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Review Article

Capsule Robot: A Theranostic Approach

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Abstract

Increasing development in healthcare systems and availability of efficient miniaturized components or systems that are economic has led to profound scope for research in many new fields. Capsule robot was one such fictional idea that turned into factual reality because of use of applicative miniaturized components. Initially capsule robots were developed for endoscopic applications. These travel inside the gastrointestinal tract and thus capture images of the gastrointestinal tract and related areas. Later, capsule robots were developed to be used as the unique tool to construct micron and sub-micron sized drug delivery systems for target delivery and treatment. This article highlights on various aspects of capsule robots in diagnosis and therapy of various disorders and diseases, together called theranostic approach in drug delivery systems.

Keywords: Capsule Robot; Endoscopy; Diagnosis; Therapy

Introduction

The rising demand for non invasive methodology for diagnosis and treatment led to the invention of capsule robots. The submarine type capsules which travel inside the body were used for endoscopy with a chief role in targeted drug delivery systems. Traditional endoscopy involves usage of a pliable endoscope which is inserted into the body cavity by a doctor for medical imaging of a diseased part inside the body. It has been successful in aiding physicians for viewing gastrointestinal tract, respiratory tract, urinary tract and other cavities in the human body. But these endoscopes have drawbacks such as risk of infection, forming perforations and tear. Endoscopic capsules are non invasive, painless and more secure to be employed for long term screening purposes [1]. The main advantage is that they can access difficult body parts that were not possible to reach before with standard endoscopy such as small intestine [2]. Wireless capsule endoscopes with advanced functionalities such as biopsy or drug delivery are highly advisable. For the release of drugs at different sections of GIT in controlled manner, Drug Delivery System (DDS) capsule endoscopy was designed. There are quite a number of research studies using Microelectromechanical Systems (MEMS) for evaluating the drug release. In 2001 Given Imaging launched first commercial capsule endoscope, PillCam into the market [1].

Design

Capsule robots are used for both diagnosis and therapy i.e. drug delivery. The design of the capsule robot is based upon its end use and therefore accordingly the components change.

Capsule robots for endoscopy

Wireless Capsule Endoscope (WCE) is used to diagnose disorders of various parts of the GI tract. The capsule endoscope possesses different characteristics depending on the organ for which it is used.

Capsule endoscope for oesophagus

In the oesophagus, ingested substance has very fast transit time i.e 10s so a dual camera system and faster image capture speed is required. The marketed capsule is PillCam ESO and has a frame rate of 14 frames/s [3,4].

Capsule endoscope for stomach

There is a requirement of floating capsule. To give 3D steerable locomotion property a propeller is used. The marketed capsule is PillCam ESO 2 and has a frame rate of 18frames/s [5,6].

Capsule endoscope for small intestine

Capsule travels through the small intestine by peristaltic movement. There can be active locomotion. If the capsule is intended to detect symptoms in the small intestine for a long time interval, a powerful battery backup is required. The marketed product is PillCam SB2 with frame rate of 2frames/s. Other marketed capsule endoscopes are PillCam SB, OMOM, Endocapsule and MicroCam Capsule [3].

Capsule endoscope for large intestine

As the diameter of the large intestine is large, active locomotion is needed to view the entire surface area of internal intestinal wall. Capsules can be longer in length compared to other capsule endoscopes. The marketed capsule is PillCam colon with the frame rate 4-35 frames/s [4].

Components [7]

A typical capsule endoscope consists of

- External biocompatible shell of a large antibiotic pill size with 11mm in diameter and 26mm in length
- Camera
- Control and communication unit
- Energy source
- Capsule case
- Optical dome
- Light emitting diode
- Optical head
- Complementary metal oxide semi conductor(CMOS) or charge coupled device (CCD) image sensor
- Microelectromechanical System (MEMS) magnetic switch
- Printed circuit
- Battery
- Receiver-transmitter

Fabrication [4]

The main challenge while developing a capsule robot is to accommodate various components in a small space. A capsule endoscope consists of different components to carry out functions like vision, locomotion, telemetry, biocompatibility, localization, sensors, power source and other interventional systems. The presence of these components depends on the end use.

