DESIGN, IMPLEMENTATION, AND TESTING OF A MINIATURE SELF-STABILIZING CAPSULE ENDOSCOPE WITH WIRELESS IMAGE TRANSMISSION CAPABILITIES.

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Abstract: Video capsule endoscopy (VCE) enables examination of the small intestine. In large-lumen organs of the gastrointestinal (GI) tract (e.g. the stomach and the colon), the capsule tumbles around and therefore cannot image systematically. This limitation underscores the need for a novel approach that allows capsule imaging of these organs without tumbling. This paper describes the design and implementation of a self-stabilizing capsule prototype for colonic imaging. The present design consists of a capsule endoscope (CE) coupled to an expandable stabilizing component comprising a liquid-permeable sac filled with dry superabsorbent polymer granules (swellable material) integrally covered by an outer colon-targeting coating. Once the capsule enters the colon, the outer coating dissolves and this allows the expansion of the swellable material attached to the back side of the capsule endoscope. This volumetric increase of the expandable component provokes peristalsis by activating colonic mass reflex. The expanded end of the capsule stabilizes the entire implement, preventing it from tumbling, and at the same time activating the capsule endoscope. Once activated, the capsule begins to record images and to transmit them to an external receiver, which records the data to a computer. As a safety measure, the expandable component can be electronically separated from the capsule at any time. The capsule is eventually expelled out of the body as a fecal matter. A prototype of the self-stabilizing capsule has been developed conceptually and electronically to fulfill the requirements of image stabilization while coping with the restrictions of commercial CEs. Self-stabilizing CEs and non-stabilized CEs were comparatively tested in laboratory and canine experiments. The self-stabilizing CE eliminated the tumbling effect and demonstrated its potential to greatly improve colonic imaging.

Keywords: Colon, Gastrointestinal Tract, Video Capsule Endoscopy, Wireless Image Transmission,

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Introduction

A. Capsule Endoscopy

Video capsule endoscopy (VCE) is a new technology that has been developed for investigation of the small bowel [1]. VCE represents a major advance in screening the small intestine because it is simple, safe, non-invasive, reliable, and well tolerated by patients [2].

The size of the small intestine below the duodenum is just right to allow the capsule to be carried through this tubular organ without significant tumbling [3]. Thus, in this part of the small intestine, the entire surface is visualized as the capsule travels through [4]. Captured images are transmitted through the human body to an external receiver [5]. No control of travel, orientation and/or posture is available because the device is conveyed

by natural peristalsis [6]. Therefore, mass lesions located in the proximal small bowel may be missed on the basis of capsule velocity or tumbling [7]. There are several possible reasons that small bowel mass lesions are missed by capsule endoscope (CE). As the capsule passes along the duodenal sweep, it may increase in speed resulting in a missed lesion [8].

The time of passage of a capsule through the entire gastro intestinal (GI) tract is about 8–10 h, with approximately 1 h spent in the stomach, 4 h in the small intestine, and 5 h in the colon [9]. However, GI motility varies widely in the general population. Twenty-four to 48 hours for a CE to go through the entire GI tract as a result of its passive movement were reported in some cases [10]. Generally, in 20% to 30% of the VCE procedures, the capsule does not reach the cecum within recording time, with incomplete imaging of the small bowel, which limits the value of CE [11,12].

Recently, commercial CEs have also been extending their reach into other parts of the GI tract including the esophagus and the colon [13]. However, with the current design approach, the application of VCE is currently limited to small-lumen organs [14].

B. The Problem of Information Transmission in the Colon

The colon measures about 150 cm in length and 6 cm in diameter [15]. It consists of at least two anatomically distinct sections: 1) the sigmoid, which is relatively narrow and typically has one or several sharp angulations or bends, and 2) the more proximal colon which is distinguished by relatively straight sections that progressively widen in luminal calibre. These disparities in the anatomy of the colon create the greatest challenge for VCE imaging. Thus, it is important to emphasize that current capsule endoscope design is not suitable for colonic imaging [16]. Autonomous swallowable video capsule has dimensions (31 mm x 11 mm) that are smaller than the lumen diameter of the colon and the capsule may toss, tumble, turn, and vibrate as it passes through the colon [17,18]. With the tumbling of the capsule in this wider space, important lesions may be missed and generally the entire internal surface cannot be viewed [19]. During the capsule transit, the lens hood can be buried in the mucosa of the colon resulting in an incomplete imaging [20]. The capsule may stagnate in some sections of the colon, may pass quickly over other sections, and may retract for a distance [21]. Therefore, it may be difficult to determine the exact location of the in-vivo device in space, in what section of the colon a point of interest pathology may have been detected or important pathologies could be completely missed [22].

During a quick passage of the tumbling capsule in large lumens, the solid capsule body can create air bubbles in the liquid environment that along with debris can significantly obscure the view of the colonic mucosa. Such obscuring of the visual field may reduce the diagnostic yield. Therefore, it is essential to reduce these potential causes of poor visualization by eliminating the tumbling and optimizing the bowel preparation for capsule endoscopy [23]. In addition, collapsed bowel, large folds, cincturing of bowel by tumors and blood in the lumen may obscure visualization of an underlying mass lesion with the current design of capsule endoscopes [24,25].

The PillCam Colon capsule (Given Imaging, Yoqneam, Israel) is the only CE currently in use for colonic investigation. In the most recent study of 56 patients, colon capsule endoscopy (CCE) was followed by conventional colonoscopy (CSPY). Polyp detection rate (per patient) was 50% (n = 28) for CSPY and 62% (n = 35) for CCE. For relevant polyps (>5 mm) there was a correspondence in the detection rates of both methods ($p < 0.05$). The mean sensitivity was 50% (95% confidence interval [CI], 19 to 81), the mean specificity was 76% (95% CI, 63 to 86), the positive predictive value (PPV) was 20% and the negative predictive value (NPV) was 93% [26]. An European study from 2009 has shown CCE being able to diagnose 64% of total polyps, which were

detected by CSPY [27]. These results indicate the general problem of CE tumbling during its transit in the colon and the need for CE stabilization.

It has been hypothesized that VCE may, by reducing the indignity and discomfort of endoscopic procedures, have the additional benefit of encouraging many who currently forgo medically recommended examinations (particularly colonoscopy) to have it done [28].

The VCE could have a place as a non-invasive screening procedure for colon cancer, which can be performed more safely, more tolerably, and more often than standard colonoscopy. The issue to be solved is improvement of the sensitivity of this modality by eliminating the unwanted tumbling and tossing effects [29].

C. The e-Stool Concept

The e-Stool concept seeks to eliminate the unwanted tumbling and tossing effects of CE traversing the colon by an expandable stabilization apparatus attached to the back-end. The stabilization apparatus can be narrow and short enough to negotiate the narrow portions of the colon, yet it adjusts to the wider luminal calibre of the organ. This design brings a new revolutionary VCE concept to increase the sensitivity and provide systematic visualization of the large intestine.

As the expandable component is fluid-permeable, an obstruction in the small intestines is not created. The risk of stagnation of the capsule in the case of bowel obstruction is eliminated by installing a separation mechanism within the capsule. As the expandable component is activated it can be electronically separated from the capsule at any time.

In addition, the expandable component is biocompatible and is able to disintegrate in the GI tract after a certain period of time.

