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Shape memory alloy–based biopsy device for active locomotive intestinal capsule endoscope

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Abstract

Recently, capsule endoscopes have been used for diagnosis in digestive organs. However, because a capsule endoscope does not have a locomotive function, its use has been limited to small tubular digestive organs, such as small intestine and esophagus. To address this problem, researchers have begun studying an active locomotive intestine capsule endoscope as a medical instrument for the whole gastrointestinal tract. We have developed a capsule endoscope with a small permanent magnet that is actuated by an electromagnetic actuation system, allowing active and flexible movement in the patient's gut environment. In addition, researchers have noted the need for a biopsy function in capsule endoscope for the definitive diagnosis of digestive diseases. Therefore, this paper proposes a novel robotic biopsy device for active locomotive intestine capsule endoscope. The proposed biopsy device has a sharp blade connected with a shape memory alloy actuator. The biopsy device measuring 12 mm in diameter and 3 mm in length was integrated into our capsule endoscope prototype, where the device's sharp blade was activated and exposed by the shape memory alloy actuator. Then the electromagnetic actuation system generated a specific motion of the capsule endoscope to extract the tissue sample from the intestines. The final biopsy sample tissue had a volume of about 6 mm^3, which is a sufficient amount for a histological analysis. Consequently, we proposed the working principle of the biopsy device and conducted an in-vitro biopsy test to verify the feasibility of the biopsy device integrated into the capsule endoscope prototype using the electro-magnetic actuation system.

Keywords

Biopsy device, capsule endoscope, shape memory alloy, electromagnetic actuation system

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Introduction

In recent years, the technology of capsule endoscope (CE) has become a common solution for the investigation and diagnosis of various diseases in the gastrointestinal (GI) tract. The untethered CE is the size of a pill that can be swallowed and passively moved by the peristaltic motion of the digestive organs. Video images of the GI path are captured with the CE's tiny high definition camera, and the captured images are then transferred to one portable receiver device through the CE's telemetry module. The transferred images are recorded and provided to medical doctors for the diagnosis of digestive diseases. Commercialized CEs include PillCam (Given-imaging, Israel), OMOM (Jinshan, China),[1] Endo capsule (Olympus, Japan),[2] and MiRo (Intromedic, Korea).[3] The peristaltic motions of digestive organs move these CEs passively through the GI tract, where they capture images or sense some physiological parameters such as pH value and temperature. Owing to this passive motility, most CEs have limited applications restricted to tubular organs such as the esophagus and the small intestine.

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For the investigation of the whole GI tract, an active locomotive intestinal capsule endoscope (ALICE) should be developed. We previously reported an ALICE actuated by an electromagnetic actuation (EMA) system.[4,24] Because the ALICE has a small permanent magnet, it could be manipulated through the magnetic field from the EMA system. Consequently, the ALICE showed an active and flexible movement in the patient's gut environment. However, for the definitive diagnosis of digestive diseases, various functions such as biopsy and drug delivery should be developed and integrated into the ALICE.

In this article, we focused on a biopsy function which can be incorporated into the ALICE. Generally, a polypus in a digestive organ should be extracted using a biopsy function, and the sampled tissue should be histologically analyzed to check whether the tissue is malignant. Many researchers have previously reported several capsular biopsy tools. First, Kong et al.[5] proposed a wireless biopsy module with a rotational tissue-cutting razor which is attached to a torsional spring and triggered with a paraffin block. The module can operate the following sequential procedures: extracting the tissue using the quick rotation of the cutting razor and then sealing and fixing the extracted tissue, where the biopsy module dimension is small enough (10 mm in diameter and less than 2 mm in thickness). Park et al.[6] proposed a micro biopsy spike which was fabricated through the conventional *Lithographie, Galvanoformung, Abformung* (Lithography, Electroplating, and Molding) (LIGA) process and triggered by a shape memory alloy (SMA). The micro biopsy spike was moved forward and backward using a slide-crank mechanism. However, the above two biopsy tools can extract only a small amount of tissue, and it is not yet clear whether they produce a sufficient sample volume for accurate external histological analysis. In addition, the insufficient reaction force from the biopsy mechanism acting on the tissue may jeopardize the extracting effectiveness of the biopsy sample. Therefore, anchoring biopsy modules were introduced with complete visual guidance.[7] This type of module may solve the above problem of the reaction force, but technical challenges remain. In particular, it requires a wired external power supply since four SMA actuators and the trigger components consume too much energy to be supplied by a battery in a CE. In addition, Simi et al.[8] proposed a wireless biopsy capsule (9 mm in diameter and 24 mm in length) which used a magnetic torsion spring, a cylindrical blade, and a hole in the capsule body. The biopsy device is triggered by a big external permanent magnet combining with one concentric couple of fixed and freely rotated cylindrical permanent magnets inside the capsule. However, the biopsy capsule is too large in size and is hard to be integrated into a CE. In addition, for attracting and cutting procedures, because the biopsy device with fixed and freely rotated cylindrical magnets is controlled by an external magnet, it cannot show a flexible motion by the external magnet.

