Techniques in Gastrointestinal Endoscopy 17 (2015) 40–46

Contents lists available at ScienceDirect

Techniques in Gastrointestinal Endoscopy

journal homepage: www.techgiendoscopy.com/locate/tgie

Emerging issues and future developments in capsule endoscopy

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ARTICLE INFO

Article history:
Received 14 December 2014
Accepted 22 February 2015

Keywords:
Medical robotics
Magnetic manipulation
Localization
Locomotion
Image enhancement

ABSTRACT

Capsule endoscopy (CE) has transformed from a research venture into a widely used clinical tool and the primary means for diagnosing small bowel pathology. These orally administered capsules traverse passively through the gastrointestinal tract via peristalsis and are used in the esophagus, stomach, small bowel, and colon. The primary focus of CE research in recent years has been enabling active CE manipulation and extension of the technology to therapeutic functionality, thus, widening the scope of the procedure. This review outlines clinical standards of the technology as well as recent advances in CE research. Clinical capsule applications are discussed with respect to each portion of the gastrointestinal tract. Promising research efforts are presented with an emphasis on enabling active capsule locomotion. The presented studies suggest, in particular, that the most viable solution for active capsule manipulation is actuation of a capsule via exterior permanent magnet held by a robot. Developing capsule procedures adhering to current health care standards, such as enabling a tool channel or irrigation in a therapeutic device, is a vital phase in the adaptation of CE in the clinical setting.

1. Introduction

Since 1950, orally administered capsules with radiofrequency (RF) transmission capability have been prototyped with an aim to study the physiological parameters of the gastrointestinal (GI) tract. A dearth of miniaturized electronic technology such as semiconductors and integrated circuits prevented development of these capsules until the beginning of the 21st century [1]. Working independently, Gavriel Iddan (Israel) and Paul Swain (UK) introduced capsule endoscopy (CE) in 2000 as a means for providing patients with endoscopic imaging of the small bowel [2]. First CE human trials were presented in 2001 by Given Imaging Ltd. (Yoqneam, Israel), which was the first to commercialize the technology [1]. Given Imaging's first clinical CE, marketed as M2A (Mouth-to-Anus), was awarded approval from the Food And Drug Administration (FDA) in 2001. The second capsule to gain FDA approval was the M2A Plus, which was later remarketed under the now familiar name: PillCam. Since the first FDA CE approval, more than 2 million capsules have been ingested worldwide [3]. The PillCam series of capsules now encompasses approximately 95% of the CE market and has been used in more than 1.7 million procedures worldwide and in more than 1900 clinical studies (www.givenimaging.co). Today, leading CE companies include the following: Medtronic Inc (USA) (Given Imaging Ltd was acquired by Covidien Ltd, which was, in turn, acquired by Medtronic Inc in 2014), Olympus Corporation (Japan), Chongqing Jinshan Science & Technology Co Ltd, (China), IntroMedic Co Ltd, (South Korea), and CapsoVision Inc (USA). Originally developed for diagnostic use in the small bowel, CE application has spread to use in the esophagus, stomach, and colon. CE is still most widely used in the small bowel owing to a lack of a noninvasive alternative. This review examines current technology in clinical CE as well as the latest developments in image enhancement, investigation of active locomotion, and therapeutic possibilities.

2. Clinical capsule endoscopes

2.1. Esophageal CE

As opposed to the slow CE propagation through the small bowel, CE traversing the esophagus can reach speeds as high as

The author reports no direct financial interests that might pose a conflict of interest in connection with the submitted manuscript.

The research reported in this publication was supported in part by the National Institute of Biomedical Imaging and Bioengineering, USA of the National Institutes of Health under Award no. R01EB018992, and in part by the National Science Foundation, USA under grant no. CNS-1239355 and no. IIS-1453129. This material is also based on work supported by the National Science Foundation Graduate Research Fellowship Program under Grant no. 1445197. Any opinions, findings and conclusions, or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Institutes of Health or the National Science Foundation.