D. Aim of the Study

The aim of the present study was to design a 1:1 prototype of the e-Stool CE, and to demonstrate the practical feasibility of VCE self-stabilization and separation concepts.

Method

The complete block diagram of the self-stabilizing CE prototype is shown on Fig.1.

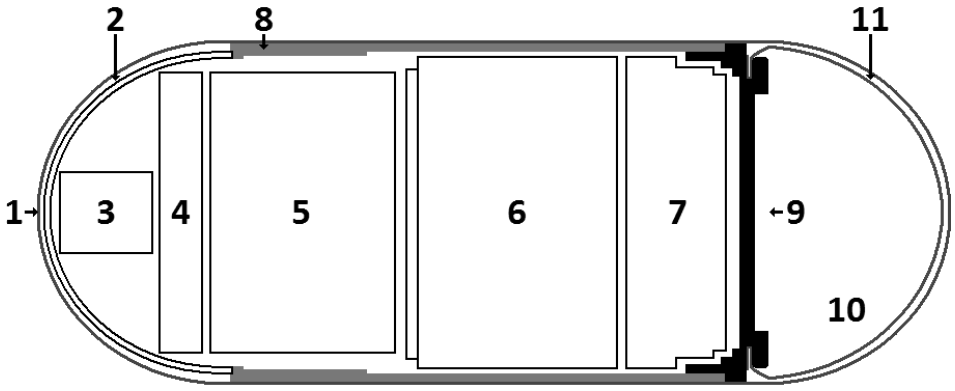


Fig. 1: Self-stabilizing CE Prototype. 1 – outer coating, 2 – optical dome , 3 – longitudinally positioned CMOS color camera, 4 – illumination system (LEDs), 5 – transmitter, 6 – battery, 7 – micro-heater, 8 – tapered cylinder, 9 – sealable lid, 10 – superabsorbent granules, 11 – PGA mesh.

The design consists of an outer coating, capsule endoscope and expandable component, which comprises the superabsorbent polymer granules contained in a porous PGA mesh that is attached to the back-end of the capsule using polydioxanone (PDS) suture. The CE comprises of complementary metal–oxide–semiconductor (CMOS) camera, radio frequency (RF) transmitter, light emitting diodes (LEDs) illumination system, battery, and a microheater. The outer coating is made of the colon-targeting agent Eudragit, a coating resistant to gastric acid that dissolves only in the intestinal tract at a pH range of 5.5-7 [30]. Therefore, when the capsule reaches the lower portion of the small intestine (the ileum) or the colon, the Eudragit coating starts to dissolve due to the change in pH. The electronics inside the capsule is activated by moisture switch and the expansion of the stabilizing material is initiated when the gastric juices start permeating the PGA mesh. The expansion process is continuous and results in volumetric and mass increase of the stabilizing component. In general, the peristaltic reflex can be elicited in the large intestine by local distension of the colonic wall, which involves activation of both ascending excitatory and descending inhibitory neural reflex pathways to the neighboring colonic smooth muscle layers [31]. Therefore, the volumetric increase activates the peristaltic reflex in the colon, which ultimately provokes natural peristalsis that propels the capsule. The expansion is completed before the peristalsis starts, allowing systematic colonic visualization starting in the cecum. As the natural peristalsis moves the capsule smoothly and painlessly through the colon, an intraluminal video is acquired at an appropriate frame rate. This video is subsequently wirelessly transmitted to a PC via an RF link. The expanded implement at the back-end of the capsule stabilizes it and prevents it from tumbling while it slides through the colon towards the rectum.

Some portions of the colon are convoluted, namely the cecum, the hepatic flexure, the transverse colon, the splenic flexure, and the sigmoid. [32]. As a safety layer to eliminate device obstruction in the gut, a separation mechanism was designed. After the expandable component has been activated it can be electronically detached from the capsule at the operator's command by enabling a fast reacting micro-heater placed onto the capsule cap. The stabilizing (expandable) component is affixed compactly to the capsule using a mechanism made of low melting point biodegradable PDS suture. The micro-heater activates the heating of a Ni-Chrome filament in the presence of a magnetic field. The heating filament reaches a suitable temperature to melt the PDS suture (≈107˚C) when a current is fed through it. This results in eliminating the point of attachment between the capsule and the expandable component, leaving the PGA mesh opened. The natural peristaltic movement of the colon completes the separation of the expandable component and the capsule. The superabsorbent polymer granules, PGA mesh, and PDS suture are bio-absorbable and biocompatible, and therefore can safely be disintegrated in the GI tract after a relatively short time period.

A. Design of the Capsule Body and the Optical Dome

The capsule endoscope must be sealed and resistant to decay within the gut to protect the internal components from conditions inside the patient's body. It is composed of three parts, a tapered cylinder, an optical dome window, and a sealable cap. The dimensions of the capsule were determined to allow it to fit inside the outer casing (Torpac #13 3.2 ml; Torpac Inc., Fairfield, NJ, USA), and to leave enough space for the 0.7 ml expandable component required for the stabilization. The design encompassed threaded cap with a recessed groove, which was used to compactly attach the stabilizing component to the body of the CE using PDS suture. The threaded cap provided a water-proof seal for the capsule and at the same time it maintained a point of attachment for the stabilizing component. The cap material that was chosen had to encompass the following properties, high wear resistance, low surface friction, high strength, and great rigidity. Hence aluminum was selected as the cap

material for the prototype. The final step was to seal the cap to the capsule body using an ultra-thin soft polytetrafluoroethylene (PTFE) film.

An optical dome of hemispherical shape was selected, because it is easier for a patient to swallow the capsule, and body fluids cannot remain on the front cover [33]. The sturdy optical dome is in front of the CE to improve the luminous uniformity and to match the lens in the back of the dome. This dome houses the CMOS imager, the lens, and the illumination system. The lumen of the bowel is illuminated through the optical dome by an illumination system. The images are to be obtained as the gut wall sweeps past the optical dome of the capsule during peristalsis. Subsequently, the obtained image is focused by a short focal aspherical lens onto the CMOS imager.

The intensities of reflections from interfaces of the optical dome are minimized when the angle of incidence and the angle of reflection are near zero, in other words, rays of light are incident perpendicular to the plane of the interface [34]. The optical dome has a shape that prevents the light reflected by the dome itself reaching and saturating the imager thus degrading image quality.

The optical dome was designed from a glass which was selected and adjusted for this design at 1-mm thickness. The dome was attached to the tapered part of the cylinder using a medical grade biocompatible epoxy resin EPO-TEK® 301-2 (Epoxy Technology, Inc., Billerica, MA, USA).

Another important efficiency consideration is how much of the light from each LED source can be collected by the optics. Distribution pattern-matched efficiency accounts for how well the optics is expected to direct the light from the LEDs into the desired distribution shape. The pattern-matched efficiency worsens when the design volume is constrained since the optic is relatively small and close to the LEDs. Light collected by any point on the optics will subtend a greater solid angle when compared to a larger optics. Smaller optics has less control over how well light is redirected.

The distance between the lens and the optical dome was chosen to be 5.4 mm. The outside curvature of the optical dome was 6.7 mm, the inside curvature was 5.9 mm, and thickness was 0.8 mm.

