireless devices for monitoring or treatment. In particular, endoluminal applications are attractive because the access is easier. For example, currently there are several commercial systems for endoluminal capsule monitoring. A miniaturized wireless radio transmitter is embedded in an ingestible capsule along with certain types of sensors. The patient swallows the capsule with water. The capsule travels through the gastrointestinal tract and broadcasts signals to the outside. The signals contain sensor information such as pH and motility or images. The signals are received by a radio receiver worn on the body. The signals are then processed and stored on a memory card from which data will be transferred to a computer later. Several commercial camera-based imaging capsules [12–15] have been developed targeting esophageal [16,17], colon mucosal [18,19], and small bowel [20–25] visualization. As the capsule travels through the area of interest, it takes photographs with lighting from LEDs mounted at the ends of the capsule. Some examples are shown in Figure 1.1. As disposable devices, the imaging capsules mostly use cost-effective technologies such as complementary metal-oxide semiconductor (CMOS) sensors and coin batteries and operate at a lower frequency band [26]. For example, PillCam capsules, with sizes of 26 or 31 mm in length and 11 mm in diameter, transmit unidirectional signals at 434.1 MHz in a bandwidth of $\pm$10 MHz with a power consumption of 5.2 mW and a data rate of 2.7 Mb/s [27]. The battery life for imaging the esophagus is designed to be 20 minutes, small bowel is 9 hours, and colon is 10 hours. Another example is the SmartPill, with dimensions of 13 mm in diameter and 26 mm in length, housing three sensors that can measure pressure, pH, and temperature as it travels through the GI tract to assess motility in the evaluation of suspected gastroparesis and colonic transit in the setting of chronic constipation [28,29]. It measures the temperature (25–49°C), pH (0.05–9.0), and pressure (0–350 mmHg) of its immediate surroundings with a battery life of 12 hours. The data are transmitted with amplitude-shift keying (ASK) modulation at 434 MHz to a reader outside.

Telemetry is a critical element in wireless implants or capsules. Endoluminal applications present further technical challenges because the wireless signals have to go


**Figure 1.1** Examples of commercially available camera capsules for GI tract visualization [26].

through much thicker tissues and environments with complex signal scattering compared to transdermal applications. Efforts have been underway to develop systems with low power consumption, low biasing voltages, and high data rates. A 2 Mb/s frequency-shift keying (FSK) transmitter at 144 MHz was demonstrated in benchtop experiments, consuming 2 mW at 1.8 V, to provide 15 to 17 frame/second (fps) image transmission rates for inductively powered endoscopic capsules [30]. A 1.2 GHz receiver for capsule endoscopy was designed with the intention of increasing transmission data rates and tested with a field-programmable gate array (FPGA) circuit in benchtop experiments [31]. A data rate of 20 Mb/s was achieved with a sensitivity of −71 dBm. ASK was also used for modulation in imaging capsules by switching on and off a driver amplifier [32] in a carrier at 900 MHz. The transmitter was fabricated using the 0.18-μm CMOS process. The signals were carried through inductive coupling with a peak output power of 1 dBm. The power consumption was 7.2 mW for a data rate of 15 Mb/s.

A system for capsule endoscopy was developed by minimizing propagation losses and link budget calculated from an analysis of the human body channel at 500 MHz [33]. Both receiver and transmitter were fabricated by the 0.13-μm CMOS process. On-off keying (OOK) modulation was used to achieve low power consumption. Output power in the transmitter of −1.6 dBm at a supply voltage of 1.2 V and minimal sensitivity in the receiver of −80 dBm were achieved at 20 Mb/s. The system was tested in both a human phantom and a pig, resulting in clear captured images of a 340 × 340 pixel resolution at 10.5 fps [33]. A transmitter designed with the 0.13-μm CMOS technology to operate at 433.92 MHz was also demonstrated with current consumption of 1.57 mA at a 1.2 V biasing voltage. It provided a data rate of 3.5 Mb/s for the imaging capsule [34].

Impulse-radio ultra-wideband (IR-UWB) communication for body area networking transmits data in short pulses that are only a few nanoseconds and consumes low power owing to its low duty cycles. High data rate and low power consumption make the data efficiency higher in signal transduction. Using the 90 nm CMOS technology, an IR-UWB transceiver was demonstrated with a 1 Mb/s data rate at 3.8 GHz. The device used 1.5 pulse/bit synched-OOK modulation and achieved a power efficiency of 10.4% at 3.82 nJ/bit in benchtop experiments. A transceiver chip using OOK modulation for scalable data rates up to 10 Mb/s has been implemented with the 0.18-μm CMOS process [35]. The average power consumptions of the receiver were 6.1 and 62 mW for 1 and 10 Mb/s data rates, respectively, achieving energy efficiency at 6.2 nJ/bit in benchtop experiments. The imaging capsule was inserted into a pig's stomach with a receiver antenna 20 cm away from the body. The image data were successfully transmitted at 2.5 fps [35].