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http://dx.doi.org/10.1016/j.tgie.2015.02.006
0049-0172/

20 cm/s, leading to difficulties in assessing for pathology [4]. Esophageal capsule primary indications include diagnosing reflux esophagitis, Barrett esophagus, and varices [5]. The most prevalent esophageal capsule, the PillCam ESO (Given Imaging Ltd), captures images at 7 frames per second (fps) from each of 2 cameras at its longitudinal ends, for a cumulative 14 fps. During a 2006 study of 42 patients with gastroesophageal reflux disease, a PillCam ESO capturing images at 4 fps was compared with one capturing at 14 fps. The higher image capture rate was observed to be superior in visualization of the entire esophagus (76% vs 12%, $P < 0.01$) making higher frame capture rate essential for esophageal CE [4]. The diagnostic sensitivity and specificity reported for the ESO were 85.8% and 80.5% for varices, 98% and 100% for gastroesophageal reflux disease, and 97% and 100% for Barrett esophagus [6]. Currently, the FDA-approved PillCam ESO3 captures images at 35 fps compared with the ESO's 14 fps, has a field of view of 169°, and an operating time of no more than 30 minutes. CEs in the esophagus are well tolerated but remain limited by poor visualization, passive motion, and lack of therapeutic ability, and thus have not replaced flexible endoscopy for esophageal evaluation [5].

2.2. Small bowel CE

CE is considered the gold standard for small bowel evaluation in patients with inflammatory bowel disease, suspected small bowel neoplastic lesions, and obscure GI tract bleeding [6-9]. The PillCam (Given Imaging Ltd) is the most widely used capsule worldwide, and the latest version, SB3 (FDA approved in 2013), acquires images at an adaptive rate of 2-6 fps.

The OMOM Smart Capsule (Chongqing Jinshan Science and Technology Co, Chongqing, China) is the first capsule to include 2-way data transmission via wearable RF sensors. This bidirectional communication allows for real-time adjustment of image capture rate and light intensity [10]. The MiroCam (IntroMedic Co, Ltd, South Korea) has similar parameters but is the only capsule to use electrical field propagation through the body—what is referred to as Human Body Communication (www.intromedic.com). The EndoCapsule (Olympus Corporation, Japan) operates similarly to the PillCam small bowel (SB) but uses high-resolution charge-coupled device technology for imaging rather than a complementary metal oxide semiconductor sensor (www.olympusamerica.com) [6].

CapsoCamSV-2 (CapsoVision Inc, Saratoga, CA) is the newest commercial CE and is the only one to employ onboard flash memory therefore requiring the patient to retrieve the capsule after passing it in their stool. Having undergone human trials [11], the CapsoCam takes a novel approach in providing a 360° panoramic view using 4 centralized cameras, each with >90° field of view. The CE has a battery life of 15 hours and captures images at 20 fps for the first 2 hours of operation and 12 fps for the duration of the procedure [12]. The CapsoVision system consists of the capsule, a stool retrieval tool: CapsoRetrieve, the CapsoAccess data retrieval system, and the CapsoView application for viewing the images. Head-to-head trials with the aforementioned small bowel capsules have suggested comparable diagnostic yield, image quality, and completion rate [3]. Various commercial capsules and related specifications are reported in the Table.

2.3. CE in the colon

Each year, colorectal cancer is the cause of nearly 608,000 deaths with approximately 14.5 million colonoscopies performed worldwide [13,14]. As reported by www.cancer.org, nearly 100,000 cases of colon cancer are being diagnosed annually in the US alone, and the number of occurrences is expected to increase by 62% by the year 2030 [15]. Introducing a less-invasive platform could prevent millions of patients from evading colonoscopy owing to fear of an invasive procedure, procedural discomfort, bowel

Table
GI capsules in clinical use today.