The final CE endoscope prototype length was 22 mm and its outer diameter was 14 mm.

B. Design of the Imager

The proposed design uses a CMOS imager (color camera) which captures images of the colon walls and also suits the space constraint in the capsule.

In the front of the CMOS imager is a short focal-length aspherical lens (0.77mm/f3.0<110°>) that is manually focused at the optical dome and a few centimeters beyond, so that the bowel laying against the optical dome would be in focus. Wide-angle lens selection permits more efficient examination of the large intestine. Improvements in image quality can be achieved by careful attention to the positioning of the lens relative to the imager. The position of the entrance pupil of the optical lens should coincide with the center of the curvature of the optical dome window to prevent any of the reflected light from entering the CMOS imager [35, 36]. A special lens holder was used to position miniature lens over the CMOS imager with high degree of accuracy using a microscope. Lens holder kept the lens' optical axis centered on the active area of the imager and perpendicular to the imager surface.

Initially the lens holder was positioned and tightly fixed to the imager to avoid dislocation during capsule transit. The top of the holder contained a thread which allowed screwing in the lens with the same thread type. The final

optical arrangement allowed the tissue to be in focus even if it is in contact with the optical dome window but also to remain in focus over 4cm if the lumen is opened with residual air or fluid. The imager uses a narrow aperture to increase the depth of field.

The selected image sensor for the final prototype was the 1/18" Color CMOS camera MO-B802-105 (RF-LINKS, Toronto, Ontario, Canada). The camera operates at 3V, 18-19mA, its minimum required illumination is 2Lux at f1.2, and number of effective pixels is 320x240 (NTSC). This CMOS imager is very precise and can detect objects (polyps) as small as 2 mm.

C. Illumination System

The challenge in developing LED illumination system for a capsule endoscope is obtaining uniform illumination [37] on the observed object. This is difficult for several reasons:

- ♣ the optical path of an LED light source is not parallel to the optical axis of the adjacent imaging lenses,
- ♣ the light pattern of the LED depends sensitively on the driving current, location, and projection angles,
- ♣ the object plane of the observed intestine is not flat,
- ♣ the luminescence of an LED is different at different angles.

In general, the spatial light distribution is not uniform at the object plane in front of the capsule endoscope, resulting in a reduced image quality from the CMOS sensor. In some regions of the object plane, the luminance is very small and in other regions it could be very large. In order to solve this problem, the positions and the angles of multiple LEDs were arranged to improve the luminous uniformity of the designed capsule endoscope. Due to space constraints in the capsule, the LEDs must be small and yet provide enough luminous intensity for decent images to be obtained. Their luminous intensities should also be able to provide enough light for the worst-case scenario where the lumen of the colon is very large: in the cecum and in the ascending colon. The power required by the LEDs is dependent on the number and the type of LEDs used.

Nichia NSSW156T LEDs (NICHIA Corporation, Tokyo, Japan) were selected based on their luminous intensity, viewing angle, and dimensions (3.0x1.4x0.8mm). Four white flat top, wide-angle, surface-mount LEDs were utilized to minimize the space volume and the current draw, while still providing adequate illumination to cover ≈ 140° range.

The experimental luminous intensity of a single LED is above 130 mcd at a forward current of 1mA. This provides sufficient combined illumination for the CMOS imager to clearly view an image inside large intestine when the four white LEDs are circumferentially positioned at the camera side end of the capsule.

Additionally, to be effective, the illumination needs to provide an adequate amount of uniform light and to be coming from a correct angle, so as to avoid shadow effects. In general, LEDs light distribution characteristic deviates from its center. When the LEDs are arranged circumferentially around the imager, light from all these illuminating units overlaps at a portion that is in front of the imager and this portion is brighter than the portion where there is no overlap [36]. Because of this imbalance in brightness, the image quality of the images captured by the imager degrades. To improve the brightness balance, LEDs were disposed around the CMOS imager in such a manner that the optical axes of the illuminating units did not intersect with the optical axis of the observation unit (the CMOS imager), and the illuminating units overlapped at a substantially central portion of the image capturing area of the CMOS imager. The tilting of the illuminating units also minimized the refraction from the optical dome, thus minimizing the distorting effect and efficiently illuminating a cylindrical area of 7cm x 18cm.

The optical dome and the LEDs placement was thoroughly designed to minimize the internal light reflections and refractions. Fig. 2 shows the designed illumination system with four tilted LEDs.

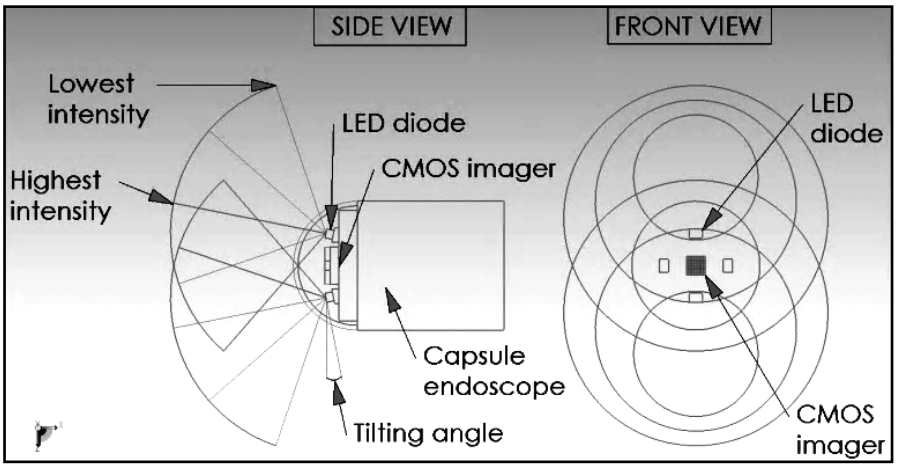


Fig. 2: Tilting of the illuminating LEDs.

The optimal tilt angle which provided adequate illumination for the self-stabilizing capsule endoscope was determined through multiple experiments to be ≈ 11 ± 2°. Three different configurations of LEDs positioning were tested. The configuration of four circumferentially placed LEDs 90 degrees apart proved to be the most effective. We found that the closer to the shell the LEDs were arranged, the lower the total flux was collected by imager. Thus, the distance between each LED and optical axis was chosen to be 5.5mm.

Protel PCB design software (Altium, Sydney, Australia) was used to produce a printed circuit board (PCB) layout of the illumination system. Subsequently, the PCB (copper single-sided board) was milled on the prototyping PCB milling machine and then tinted using a chemical bath. A custom-made ultra-small plastic ring was manufactured to provide a plane for tilting the LEDs, thus ensuring an even tilt angle for all four LEDs. Subsequently, the LEDs were partially placed on the plastic ring and soldered to the PCB with the aid of a microscope.

D. Transmitter, Receiver, and Antenna

The design of a low-power wireless transmission system capable of transmitting through the body was an integral part of this project. The human body is a medium that poses numerous wireless transmission challenges [38]. The RF transmitter must operate in a wide variety of environments and positions that can change with time, because the human body tissue will attenuate the signal variably as the capsule passes through.