In this article, we propose a biopsy device actuated by SMA which can be incorporated into an ALICE using an EMA system. The biopsy device has a razor blade which can be opened and closed by SMA and two small magnets. The biopsy device was integrated into an ALICE prototype using an EMA system. First, the ALICE prototype was positioned to the target lesion using the magnetic field generated by the EMA system. Second, the biopsy device's razor blade was opened, and the rotational motion for the extraction of the tissue was executed using the generated rotational magnetic field. Finally, when the razor blade was closed, the extracted sample tissue was reserved inside the biopsy device. The proposed ALICE can solve the reaction force problem between the cutting tool and the lumen wall. In addition, it has the ability to extract a sufficient amount of tissue for histological analysis. We evaluated the feasibility of the proposed biopsy device actuated by SMA through the locomotion and the biopsy operation of the ALICE prototype.

Material and methods

ALICE

Considered a disruptive technology, a CE has been used for diagnosis in digestive organs. However, because of its passive locomotion that relies on the peristalsis motion of digestive organs, its use was limited to small tubular digestive organs, making it ineffective in large digestive organs, such as the stomach and the colon. Therefore, in our previous research,[4] we developed an ALICE for the diagnosis of the whole GI tract. The ALICE consists of an EMA system[9] and a CE with a small permanent magnet. We demonstrated the complex motions of the CE for diagnosis and verified the feasibility of the ALICE system. The ALICE has a tubular shape, resulting in easy access to the patient, and achieves a 5-degree-of-freedom (DOF) basic motion. In addition, through the flexible motion of the CE, it is possible to closely scan the inner wall of the GI tract and thereby improve diagnostic efficiency. In this article, we developed a biopsy tool and tried to integrate it into the ALICE to allow the biopsy process to occur simultaneously with the investigation operation. The ALICE with a biopsy tool can also be driven by the EMA system. In addition, the EMA system consists two parts: part 1 is composed of one pair of Helmholtz coils and two pairs of uniform saddle coils which are fixed perpendicularly to each other in the x-, y-, and z-axes; part 2 is composed of one pair of Maxwell coils and one pair of uniform gradient saddle coils.[9,10] These coils generate a uniform magnetic field to align the CE and generate a uniform gradient magnetic field to

propel CE. Each coil pair was connected to a power supply MX12 (3EA) from California Instruments (USA), which was controlled by a peripheral component interconnect (PCI) controller with LabVIEW software (National Instruments, USA).

ALICE prototype with biopsy device

Design consideration of biopsy device

Most CEs are shaped liked pills and consist of one camera, illuminating light-emitting diodes (LEDs), integrated sensors, programmed electronics, wireless communication, and a battery for power.[11] The biopsy device for CE should satisfy the following requirements. First, the biopsy device should be sufficiently small enough to be integrated into a swallowable CE. In this article, we aimed for the prototype to have a similar size as the PillCam COLON video capsule with a diameter of 12 mm and a length of 33 mm because it has been approved by the US Food and Drug Administration (FDA). Second, to realize the biopsy function, the CE should have a localization method and move to a desired target position. That is, the biopsy device should be integrated into the ALICE for the realization of the biopsy function. Third, the biopsy tool must have the ability to be activated and stabilized during the sampling process. After the tissue sampling, the biopsy device should be unactivated and the sampled tissue should be stored. Fourth, the biopsy mechanism should provide a sufficient cutting force to extract tissue samples. From human cadaver trials, it was reported that GI tract tissues have an average destructive stress of 20 MPa at the tool–tissue interface.[12] Fifth, the sampled tissue must have a sufficiently large volume (at least 1 mm^3) for a doctor to histologically analyze,[13,14] and it is usually necessary to have several biopsy specimens in order to avoid diagnosis misinterpretation.[15,16] After the extraction of the tissue sample, the biopsy sample should be preserved safely in the CE with fixating solution in order to remove the contamination of the biopsy tissue.[17] Sixth, because CEs are operated by a small, coin-type high-rate lithium battery, the power consumption of the biopsy device should be minimized. Finally, the biopsy device should provide a safe sampling mechanism without the risk of lumen perforation.[18]

Design of SMA-based biopsy tool

Figure 1 shows a design of our proposed biopsy device and a schematic design of the ALICE with the biopsy tool. In the schematic design of Figure 1(a), the proposed biopsy tool should be designed to integrate into the ALICE, which includes two permanent magnets for EMA. The ALICE was manipulated by our proposed EMA system, as shown in Figure 2. The EMA system consists of one pair of Helmholtz coils, two pairs of uniform saddle coils, and one pair of Maxwell coils. The