Material for fabrication [7]

The device developed must be biocompatible with the body. Casing of the WCE should be biocompatible, safe and inert to the stomach acid and intestinal flora and should be easy to swallow. The casing should be transparent for optical dome. Mostly polycarbonate material is used for capsule casing.

Imaging

It is the most important part of a WCE. The main aim of this system is to capture clear images of the GI tract with high resolution. It consists of a lens, LED, vision sensor and a chip to compress the images [4]. Earlier CCD was used but now CMOS has replaced it. Critical challenge faced is the compromise between image quality and power consumption, size, image resolution and frame rate. The image resolution of WCE is between 256*256 pixels and 1000*1000 pixels. The frame rate varies from 2 to 7 frames per second (fps) [8]. Good illumination is also important for taking quality images. For this purpose most of the WCE have installed LEDs. Fluorescent Imaging was developed to enhance the view of the GI tract. To image tissue auto-fluorescence and targeted florescence via fluorophore labeling of tissue a novel FI technique is used. CMOS single photon avalanche detecting imaging array, miniaturized design, wireless technology and low power consumption is used in this technique [9]. Another critical parameter is the frame rate which decides the rate at which the acquired image is sent. Usually the frame rate is 2-7 fps which can be increased to as high as 18 fps for oesophageal endoscopy [3].

Measurement of transmission

The acquired image is transmitted to the external receiver. Microsemi's ultra low power Radio Frequency transmitter chip is used in PillCam during endoscopy [10]. Most of the WCEs have only unidirectional communication system i.e. sending images from the capsule. The main disadvantage is that there is no possibility to adjust the operation of the capsule for target research area before the endoscopy [11].

Power supply [10,11]

For appropriate power back up, limited battery space and power output are the two main challenges. Lithium ion polymer batteries and carbon nanotube based systems not only improve power supply but also reduce the required battery space. Lithium batteries can improve power supply with less battery space as they can peak up to 20 times their nominal values. The next generation power demand can be met by Wireless Power Transmission (WPT). WPT transfers electrical power from the transmitter to receiver wirelessly.

It is classified as Inductive coupling and Radiative coupling. Inductive coupling is useful for short distance transmission. Radiative coupling is useful for far field transmission. In inductive coupling there is electromagnetic induction between two coils. The receiving coil placed inside WCE derives power from the magnetic field generated by external transmitting coil. The generated electromagnetic field must not harm human tissues. The size of the receiving coil must be small so that it can fit inside the capsule. The main problems with WPT technology are non-uniformity in magnetic fields near WCE operating area, misalignment between receiving and transmitting coils and difference in the electrical parameters. Extensive research in this field is required to make WPT a great technology to power WCEs.

Locomotion

Segmentation and peristalsis helps a WCE to move through the GI tract. In segmentation, alternate contraction of different rings of circular muscle occurs and in peristalsis, sequential contraction and relaxation of continuous rings of smooth muscles occur [4].

An important feature of active capsule endoscopy is the actuator. The critical properties that one should remember before designing a locomotion system are:

1. The speed should be within the range of natural GI tract motion i.e. around 15 cm/min.
2. Power consumption should be less.
3. The diameter of capsule shall be not more than 1.5 cm diameter and 3 cm in length or it would be difficult for a person to swallow.
4. The temperature of the capsule should not be more than 43°C.

The locomotion methods can be classified as internal locomotion, external locomotion and other locomotion methods [12].

Internal locomotion

The actuator is present inside the capsule. Following are the methods used for internal locomotion.

Worm like mechanism

Due to alternate contraction and elongation of smooth muscles, worms move ahead. Such mechanism is mimicked in capsule robots which includes three basic functions of anchoring, elongation and contraction which is driven by Shape Memory Alloy (SMA) actuators. The SMA alloys are metals like nickel–titanium alloy, copper–aluminum–nickel alloy or iron–manganese– silicon alloys, which change their shape, position and other characteristics as a response to the temperature or electromagnetic fields [12].