There are several critical requirements for the transmitter in a capsule endoscope, including size, power consumption and data rate. Small size is essential, since there is very little room to fit it into the device along with the other components. The hardware needs to be robust in order to withstand the knocks and bumps of normal human body movement. The transmitter layout complements the other electronic components, making the most out of the small space inside the capsule. The antenna connection must be very short to minimize losses and to keep the impedance constant. The length of the antenna must be small enough to fit in the capsule. However, if

the compact antenna in the capsule endoscope is too small, its bandwidth at low frequency will not be wide enough and its radiation efficiency cannot be very high. In addition, in order to transmit the diagnostic real-time high-resolution image data at high speed and because of the effect of human body tissue on signal propagation characteristics, the transmission frequency may slightly shift during operation [39]. Thus, a wide-bandwidth, higher transmission frequency needs to be employed along with a tunable receiver. Unfortunately, an antenna with a higher transmission frequency may cause higher radiation absorption especially in the backmost portion of the intestine and decay the communication link performance in the human body. Since more energy will be absorbed by the human tissue at higher frequencies, many problems exist such as power consumption and the way various positions and orientations of the radiation source influence its characteristics [40]. Consequently, careful selection of transmitter, antenna and frequency for in vivo use is very important. With CMOS technology, the output frequency typically increases as the physical size diminishes. Among the industrial, scientific, and medical (ISM) frequencies, 1.9 GHz is frequently used for transmission, and the smallest transmitters that are commercially available operate in this range.

An RF transmitter chip is used to send data from the CMOS imager wirelessly to be recorded in the computer. The selected transmitter in the final prototype, DX-5A (RF-LINKS, Toronto, Ontario, Canada) operates at 1900MHz (channel frequency), and draws 8mA from a 3V source. This transmitter is ultra-small (4 mm x 5 mm), gain-tunable, and is capable of transmitting a standard NTSC signal.

The transmitter antenna size and shape needed to be modified in order to achieve maximum efficiency in human body environment, fit in the capsule along with all other components, and minimize antenna coupling to the battery. The capsule travels passively in the GI tract, and therefore is randomly oriented. Thus, the direction of transmission radiation is uncontrolled, and to detect the transmitted signal independently of transmitter position, the antenna is required to emit an isotropic radiation pattern [41, 42].

The selected external receiver VRX-2000M (RF-Links, Toronto, Ontario, Canada) outputs the received video signal from the in-vivo sensing device into a video capturing device DVD Xpress DX2 (ADS Tech, Walnut, CA, USA). The small external receiver can monitor the 1900-2100 MHz video bandwidth and the frequency is controlled in 0.25MHz steps, which is entirely sufficient for stable real-time recording and display of the results. The receiver provides very high sensitivity of -86dBm. In addition, it has a built-in special Automatic Frequency Tuning (AFT) control function for best signal receiving stability.

The DX2 outputs the video signal to a PC display via a fast USB 2.0 connection while the CE is inside the patient's body. Using video capture software, the video was captured to computer's hard drive for further analysis.

E. Design of the Self-stabilizing Component

The stabilizing component should be able to deform under external pressure but revert to its original shape when the pressure removed. To provide a maximum safety to patients, necessary requirements for the stabilizing component are: permeability to fluids and gases, compliance characteristics mimicking soft stool, and biodegradability in 2-3 days. The expanded implement should also maintain its consistency and not change state under the influence of water or colonic fluids. In addition, the super-absorbent polymer has to be biocompatible, to swell extensively, to swell in a relatively short period of time, to exert a reasonable swelling pressure on the walls of the lumen, and to withstand the maximum luminal inner pressure in the colon.

The faster the expansion process is completed, the more rapidly the imaging capsule would stabilize in the colon, allowing systematic imaging of the organ once the capsule enters the cecum. Therefore, the expected overall expansion time should be less than 1 min.

The materials that had the desired properties to design the expandable component were categorized according to the preferred mechanism of expansion, osmosis (release of potential energy) and expansion rates. The release of potential energy results in an expansion of the material that possesses the potential energy. Osmosis has proven to be effective in several medical applications such as stents that help relieve pathological obstruction of tubular structures in vascular, urologic and GI systems, as well as in self-expanding prostheses [43].

The swelling behavior of superabsorbent osmosis-based materials depends on pH, temperature, ionic strength, or solvent composition. The rate of expansion in osmosis depends on numerous factors, including the structure of the material, the membrane and the concentration of the solution. On the other hand, the release of potential energy is rapid, almost instantaneous. The superabsorbent material used in this design was cross-linked sodium polyacrylate polymer granules. These granules exhibit strong hydrophilicity and can absorb hundreds of times their weight in water without dissolving upon swelling [44].

The stabilizing component adapts to the inner lumen shape, maximizing the contact surface area between the two. The dynamic viscosity of the swollen superabsorbent (hydrogel) is in the range of 900-7000 centipoises (cPs) [45], which is considerably less than healthy human feces viscosity (semiliquid; <50000cPs) [46]. When the tissue of the wall is stretched, the friction will increase rapidly. This is very important during the CE transit in the colon since it allows for a very smooth movement of the capsule by reducing friction between the expanded implement and the intestinal wall. The selected superabsorbent polymer provides high fluid retention even under pressure.

To overcome sharp colonic turns such as the hepatic and the splenic flexures the expandable component must behave similarly to the way formed stool does, which has been incorporated as an important feature of this design. This bending capability should be uniform up to the base of the expandable component that is attached to the rigid, but relatively small imaging component.

The pressure exerted on the walls of the colon upon expansion should not be harmful. The colon wall of the human body can bear≈ 7.71 pound -force/square inch (398.72 mmHg) [47]. The forces due to the internal pressure of the stabilizing component acting on the colonic walls can potentially harm the walls. As a result, stresses in the colonic wall on the cross-section along the colonic axis and on the cross-section perpendicular to the axis are created. Generally, these stresses are tensile and are known as circumferential (hoop) and longitudinal. The normal colonic wall thickness ranges from 0.1 to 2 mm in colonic segments with a diameter of ≥4-6 cm, from 0.2 to 2.5 mm in colonic segments with a diameter of 3-4 cm, from 0.3 to 4 mm in colonic segments with a diameter of 2-3 cm, and from 0.5 to 5 mm in colonic segments with a diameter of 1-2 cm [48].

Thus, the colon can be regarded as a thin walled cylinder if certain assumptions are made. Firstly, the stress differences across the thickness of the bowel wall should not be considered significant and secondly the weight of any bowel contents should also be considered insignificant as a stress raiser. These are reasonable assumptions in the bowel if the internal diameter is greater or equal to 10 times the thickness of the bowel wall and the bowel wall receives no external support. Generally, it is known that in the particular case of a thin-walled cylinder, the longitudinal stress is half of the hoop stress [49]. Hence, the permissible stress in the colon should be less than the hoop stress. Thus, in a distendable biological tube like the large intestine, the principal stress of interest is the

hoop stress [50]. Fig. 3 illustrates a simple model of the pressure P_(expan.) exerted upon the expansion of the stabilizing component on the colonic walls during peristalsis.

