Testing and Evaluation of Foldable Biopsy Tools for Active Capsule Endoscope

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***Abstract*—This paper describes the development of passive foldable biopsy tools and the improvements of active capsule endoscope as future medical devices for intestinal inspection. The present's active locomotive capsule endoscope is a micro-robot that can travel along the way of the digestion system with wireless control and position abilities. The capsule endoscope has been integrated with novel micro-biopsy tools armed to extract tissue samples from the small and larger intestine. The entire capsule system has abilities of target random biopsies at any position of the intestinal system by magnetic control and shortly 3D sensor localization and position methods. The Active capsule endoscope system could reach the target place, be controlled at real-time by the doctor, and be able to cut-off and keep on-board of its body's as much as possible of intestinal tissue for further analysis. The biopsy mechanism is a novel passive triggered mechanism with a highly accurate magnetic actuator for positional control and localization.**

I. Introduction

Nowadays, wired endoscope process consisted of unplaced devices of around 2 meters that travel along the way of the digestion system via natural orifices. One alternative and relatable comfortable is the capsule endoscope that can travel and take several pictures in the entire digestion system or until its battery last (around 10 hours depending on the configuration for each factory). Since 2002, a commercial version of capsule endoscope was widely released into the medical market like Korean Miro Pill and PillCam, Olympus EndoCapsule (Olympus, Japan), Given Imaging (Yokneam Israel), OMOM capsule endoscope (jinshangroup, China), and several other [1].

The capsule endoscopy systems usually use wearable sensors, video analysis software and data acquisition devices. About 55,000 images are take/sent thrown the devices during a typical lower bowel CE procedure that later are them post-processed [2]. Clinicians are unable to observe these entire procedures in real-time leading to the development of CE image processing typically produced by the capsule manufacturer. These capsule endoscopes are normally deal with gastrointestinal (GI) diseases examination on upper or lower visual endoscopy procedure on the small and large intestine. Unfortunately, the whole capsule endoscopes have a similar disadvantage in terms of (active/passive) locomotion where all of them exclusively travel by peristaltic motion of the human digestive system. [27][28] This passive locomotion in term of control, speed and precise position of affected areas will soon make them relatively useless due to lack of orientation and number of pictures in the abnormal region on the intestinal system. Several alternative systems on these difficulties have been reported by developing an active motion in the capsule endoscope (CE) by driven with external electromagnetic actuation system [3] [4] [5] [6] [7].

Taking advantages of the actual technology, the new generation of capsule endoscopes should carry on-board multi-functional tools like a biopsy, drug delivery, tattooing, etc. Doctors require being able to solve critical priorities of endoscopy procedure when are treating gastrointestinal diseases, defining abnormal cell or areas; and mainly, absorb any tissue sample for further analysis given back a mark location of the affected area in the small and larger intestine for further operation.

Several conceptual designs for active capsule endoscopes with biopsy functions or drug delivery system (DDS) had been reported, where almost all of them are promising soon. [21] [23] One alternative presented with an elastic element called magneto-mechanical that can be loaded remotely by varying the magnetic field surrounding it. It is capable to store and release its energy by mechanical spring and be activating externally. This proposal micro-robot stored multiple samples of about 1 mm3 thanks to one reservoir underneath of its cylindrical rotating blade [8]. The mechanism is achieved by rotation of two axial permanent magnets, where one of them is locked on its body and the other generates the turn by a highly magnetic field.

Another alternative is mechanically powered micro-motor actuator with a biopsy tool placed in a cylindrical body shape acting as a capsule. Its biopsy tool has the ability to stretch into to affected area bite, cutting off and return with a small amount of tissue to body´s capsule; all these processes are doing automatically [9]. Further design most presented due to the size is relatively large considering the regulations approved by food and drugs administration in 2001, but, its applications focus exclusively in the large intestine.

