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Wireless capsule endoscopy: from diagnostic devices to multipurpose robotic systems

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Abstract In the recent past, the introduction of miniaturised image sensors with low power consumption, based on complementary metal oxide semiconductor (CMOS) technology, has allowed the realisation of an ingestible wireless capsule for the visualisation of the small intestine mucosa. The device has received approval from Food and Drug Administration and has gained momentum since it has been more successful than traditional techniques in the diagnosis of small intestine disorders. In 2004 an esophagus specific capsule was launched, while a solution for colon is still under development. However, present solutions suffer from several limitations: they move passively by exploiting peristalsis, are not able to stop intentionally for a prolonged diagnosis, they receive power from an internal battery with short length, and their usage is restricted to one organ, either small bowel or esophagus. However the steady progresses in many branches of engineering, including microelectromechanical systems (MEMS), are envisaged to affect the performances of capsular endoscopy. The near future foreshadows capsules able to pass actively through the whole gastrointestinal tract, to retrieve views from all organs and to perform drug delivery and tissue sampling. In the long term, the advent of robotics could lead to autonomous medical platforms, equipped with the most advanced solutions in terms of MEMS for therapy and diagnosis of the digestive tract. In this review, we discuss the state of the art of wireless capsule endoscopy (WCE): after a description on the current status, we present the most promising solutions.

Keywords Wireless capsule · Capsule endoscopy · Active capsules · Medical robots · Robotic capsule

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Introduction

Endoscopy, intended as a methodology to assess the mucosa of the gastrointestinal (GI) tract, was born in 1868 when G. and R. Schindler pioneered methods of performing gastroscopy with a semiflexible gastroscope (Salmore, 1998).

Nowadays flexible endoscopes enable diagnosis inside esophagus, stomach, colon and in part to small bowel, thus helping to understand its structure, functions and pathologies. Flexible endoscopy induces little trauma to the patient and is generally well accepted.

However, some areas of the GI tract are still difficult to reach with flexible endoscopes, such as the largest part of the small bowel. At least a fraction of the patients fears flexible endoscopy due to pain and. This limits the willingness of patients to undergo endoscopy, especially in the field of cancer prevention and screening.

In this sense wireless capsule endoscopy (WCE) has been playing an important role since its introduction and promises to revolutionize endoscopy because it can greatly reduce the level of discomfort to be tolerated by patients (Bradbury, 2000). While this has initially been limited to small bowel endoscopy, WCE is now branching off into other indications, such as esophagoscopy or colonoscopy, although this expansion of indications will not happen to a larger extent without significant technology advancements. In the future

WCE may integrate mechanisms for active locomotion inside the GI tract, cutting edge microsensors for diagnosis and therapy and microtools for minimally invasive surgery (MIS) (Fireman et al., 2004; Polla et al., 2000; Bashir, 2004; Zahn et al., 2000).

In this regard, several privately held companies and research centers throughout the world are trying to leverage their technological background in order to enhance the capabilities of WCE from a mere video acquisition tool for diagnosis to a complete and autonomous medical platform also for therapy and MIS, thanks to the advancements and harmonization of various engineering disciplines, including: microelectromechanical systems (MEMS), user friendly control interfaces and high precision mechanics.

Present of wireless capsule endoscopy

Given Imaging

The idea of a capsule able to take pictures inside the small bowel traces back to the 1980s, although at that time it seemed mere figment because of the technological limitations hampering its feasibility, among which the high power consumption of charged couple device (CCD) image sensors. However, in the early 1990s complementary metal oxide semiconductor (CMOS) technology, along with progresses in application specific integrated circuit (ASIC) for control systems and light emitting diode (LED) for illumination, paved the way for the advent of WCE.

In 2000, during the Digestive Disease Week Conference in San Diego, California (USA), P. Swain, an endoscopist from the London Royal Hospital, and Given Imaging Ltd., a Yoqneam (Israel) based company, announced the M2A™ pill, the first swallowable capsule able to capture images inside the small bowel (Iddan et al., 2000; Pennisi and Kerr, 2004; Moayyedi and Ford, 2002). This has been possible thanks to the collaboration between P. Swain, working on wireless endoscopy, and G. Iddan, an engineer dealing with imaging devices for defense missiles at Rafael Ltd., the R&D group of the Israeli Ministry of Defense (Meron, 2000; Iddan et al., 2004).