There are two possible scenarios in the colon. In the first scenario only expansion is present but no peristaltic activity. In this case the following assumption is made:

$$\boldsymbol{P_{expan.}} < P_{\boldsymbol{net}} \tag{1.1}$$

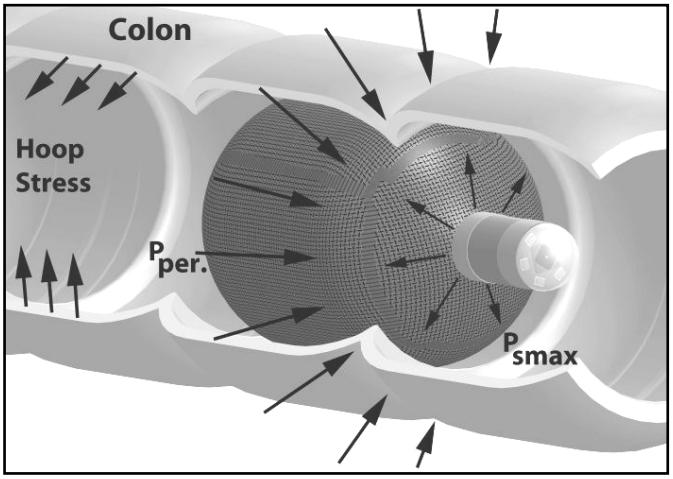


Fig. 3: Pressure in the colon during expansion.

The net pressure that the walls of the colon can bear, P_{net} can be calculated using equation (1.2) [51], assuming that the pressure applied on the walls would mainly result in a hoop (tensile) stress and in a negligible longitudinal stress:

$$\boldsymbol{P_{net}} = \frac{\sigma_{\boldsymbol{h}}\boldsymbol{t}}{\boldsymbol{R}} \tag{1.2}$$

where:

$\boldsymbol{P_{net}}$ = Net pressure that the walls of the colon can bear upon expansion, Pa;

$\boldsymbol{P_{expan.}}$ = Maximum swelling/expanding pressure on the walls of the colon upon expansion, Pa;

$\sigma_{\boldsymbol{h}}$ = Hoop (tensile) stress of the colon, N/m^2;

$\boldsymbol{t}$ = Thickness of the colonic walls, m;

$\boldsymbol{R}$ = Inner radius of the colon, m;

The colon tensile strength is 81 to 139 g/mm^2 [52]. Using equation (1.2), we estimated the maximum $\boldsymbol{P_{net}}$ of 13.9 kPa (104 mmHg). Previously, it was found that during colonoscopic air insufflations colon perforation can occur at intraluminal pressures greater than 140 mm Hg (or 18.67 kPa) [53, 54]. The estimated $\boldsymbol{P_{net}}$ of 104mmHg is well below the reported critical value of 140 mmHg which can perforate the colon.

The second scenario assumes expansion and peristalsis acting simultaneously. Thus, the net pressure applied on the walls of the colon is the difference between the maximum swelling/expanding pressure applied by the stabilizing component, $\boldsymbol{P_{expan.}}$ and the pressure exerted on the device by the colonic walls, $\boldsymbol{P_{per.}}$ and is shown in

equation (1.3). The difference between the maximum swelling/expanding pressure $P_{expan.}$ and the peristalsis pressure $P_{per.}$should be less than the net pressure, P_{net} so that no harm is caused to the colonic walls:

$$P_{expan.} - P_{per.} < P_{net} \quad (1.3)$$

where:

$P_{per.}$ =peristaltic pressure in the colon, Pa;

The mean peak amplitude of antegrade propagating pressure waves is 41.8+/-2.3 mmHg with a range of 5-169 mmHg [55]. It can be seen that the difference between the swelling pressure and the peristaltic pressure should be lower than P_{net}. However, it is important to simultaneously include in this analysis the antegrade propagating wave. Therefore, the stabilizing component was designed to create maximum swelling pressure of 90 ± 15 mmHg, because if this pressure is higher than the antegrade propagating pressure, severe constipation or perforation might result [56]. The self-stabilizing capsule before assembly is shown in Fig.4

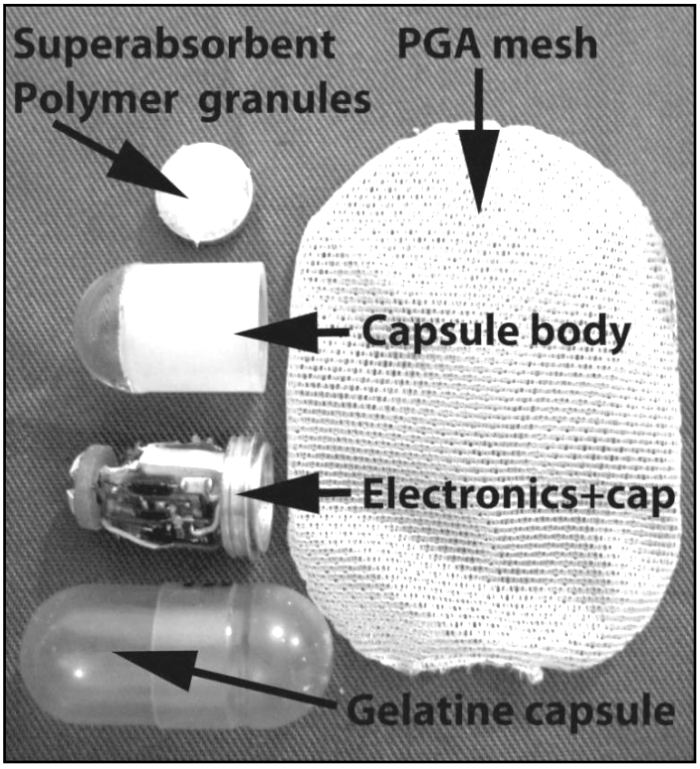


Fig. 4: The self-stabilizing capsules before assembly. The expandable component made from permeable PGA mesh filled with superabsorbent polymer granules was attached to the CE prototype containing the batteries, the imager, and the lens. Subsequently, the entire implement was put in a gelatin capsule.

The self-stabilizing component selected for the final prototype was a woven, bioabsorbable liquid-permeable, flexible polyglactin 910 mesh (Vicryl, Ethicon Inc, Somerville, NJ, USA) filled with superabsorbent polymer granules (Favor PAC, Evonik Industries, Stockhausen, Germany).

Initially, the mesh was thermally processed to obtain oval shape (side length=2cm, radius=2cm) followed by cutting a slit (5mm) through which the polymer (≈ 0.7 ml) was inserted into the oval-shaped mesh. Subsequently,

the mesh was pulled over the end part of the CE through this opening, compactly attached to a specially designed cap using PDS absorbable suture, and covered with an outer casing.

F. Design of the Attaching Mechanism

Due to the geometry of the self-stabilizing CE and the pressure applied in the colon, there is a higher risk of the stabilizing and the imaging components disassociating from each other as a result of shearing. Consequently, the attachment point on the cap has been designed to maintain a strong connection between the CE and the stabilizing component utilizing PDS II (USP 5-0) absorbable suture (Ethicon, Inc. in Somerville, NJ, USA). The attachment of the stabilizing component around the circumference of the sealable cap uniformly distributes the tensional load. This increases the strength of the connection, and prevents the two components from flexing. In addition, this type of attachment normally preserves a common central axis between the stabilizing component and the capsule, while ensuring the necessary flexibility to systematically visualize convoluted portions of the colon.