Another biopsy micro actuator idea for capsule endoscope was development with the cylindrical shape of 10 mm diameter and 18 mm length. Its actuator is founded in a spring locked by polymer string; when the target is selected the actuation is executed by heating an SMA wire that makes the

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polymer to meld resulting on triggered micro-spike moved forward and backwards using a slider-crank mechanism [10]. The SMA (shape memory alloy) is the most promising material as a bidirectional actuator device for active capsule endoscope with biopsy tools. Its characteristics and relatable small size permit to locate it in a very narrow space. We had used SMA as an alternative of an active actuator connected with a razor-sharp blade. This biopsy device measuring 12mm in diameter and 3mm in length was integrated into a capsule endoscope prototype. Furthermore, the electromagnetic actuation (EMA) system generated a specific algorithm motion affected directly the capsule endoscope orientation, resulting in cut and store one small sample of tissue from the intestines. [11] [29] [30]

We had reported a micro-hydraulics conceptual design of modular capsule endoscope with biopsy tools placed next to the camera, due to the necessary expectation of the doctor and procedure [12] [13]. Now, this paper present the further development of the capsule endoscope system merged the conceptual platform of passive/active locomotion, the integration of passive biopsy tools powered by an external magnetic actuator (EMA). This new capsule endoscope can navigate to specific targeting lesion in the intestinal system, and then deploy the biopsy tools to extract and store a specific amount of tissue sample for further analysis. The method of biopsy collected material is compatible with pill-shaped capsule endoscopes which are already commercialized. Several experiments in-vitro and in-vivo were carry-out to test the performance of the tools. The animal test was conducted on a pig stomach to evaluate the feasibility and the potential ideas of the biopsy tools with successfully results presented in this paper.

II. Capsule Design Specifications

The new capsule endoscope is required to be combining with vision system, wireless communication unit, batteries or energy source and biopsy tools. All of these features most be packet into pill-size with external bio-materials container. The capsule aims to meet the restrictions and/or conditions approved by food and drugs administration (FDA) wherein 2001 the size approved was (11mm in diameter, 26 mm in length) for use in adults and in 2003 was accepted to use in children older than 10 years [14]. Recently, PillCam-Colon received clearance under the direct of Novo classification for devices with low to moderate risk that has not yet established on the market. These dimensions are been stretched and approved by FDA to (12 mm diameter, 33 mm length) in 2013 for use in adults within the condition of a capsule endoscope. The risks of capsule endoscope size include capsule retention, aspiration and skin irritation. The risks associated with colon preparation are allergies or other known contraindication to any preparation agents or medications used for the PillCam-Colon regimen, according to laxative medication labelling and per physician discretion [15].

Nevertheless, based on a wireless capsule endoscope develop the new goals is not just miniaturization of one camera and lighting system squeezed in a pill-sized; the aim is to step further the capsule from passive motion to active motions through the digestive system, enables visualization of the GI tract without discomforts and hopefully carry all the features on-board. [22] [25] The present research is expecting to carry and deploy biopsy tools and take and collect tissue´s samples without breaking the regulations of size for low or moderate risk.

The actual capsule is loading with wireless communication module built to send 3 to 12 pictures per seconds trough human body and then been captured by with several electrodes-cups placed around the patient abdomen, similar to long-term electrocardiogram exams and stored. The ideal solution is to have a real-time image´s capture while the capsule is swallowed in the digestion system; the peristaltic motion rates about 1–2 cm/min. however, better images quality is possible but is also necessarily an automated brightness control of around 4 to 6 white led lights that would affect battery consume vs. working time (around 10 hours). Besides, batteries that take about 50% of the actual capsule inner space or can be replaced or mix with energy source transmitted wirelessly by an external electro-magnetic system or any other source.

The advantage of having an active capsule endoscope is to be able localized, manipulate and control wherever the medical doctors require to be focus-on the affected areas of GI tract; these could be given by the electromagnetic actuation (EMA) system as an energy source; optimistically with a micro-magnetic 3D sensor (not implemented yet) to avoiding the risk of unlucky perforation, loss localization in GI track and/or retention. [14] [26]

Computing the collected images requires a software recognition that would support the endoscopy´s doctor to identify suspicious damage areas of the GI tract. The bowel preparation procedure is similar to the traditional flexible wired endoscopy, it requires ingestion of a strong laxative to ensure adequate bowel cleanness and facilitate the progression of the capsule through the GI tract.