Capsule	Purpose	Company	FDA	FPS	Size (mm)	Software	Related devices
PillCam ESO 3	Esophageal imaging	Given Imaging Ltd (Israel)	Yes	35	26.0 × 11.0	RAPIDv8.0	PillCam recorder DR3, PillCam Express, Sensor Belt
PillCam SB 3	Small bowel (SB) imaging		Yes	2-6	26.0 × 11.0		
PillCam COLON 2	Colon imaging		Yes	4-35	31.5 × 11.6		
PillCam SmartPill	Sensory		Yes	No imaging	26.0 × 13.0	N/A	N/A
Bravo capsule	Sensory		Yes	No imaging	26.7 × 6.3 × 5.4	N/A	N/A
Agile patency capsule	Patency		Yes	No imaging	26.4 × 11.4	None. Dissolvable capsule	None
CapsoCam SV-2	SB Imaging	CapsoVision Inc (USA)	No	12-20	31.0 × 11.3	CapsoView	CapsoRetrieve, CapsoAccess CDAS2
MiroCamv2	SB imaging	IntroMedic Co, Ltd (South Korea)	Yes	3	24.5 × 10.8	MiroView v2	MiroCam Receiver
MiroCam Navi	SB Imaging and Navigation	IntroMedic Co, Ltd (South Korea)	N/A	3	24.0 × 11.0	MiroView v2	MiroCam Receiver
OMOM Smart Capsule	SB imaging	Chongqing Jinshan Science & Technology Co., Ltd (China)	Yes	2	27.9 × 13.0	OMOM workstation	OMOM image recorder
OMOM Controllable Capsule (Magnetic Control)	SB Imaging		N/A	N/A	N/A		OMOM image recorder, hand-held steering magnet
EndoCapsule	SB Imaging	Olympus Corporation (Japan)	Yes	2	26.0 × 11.0	Olympus VE-1 Real Time Viewer	EndoCapsule recorder set
IntelliCap	Sensory or drug delivery	Medimetrics, a Philips Company (Netherlands)	N/A	No imaging	26.7 × 11.0	N/A	N/A
Enterion capsule	Sensory or drug delivery	Quotient clinical (England)	N/A	No imaging	32.0 × 11.0	N/A	N/A

N/A, not applicable.

preparation, risk of adverse events, and the potential need for sedation [16,17]. The most prevalent capsule for colonoscopy is the PillCam COLON2 (Given Imaging Ltd). The 31.5 mm × 11.6 mm capsule, which like the PillCam ESO2, has a camera at both longitudinal ends and has capability of adjusting image capture rate from 4 fps in stasis to 35 fps when in motion [6]. In a study of 104 patients, the PillCam COLON2's sensitivity and specificity for polyps ≥6 mm and ≥10 mm was 89% and 76%, and 88% and 89%, respectively [18]. To accelerate CE transit through the colon and distend the lumen around the capsule, sodium phosphate has been added to the traditional preprocedural patient solution of polyethylene glycol [19]. The PillCam COLON2 is actively used in Europe and Japan and has gained FDA clearance in 2014 in the United States for use in patients following an incomplete colonoscopy (www.givenimaging.com). Capsule colonoscopy is not yet considered a replacement to traditional colonoscopy owing to specificity rates recorded as low as 64% [20]. Effect owing to lack of active steering techniques and inability to distend collapsed tissue may lead to reduced visibility [20].

2.4. Software

Apart from the capsule, CE systems generally include wearable sensors, data acquisition equipment, and video analysis software [6]. Approximately 55,000 images are captured during a typical lower-bowel CE procedure that are then postprocessed [7]. Clinicians are unable to observe these entire procedures in real time leading to development of CE image processing typically produced by the capsule manufacturer (ie, Given Imaging's Rapid Reader, CapsoVisions's CapsoView, IntroMedic's MiroView, and Olympus' VE-1 Real Time Viewer). The most widely used software of these is Given Imaging's Rapid Reader 8.0. Postprocessing of data in software allows for filtering bandwidth to enhance surface contrast, make regions of interest more distinguishable, and apply algorithms to improve identification of blood. The most widely used tool in digital CE chromoendoscopy is Fujinon Intelligent Colon Enhancement (FICE, Fujifilm, USA), which is used in the RAPID software and decomposes images into RGB wavelengths, increases contrast of each, and then reconstructs the image system [5,21,22].

Clinical CE systems have also incorporated a capsule localization feature in the wearable hardware. RF signal strength measured via wearable sensor allows for triangulation to determine CE position without the need for additional hardware. Though a seemingly simple solution to a convoluted problem of determining capsule position, using RF signal strength can, at best, be used to determine global capsule coordinates, rather than locations with respect to anatomical landmarks. Further developments are needed to produce relevant localization data. Given Imaging has recently introduced the PillCam Recorder DR3 Simulator, an interactive data acquisition that readily acquires and analyzes capsule images during the procedure. This allows the image frame rate to be adjusted from 4-35 fps in accordance with capsule motion detected by image processing.