Several reports have summarized the development of GI capsule applications. McCaffrey et al. [36] described briefly the history, state of the art before 2008, ongoing research, and technical challenges of swallowable capsules for GI tract diagnosis. Twomey et al. [37,38] discussed a wide spectrum of sensing modalities beyond imaging, as well as drug delivery, motion control, and batteryless power mechanisms that can open many innovative clinical applications. The authors also pointed out the potential development directions for the future. Pan et al. [39] and Ciuti et al. [26] summarized the status of capsule endoscopic devices available and under development as well as the open challenges in navigation, vision, telemetry, energy sources, capsule localization, diagnostic modalities, and treatment. It is quite clear that the clinical and financial advantages of wireless devices are well recognized because they present comfort and convenience to patients, eliminate the need to sedate patients during diagnoses (thus reducing risks significantly), and have proven feasible for prolonged diagnoses. These advantages would further encourage a larger population of patients to undergo GI tract examinations and will benefit many people by detecting and treating diseases in early, treatable stages. Thus both academia and industry are working toward the goal of providing appealing alternatives with small wireless implantable or navigable devices to replace traditional diagnostic techniques.

In the next section, the discussion is focused on one particular endoluminal application: monitoring of reflux in the esophagus for diagnosis and prognosis of gastroesophageal reflux disease. The review is one example of using wireless sensor implants for many potential clinical applications.

## 1.5 An Endoluminal Application Example: Reflux Monitoring

### 1.5.1 Significance

*Gastroesophageal reflux disease* (GERD) is a medical condition that affects approximately 15% of the adult population in the United States. It is one of the most common clinical conditions afflicting the GI tract [40]. GERD refers to symptoms or tissue damage caused by the reflux of stomach contents into the esophagus and pharynx. Refluxants can be both acidic and nonacidic fluids [41–43]. While mostly GERD refers to acidic refluxes that are painful and obvious to patients, when patients experience frequent nonacidic refluxes, the symptom is not so pronounced to patients. It is referred as *nonerosive esophagus reflux disease* (NERD) [44–46]. The most common symptom of GERD is heartburn, which is a burning sensation in the chest as the acid triggers the pain responses in the nerves of the esophagus. However, NERD is the most common phenotypic presentation of GERD that has functional heartburn symptoms but without or with minor esophageal mucosal injury. Compared to patients with erosive esophagitis, NERD patient groups are complex and heterogeneous. The first factor makes it difficult to diagnose accurately with conventional means such as endoscopic visualization. The second factor further restricts doctors to focus on a certain risk group for frequent checkups or tracking. Recent clinical research has found that a daily standard dosage of proton pump inhibitors (PPIs) is less effective in NERD patients than in those with erosive esophagitis. Currently, doctors have to deal with a growing number of GERD patients who are referred due to failed PPI treatment for reflux symptoms. Most of these patients originate from the NERD group [46]. Unfortunately, NERD is still considered a mild form of GERD by hospitals and insurance companies, so prescribing PPIs is commonly discouraged. Often patients are treated with long-term $H_2$-blockers, which research has shown to have very limited efficacy in NERD patients [47]. This means an effective diagnostic method is needed for nonerosive esophagus reflux disease, which can be undetected during endoscopy, in order to find appropriate treatment for patients. Furthermore, a comfortable means to monitor therapeutic progress, especially for diverse, nonspecific patient groups, is as yet an unmet need in clinical practice.

Because the sensation of heartburn affects quality of life, GERD can further lead to long-term complications such as lung damage, Barrett's esophagus [48,49], and esophageal cancers. As the stomach contents rush into the esophagus, they can reach the throat, which causes persistent sore throat, laryngitis, and odynophagia (pain in swallowing), or mouth, which worsens dental diseases. The contents can even be aspirated into the windpipe, which causes sinusitis, chronic cough, asthma, pneumonia, and possibly suffocation. Barrett's esophagus is a condition in which the epithelial tissue lining of the esophagus is replaced by tissue similar to the intestinal lining. This process is called *intestinal metaplasia*. GERD has been recognized as a major risk factor for Barrett's esophagus. It was reported that 5% to 10% of people with GERD develop Barrett's esophagus [50]. People with Barrett's esophagus are at increased risk for a type of cancer called *esophageal adenocarcinoma*.