M2A™ and PillCam™ SB

The first ingestible capsule by Given Imaging for diagnosis in the small bowel was the M2A™ (Fig. 1(a)), a disposable pill measuring 26 mm in length and 11 mm in diameter with a weight of 3.7 grams (Swain, 2003; Qureshi, 2004). The components hosted inside the body of the pill are shown in Fig. 1(b). A portable hard-drive and a personal computer workstation with proprietary software complete the diagnostic system. Image features include a 140° field of view,

Fig. 1 M2A™ Capsule (a) and schematic diagram of its components (b): optical dome (1), lens holder (2), short focal length lens (3), four LEDs (4), CMOS image sensor (5), two silver oxide batteries (6), ASIC radio-frequency transmitter (7) and external receiving antenna (8)

a factor magnification of 1:8 and a resolution of 0.1 mm (Qureshi, 2004). The short focal length lens comes with a narrow aperture to vary the depth of view from 1 to 30 mm: in this way the GI tissue can be brought into focus when it is both close and far from the camera.

Before undergoing WCE patients are usually placed on a liquid diet starting after lunch the day before the examination (de Franchis et al., 2005; Cave, 2006). Once ingested, the pill is carried passively through the GI tract by peristalsis and captures two images per second. Considering a typical transit time of eight hours, the capsule acquires more than 55 thousand pictures. These are sent, via radiofrequency communication operating at 432 MHz, to an antenna array of eight aerials, taped to the abdomen. These are connected by wires to a portable storage unit, placed in a belt and worn by the patient. Data are then downloaded to a PC workstation. The RAPID® proprietary software allows the physician to review the images.

In 2002 the company introduced M2A™ Plus, making it possible to know the location of the capsule, with an accuracy of about ± 3 cm, by means of a triangulation process of the signal strength received by three adjacent aerials (Swain, 2003). Then, the suspected blood indicator (SBI) utility was implemented in order to decrease the time to interpret WCE recordings (Swain, 2003; Mishkin et al., 2006).

The time to evaluate the video sequence depends on several factors, among which the endoscopist experience (Cave, 2004) and the frame speed at which the video is viewed. It generally takes between 30 to 60 min.

At present, the Given Diagnostic System is made of the PillCam™ SB (Fig. 2(a)), the DataRecorder 2 (Fig. 2(b)), the RAPID® 3 Software and the Given Workstation.

The latest edition of RAPID® software, called RAPID® 4, comes with the following features: Automatic Mode v4 for increased reading efficiency, QuickView v4 for fast preview of the video while highlighting images of interest, Circumference Scale for assessment of circumferential involvement of findings such as esophageal varices or small bowel ulcers, and RAPID® Atlas to compare on-screen images.

Fig. 2 PillCam™ SB (a) and DataRecorder 2 (b)

Remote capsule endoscopy is a recent modality to transfer the acquired data by WCE from Satellite Sites, equipped with a DataRecorder, to a Central PillCam Site with a Given Workstation. The usage of this technology should be encouraged in those geographical areas, such as the Scandinavian mainland, with scattered population, high distances between hospitals and where travelling is difficult, especially during winter.

The device obtained approval from Food and Drug Administration (FDA) in 2003.

In October, 2003 Given Imaging got clearance to market capsule endoscopy for use in pediatrics patients with an age from 10 to 18 years.

Clinical applications

To date over 340,000 patients worldwide have experienced WCE without the invasiveness and discomfort of more conventional procedures. In fact WCE does not require sedation, nor entails radiation absorption for patients.