3. Current research in CE

3.1. Image-enhanced CE

Image enhancement is used to improve standard colonoscopy procedures and is beginning to be applied in CE [22]. Compared with healthy tissue, neoplastic intestinal tissue has been shown to exhibit a lower autofluorescent response to blue or ultraviolet light. A sarcoma-detecting capsule prototype has been developed that uses an autofluorescence intensity system. Narrow band imaging and white light imaging would complement the system owing to the high false-positive rate of autofluorescence intensity imaging. Further work is yet to be done to conduct in vivo trials [23]. A method was introduced for gathering pathologic data from imaging. Tethered capsule endomicroscopy was introduced, which utilizes optical frequency domain imaging technology in which images are obtained for single-wavelength scattered light. Gora et al introduced tethered capsule endomicroscopy, another imaging method utilizing optical frequency domain technology in which images are obtained for single-wavelength scattered light. A tethered capsule produces 3-dimensional (3D) microstructural images of the esophagus while traversing passively via peristalsis and can be retracted after imaging is complete [24]. This technology was first developed by NinePoint Medical Inc under the name NvisionVLE (Cambridge, MA), and the FDA approved it in 2013 for use in standard endoscopes but is not cleared for capsule use.

3.2. Capsule localization

Accuracy in CE localization is vital for obtaining diagnostic information that can be used for planning treatment and for effectively actuating CEs via an external robot with a mounted magnet [25-27]. Localization can be referred to in 2 respects: relative to a point of interest inside the GI tract, such as a lesion (diagnostic localization), or relative to a universal frame shared by an external driving robot (global localization). Owing to the deformable nature of the GI tract, we cannot rely solely on global localization to locate target areas. Conversely, knowing only the distance from a capsule to a target area cannot provide enough information for control via an external robot. Though groups have reported 3D localization with an error of 1 mm using fluoroscopic imaging [28], developments must be made in describing a CE's location with respect to anatomical landmarks. The recently prototyped OdoCapsule targets this challenge by providing real-time distance from point of duodenal entry to exit from the ileum via mounted passive wheels on its side that operate as an "odometer." In vivo testing is pending to establish proof of this concept [29]. In 2014, a hybrid localization technique utilizing video motion tracking and RF was introduced by Bao et al. Experimental results show a localization error of less than 2.3 cm and a promising platform with no additional CE hardware [30]. External magnet systems with hall-effect sensors have been studied for localization and position and orientation detection [26], demonstrating very promising results in 2 different in vivo studies on porcine models [31,32].

3.3. Capsule locomotion

3.3.1. Upper GI tract and stomach

As seen in the Table, nearly all commercially available CEs are limited to passive and random movement, hindering the technology from becoming a prevalent diagnostic technique throughout the entire GI tract [33]. An upper GI tract CE actuation technique must allow for resistance of peristaltic force in the tubular esophagus, remain dexterous enough to directly observe the gastroesophageal junction by rotating the capsule body 180°, and maintain compliance while moving through the open fluid-filled gastric lumen, pylorus, and duodenum. Tortuous design requirements like these have provoked a ubiquitous need for an active capsule actuation method. The varying geometry throughout the GI tract has resulted in a research focus on CE actuation using a magnet maneuvered on the outside of a patient's body. Magnetic coupling, a means of exerting forces across a physical barrier, has been a focus of CE active locomotion research in the past 4 years and is one of the 4 "grand challenges" of CE, along with magnetic field gradient control, accurate localization, and enabling

diagnostic and therapeutic functions [17,33]. Applying force from outside the body enables a clinician to control the point of desired manipulation on a capsule, such as direct steering of the camera, vs pushing from the distal end of the endoscope. Benefits of magnetic capsule endoscopy (MCE) as outlined has made MCE an American Society for Gastrointestinal Endoscopy emerging technology focus and subject of research worldwide [34].