Tissue cutting pressure is necessary to be considered to deploy the biopsy tools in the affected area, collect the maximum size of tissue samples (at least 5 mm3) and ensure a sufficient force for an efficient cut of slide-test; this force is being experimented by the reference (about 10N) [10]; besides, the tissue sample must be kept in a capsule´ reservoir for further analysis and to avoid altering the diagnostic it must store up to 24 h on gauze soaked with liquid solution [10] [24].

III. Wireless Actuation and Control by EMA System

With a specific arranges the electromagnetics coils are one of the most used wireless technologies in medical applications and until now is the most successful way of power and control micro-robots. The reason of uses wireless systems as actuators is due to the microrobot cannot have enough room to store batteries, sensors and actuators where electromagnetic actuation (EMA) system can effectively solving some of the problems. EMA system could be combined in 2D, 3D electromagnetic coils arranged at 90 degrees with at least one pair of Helmholtz, Maxwell, Uniform or Gradient coils that can generate a uniform magnetic field in x, y, z axes, rotational magnetic field and oscillating magnetic field. These pair of coils generally consists of two identical circular magnetic coils, where the radius of the coils is equal to the distance between them for Helmholtz configuration and √3 of the radius for the Maxwell configurations [16]. Also, there are some other EMA configurations designed to obtain higher magnetic field in the region of interest (ROI) like Octo-magnet coils [17] or for increasing the room of ROI like saddle coils [18].

The EMA can generate and induces in any direction magnetic fields that will affect any ferromagnetic material placed in the ROI, as a result, micro-robots could be controlled and align to any direction and thrust to the desired position [3]. For align, any micro-robot at the same direction of magnetic field torque is generated and can be voiced in Eq. (1):

$$\tau = V\mathbf{M}\times \mathbf{B} \tag{1}$$

Where τ means torque, and V, **M**, **B** denotes volume and magnetization in the micro-robot body and electromagnetic field generated by Helmholtz coil. In addition, to produce a thrust force on the micro-robot, this could be generated by gradient magnetic field and it is expressed in Equation (2):

$$\mathbf{F} = V(\mathbf{M}\cdot\nabla)\mathbf{B} \tag{2}$$

Where **F**,∇ are propulsion force of magnetic body and the gradient symbol.

Several alternatives of path locomotion and algorithms can be arranged for capsule endoscope acting as a micro-robot; it needs to carry on-board a magnetic material (permanent magnet) and by using magnetic field control, the EMA system reproduces any specific trajectories by combined different pair of coils. As an example, we set 3-pairs of mutually orthogonal Helmholtz coils and uniform coils for *x*, *y-axis* and 1-pair of gradient coils placed in the z-axis, as shown in Figure 1.

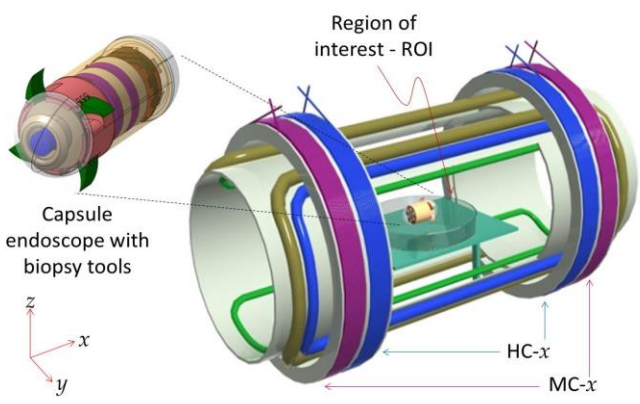

Figure 1: Schematic diagram of EMA system and capsule endoscope with biopsy tools.

The EMA generates along x-axis uniform magnetic field that aligns the micro-robot at the same directions placed and expressed as follow in Eq. (3) and (4):

$$H_h = [d_h \;\; d_u \;\; 0]^T \tag{3}$$

$$d_h = 0.7155\, i_h \times n_h / r_h \tag{4}$$

Where i_h, n_h, and r_h denote applied current, turns and radius of the Helmholtz coils and uniform.