Thanks to the ability to acquire images, while passing through the entire small intestine, WCE has been shown successful, in many cases providing better results than traditional techniques, in the diagnosis of occult gastrointestinal bleeding (OGIB). This is defined as bleeding of unknown origin which persists or recurs after a negative initial or primary endoscopy result, e.g. esophagogastroduodenoscopy (EGD) or colonoscopy (Zuckerman et al., 2000). In particular, each year in the United States 1 new case of GI bleeding per 1000 persons arises, with obscure bleeding representing 5% of all new recurrences of GI bleeding (Pennazio et al., 2005; Triester et al., 2005).

Crohn's disease is another clinical application which can benefit from WCE (Herfarth et al., 2005). It is an inflammatory bowel disease (IBD) of unknown origin which can recur in any site of the digestive tract, in 30–40% of cases in the small intestine (Kornbluth et al., 2005; Hara et al., 2006).

In Fig. 3 the jejunum of patient with suspected Crohn's disease, showing thickened infiltrated folds, is illustrated.

The possibility to view the intestinal mucosa has allowed to detect the villous atrophy, which is a common symptom

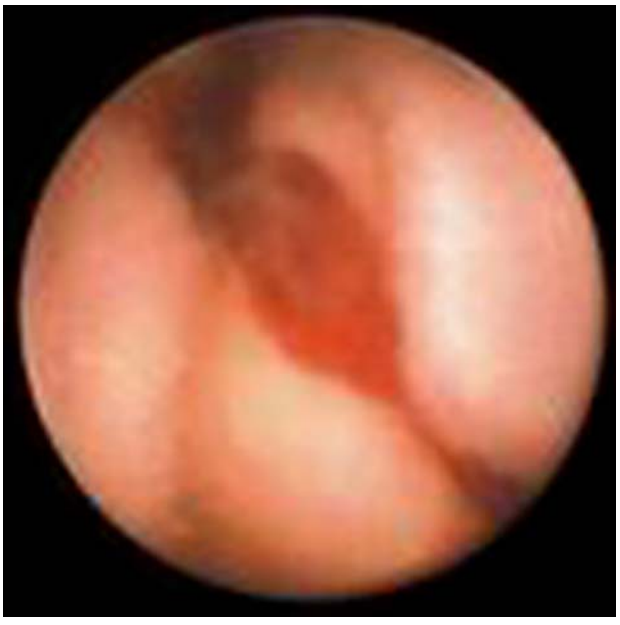


Fig. 3 Jejunum of patient with suspected Crohn's disease showing thickened infiltrated folds

of celiac disease (Kesari et al., 2005). This is an inflammatory intestinal pathology affecting people with intolerance to gluten, a wheat protein, with a prevalence of almost 1 in 100 persons in western countries (Green et al., 2006; Dube et al., 2005; Maki et al., 2003). Interesting findings have been reported also in the diagnosis of small bowel tumours (Urbain et al., 2006).

Then, WCE has found applications in pediatrics. It detected the presence of OGIB even in 2.5 years old child, so far the youngest patient who has received WCE treatment (Kavin et al., 2006).

PillCam™ ESO

Besides PillCam™ SB, Given Imaging produces PillCam™ ESO (Fig. 4), marketed in the U.S. by the InScope Division of Ethicon Endo-Surgery Inc., Johnson & Johnson Group, Cincinnati, Ohio (USA), which may represent an alternative