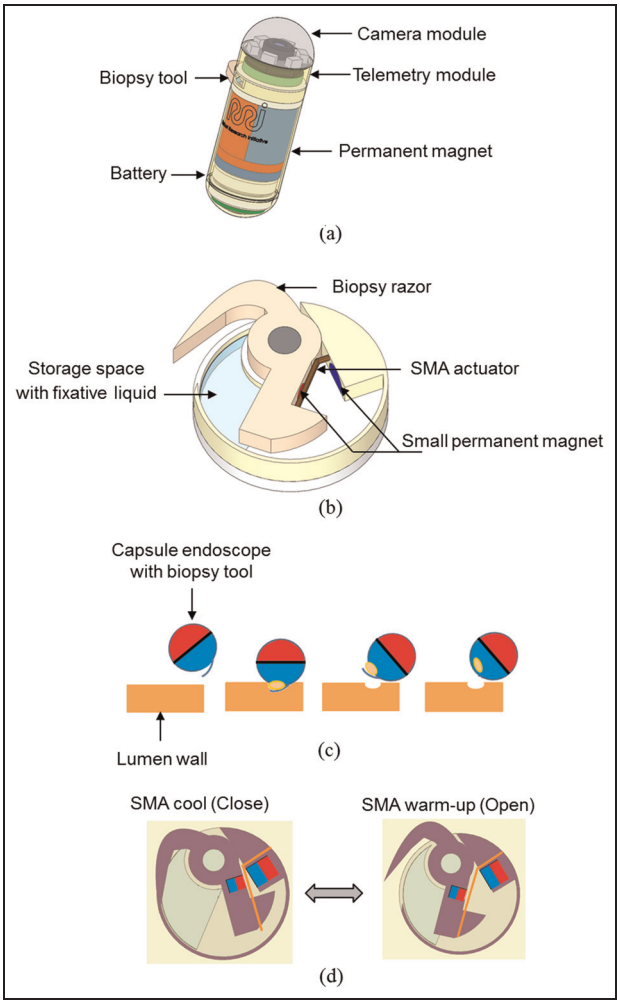

Figure 1. Design of proposed biopsy device of active locomotive capsule endoscope: (a) schematic ~ design of active locomotive capsule endoscope with biopsy tool, (b) design of biopsy tool with SMA actuator and magnets, (c) concept of biopsy procedure, and (d) working principle of tissue-cutting razor.

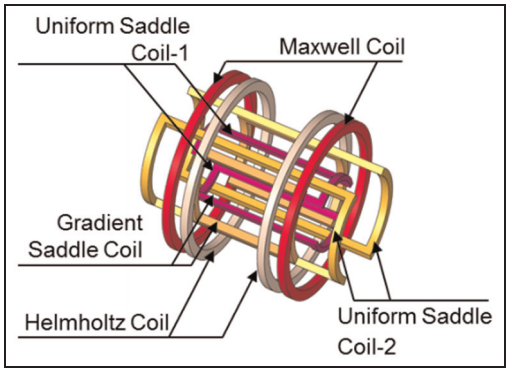

Figure 2. Schematic representation of EMA coil system.

biopsy tool depicted in Figure 1(b) consists of a tissue-cutting razor connected with an SMA actuator, two face-to-face small magnets for the restoration of the biopsy mechanism, and a storage space for the biopsy sample tissue with fixative liquid. Figure 1(c) illustrates

the biopsy procedure of ALICE with the biopsy tool, and Figure 1(d) shows the open and close mechanism of the tissue-cutting razor through SMA actuation. In detail, first, through the generated magnetic field of the EMA system, the prototype actively moved to a target lesion. Second, the biopsy razor tool was opened by SMA actuation. Third, when the prototype was rotated by the rotating uniform magnetic field, the biopsy tissue sampling procedure was executed, and the sampled tissue was kept inside the storage space which may be filled with the fixation liquid.[17,19] Finally, the biopsy razor tool was closed through the restoration magnets. Generally, most clinically suspected lesions in a small intestine are located within 1.0–2.0 mm depth.[20,21] Therefore, the proposed biopsy device was designed with its storage space about 157 mm^3, which has the thickness of 2.0 mm and the diameter of 10.0 mm, in order to store more than 10 times extracted tissue samples.