Keller et al performed the first human MCE studies in 2010. During the first study, a PillCam COLON was modified to house a permanent magnet and was manipulated by a hand-held magnet in a volunteer's esophagus and stomach [35]. Later that year, Keller et al performed separate studies on MCE manipulation in both the esophagus and stomach, also actuated via hand-held magnet. During the esophageal study, PillCam ESO2 capsules with embedded permanent magnets were swallowed by 10 healthy subjects and actuated by an external hand-held magnet. Although the procedure was reported as safe and feasible, magnetic forces were not strong enough to resist esophageal peristalsis [36]. During the latter study, CE maneuverability in 7 of 10 subjects in the stomach was referred to as excellent, but visualization of the gastric mucosa was not complete as magnetic forces were not strong enough to overcome passage from the antrum to the duodenum during phase III motility [37]. Since these feasibility trials, 2 MCE systems that use a hand-held external magnet have become commercially available: the OMOM Controllable Capsule System (Chongqing Jinshan Science & Technology, China) and the MiroCam Navi (IntroMedic Co, Ltd, South Korea). The authors have no knowledge of effectiveness of these systems at the time of writing this review.

Although hand-held magnet control may allow for faster movement through a straight trajectory, the use of an external robot with a permanent magnet mounted to the end effector has been shown to be more precise when approaching a target point, which is imperative for diagnosis and therapeutic maneuvering [38]. One of the first groups to study external robotic control was Carpi et al who first conducted proof-of-concept in vivo porcine studies (2009-2011). During this study, a PillCam capsule was actuated via the Niobe magnetic navigation system (Stereotaxis, Inc, St. Louis, MO) in a porcine model [28,39].

Human trials using external robotic actuation were presented in 2010 by Rey et al who conducted a feasibility study on the magnetically guided capsule endoscope introduced by Siemens Healthcare and Olympus Medical Systems Corporation. The study included 53 subjects who were placed on a bed and positioned under a magnetic guidance system that produced gradients in 3D space around the subjects' water-distended stomachs. Capsules were guided magnetically using the magnetic resonance imaging-like system and could be maneuvered at the gastric water surface or made to dive to the bottom of the gastric lumen. To improve capsule mobility, subjects were at times asked to rotate their body while lying on the bed suggesting a deficiency in the control method. The procedure lasted an average of 30 minutes with an overall technical success rate of 98% with full visualization of the antrum 98%, body 96%, fundus 73%, and cardia 75% [40]. A similar study was conducted in 2012 where a 5-degree of freedom (DOF) robot was used to actuate capsules. An assessment of the actuation system was conducted on 34 healthy volunteers who ingested magnetic capsules and powder for gastric distension. The authors concluded that examination of the human stomach via MCE is feasible and safe [41].

The use of magnetism for GI CE control has not been limited to manipulation by an external robot. Conversely to the aforementioned robot manipulation techniques, Kim et al in 2014 studied the feasibility of patients wearing a belt with an array of 17 total magnets to prohibit a swallowed capsule from advancing past the stomach. A modified MiroCam (IntroMedic Co, Ltd, South Korea) capsule was equipped with internal permanent magnet disks, and results suggest that real-time monitoring of gastric motility via MCE is feasible [42]. Besides magnetic actuation in the stomach, investigators have studied feasibility of submarinelike capsule robots for enabling omnidirectional swimming through a fluid-filled gastric lumen. This technology remains in preliminary stages of development [43,44].

3.3.2. *Lower GI tract*

Although the narrow diameter of the small intestine allows for adequate tissue visibility with CE, the larger diameter lumen of the colon tends to collapse, inhibiting visibility. Maneuverability through such collapsed tissue is necessary for inspecting behind folds and thus performing a complete examination. Since the advent of the technology, the main actuation modes of CEs can be categorized as onboard or external. Onboard actuation consists of miniaturized mechanical hardware built into the capsule allowing them to self-propel through the GI tract, whereas external actuation consists of pulling a capsule via magnetic coupling.

The most commonly studied onboard actuation techniques are legged locomotion and treaded driving. A number of legged capsule prototypes were developed in hopes of enabling crawling actuation in the small bowel. Mechanical complexity and convoluted control of such legged capsules has hindered further development and seems to lack feasibility for commercialization [45-47]. In 2012, the tethered robotic capsule endoscope was developed which is driven via 4 series of treads on each of its sides. Designed for mobility in a collapsed lumen, the treads are made to maximize contact area with tissue thus increasing friction. Owing to agility and virtually unlimited power supply, capsules like such can be incorporated into other areas of minimally invasive surgery [48-50]. Onboard actuation techniques allow for accurate relative motion but are limited by high power consumption, increased capsule volume (needed for hardware), and general complexity of miniature mechanical systems.