Fig. 4 PillCam™ ESO

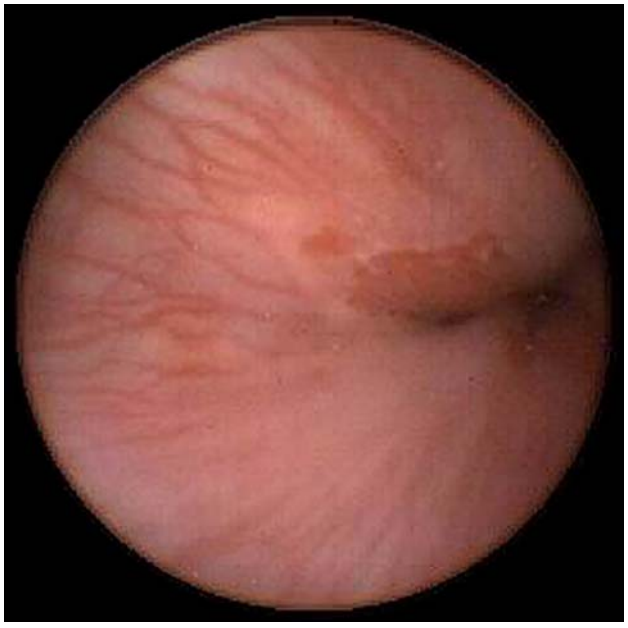


Fig. 5 Image of an esophagitis taken by PillCam™ ESO

to traditional upper GI endoscopy techniques for the investigation of pathologies in the esophagus.

The body of PillCam™ ESO harbors two cameras, one on each side and, while it proceeds along the esophagus, it captures 14 images per second. Other features, concerning dimensions, field of view and resolution, are the same as the PillCam™ SB.

In this case the diagnostic procedure begins when, after a two-hour fast, the patient swallows the pill lying down. Then he is raised in a series of inclinations over a total of five min. During this stage the PillCam™ ESO acquires images which are directly transmitted to the sensor arrays and then to the storage unit. At this point, the patient is allowed to get up and can either walk or remain seated for additional 15 min to ensure the capsule has entered the stomach.

The first clinical trial on PillCam™ ESO concerned gastroesophageal reflux disease (GERD) (Eliakim et al., 2004). GERD is a frequent and/or severe form of heartburn, when the contents of the stomach backflow into the esophagus. Persons with chronic GERD may develop Barrett's esophagus, a premalignant condition, whose incidence has been increasing steadily since 1970s. Barrett's esophagus may in turn lead to esophageal adenocarcinoma, one of the fastest growing cancers in western countries (Ronkainen et al., 2005; Bollschweiler et al., 2001).

Controindications

Both PillCam™ SB and PillCam™ ESO are contraindicated in those patients with known or suspected GI obstruction,

Fig. 6 Patency capsule

strictures, or fistulas, swallowing disorders and cardiac pacemakers or other implanted electromedical devices. In particular, Leighton has proven that patients with portable electric cardiac devices, such as pacemakers, can undergo WCE examination (Leighton et al., 2005).

Furthermore, a serious concern is represented by capsule retention, which may lead to acute small bowel obstruction and in some cases surgery may be required to remove it. In the case of OGIB the most quoted retention rate is 0.75% (Barkin et al., 2002). For patients with Crohn's disease, retention may happen in 6.7% (Buchman et al., 2004). It represents a concrete risk also for those undergoing esophageal capsule endoscopy, if they have a history of dysphagia, i.e. a difficulty to swallow. In order to avoid this inconvenience, Given Imaging has developed the Agile™ Patency System (Spada et al., 2005), a self-disintegrating pill, shown in Fig. 6. This has the same dimensions as the PillCam™ SB (11 mm × 26 mm), is made of a lactose body, has a paraffin plug, contains a microchip for radiofrequency identification (RFID), a timer and 100 ml of barium sulfate to enable detection by fluoroscopy. A parylene layer covers the whole body, with the exception of the area in contact to the plug. The dissolution of the patency capsule starts approximately 40 hours after ingestion and is due to lactase, an enzyme produced by intestinal mucosa cells in the jejunum (Gay et al., 2005). The RFID plaque, measuring 2 mm × 12 mm and placed inside the body, can be detected by a RFID scanner which stays outside (Boivin et al., 2005). The Agile™ Patency capsule received approval from FDA in May 2006.

Olympus

In October 2005 Olympus Corporation, Tokyo (Japan), launched in Europe EndoCapsule, a disposable and passive pill for small bowel endoscopy, 26 mm in length and 11 mm in diameter, with a CCD sensor camera (Fig. 7(a)). This boasts a depth of field varying from zero to 20 mm, automatic brightness control to adjust the illumination, ensured by 6 LEDs, and an operational time of 8 h. An antenna sends two images per sec to the recorder. Moreover, thanks to the Real Time Viewer (Fig. 7(b)), physicians can view real-time images and estimate the capsule position.