The PGA mesh was pulled up over the perimeter of the lid, in such a way that it covered the entire circumference of the external groove. Then, looking at the back of the lid, a suture was threaded into the upper left hole and out through the mesh into the groove. It was then wound tightly one full turn clock-wise around the outside of the mesh pulling it into the groove. Next, it was threaded out the other hole to the back of the lid where the two ends of the suture thread were then tied tightly together.

The breaking strength of the stabilizing component should be greater than the maximum possible pressure in the colon if the worst-case scenario is considered. In this scenario, the peristaltic pressure holds one end of the stabilizing device fixed, while random pulling pressure is applied on the rest of the capsule. The random pressure is assumed to have a pulling effect, i.e. a lateral pressure of the same magnitude as the transversally applied random pressure. Figure 5 shows the worst-case scenario where one end is held and the other is pulled laterally and circumferentially.

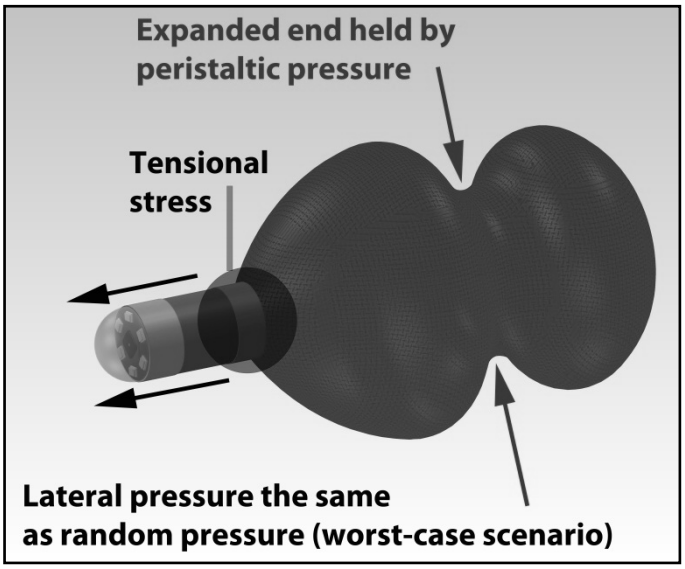


Fig. 5: Worst-case scenario for the stabilizing component where one end is held and the other is pulled by lateral and circumferential forces.

Previously, it was found that the mean peak amplitude of antegrade propagating pressure waves for all colonic regions is significantly greater than that of the retrograde propagating pressure waves [57]. The colonic pressure activity is complex and usually ranges from 25 mmHg up to 400 mmHg [58]. A value of 400 mmHg was used to calculate the worst-case scenario for the attachment between the CE imager and the expandable component.

G. Design of the Separation Component

The separation component was designed utilizing an electronically-controlled microheater. The general requirements for the microheater module can be summarized as follows: excellent temperature uniformity over the sensitive area, very low input power and ultra- small dimensions. For the final prototype, the material selected for the microheater's heating filament was a non-magnetic alloy of nickel and chromium (80% nickel and 20% chromium). Ni-Chrome converts heat into electricity through Joule heating. This alloy has a high melting point of about 1400 °C. The Ni-Chrome based microheater is controlled via two specially disposed miniature magnetic dry reed switches (contact layers: gold, sputtered ruthenium). These switches are of the double-ended type and may be actuated by an electromagnet, a permanent magnet or a combination of both. The connection between these switches is flexible and partially movable to improve reliability and sensitivity of switching. The diameter of the Ni-Chrome filament is very small (0.001mm), which allows it to heat up quickly when exposed to a relatively small current. Unfortunately, this means that the filament is very fragile, and could be severed during assembly when the PDS suture is tensioned on top of it. This situation was avoided by using a diameter of Ni-Chrome wire that was small enough to be partially concealed within the uneven surface features of the sealable cap. Thus, an additional structural support to the Ni-Chrome wire was provided by the sealable cap, which effectively increased the breaking point of the wire. Using a microscope, the PDS suture was positioned on the top of the heating filament (1.4 mm in length) making a very slight contact with it.

The magnetic reed switches activate the heating of Ni-Chrome filament in the presence of a magnetic field, and deactivate it once the field is removed. When a current passes through the filament, it achieves the requisite temperature (melting point of 107°C) to melt the PDS II suture [59], separating the capsule from the expandable material. In the specific design the switching time was less than 100 ms and the separation time was 1.5 seconds using an 89-mA pulse delivered from the power supply. The effective magnetic field of operation was determined by multiple experiments and was in a range of 2-15Ampere-Turns (current in the coil multiplied by the number of turns). Fig. 6 illustrates a CAD-rendering of the microheater module.

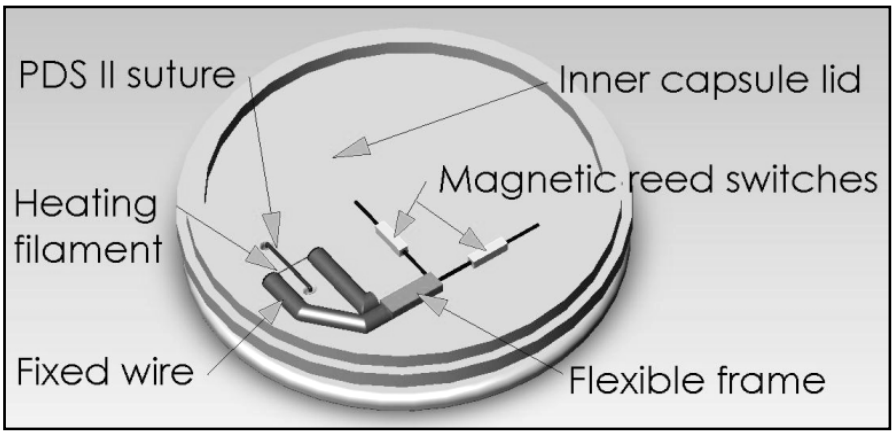


Fig. 6: Microheater module.

H. Power Supply and Encapsulation

Commercial CEs use small silver oxide batteries (usually two), which account for more than half of the weight of the capsule. In all applications of capsule endoscopy it is imperative to consider battery life/performance trade-offs and toxicity of the battery technology. Careful component choice and efficient electrical design are important in extending the life and improving the performance of the capsules.

Since there are only certain types of batteries commercially available that can fit in the limited space of the capsule, the power supply needs to be designed very efficiently. The CR 1/3N battery (Duracell Canada Inc, Mississauga, Ontario, Canada) provides enough continuous current to allow for the reliable operation of all electronics inside the capsule. The operational voltage, continuous discharge current, small weight, and small dimensions were deciding factors when selecting an effective power supply. Another important parameter to consider was the internal resistance as the battery must provide enough continuous discharge current of 28-30mA for the electronics and 400 msec/80mA pulse to trigger the microheater simultaneously. The lower the internal resistance, the less restriction the battery encounters in delivering the needed power spikes. Moreover, the smaller the battery (i.e. its diameter), the higher the internal resistance. Using a DC load test the internal resistance was measured to be in range of 250 mOhms.

For the initial prototype model, the outer casing is a hard-shell gelatin capsule from Torpac, Inc. (Fairfield, NJ, USA) which dissolves very rapidly (2-3 minutes) in water. This capsule is sized for animal testing, and with the design limitations in mind, a capsule of size #13 (1/8 oz. 3.2 ml) was chosen. The gelatin capsule provided an adequate space for the CE containing both the electronics and the self-stabilizing component. In the present prototype, the emphasis is on demonstrating stabilization and separation, and the testing assumes that the outer casing has reached the targeted organ.