To generate an attraction force between the capsule and the intestine wall, scientists have used microfibrillar adhesives from Polydimethyl Siloxane (PDMS). The Adhesive pads are made from high density, high aspect ratio microfibers of PDMS. The SMA wire, compression spring, capsular casing and six adhesive pads form the design of capsule robot. The SMA wire is activated by heat by passing a current. The capsule moves forward by sequential actuation and cooling of SMA wire makes the capsule to contract and elongate [13]. These capsules are larger in size than the marketed PillCam WCEs. The SMA wire and compression spring are used as actuators in another capsule as mentioned above with the only difference that the stopping mechanism is based on suction cups and pitch depth [14,15].

Legged/paddle based mechanism

By introducing legs on the capsule, the anchoring and locomotion becomes easier. Legs can prove to be beneficial when there is a need for long term monitoring or to work against body's peristalsis and adhere to a surface. A 3-legged system can be developed for providing adherence to the oesophageal tract which is required for pH monitoring in case of Gastroesophageal reflux disease (GERD). SMA wires actuate the legs. These legs are inserted in the grooves present on the capsule casing. The legs are closed at the time of swallowing. To stop the device inside the oesophageal tract, the doctor sends the signal wirelessly using the user interface to open up the legs suddenly and stop the device inside the oesophageal tract. The friction with walls of oesophagus can be avoided by coating the legs with soft material like PDMS [17].

Hydrodynamic based method for locomotion

These robots are developed to navigate through the stomach. They are also known as swimming robots. By traveling like a submarine through the stomach they help to capture images of critical areas in stomach endoscopy. They have similar power consumption like paddle based capsule endoscopes but they have an ability to swim in both directions. These robots navigate with a high velocity leading to chances of missing critical areas [5,12].

Vibration based method for locomotion

A vibratory motor produces a centripetal force that overcomes the net force acting on the capsule and helps it to navigate in the forward direction. The vibration based capsule helps in reduction of frictional forces along the walls of the small intestine [12,19].

External locomotion

Using a permanent magnet or electromagnetic coil externally to actuate the capsule a magnetic field is created. An internal magnet is placed inside the capsule. The doctor navigates the capsule to observe the desired area. A permanent magnet is kept inside the capsule. When an external rotating magnetic field is applied, the capsule rotates in a helix. The mucus membrane is pushed backwards and the capsule moves in a forward motion. The capsule size is 11× 40 mm while the average velocity is 1200 mm/min. Another method to control the locomotion of a capsule robot is magnetic platform method. The external locomotion has advantage that there is no need of an internal battery to power the locomotion and it can precisely control and position a capsule [20,21].

Capsule for drug delivery

The designing of Medical Capsule Robots (MCRs) is complicated because it has to address severe cross-cutting constraints such as size (to gain non-invasive access, MCR diameter is limited to about 1 cm), power consumption (limited space for battery is available onboard), and fail safe operation (MCR operates deep inside the human body). MCR design and development demands significant skills and efforts in embedded systems, miniaturized electronics, packaging, debugging and mechanical miniaturization of the device [22].

It consists of

- A drug chamber
- Two coils
- Magnetic piston
- Diameter = 7.94 mm
- Length = 6.35 mm
- Volume = 314.42 mm3

The distance between outer diameter of the magnetic piston and inner diameter of the chamber is 0.4 mm. This value assures a low friction with the magnet and therefore no leakage of the drug and the actuating mechanism. The drug is released into the environment from the distal collar edge of the chamber that has twelve circular holes (each with a radius 0.8 mm). For deploying the drug uniformly without being affected by capillarity, the number of holes and radius should be chosen accordingly. The number of holes as well as their dimensions can be adjusted if the drug with different viscosities is used. The incorporation of proper drug viscosity and aperture size prevents drug leakage for any possible orientation of the capsule [22].

Capsule robots are broadly divided in two domains i.e. Microelectromechanical Systems and Non mechanical Systems.

Microelectromechanical systems

They may or may not use mechanical systems in order to align at a particular area and release the drug on receiving wireless signals.