Similar to the upper GI tract, research into active robotic CE driving began with passive movement of a permanent magnet mounted on a robotic arm. Early in vivo trials involving actuating a MCE through the lower GI tract via a passively actuated external magnet mounted on a hydraulic arm occurred as early as 2008 [51]. Since then, robotic platforms have been developed in pursuit of intuitive closed-loop CE control via an external permanent magnet in various quantities and configurations. Procedural accuracy of control using an external industrial robot for MCE has been studied and concluded to be feasible [52,53]. In 2014, Sun et al presented a magnetic driving system consisting of 2 external magnets placed on the lateral and medial side of a patient to produce coplanar motion of an internal capsule with the magnets. The study involved magnetic and hybrid (legged) capsule actuation, where purely magnetic driving was concluded as best [54].

As opposed to the aforementioned techniques of pulling a CE via magnetic field gradient, an actuation approach using rotating magnetic field generated by spinning an external permanent magnet has been developed. First introduced in 2003 by Olympus Optical Co Ltd (patent no. US20030181788 A1), these screw-type capsules are rotated about their longitudinal axis. Threadlike features on the external capsule shell allow for translation of magnet-induced rotation to lateral capsule motion. Studies on spiral actuation were conducted in 2012 by equipping a PillCam SB2 with external threads [55]. As opposed to direct magnetic gradient dependence of aforementioned MCE guidance techniques, MCE actuation via rotating permanent magnet is governed by torque induced by magnetic field intensity that decays slower with distance and can allow for more controlled actuation [55-57].

A locomotion technique utilizing both onboard and external actuation has been developed. Hybrid locomotion, defined by Simi et al in [58], as a combination between internal actuation mechanisms and external magnetic dragging, can provide a way for CEs to anchor against peristalsis and make accurate movements without the need for onboard elements to provide total drive power, thus reducing power requirements [59]. One of the first hybrid designs was developed in 2009 and tested in vivo via porcine model that was actuated via external magnetic fields and, with a 3-leg mechanism, was able to distend collapsed tissue [58]. Another hybrid system was proposed by Ciuti et al [60] who used vibration to reduce contact friction between a CE and tissue while the capsule was dragged magnetically.

Adverse events in colonoscopy generally arise owing to the mechanics of pushing a flexible, yet stiff, colonoscope through a pliable lumen, where device buckling or colon looping can occur. Such events can be averted by pulling the device through the colon via external magnetic force [17]. Aforementioned studies show that MCE driving via external robot is a favorable capsule actuation technique; however, research addressing tissue interaction must be performed. Researchers are challenged with designing MCEs to meet miniaturized size constrains, ability for active locomotion, and adequate power supply, parameters which are unfortunately antithetical. The most pragmatic solution is to introduce a tether with tool channel to enable standard instruments to be used under robotic manipulation of the MCE. Valdastri et al introduced a tethered MCE system with tool channel in 2011. The Magnetic Air Capsule (MAC), pictured in the Figure, is steered via 6DoF industrial robot and contains a camera, illumination, and a tool channel as used in standard colonoscopes. During in vivo trials, biopsy samples were collected with the MAC that were of the same size as those collected during traditional colonoscopy [61]. A 2012 MAC feasibility study including 22 subjects using a 7 DoF robot assessed navigation of an MCE through an ex vivo porcine colon where experts and trainees were tasked with detecting 672 pins. Pin detection was 80.9% for CE and 85.8% for traditional colonoscopy with appropriate diagnostic yield. The authors concluded that MCE was a feasible procedure [53]. Real-time localization must be applied to the system to enable closed-loop control [26]. Global localization will prevent loss of magnetic coupling between robot and MCE, whereas diagnostic localization will maintain physician awareness of lesion position. The act of pulling a small capsule with flexible endoscope will reduce risk of tissue stress and colon looping and show pursuit of promise in replacing traditional colonoscopy [17].

3.4. Interaction with tissue

Studies on therapeutic capsules have been conducted that address wireless power transfer to CEs by induction, utilizing autofluorescence in diagnosing tissue, and various tissue biopsy techniques [23,62-66]. In 2014, a novel capsule targeted for drug delivery in the GI tract was introduced. In vivo porcine studies were conducted on the drug-delivery needle capsule targeted for delivery of biological therapeutics that could otherwise be adversely affected by bacteria and pH levels in the GI tract. The capsule is covered with radially oriented needles embedded in a pH-sensitive coating that both protect tissue while the capsule is swallowed and keeps drug contained. Once the capsule reaches the target delivery site, the coating dissolves and the drug is squeezed out via peristalsis into hollow needles that penetrate tissue, and detach from the capsule, remaining embedded in tissue, allowing for steady drug release [67].