In a final design, a colon targeting film cover can be utilized such as the recently proposed coating prepared by mixing Eurylon VII [high amylose maize starch (Roquette, Lestrem, France)] aqueous dispersion and Eudragit S ethanolic solution (Evonik, Darmstadt, Germany) (ratio 3:7 solids) [60].

I. Laboratory Testing

1) Image Transmission Test

A medium approximating human flesh, a fatty beef tripe was selected in order to confirm that an image can be transmitted successfully through. The prototype of the capsule endoscope was placed between two pieces of the tripe (>5cm thickness each) and was fully covered, with the CE being positioned in the center. The receiver antenna was placed 2m from the outer tripe surface to sense the receiving signal. The tripe was manually squeezed both periodically and randomly to simulate the dynamic impedance change of moving flesh, at a distance of 2m from the receiver. The squeezing continued for five minutes, monitoring the PC screen for qualitative changes in the clarity of the images.

2) Vertical Drop Test

A 1.5-liter transparent acrylic tube (4.5 cm diameter, 90 cm length) was sealed at one end, filled with water/oil (1:1), and a non-stabilized or stabilized capsule was set to fall down its entire length. The oil-water mixture reduced the speed at which the capsules fell, and enabled more consistent video comparison.

Agitation of the cylinder was delivered manually, with a displacement of 18 cm from the center of the tube at a frequency of approximately one back and forth oscillation per second. A scaled paper grid was placed on the

floor below the center of the acrylic tube for the purpose of amplitude control while agitation of the tube was performed (Fig. 7).

3) Separation Test

The self-stabilizing CE was activated by placing it into a container filled with saline solution. Once the stabilizing component achieved its final swollen state it was manually removed from the container. Subsequently, a magnetic field was created with intensity in the 5-15Ampere-Turns range to which the expanded self-stabilizing CE was subjected to. The separation time and the needed force that resulted in physical separation between the capsule and stabilizing component were recorded.

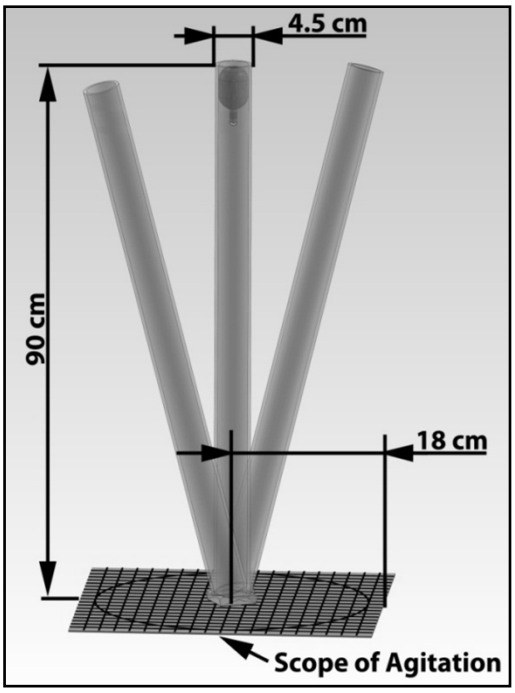


Fig. 7: Self-stabilizing CE-acrylic tube test.

J. Pilot Animal Testing

Two mongrel dogs (1M, 1F, 25.3+/-4.5 kg) were included in an acute testing of the stabilized and the non-stabilized capsules. Colon preparation involved a 48-hour liquid diet and the administration of phosphosoda enema in the morning before the surgery. At the end of the experiment the animals were euthanized with an intravenous injection of Euthanyl, (480mg/4.5kg, Bimeda-MTC Animal Health Inc., Cambridge, ON, Canada). This research was approved by the Life and Environmental Sciences Animal Care Committee, University of Calgary, Calgary, Alberta, Canada.

Each of the animals underwent an induction with an intravenous injection of thiopental (Thiotal 15 mg/kg IV, Vetoquinol Canada, Lavaltrie, QC, Canada) and was subsequently maintained on inhalant isoflurane and oxygen (Halocarbon Laboratories, River Edge, New Jersey, USA) with a vaporizer setting of 1-3%.

A laparotomy was followed by exteriorization of a 15 cm segment of the proximal descending colon while preserving intact the mesenteric innervations and blood supply. A 1-cm transverse full thickness incision was made in the colon 2 cm proximal to the beginning of the chosen colon segment.

A single CE, either with stabilizing component or without stabilizing component was inserted using forceps through the incision into the lumen of the colon. Subsequently, the incision was temporarily closed with 4-0 Dexon

suture (Covidien, Mansfield, MA) and 200ml saline was injected at the level of the capsule. Each animal was then administered an intravenous injection of Neostigmine (0.04mg/kg, APP Pharmaceuticals, Schaumburg, Illinois, USA) to speed up the transit time by inducing pharmacologically colonic peristalsis. The inserted capsule was propelled distally through the colon and expelled naturally through the anus as a result of the Neostigmine-induced colonic peristalsis. Upon the expulsion of the capsule through the anus, the video data which was collected by the RF receiver were transferred to the PC for further image processing. After the clearance of Neostigmine from the circulation, another capsule was administered in a similar manner. Ultimately, 2 such administrations per animal were sequentially performed, two with the non-stabilized and two with the stabilized capsules.

Results

A. Capsule Dimensions and Performance

The volume of the expandable component (polymer and mesh) was 0.9±0.5 ml before expanding and 67±7 ml after the expansion in water. The fully expanded volume in saline decreased to 54±5 ml. This was because the saline solution contained heavy ions, which slowed down the osmosis process and lowered the volume of the fully swollen expandable component The total volume of the self-stabilizing unit and the dry expandable stabilizing component) was in the 3ml range, which is very close to the volume of 2.7 ml of the Given's PillCam Colon capsule.

Prior to swelling each mesh had an oval shape of 5.5 cm length and a diameter of 4 cm. The expansion time was less than 1 min in water and less than 2 minutes in a saline solution.

The average maximum swelling pressure that the expandable component exerted on the colonic walls was measured to be 95±18 mmHg at 136 gram force per square cm, gf/cm2. This value is well within the pre-design constraints. The tensile strength of the mesh was 341±8 mmHg.

The minimized overall weight (5.1g) of the designed capsule endoscope allowed a common centroid axis for the capsule endoscope and the expanded implement.

The average operating time of the capsule endoscope prototype was 76 minutes and its total power consumption was 84 mW.The fully expanded capsule is shown in Fig.8.