Esophageal cancers including adenocarcinomas and squamous cell carcinomas are often incurable and can spread quickly. They are the fastest-growing cancers in developed countries [51–54]. In the United States, esophageal cancers account for 10,000 to 11,000 deaths per year and also have the fastest-growing incidence rate of all cancers. The clinical GI community has identified GERD as the primary risk factor for esophageal cancers [55,56].

### 1.5.2 Monitoring and Diagnostic Methods

Monitoring GERD and NERD symptoms accurately, reliably, and comfortably for diagnosis and prognosis of the diseases before and during treatment is important to provide precise information to doctors for choice of treatment. It often requires days, if not weeks, to monitor the symptoms. This is particularly critical for diagnosis in children, who are not good at expressing their feelings about the symptoms. It is also important to provide the right treatment to children as early as possible to prevent long-term tissue damage and reduce their risk of developing Barrett's esophagus. Giving children unnecessary drugs to reduce acid production may create side effects that are harmful in the long term. As GERD and NERD symptoms persist, the stomach reflux may induce Barrett's esophagus, for which the patients experience less pain and mistakenly think that the symptoms are improving. A patient who has Barrett's esophagus without proper treatment has a much higher risk of developing an esophageal cancer.

Sixty million Americans experience reflux symptoms monthly. Nineteen million of them suffer daily and thus may have GERD [57]. Screening such a large population effectively becomes an issue. A comfortable, safe, cost-effective yet accurate screening method is lacking in clinical practice for the diagnosis of GERD/NERD. Further, doctors have no method to monitor patient progress in real time or continuously for prognosis purposes when they are taking medicines or under treatment

### 1.5.3 Multichannel Intraluminal Impedance (MII) Probe

A multichannel intraluminal impedance (MII) probe is one of the currently available instruments used to correlate symptoms with episodes of gastroesophageal reflux [58–61]. It consists of several metal impedance and antimony pH-sensing electrodes on a wire for detecting activity at multiple points along the esophagus. The probe and system configuration are shown in Figure 1.2. Whereas electrical conductivity is directly related to the ionic concentration of the intraluminal content, materials with high ionic concentrations, such as gastric juice and food residues, have relatively low impedance compared to those of the esophageal lining or air [60]. When reflux occurs, the content passes the electrode, inducing impedance variations. The transit time of impedance change in each electrode indicates the reflux period at the location of the electrode. Depending on the severity of the reflux episode, the signal changes in the spatially arranged electrodes indicate how far the refluxant reaches toward the throat. With data acquisition into a graphical user interface, the signals are separated into multitrack plots continuously in the time domain. The visualization of a certain impedance change across the length of esophagus and the transit time for such a change in each electrode location provide the dynamics of one reflux episode, showing how the reflux moves along the esophagus. Figure 1.3 shows a sample plot [62]. By both the temporal and spatial responses, the information indicates the timing and moving direction of the refluxant and the severity of the reflux. The same data are applied to the swallowing of food and liquid because the direction of impedance variations over time