Since the volume in the CE is too small and the energy for the CE is also strictly limited, the selection of the actuator for a biopsy tool is very difficult. In addition, according to the guidance document of FDA about the GI capsule imaging system,[22] the material to build the CE should be biocompatible, electrical and mechanical safe, cause no change in chemical reaction in digestive environment, functionally reliable including structural integrity, and cause no intestinal obstruction or injury and misinterpretation of the captured image. Considering these requirements, an SMA actuator can be a promising candidate which satisfied all the mentioned requirements. It has been already used widely in clinical applications such as implant materials for bone-cells, surgical devices, and minimal access surgery or in orthopedic application.[23] Since it also shows a reliable and smooth response, we selected the wire-type SMA actuator as an actuator for the biopsy tool. The SMA actuator of various types with different dimensions can be purchased on the commercial market. Due to the limitation of the battery energy for the biopsy process, the SMA actuator should have low energy consumption. Therefore, we selected the nickel–titanium SMA with a small diameter of 0.08 mm and the length of 7 mm. The chosen SMA wire needs a power of 19.57 W to be activated and consumes about 14.5–24 mWh, which is 2.5%–5.0% total energy of cell battery 3.0 V, 160 mAh (475 mWh), for each biopsy process which often takes about 3–5 s. Before attaching the SMA actuator to the biopsy razor, the SMA wire should be pre-formed as a straight wire type. In the extraction procedure (Figure 1(c)), a small current was supplied to the SMA actuator, which returned to its straight wire shape and exposed the razor blade. When the biopsy process was completed, the applied current to the SMA actuator was removed, and the biopsy razor returned to its initial position by the restoration magnets, as shown in Figure 1(d).

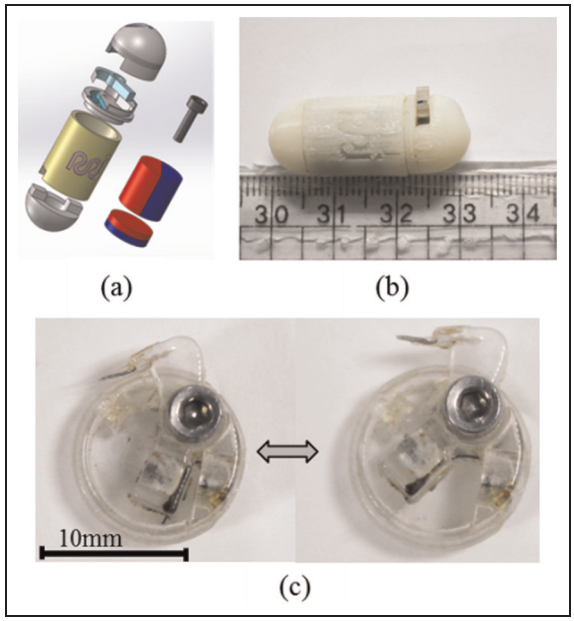

Figure 3. Prototype of biopsy device for ALICE: (a) schematic design of ALICE with biopsy device, (b) ALICE prototype with biopsy device, and (c) SMA-based biopsy tool.

Design and fabrication of ALICE prototype with biopsy device

To extract biopsy tissue, the razor tool should generate a shear stress larger than the destructive stress of the tissue (τ_{des} = 20 MPa).[12] The resulting shear stress (τ_{ex}) induced by the razor tool was calculated by the following formula

$$\tau_{ex} = \frac{F}{t \times s} \quad (1)$$

where F denotes the cutting force acting on the tissue, and t and s are the thickness and width of the razor, respectively. To reduce the cutting force, the values of t and s need to be minimized; in other words, we need to design and fabricate a sharp razor with a small width. In this proposal, we selected a razor tool with a thickness of t_1 = 0.1 mm and a sharp end thickness of t_2 = 0.03 mm, similar to a shaving razor. The necessary volume of the biopsy tissue sample is known to be about 1 mm^3, and the razor width was selected as s = 1.5 mm. After the selection of the main design parameters of the biopsy device, an ALICE prototype with the biopsy device was designed and manufactured. The capsule chassis was fabricated by a rapid prototyping three-dimensional (3D) printer with the real dimensions. All other components including a razor blade, a SMA actuator, and two permanent magnets were assembled. Figure 3 shows the fabricated ALICE prototype with the biopsy device. Figure 3(c) and the sub-material clip show the closed and opened status of the razor tool of the biopsy device.

