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A soft-magnet-based drug-delivery module for active locomotive intestinal capsule endoscopy using an electromagnetic actuation system

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ABSTRACT

Nowadays, capsule endoscope (CE) technology is highly evaluated as a promising medical apparatus for minimally invasive diagnosis and therapy. Active locomotive capsule endoscopy (ALICE) using an electromagnetic actuation (EMA) system is one of the new state-of-the-art solutions that effectively increase the diagnostic ability of CE. Together with a locomotive CE, there are various requests for multifunctional modules that can deliver drugs or execute biopsy functions. This paper presents a drug delivery module for ALICE using EMA, where we adopt a soft magnet due to its special physical properties. The drug-delivery module consists of two ring-type soft magnets and a simple plastic hinge; it has a volume of 0.78 ml, which is approximately 26% the total volume of a conventional active CE. The drug-delivery module can be integrated with ALICE. First, the drug is encapsulated into the module by the attracting force between two axially magnetized soft-magnetic rings. Second, ALICE with the drug delivery module can be driven by a precisely controlled external magnetic field to investigate and situate correct drug delivery to a target lesion. Third, at the target lesion, the external magnetic field is turned off and the two axial magnetized soft-magnetic rings of the drug-delivery module are demagnetized. Fourth, when we apply a strong pulsating magnetic field in a radial direction, the drug-delivery module is opened by the repulsive force between the two radially magnetized soft-magnetic rings, and the encapsulated drug can be released. After the drug release, the drug-delivery module can be returned to its initial shape thanks to an integrated plastic hinge in the drug delivery module and the attracting force between two axially magnetized soft-magnetic rings. Finally, the active CE can continue to show its intrinsic diagnostic work. Consequently, we demonstrate the feasibility of the drug-delivery module which is integrated in ALICE.
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1. Introduction

To date, several types of capsule endoscopes (CEs) have been developed from the first generation of small intestinal capsules (M2A, Given Imaging, Israel) [1] to the improved esophageal and colonic capsules [2,3]. Recently, a later version of CE has been widely commercialized as PillCam (Given Imaging, Israel), EndoCapsule (Olympus, Japan), MiroCam (IntroMedic, Korea), and OMOM (Chongqing Jinshan Science and Technology Co., China). However, CEs have a common weak point in terms of their passive locomotion, where they rely on the peristaltic motions of the human digestive system. Due to their passive locomotion, the CEs might miss some abnormal lesions. As a promising solution to this problem, an active locomotive intestinal capsule endoscope (ALICE) was previously reported, which was driven by an external electromagnetic actuation (EMA) system [4].

Besides the locomotive function of CEs, different functions have been requested by several physicians, including biopsy, pH sensing, and drug delivery. These functions can be used for the diagnosis and treatment of gastrointestinal (GI) diseases. In this paper, we present a prototype of a drug-delivery function module for ALICE that can deliver a therapeutic drug to a specific target region in the GI tract. We expect that the ALICE with the proposed drug delivery function module can be used for the treatment of the GI diseases. In addition, it can be also applied for the drug absorption research of a therapeutic drug in the GI tract, as the efficacy evaluation of the therapeutic drug is very important and often costs the pharmaceutical industry millions of dollars per year to carry out [5–7].

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There have been several reports on the CE drug-delivery function. First, a drug-delivery capsule using a small gas-producing cell was proposed, where the cell was activated by a high-frequency current induced from its oscillating circuit [8]. The activated gas-producing cell generates sufficient pressure to push the piston forward and release the drug from the reservoir. This system demonstrates the feasibility of controlled drug release. However, only 16% volume of the capsule was used for the drug loading and the activation time for releasing a dose takes an hour. Second, an active drug-delivery CE using a micro-thruster was reported [9]; this had a large volume for the drug loading (about 30% volume of the CE) and a relatively fast activation time. However, because the active drug-delivery CE does not have any locomotive function, it cannot be positioned to deliver to a specific target lesion in an intestinal tract. Third, Stephen et al. developed a CE comprising a holding or anchoring mechanism with a C-shaped tip legging mechanism [10]. However, because the CE was composed of complex and large mechanisms, it was very difficult to apply it to the intestinal tract. In addition, the CE does not also have any locomotive function. Finally, Yim et al. proposed a soft-capsule with two magnetic parts, where the two magnets were attracted to each other with an appropriate magnetic force to keep the drug encapsulated inside the capsule during its traveling through the GI tract. When the capsule reached the target position, an external magnetic field from the external permanent magnet was used to extract and release the drug [11]. We found that the drug delivery capsule includes a targeting mechanism, and at the same time, an active drug-releasing mechanism. Therefore, it is considered as a feasible method for a drug delivery CE. Nevertheless, the drug-releasing module can be integrated with only a soft-capsule endoscope and it not compatible with the popular pill-shaped CEs or ALICE.