For gradient coils, composed of two solenoids has the relation that distance of the coil (d) is the same to 1.3857 times the coil radius (r). The current direction applied to two coils is reversed, and the amplitude is equal to each other. By using this relation, the micro-robot is powered to the desired direction, and the propulsion force is expressed as Eq. (2). The Maxwell coil of the proposed system can be explained as shown in Eq. (5) and (6)

$$\mathbf{H}_m = [-0.5g_m x \;\; -0.6g_m y \;\; g_m z]^T \tag{5}$$

$$g_m = 0.6413 i_m \times n_m / r_m^2 \tag{6}$$

Where i_m, n_m, and r_m are applied current, turns and radius of the Maxwell coils [19, 20].

As a result, by combining these expressions the micro-robot can align, propel, turn and rotated in the ROI to desired pattern direction. In additions, there is a pair of gradient coils along the z-axis, the capsule endoscope can realize not only ascending but descending motion also propulsion force on the 2-D plane as showing in figure 2.

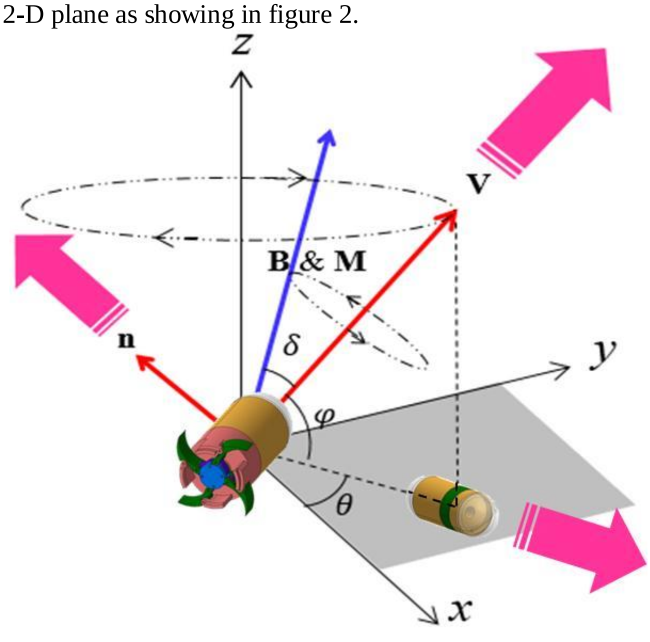

Figure 2: Diagram of helicoidally and planar motion for capsule endoscope

Figure 2 is showing a schematic diagram of helicoidally motion and planar motion of the capsule endoscope place in ROI in the central spot of EMA. The desired magnetization direction (φ) from the axial direction generates the spiral motion using the revolution of alignment vector; as a result, the EMA system creates a 3D alignment vector of the capsule endoscope by applying the equation expressed as follow:

$$\begin{aligned}\mathbf{B}_{rot.} &= M\cos\delta[\cos\varphi\cos\theta,\ \cos\varphi\sin\theta,\ \sin\varphi]^T \\ &+ M\sin\delta[-\sin\varphi\cos\theta\cos2\pi\omega t + \sin\theta\sin2\pi\omega t, \\ &-\sin\varphi\sin\theta\cos2\pi\omega t - \cos\theta\sin2\pi\omega t, \\ &\cos\varphi\cos2\pi\omega t]^T\end{aligned} \tag{7}$$

In conclusion, by generating a spiral motion as shown in figure 3 the capsule endoscope moves upward or downward of the digestive system and also allowed to stick in the inner wall of the larger or small intestine with the aim of generates better images results in the target position and accurate diagnosis by the endoscopy doctor. [5]