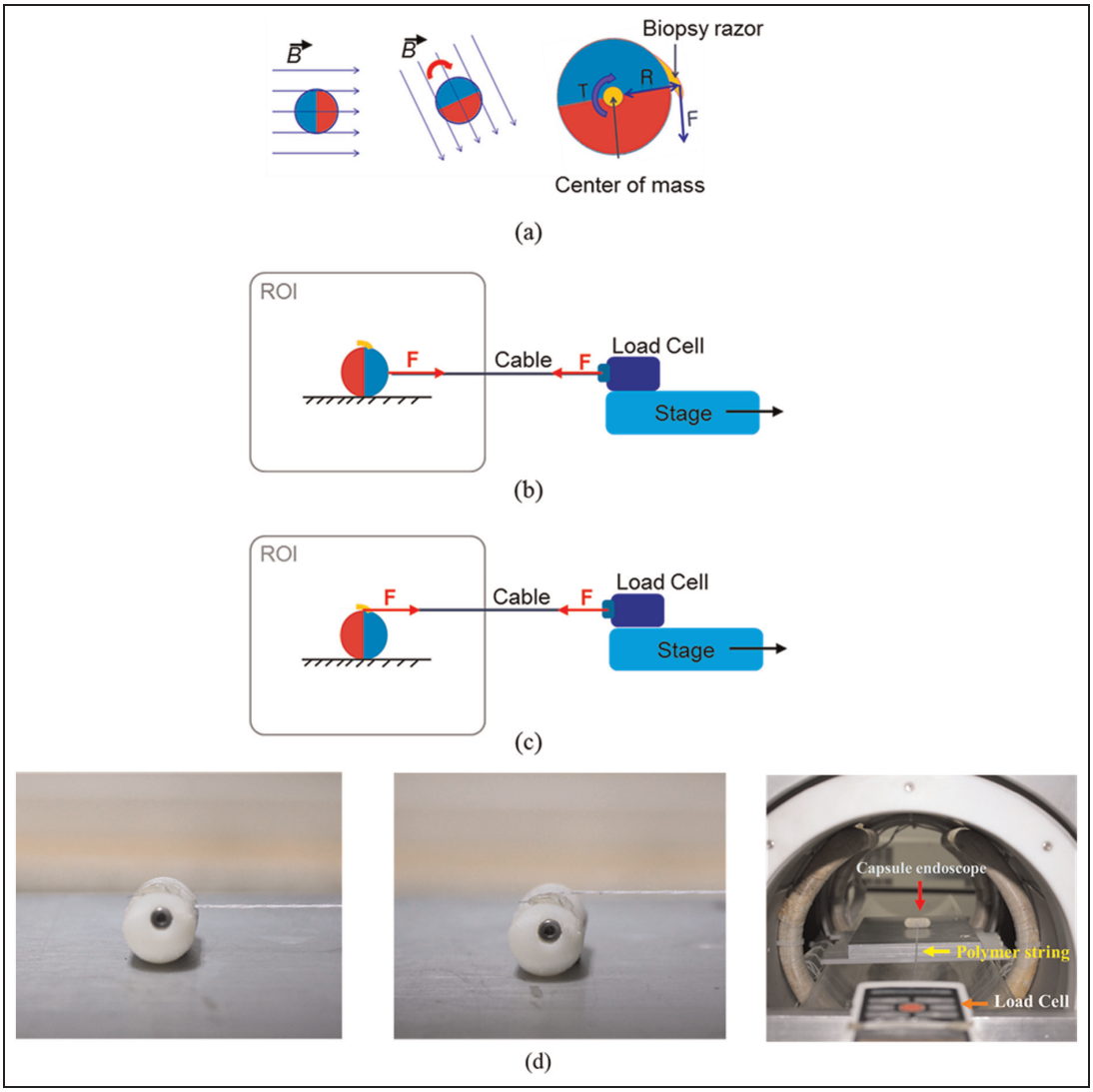

Figure 4. Schematic representation of experimental setup: (a) rotational torque and cutting force through th erotation of uniform magnetic field for biopsy device, (b) propulsion force measurement, (c) cutting force measurement, and (d) experimental setup with EMA system and load cell.

When we designed the biopsy tool with the given razor dimensions, we could estimate the necessary punching force through the lumen wall ($F \geqslant \tau_{des} \times t_2 \times s = 0.9\,\mathrm{N}$), the necessary cutting force to extract the tissue ($F \geqslant \tau_{des} \times t_1 \times s = 3\,\mathrm{N}$) from equation (1), and the destructive stress of the tissue ($\tau_{des} = 20\,\mathrm{MPa}$).

In order to extract a biopsy sample, the ALICE has to create active and complex motions and has to have enough large pushing force and rotational torque on the intestinal wall. When we introduced our previously developed EMA system[10,24] in Figure 2, the magnetic fields near the center of the Helmholtz and Maxwell coils are described as follows

$$\vec{H}_{\mathrm{Helmholtz}} = [\,d_h \quad 0 \quad 0\,]^T \tag{2}$$

$$d_h = 0.715 \frac{i_h n_h}{r_h} \tag{3}$$

$$\vec{H}_{\mathrm{Maxwell}} = [g_m x - 0.5 g_m y - 0.5 g_m z]^T \tag{4}$$

$$g_m = 0.641 \frac{i_m n_m}{r_m^2} \tag{5}$$

where i_h and i_m are the current intensities; r_h and r_m are the coil radii; and n_h and n_m are number of turns of the Helmholtz and Maxwell coils, respectively.