Designing CEs to achieve accurate CE locomotion and ability to resist or drive against bowel forces requires GI force characterization. Terry et al were the first to quantify contractile strength of the porcine small intestine in vivo while studying force variability in the proximal, middle, and distal regions. Measuring the migrating motor complex force with sensor balloon segments, contact force values in the distal small bowel were observed to be 92% larger than in the proximal small bowel [68]. Knowledge of aforementioned force variations is vital for control algorithm development. In 2014, Natali et al presented a real-time platform for quantifying the propelling force required for traversing the GI tract. The capsule, while coupled with an external permanent magnet, sent wireless data to an external transceiver consisting of intermagnetic force and capsule acceleration, from which a force model was developed [32]. Care must be taken in MCE to maintain streamlined capsule motion while preventing overstressing of tissue owing to excessive magnetic link strength that may cause patient discomfort, tissue ischemia, or tissue perforation.

4. Conclusions and future direction

CE is the primary mode of small bowel examination, and the technology has expanded to clinical applications in the esophagus, stomach, and colon. Current CEs are limited to acquiring images of the mucosa while being passively moved throughout the GI tract via peristalsis. The primary focus of CE research in recent years has

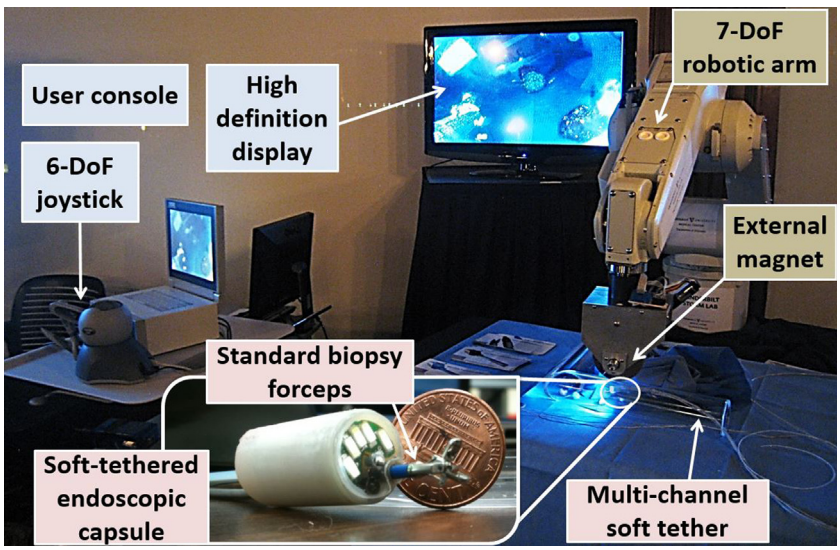

Fig. Magnetic air capsule system. (Color version of figure is available online.)

been enabling active CE manipulation and extension of the technology to therapeutic functionality. The most promising mode of CE control involves actuating tethered capsules via external permanent magnets manipulated by a robotic controller. Actuation of magnetic or hybrid capsules will allow for more thorough bowel examination and the ability for therapeutic intervention. Attaining such control in the clinical setting will serve as a paradigm shift. Development of these control algorithms may contribute to the advancement of CE's use in practice and possibly eliminate the need for patient sedation within the next 5-10 years.

CE development is a labor- and resource-intensive task involving determination of functional parameters, designing mechanical components, developing miniature circuitry, and integrating custom hardware and software into a functioning model. Work has recently been done to develop open-source hardware and software for expediting CE development and a web-based collaborative design environment [69]. Creating easy-to-use components may enable researchers to avoid the time-consuming process of gaining expertise in various domains such as low miniaturized electronics or level programming and skip to design for creative application. Efforts like these, and the research ventures outlined in this review, suggest vast advancements in CE technology in the coming 5 years. The future of CE is promising, and further clinical applications of CE actuation technology and therapeutic ability are expected.

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