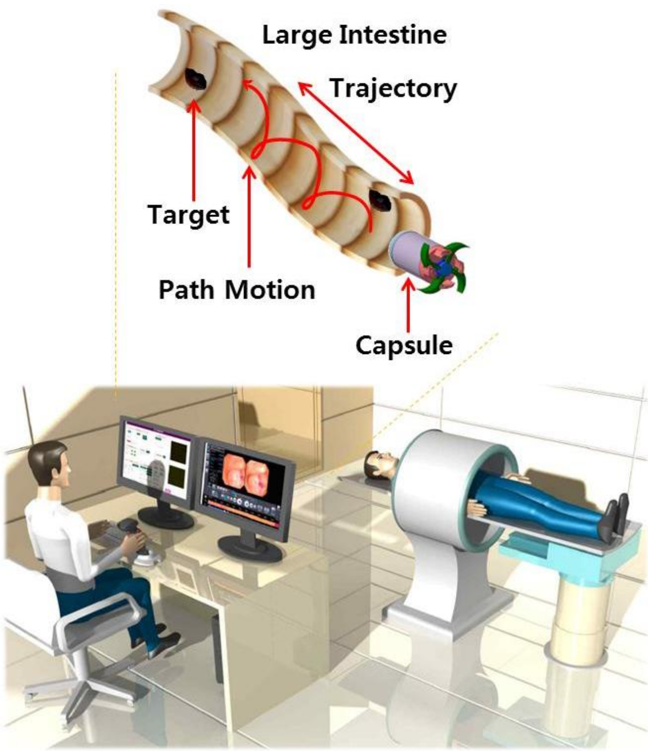

Figure 3: Schematic diagram capsule endoscopy system and helical motion in the large intestine [14]

IV. MICRO ROBOT DESIGN

The capsule endoscope is required to be a microrobot with active and complex motion to extract the biopsy sample with foldable tools; it has to reproduce enough force and torque on the wall surface of the intestines. [11] Based on other experimental researches the given design of capsule endoscope most generates a minimum cutting force to successfully extract biopsy tissue (larger than 2N) [10]. Generally, when electrical current flows in a wire, a magnetic field is generated according to Biot-Savart theory [16]. Electrical current flows in a solenoid coil, it will create magnetic flux intensity in the centre region. With the circular shape of the coil and current intensity of *i*, it can use the previous formulas to calculate the magnetic field along the axis of the coils; equations (1) (2).

By alignment the magnetic field the torque acts on the permanent magnet place in the capsule and became the cutting force of the biopsy tool; besides, the CE is an asymmetric structure where the centre of mass lies at the centre axis through the whole CE, the relation between cutting force and alignment torque can be estimated by equation (8) and the diagram is showing in figure 4.

$$F = \tau / R \tag{8}$$

Where F is the cutting force of biopsy tool razor on wall tissue and R is the distance from the centre of a permanent magnet to the out part of the tool razor.

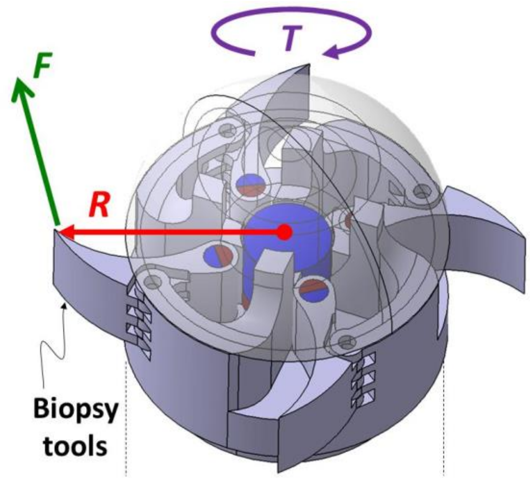

Figure 5: Diagram of biopsy tools and cutting force analysis.

Based on EMA parameters presented above, the apply voltage and current injected into the coils where directly affected the micro-robot (capsule endoscope). There is a hindrance due to the restrictions in dimensions of FDA regulation; so, the incognito relied on the maximum permanent magnet size to be placed to generate the cutting force, bigger magnet larger cutting force generated. Considering using one neodymium magnet (NdFeB) with a cylindrical shape, radius R, thickness h and magnetization (M) of 955000 A/m; by computing these parameters the results are showing in figure 6 with regard of current supplied by EMA system, the dimension of permanent magnet inside the CE and the maximum cutting force.