Fig. 7 Olympus WCE system: EndoCapsule (a) and Real Time Viewer (b)

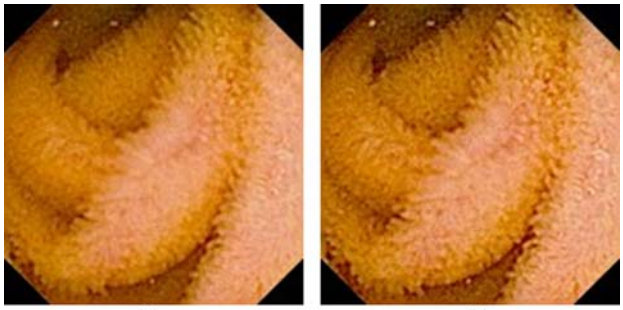


Fig. 8 Image of normal villi structure, taken by EndoCapsule: without (a) and with structure enhancement (b)

Then, the EndoCapsule Software allows the management of the acquired data. Its main features are: a multi display function for optimal observation, structure enhancement and enlargement display function to highlight the tiniest details (Fig. 8), red colour detection function to highlight suspected bleeding symptoms, and auto speed adjustment function to optimise the review speed Clinical testing is still under way in the United States and Japan, and the company needs to receive full approval before selling its device in these markets (Fuyuno, 2005).

The efficacy of EndoCapsule was demonstrated During Digestive Disease Week 2006, in Los Angeles, California (USA).

Technical limitations

The usage of an internal power source, such as a battery, is a critical issue as to toxicity and length. In particular, the latter sets a limit on the amount of available energy devoted to the acquisition of pictures. This affects the choice of the image sensor: CMOS technology may be preferable since it ensures a lower power consumption than CCD, but at a price of a poorer image quality (Litwiller, 2005).

Moreover, the limited energy provided by a battery makes it impossible to add other functional modules to endoscopic capsules, especially those for the locomotion and control of movement. If a capsule had an active locomotion it could vary its speed, thus reducing the transit time, and with stop mechanisms it might stay at a specific point of diagnostic interest for a prolonged time. This would enable the physician to conduct a more thorough analysis, whenever he spots interesting sites. The integration of sensors could also make other diagnostic and therapeutic tasks feasible, e.g. biopsy and drug delivery.

Table 1 reports a comparison of the WCE which have received approval for usage in clinical environments.

Future prospects of WCE: better images, therapy and active locomotion

The importance of image sensors with finer resolution than current systems is motivated by the need to enable the detection of pathologies at an earlier stage, which are smaller and for this reason invisible at present. As a consequence, they may overcome images distortion, which recurs during the zoom of a picture every time an enlarged view is required. However the higher the resolution, the higher the power consumption of the RF transmitter. In this sense Lin et al. (2006) have developed the GICam pill with a low power image compression processor. On the other hand, if a capsule were able to move actively it would decrease the length of its journey. Furthermore, with the capability to stop at specific sites, it would help the physician to perform a thorough diagnosis in areas of major interest and to enable drug release (Raju et al., 2002). Then, steady advancements in the BioMEMS field foreshadow capsules with sensors enabling new tasks (Gourley, 2005).

In this regard, a wireless ingestible capsule endowed with three sensors for the monitoring of pH, temperature and

Table 1 Comparison of existing WCE solutions of Given Imaging and Olympus

	Given Imaging		Olympus
WCE Name	PillCam™ SB	PillCam™ ESO	EndoCapsule
Dimensions ($D \times L$)		11 mm × 26 mm	
Operative environment	Small intestine	Esophagus	Small intestine
Image sensor type		CMOS	CCD
Frame rate	2 images/second	14 images/second	2 images/second
Image acquisition		Off line	Real time
Power source		Internal battery	
Source of motion		Peristalsis	