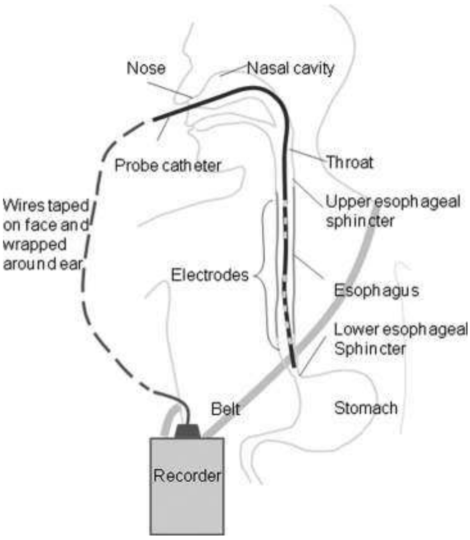


**Figure 1.2** Multichannel intraluminal impedance (MII) probe and its use on a patient.

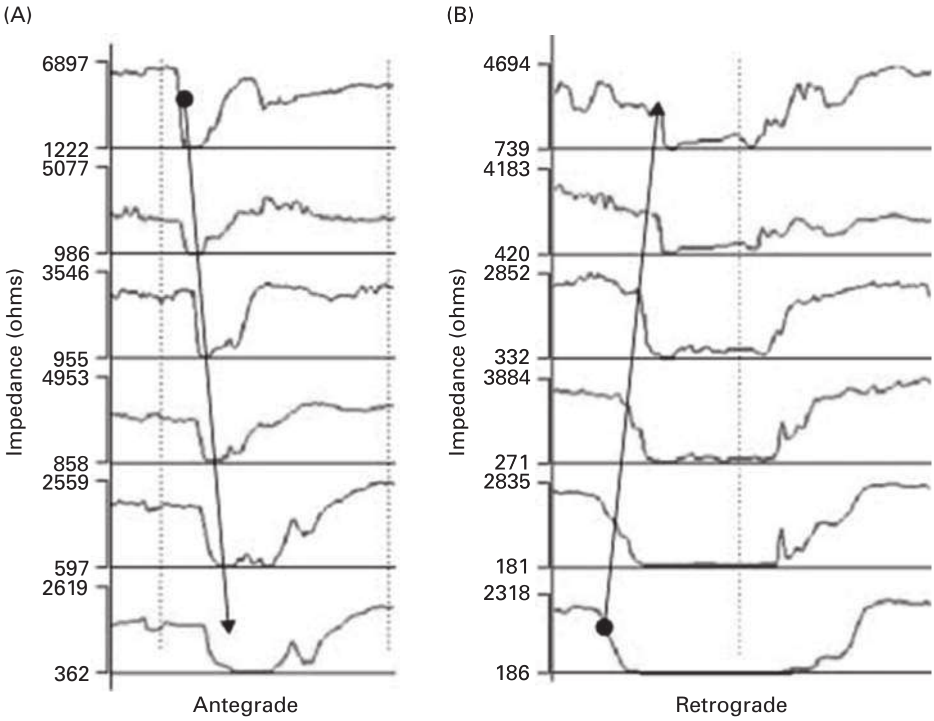


**Figure 1.3** Impedance changes during (A) swallowing and (B) reflux of a bolus measured by an MII probe [62]. The arrows indicate direction of bolus movement.

is the opposite. Thus the patient does not need to keep a log indicating eating times. The pH-sensing electrodes among the impedance electrodes indicate the pH level of moving refluxant. The ability of the MII probe to detect nonacid or weakly acidic reflux events (aerophagia) and to discern true reflux events from swallows provides more information than pH detection alone [61,63].

Although the MII probe system brings more accurate monitoring results than the conventional pH probe alone does, because of the nonselective responsivity of impedance sensing, tolerability is low in patients [64–66]. The tethered probe requires a transnasal insertion procedure. The wires connecting the electrodes to an external electronic unit worn by the patient go through the esophagus, throat, and nose. They are expected to stay in place for more than 48 hours while the patient is anticipated to resume normal daily activities. To avoid accidental removal of wires, the wires are taped on the patient's face. The presence of transnasal wires brings noticeable discomfort in patient's throat, and the patient feels self-conscious and sometimes embarrassed by the wires. Patients thus change their regular daily activities, which alters the reflux symptoms. The data collected may be a false representation due to alteration in patient behaviors. The use of wires limits the clinical utility and accuracy of the impedance-sensing technique for protracted monitoring of gastroesophageal reflux.

### 1.5.4 Wireless pH Monitoring Capsule

A wireless pH monitoring capsule (Bravo) has been used in some clinical practices [67–70]. The capsule consists of an antimony pH sensor shaped like a rod, and located in the bottom of the capsule are a microprocessor, a radio transmitter, and a chamber for tissue attachment. Inside the chamber, an insertion needle is used to attach the device to the wall of the esophagus via an endoscopic procedure. The implantable capsule has dimensions of 26.7 mm (length), 6.3 mm (width), and 5.4 mm (height) with circuit boards and batteries inside the polysulfone casing. Figure 1.4 shows the device and endoscopic apparatus for attachment. The antimony pH-sensing electrode and

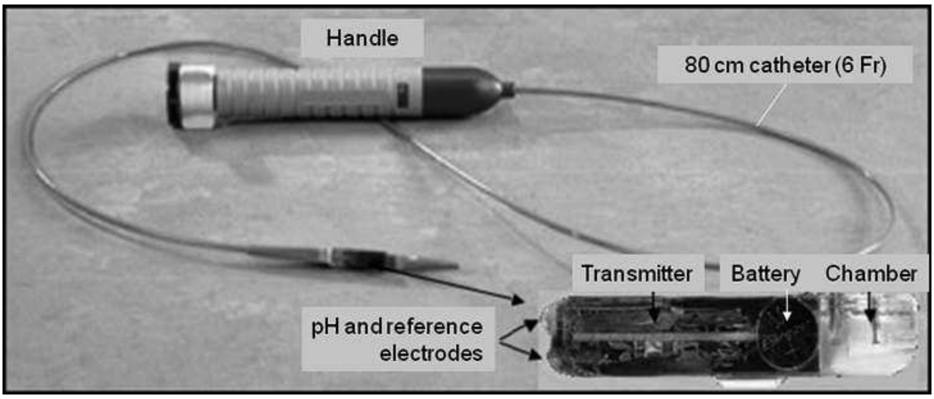


**Figure 1.4** Bravo capsule and its implementation apparatus [71].