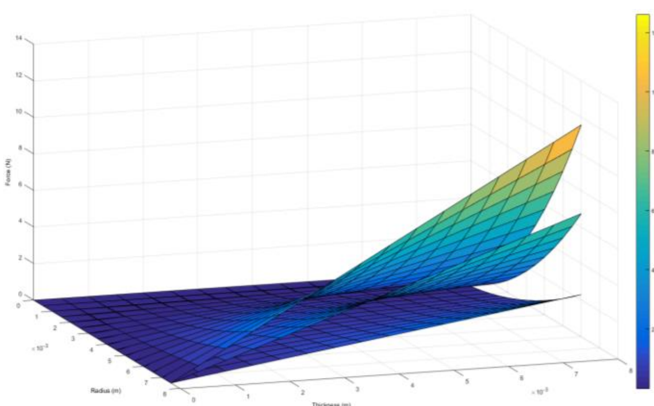

Figure 6: Diagram of biopsy cutting force with respect of radius of permanent magnet and thickness

Based on the results the suitable dimensions to place in the capsule endoscope with the cylindrical shape of neodymium magnet is 10mm in diameter and 15mm of length for cutting force produced of around 3N. These results showing that the cutting force can be generated and the dimension meet the requirement of FDA regulations.

V. EXPERIMENTAL SETUP OF TRIALS

The setup EMA system used in trials is presented in figure 5 (saddle coil); it uses the same principles like the circular coils, the only difference is that has the advantage of bigger room in the ROI and the bases of calculations are relative the same, with some modifications in the trajectory algorithms.

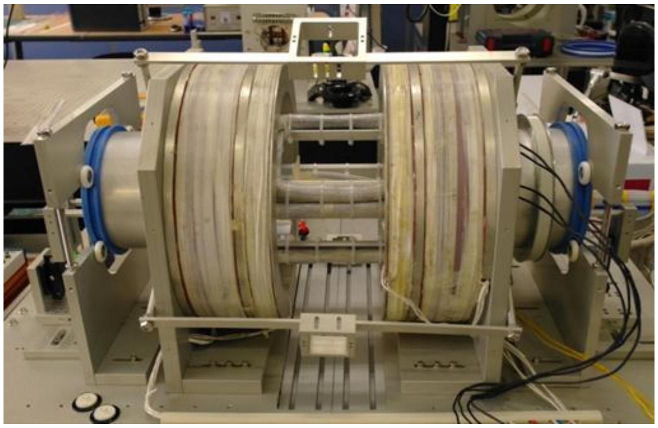

Figure 7: EMA system to drive the capsule endoscope.

To demonstrate that the micro-biopsy tool can obtain biopsy samples; in-vitro experiments were performed with a piece of the small intestine of a pig. The experimental results of the EMA are presented in figure 8 by drive the CE to a given turn angle and trajectory. As a result of the CE in the tested directions, the biopsy tool successfully extracts the tissue from the lumen wall. Additional experiments were performed to demonstrate the feasibility of the biopsy process. The cutting tissue was stored in the inner side of the biopsy tools. The figure 8 also shows the comparison of theoretical result vs. experiment results with an error that can be explained by considering dynamic friction of the CE and/or the capsule is not fully positioned in the centre spot of ROI of EMA system.

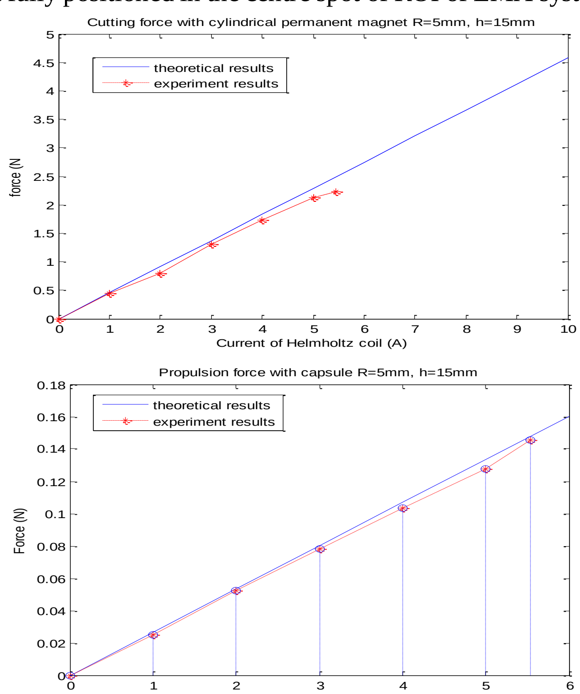

Figure 8: Cutting force and propulsion force of capsule endoscope in ROI.