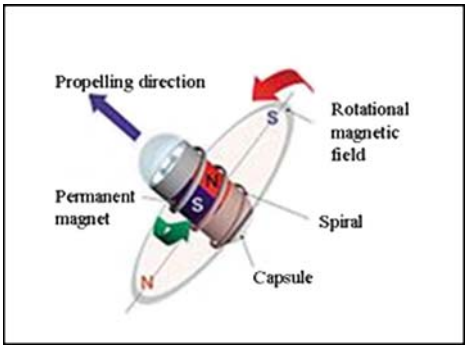


Fig. 9 Working principle of Olympus WCE with active locomotion

pressure inside the GI tract was developed by SmartPill Corporation (Dickman et al., 2006). In July 2006, this device received approval by FDA for the sale and use in the United States.

Swallowable capsules with active locomotion, based on magnetic actuation and electrical stimulation, have been recently demonstrated (Sendoh et al., 2003; Mosse et al., 2001; Woo et al., 2005; Swain et al., 2005).

In a not too distant future, robotics will significantly contribute to make WCE autonomous devices capable to bring a set of MEMS in targeted areas of the GI tract, independently from an external operator.

Magnetic actuation and therapy

Olympus

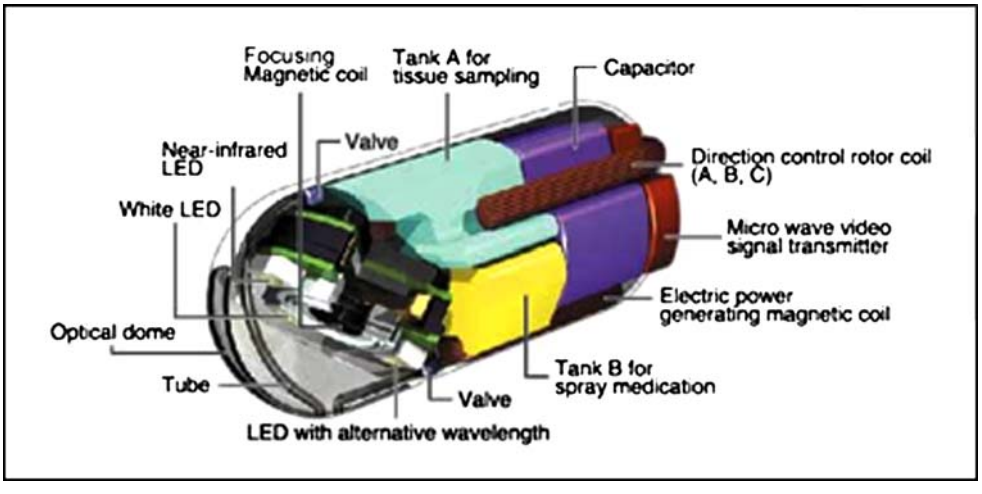
Since November 2004, Olympus has been developing also a self propelled capsule for all parts of the GI tract and with the possibility to control its movement (Kusuda, 2005). In this case, an external magnetic field generator using three pairs of opposing electromagnets creates a uniform magnetic field in any direction (Fig. 9). By varying this magnetic field, position, orientation and posture of the pill can be controlled, thanks to a built in permanent magnet. For example, the magnetic field is used to generate a second and rotating magnetic field which rotates the capsule, generating thrust through the spiral on the outer surface of the pill. In this way, control of forward and reverse motion could be achieved. Additionally, the pill is provided with an external power source: coils outside the body transmit energy to those inside the capsule, by exploiting the principle of electromagnetic induction, hence eliminating the need of an internal battery. This has two advantages: increasing the pictures acquisition rate up to 5 images per second and the possibility to remain inside the GI tract for more than eight hours. Other features include a deflatable balloon and a negatively-pressurized space, both controlled from outside the body, for respectively drug delivery and body fluid sampling. Moreover, the pill will also integrate an ultrasound scanning module, promising to deliver high resolution images.