To create the cutting torque of the biopsy tool, the EMA system generates a rotational uniform magnetic field, as shown in Figure 4(a), where the generated torque on the capsule with a permanent is calculated by

$$\tau = V\mathbf{M} \times \mathbf{B} \sin\theta \tag{6}$$

where V and $\mathbf{M}$ are the volume and the magnetization of the permanent magnet, respectively. θ denotes the angle between the magnetization direction and the magnetic field, and $\mathbf{B}$ is the magnetic flux which is defined as: $\mathbf{B} = \mu_0 \mu_r \mathbf{H}$, where μ_r is the permeability of the environment surrounding the magnet, μ_0 is the permeability

of the vacuum, and **H** is the intensity of the magnetic field.

The rotational torque of the capsule can be converted to the cutting force ($F_{cutting}$) of the biopsy razor tool as

$$F_{cutting} = \frac{\tau}{R} \tag{7}$$

where R is the distance from the center of the permanent magnet to the tool razor.

In addition, the propulsion force ($F_{propulsion}$) of the ALICE can be expressed as follows[4,24]

$$F_{propulsion} = \frac{0.3616\mu_0 \mathbf{M} V i_m}{r_m^2}\left(cos\theta\hat{i} + sin\theta\hat{j}\right) \tag{8}$$

As shown in Figure 1(a), we adopted two cylinder-shaped neodymium (NdFeB) permanent magnets with the magnetization value of **M** = 1,990,000 A/m. One magnet magnetized in the radial direction has a diameter of 10 mm and a height of 10 mm. Another magnet magnetized in the axial direction has a diameter of 10 mm and a height of 3 mm.

Experiments

Preliminary evaluation of ALICE prototype with biopsy device

First, it is necessary to evaluate the feasibility of the ALICE prototype with the biopsy device. For the biopsy procedure, the propulsion force and the cutting force of the ALICE prototype with the biopsy device are very important. Figure 4(b) and (c) shows the schematic representation of experimental setups for measurements of the propulsion force and the cutting force, respectively. Figure 4(d) shows the experimental setup using the load cell (Advanced Digital Force Gauges Series 5; Mark-10, USA). Basically, a load cell and a linear stage were installed, and the ALICE prototype was connected with the load cell using an inextensible cable. In order to eliminate the magnetic field effect on the load cell, the load cell was located outside the region of interest (ROI) in the EMA system. As shown in Figure 4(b), because the cable was connected with the center part of the ALICE prototype, we could measure its propulsion force which could push the capsule into the tissue. Figure 4(c) shows the experimental setup for the cutting force measurement, where the razor tool of the ALICE prototype was connected with the load cell through the cable. In addition, the cutting force and the propulsion force can be estimated by equations (7) and (8), respectively. Figure 5(a) shows the propulsion force of the ALICE prototype according to various applied currents of Maxwell coils. When the current of 5.4 A was applied to the Maxwell coils, the maximum propulsion force was measured about 0.20 N, where it was estimated as 0.22 N in the simulation. Figure 5(b) shows the cutting force of the ALICE prototype according to various applied currents of Helmholtz coils and

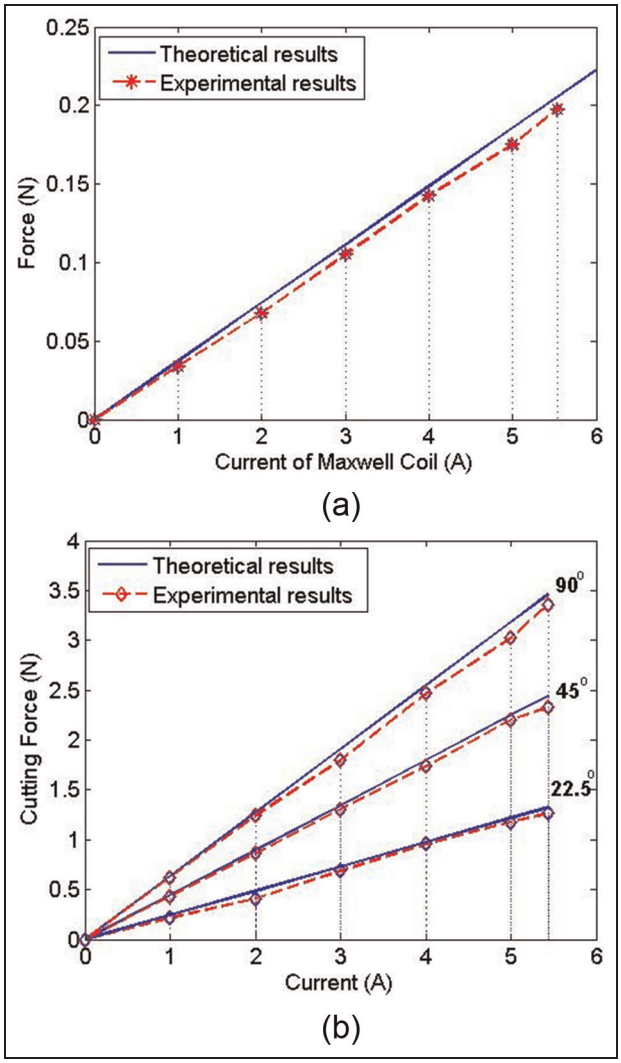

Figure 5. (a) Propulsion force of capsule endoscope created by magnetic field of Maxwell coil pair in EMA system and (b) cutting force of biopsy tool created by magnetic field of Helmholtz coil pair and uniform saddle coils.