Several capsulate prototypes were designed and printed in the 3D printer with the goal of produces one suitable concept for medical production. The entire system of active and biopsy capsules had been patented in Korea in 2015. Initially, the capsule micro robot had fixed blades to prove the magnetic calculations and the performance in-vitro and in-vivo tests. Further prototypes were tested in-vivo trials with the successful result considering that these micro-robots are early development and many conditions need to be solved. Figure 9 showing different capsule prototypes used and extracted after animal test executed in the pig´s stomach.

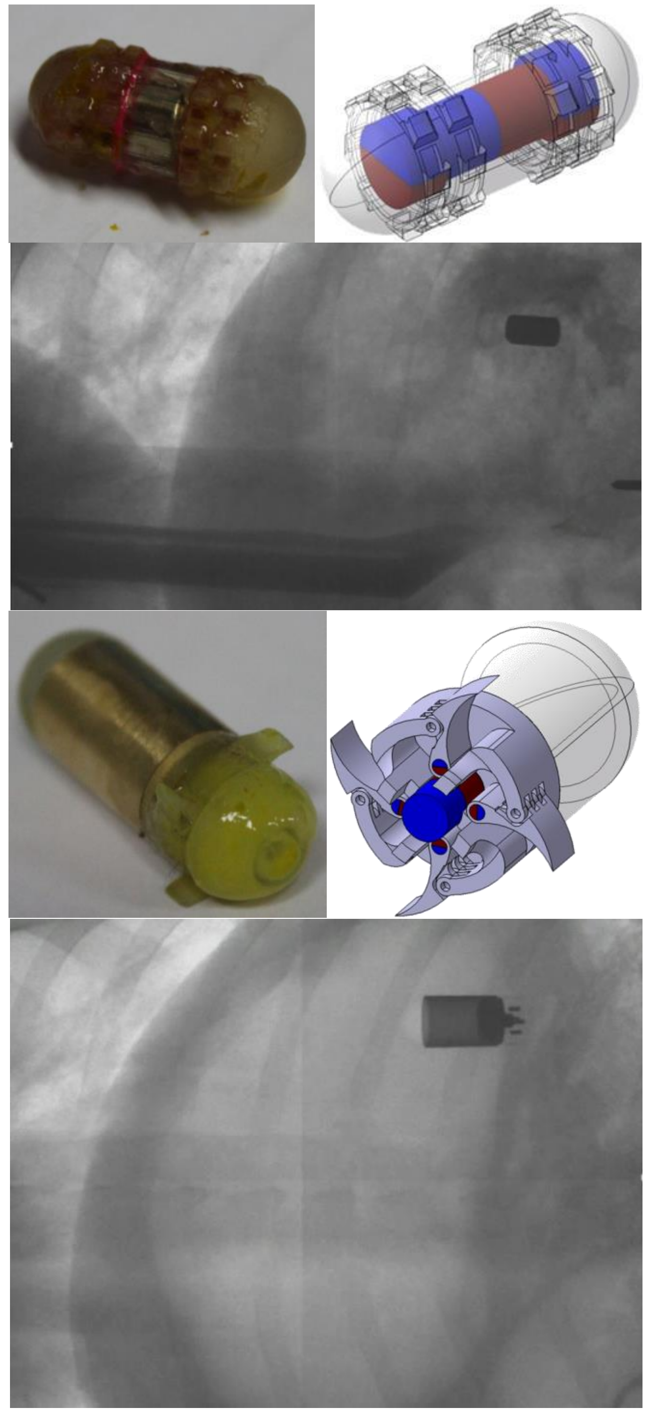

Figure 9: Capsule endoscope prototypes after performance of animal test (pig´s stomach)