Norika

Since 1998 at RF SYSTEM Lab, Nagano (Japan), the Norika Project Team has been dealing with WCE, in particular on an externally powered capsule (Fig. 10), which integrates a CCD image sensor (Uehara et al., 2003). The diagnostic system includes a pill, 23 mm in length and 9 mm in diameter, a camera, 4 LEDs for illumination, an external controller, a transmitter vest and a workstation. Data processing is performed by a digital signal processor (DSP) which consumes 94% of the total power and for this reason is placed outside the body. The camera is able to capture images at distances ranging from a few millimeters to some centimeters from its lens and features also focus adjustment.

In order to enrich diagnosis, the capsule possesses some degree of rotation enabling images acquisition at different positions during its transit. A schema of the working principle is depicted in Fig. 11.

Fig. 10 Norika WCE



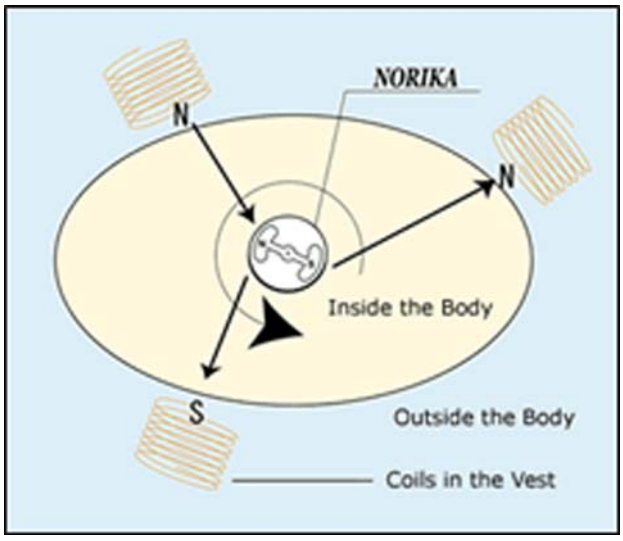


Fig. 11 Working principle of Norika WCE

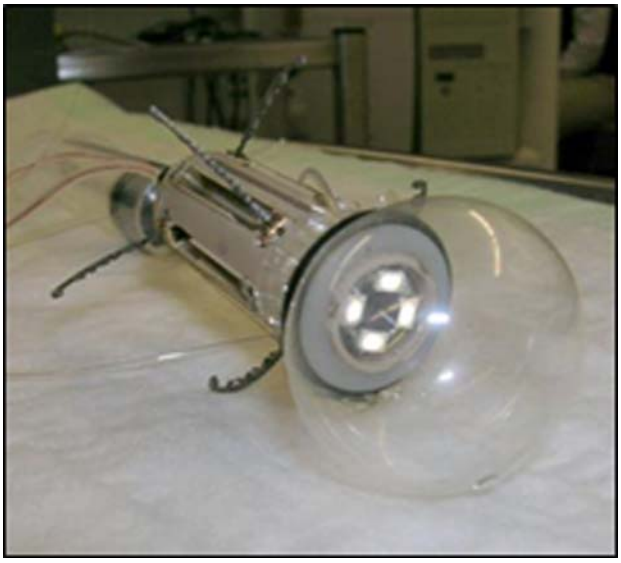


Fig. 12 EMILOC robotic capsule developed at Scuola Superiore Sant'Anna

Three coils are placed inside the capsule, acting as rotor coils. Three coils, embedded in a vest-like jacket, act as stators. The direction of stators magnetic field sets the rotative direction. Localization and tilt can be detected with respectively 5 mm and 15° of deviation. Moreover Norika Project Team has been evaluating the use of near-infrared light in the acquisition of translucent images of the stomach in order to see mucosal pathology behind gastric folds. In fact near-infrared light, with a wavelength ranging between 800 and 1200 nm, is able to pass through human body 10 times better than other types of radiation whose wavelength does not belong to this range.

In the body of the pill about 40% of the volume is free and might host reservoirs for drug delivery or miniaturized knives and scissors for MIS or sensors for advanced diagnostic tasks.

According to industry insiders, the Norika pill needs further years of development, before entering the market (Fuyuno, 2005).