different aligned angles. When the align angle was 90° and the maximum voltage (5.4 A) was applied, the maximum cutting force was generated. The maximum cutting force was measured as 3.36 N, and the estimated cutting force was 3.46 N. The measured force was larger than 3 N, giving us confidence in the feasibility of the biopsy process. The differences between the experimental results and the simulation results can be caused by the friction effect of the bottom surface and the fabrication error of the EMA system.

In vitro tests of ALICE prototype with biopsy device

We executed the feasibility test of the ALICE prototype with the biopsy device through an in vitro test. For the in vitro experiments, a segment of a small intestine from a pig was extracted and placed within the ROI of the EMA system. First, we demonstrated the flexible locomotion of the ALICE in the small intestine

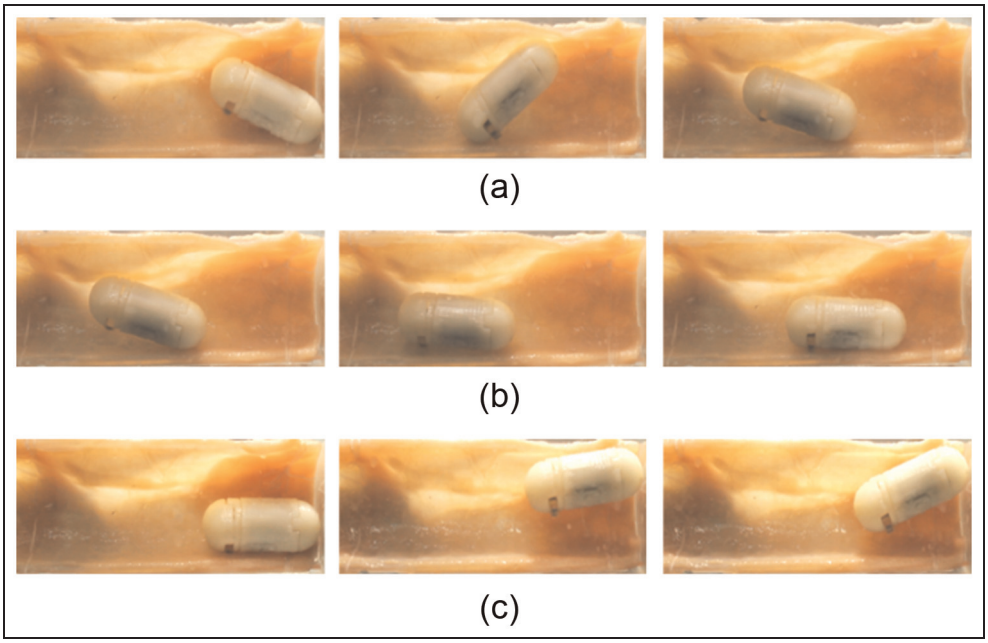

Figure 6. In vitro locomotion of capsule endoscope in small intestine environment: (a) zigzag orbit locomotion, (b) backward locomotion, and (c) flying locomotion to upper part.

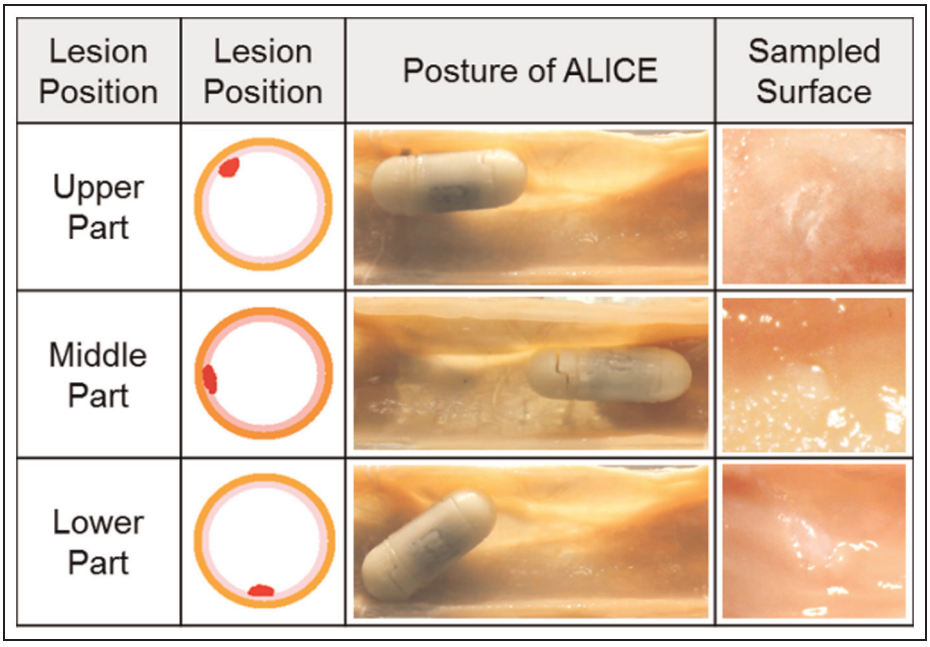

Figure 7. Biopsy process of ALICE in various positions of intestine.