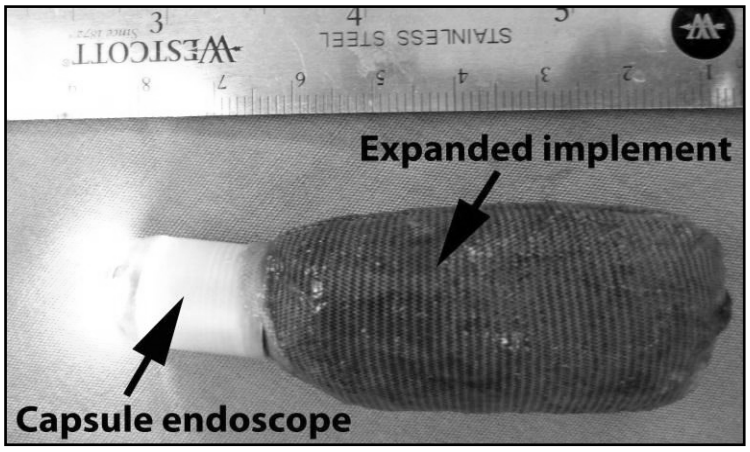


Fig. 8: Fully expanded self-stabilizing capsule endoscope. Due to its permeability, the stool-like tail swelled immediately after the degradation of the gelatin cover to provide stabilization to the imaging module.

B. Laboratory Test Results

1) Image Transmission Test

Continuous images were successfully transmitted from the capsule and were easily captured using wireless receiver without decrease in video quality.

2) Vertical Drop Test

A total of 30 laboratory video footages for each modality (stabilized and unstabilized) were collected for the vertical drop, resulting in 36 minutes of recorded video for the stabilized case and 22 minutes for the unstabilized.

The expandable portion of the stabilized capsule absorbed and attenuated the manually delivered agitation disturbances, which resulted in a minimal CE lateral movement during the agitation process.

It was clearly seen that that no tumbles have occurred in the stabilized case. Since the connection between the expandable stabilizing component and the capsule was rigid, the completed assembly was unable to deform permanently, and the CE self-stabilized itself during the agitation process.

In addition, the stabilized capsule showed significant improvement in image quality versus the non-stabilized capsule.

At no time in this testing did the stabilized capsule faced closely the cylinder wall because both the combined length of the capsule and the stabilization mechanism exceeded the diameter of the acrylic tube.

3) Separation Test

In each of the successful trials that were conducted, the expanded part separated from the capsule cap by means of gravity in less than 1.5 seconds after entering the created magnetic field. Ten trials were conducted with the complete separation mechanism, and the only failures of the system were identified to be due to poor workmanship, which was dramatically improved with the aid of a microscope. The initial difficulty was keeping close proximity between the heating filament and the PDS suture, without which the heat generated by the filament was able to dissipate through the small volume of air within the capsule. The microheater was determined to be entirely suitable for this application, with the only potential design challenge left being the reliability of its manufacturing. Fig. 9 shows the CE and the stabilizing component after the physical separation.

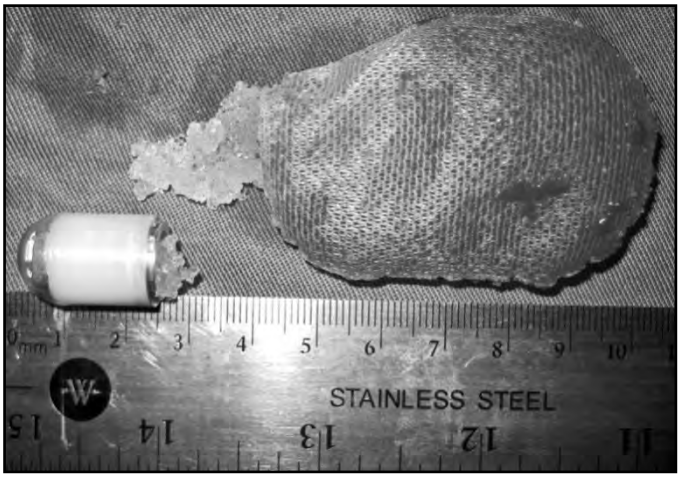


Fig. 9: Separated CE and stabilizing component.

Once the capsule was electronically separated, the average force that would result in physical separation of the device was in the range of 80gf. Thus, the peristalsis can complete the physical separation process after the electronic separation.

C. Results from the Pilot Animal Tests

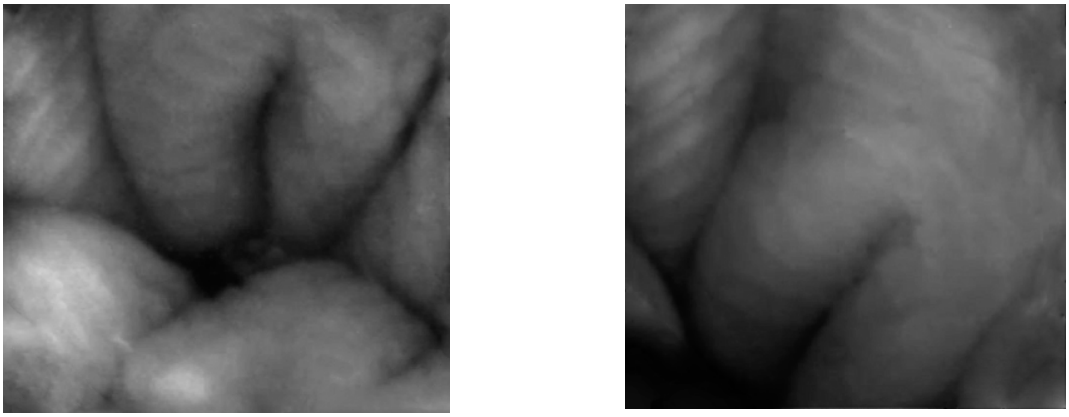
Totally, there were 4 video footages for each of the stabilized and the unstabilized cases, resulting in 28 minutes of recorded video for the former and 42 minutes for the latter.

The stabilized capsule did not miss vital intraluminal visualization of the colon during its distal peristaltic transit.

The unstabilized CE was rapidly changing its position and rendered some parts of the video completely unusable. In addition, the sensitivity of the CMOS imager was greatly decreased by this effect during peristalsis. It was evident that during rapid capsule repositioning (e.g. during rapid persistaltic activity) the stabilized capsule reacted quickly by stabilizing itself towards the centroid of the lumen.

In addition, it was observed that the unstabilized capsule faced directly the colonic wall during its tumbling movement. Thus, the unstabilized capsule could not systematically visualize the entire portion of the colon it was traversing. This inevitably resulted in missed areas.

A comparative example of images for the self-stabilizing capsule (a) and the non-stabilized CE (b) is shown in Figure 10.



(a) (b)

Fig. 10: Example of images for both modalities, (a) self-stabilizing and (b) non-stabilized CE)

At no time in this study did the self-stabilizing capsule tumbled within the colon. The simple reason for this was that both the combined length of the capsule and the stabilization mechanism exceeded the diameter of the lumen. Because the connection between the two was flexible, the completed assembly was unable to deform permanently, and the scenario in which the self-stabilizing CE could closely be facing the colonic wall became a geometric impossibility with the fully expanded stabilizing component.

Conclusion

The feasibility of self-stabilized capsule endoscopy has been demonstrated in laboratory and acute canine experiments. New self-stabilized capsule design was described. The goal of this study was the improvement of sensitivity of VCE in the colon. The proposed device has the capabilities to provide colonic images of quality comparable to the ones received from the small intestines using traditional VCE. In comparison with the conventional CE design, the proposed self-stabilizing CE delivered a significant improvement in canine colonic imaging. It has the potential to greatly improve quality of colonic imaging. Self-stabilized CE could be an alternative diagnostic modality for colon neoplasia screening. Further larger-scale clinical trials are needed to confirm and elucidate further the findings of this pilot study.

Acknowledgement

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