Autonomous robotic capsule

Intelligent Microsystem Center (IMC), Seoul (South Korea) has launched the EMILOC project (Endoscopic MIcrocapsule LOcomotion and Control) and since 2004 has been supporting a research team of Scuola Superiore Sant'Anna (SSSA), Pisa (Italy), to develop a robotic WCE able to move autonomously in the GI tract.

In this regard, the advent of robotics paves the way for a swallowable and disposable complete medical platform integrating actuators for active locomotion, sensors for diagnosis and therapy, and tools for MIS inside the digestive tract (Menciassi et al., 2005). In the recent past robotics has been successfully applied to colonoscopy (Dario et al., 2004; Swain, 2005).

The medical rationale of using micro-robotics to enable active capsule locomotion and control lies in the need to actively steer the capsule inside the digestive tract for improved diagnostic and especially therapeutic means. This medical need is unmet by current capsular technologies.

In particular the SSSA robotic capsule has an active locomotion based on a set of bioinspired legs. This solution offers various advantages: an accurate control on the trajectory allowing the capsule to pass over critical areas without touching them; adaptability to organs with different shape, such as the large and the small intestine; fine position control, by varying the extension and orientation of the legs; high velocity to reduce the length of the journey inside the GI tract.

The dimensions of the capsule shown in Fig. 12 are a diameter of 12 mm and a length of 30 mm. It has six legs, made of superelastic shape memory alloy (SMA), a well known material in the biomedical industry for its biocompatibility. Each leg has a round tip, ending with 200 μm high hooks to provide friction for locomotion. Legs can fit to organs with different geometry thanks to a flexible knee. Despite their sharpness, the hooks did not damaged too heavily the tissue during both in vitro and in vivo tests on animals, confirming what Atuma et al. had previously found (2001). Each leg is independently actuated by a SMA actuator, whereas a human machine interface (HMI) is responsible for the control of the movement.

The camera, based on CMOS technology, has a resolution of 320 $\times$ 320 pixels.

Table 2 Comparison of the future WCE of Olympus, Norika and SSSA

	Olympus	Norika	SSSA
Dimensions ($D \times L$)	11 mm × 26 mm	9 mm × 23 mm	12 mm × 30 mm
Operative environment	Whole gastrointestinal tract		
Image sensor type	CCD		CMOS
Frame rate	5 images/second	30 images/second	2 images/second
Power source	Wireless power transmission		Battery
Source of motion	External magnetic field		Bioinspired legs
Motion control	Yes		
Stop capability	Yes		
Other features	Availability of space to lodge sensors for therapy and micro tools for MIS		
	Advanced image acquisition by ultrasound		Inflatable balloon

Another feature of this capsule is an inflatable balloon useful to open the lumen, thus enabling the camera to view the largest area as possible, and to foster the locomotion.

During both in vitro tests in phantoms and in vivo tests on animals, conducted in collaboration with novineon Healthcare Technology Partners GmbH, Tuebingen, (Germany), the pill has proven to proceed successfully and stop by spreading the legs against the wall of the small bowel. In this case force exertion of the legs is only local and over a relatively small surface of tissue, making this type of locomotion very atraumatic.

When the pill will be ready to undergo clinical tests on humans, the body will be covered by a biocompatible and biodegradable layer to avoid the accidental deployment in the mouth and esophagus. Once in the stomach, the layer will be dissolved by the gastric juices and the legs will be free to move, enabling the capsule to move autonomously until the end of its journey.

Table 2 compares the most promising WCE solutions combining active locomotion with therapeutic tasks.

Concluding remarks

In the past few years wireless ingestible capsules opened the chance to conduct in a non invasive way diagnosis of a wide range of pathologies of the digestive tract, including OGIB, Crohn's disease, celiac disease and GERD. Today, cutting-edge technologies make diagnosis feasible, while in the future high efficiency power sources and micro actuators promise to increase the potentialities of WCE. In this sense robotics and MEMS will play a significant role to develop a complete medical platform also for therapy and MIS. An additional input may come from the increasingly wide number of research centers and private companies engaged to achieve the supremacy in this fast growing field.

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