environment. As shown in Figure 6, we demonstrated three kinds of locomotion, namely, the zigzag orbit locomotion, backward locomotion, and flying locomotion to the upper part. Through the various motions of the ALICE prototype, the capsule was moved to the target lesion.

Second, we executed the biopsy procedures using the ALICE prototype with the biopsy device at the three target positions: the upper part, middle part, and lower part of the small intestinal segment. Through various positioning tests of ALICE with the biopsy tool, we confirmed that the biopsy tool can be positioned with high accuracy within the range of 2.5 mm. Therefore, we could consider that the positioning accuracy of ALICE with the biopsy tool was sufficiently accurate for a biopsy process. Figure 7 shows the biopsy procedures, such as the posture of the ALICE and the final sampled surface. The sampled tissue extracted by the razor tool was stored in the storage space of the biopsy device.

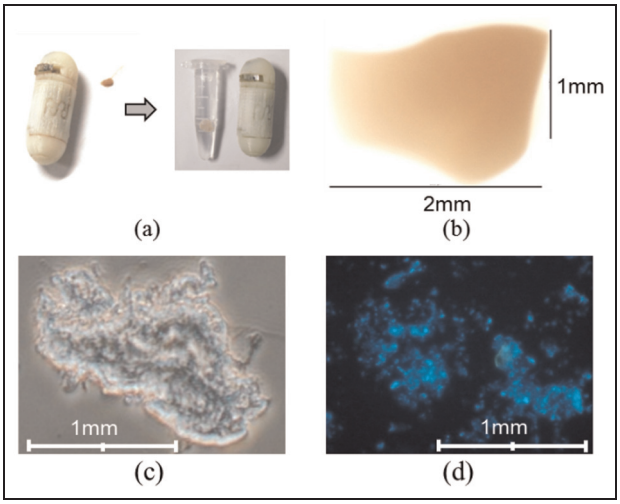

Figure 8. Analysis of biopsy tissue sample: (a) extraction of biopsy tissue sample, (b) size measurement, (c) microscopic image, and (d) fluorescent image.

Finally, as shown in Figure 8(a), after the extraction of the biopsy tissue sample from the biopsy device, the sampled tissue was characterized. For the volume measurement of the extracted biopsy tissue, it was imaged by a microscope and measured by a digital ruler, as shown in Figure 8(b). We found that the sampled tissue had a volume of about $6\,mm^3$ ($2\,mm \times 1.5\,mm \times 2$ mm). In addition, for more histological analysis of the biopsy tissue, a piece of the sampled tissue was put into a tube of phosphate-buffered saline (PBS) and homogenized through an ultra-sonication. After the centrifugal process of the sample tube, the supernatant was removed, and the sampled tissue was suspended in a solution of PBS and 4′,6-diamidino-2-phenylindole (DAPI) in a dark environment. We removed the remaining solution from the tube and obtained a tissue pellet. After suspending the tissue pellet in PBS, 1 μL of tissue suspension was placed on a glass side with a cover slip and investigated by a microscope. Figure 8(c) shows the bright field microscopic image, and Figure 8(d) shows the fluorescent microscopic image. Because the blue color in Figure 8(d) denotes the fresh animal cells in the sampled tissues, we confirmed that the ALICE with the biopsy device can execute biopsy functions to collect biopsy tissues that can be used for additional histological analysis.

Conclusion

In this study, we proposed an SMA-based biopsy device which can be integrated into the ALICE. The ALICE was controlled by the external EMA system and showed flexible locomotion and investigation of the GI tract. The ALICE prototype with the biopsy device was developed and evaluated through in vitro tests. The ALICE prototype with the biopsy device could move to the target lesion, and the SMA actuator could open the biopsy tool at the right time to extract the biopsy tissue and close it for to store the sampled tissue which may prevent damage of the sampled tissue from the intestine's digestive environment. It processed the extracting operation continuously with little amount of energy and solved the reaction force problem between the cutting tool and the lumen wall. Consequently, we expect that this study on the SMA-based biopsy device for the ALICE can be not only directly used in the extracting biopsy sampling but also applied to biomedical instruments as well as micro-surgical operational tools.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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