In this paper, a new platform for a drug-delivery function module for ALICE will be presented. The ALICE with the proposed soft-magnet-material-based drug-delivery module shows advanced features of positioning controllability and drug releasing performance due to the external magnetic field of an electromagnetic actuation (EMA) system. The new drug-delivery module for ALICE can be made compatible and integrated with other commercialized pill-shaped CEs. Through several fundamental experiments, we will evaluate the feasibility of the drug-delivery module integrated with ALICE.

2. Materials and methods

2.1. Active locomotive intestinal capsule endoscope (ALICE)

Considered a non-invasive procedure, conventional CEs have been used as an excellent and safe device for diagnosis in the small intestine and esophagus. However, because CEs locomotion is passive, relying on the peristalsis motion of digestive organs, they cannot give a sufficient diagnosis and may have many blind spots in other organs such as the stomach and colon. In our previous research, as a promising solution for this limitation of CEs, we proposed an active locomotive intestinal capsule endoscope (ALICE) that consists of CEs with an integrated small permanent magnet and an external electromagnetic actuation (EMA) system [4]. The ALICE exhibits 5-degree-of-freedom (DOF) motions through the control of the coil currents in the EMA system. As shown in Fig. 1, the EMA system consists of two parts. One comprises coils for the generation of a uniform magnetic field with a pair of Helmholtz coils and two pairs of uniform saddle coils. The other includes coils for the generation of a uniform gradient magnetic field with a pair of Maxwell coils and two pairs of uniform gradient saddle coils. Each coil pair is connected to an MX12 (3EA) power supply (California Instruments, USA) and the currents of the coils are controlled via a peripheral component interconnect (PCI) controller with LabVIEW software (National Instruments, USA). Thanks to the controllable magnetic field of the EMA system, the movement, posture, and angle of ALICE inside the digestive system can be effectively driven with 5-DOF. In addition, for accurate diagnosis of the digestive organs, a biopsy module for ALICE has been developed as a functional module of CEs [12,13]. This paper will present the functional drug-delivery module for ALICE.

2.2. Design basic specifications of the drug delivery module for capsule endoscopy

CEs have the same shape as a large antibiotic pill and consist of a camera and lighting LEDs, programmable electronics and power batteries [14]. Therefore, the size of the functional modules for CEs should be suitable for integration into the existing swallowable CEs, which are 12 mm in diameter, 33 mm in length, or 3.0 cm^3 [15]. The wireless remote actuation of a drug-releasing mechanism should consume a small amount of energy, as the available energy is limited in CEs. CEs should have an active drug-releasing function that is independent from environmental conditions, such as pH levels, different intestinal sizes, and disease condition. Moreover, the drug must be safely encapsulated without any leakage before the activation of the drug-release process. It is desirable for the drug reservoir to have a large volume ratio compared to the total volume of CEs. Finally, the drug delivery module should be easily activated and reliably controlled to ensure that the encapsulated drug will be released at the targeted position, which is an important role for the drug-delivery system required [8,16].

2.3. The drug-delivery module for the ALICE system

Fig. 1 shows a schematic diagram of the ALICE operating system. ALICE with a drug-delivery module was placed inside the EMA system and driven by the magnetic field generated from the EMA system. The EMA system consists of one Maxwell coil pair, one Helmholtz coil pair, two uniform saddle coil pairs, and two gradient saddle coil pairs arranged perpendicularly on the X-, Y-, and Z-axes; it can produce a uniform, gradient magnetic field inside the region of interest (ROI). Fig. 2 introduces the novel ALICE with the drug-delivery module. Fig. 2a presents the overall shape of ALICE with the drug-delivery module but seems to exhibit no differences from other CEs. The inside structure of ALICE is shown in Fig. 2b, where the upper part is the main part of ALICE—which is the same as a conventional CEs (camera, telemetry module, and batteries)—and the lower part is the drug delivery module using two axial magnetized soft-magnetic rings. The axially magnetized soft-magnetic rings pull toward each other to keep the encapsulated drug in ALICE. In addition, to improve the sealing of the encapsulated drug, a layer of hard gelatin shell was added, as shown in Fig. 2b. The axially magnetized soft-magnet rings help to control ALICE's movement through the external magnetic field created by EMA system. Fig. 2c describes the drug-releasing state of ALICE, where the plastic hinge on the system's shell helps the lower part connect with the main body during the drug-releasing process and assists ALICE to return to its original shape (Fig. 2a) after the drug release. Therefore, after the drug is released, ALICE can continue to diagnose the digestive organs. Since the drug-delivery module in ALICE was made with two soft magnets, the drug chamber has a greater volume and there is a higher ratio between the encapsulated drug and the ALICE capsule volume.

Fig. 3 illustrates the detaching and attaching procedures of the two soft magnets in the drug-delivery module. In step 1, the two ring-type soft magnets are magnetized in the axial direction, and the attraction force between the two soft-magnets is generated. The attraction force is sufficient to safely store the encapsulated

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