VI. Conclusion and Future Work

Several prototypes of capsule endoscope integrating with fixed biopsy tools were built and tested in-vitro and in-vivo. The EMA system successfully performed the helicoidally motions to extract a tissue sample from the intestinal wall after arriving at target lesion and increasing the magnetic field to a high level the capsule is attached harder to the intestinal wall and giving a rotation the biopsy process, as showing figure 9. The biopsy tools with a dimension of 3.5mm in length outside of its body can solve effectively the problem of reaction force against the intestinal wall, with a small amount of consumed energy. Besides, the proposed biopsy device can also be integrated into other conventional CEs without changing their telemetry module and can be triggered by an external permanent magnet and/or EMA; this opens a potential revolution for an era of biopsy capsule endoscope technology. To ensure that biopsy tools are collecting animal cells nucleic acid preparations with DAPI Stain incubate in dark space for 30 min were done on the extracted material. As a result, the ultra-violate light showing on blue colour and reflex the animal’s nucleus cells bright, while vegetable cells were also reflected as presented in figure 10.

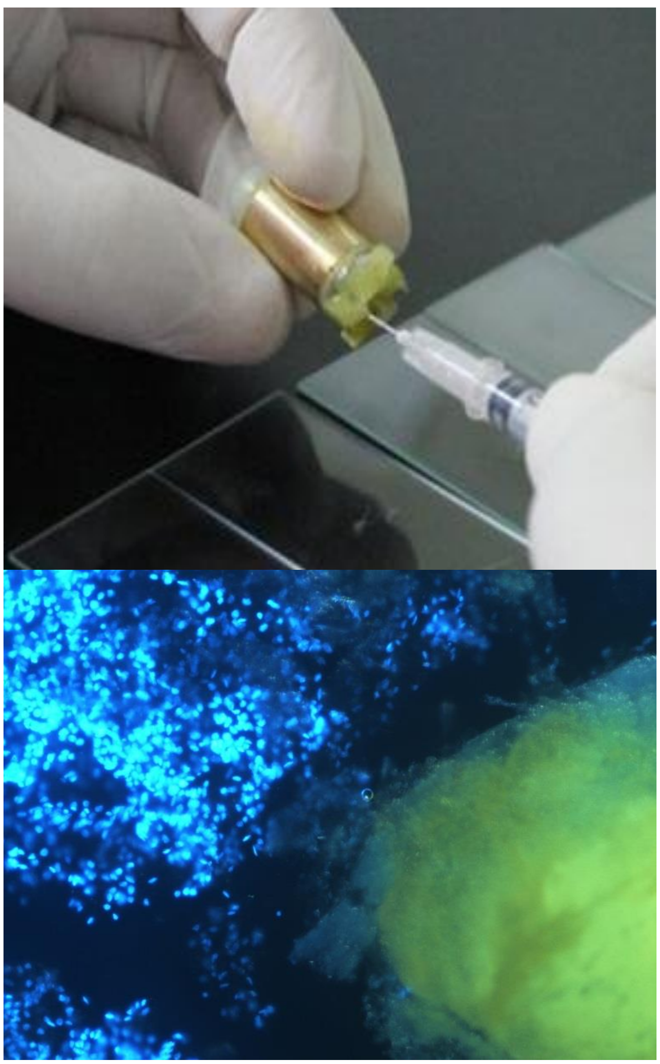

Figure 10: Nucleic Acid preparations with DAPI Stain on tissue sample extracted from the capsule with fixed biopsy tool in animal test

The EMA system is a 3D arranged magnetic field, which can be controlled in several ways by combining the Helmholtz and Maxwell coil in any orientation as an external induced power supply. However, when the capsule endoscope is travel along the way of the oesophagus the biopsies tools most be retrieved and deploy them later in a target disease area or where the doctor will require. Considering so further design of capsule endoscope with foldable biopsy tools were design and built. See figure 11. The biopsy tools of capsule endoscope can be constructed from one tool up to several of them that successful collect tissue samples as presented and proved in this paper.

Figure 11: Capsule endoscope prototype machined in biomaterial metal with foldable biopsy tools

Further research, trials and prototypes design needs to be developed to produce the new generation of capsule endoscope with active or passive biopsy tools, figure 11 presented an alternative of deploying the biopsy tools by rotation and friction. Different electronic materials for actuation the biopsy can be also as alternatives of a trigger; micro-hydraulics system controlled electro-magnetically, SMA, etc. still a long time to go, we will see in the future.

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