It is further divided into two types

Passive mechanical release mechanism: There are inner and outer sleeves. Generating a radio frequency signal from a distance of 10 cm, a resistor activates heat mechanism which allows rotation of the inner sleeve when a temperature of 40°C is reached. When the inner sleeve is rotated, it gets aligned with the outer sleeve releasing the drug contained in the inner sleeve. The total volume is 2.75ml and the capsule is 10 mm wide and 35 mm long. The ratio of volume of the drug reservoir to the total volume of the capsule is 0.29. This means that only 29% is used to load the drug and the rest 71% of the space is consumed by other components [23].

Active mechanical release mechanism: In order to have higher control over the drug release rate, the drug delivery system should be less dependent on fluid availability in the area of interest. Several studies have aimed on different techniques to propel a piston that would push the drug out of its reservoir [22-25]. It was reported in a mechanism that allowed a drug release chamber of 0.51ml in a capsule whose maximal size is 10.2 mm in diameter and 30.0 mm in length [26]. The stretchable component was released when a signal triggered a calorific element in the capsule. This signal was generated from a maximum distance of 1 m and allowed the stretchable component to push the piston that expelled the drug out of the reservoir. The total volume of the capsule is 2.45

ml. The ratio of volume of drug reservoir to total volume of capsule is 0.208. This means that only 20% is used to load the drug. The disadvantages of this device include poor reproducible release of the drug due to usage of stretchable component and the fact that only one dose can be released at a time. To overcome these two drawbacks, the propulsion of the piston by the pressure of hydrogen gas generated by a small gas producing cell was developed [27]. In this study, the capsule is embedded with a high frequency signal induced current in an oscillating circuit. The gas producing cell is activated by the electrical current that consequently moves the piston forward and empties the drug reservoir. The result of this study proposed that it is possible to activate the capsule on demand after intervals of few hours and thus get a reproducible release of the drug [2].

Non mechanical system [27-29]

In these systems, chemical interaction takes place because of certain environmental conditions to release the drug out of the capsule or use non-mechanical energy to expel the drug. These are also classified into passive and active drug delivery systems.

Passive release mechanism

Chemical interactions are triggered in response to certain conditions of the environment such as the temperature and pH. The physicochemical property of the compound is manipulated to increase intestinal concentration of drugs. This approach has shown promising results for colon targeting. It is difficult with these systems to control variables, such as the release rate, target location, number of doses and exact amount of drug released, since the properties of the GI tract can vary greatly among the patients.

Active release mechanism

It is represented by micro-pump systems where non-mechanical energy such as magneto- hydrodynamic energy is transformed into kinetic energy. This kinetic energy drives the liquid drug out of the reservoir. The advantage of this approach is that it creates a bigger volume.

Advances

Capsule micropump

Capsule micropump can be used for drug delivery. It is able to make a microflow. Capsule micropump uses Ionic Conducting Polymer Film (ICPF) actuator as the servo actuator. It consists of a two active one-way valves which make use of the same ICPF actuator and a tank. The dimension of capsule micropump is 13mm diameter and 23mm length.

The mechanism of actuation is as follows

- After application of electricity, the ICPF bends towards the anode side. The volume of the pump chamber increases which causes the inflow of liquid from the tank to the chamber.
- By changing the current direction, the volume of the pump decreases which causes the liquid to flow out of the chamber.
- The ICPF actuator is applied with a sine voltage, the micropump causes the liquid flow from the tank to the outlet [30].

The micropump is one of the micro and miniature devices, which have been installed with sensing and actuating elements that supply micro liquid flow. Micropump uses polymer actuator and piezoelectric actuator [31-33].

Magnetic capsule robot

In magnetic capsule robot magnetic properties are used in order to develop a capsule robot that remains in the abdominal cavity in order to monitor the areas of the GI tract. Ferromagnetic material in pieces is placed inside the robot and external magnetic field is used to set the robot in motion. The magnetic forces produced by mobile phones and metal items are not strong enough to move the robot, thereby avoiding unexpected movements that can endanger the patient's health. By applying strong external magnetic field, the robot travels and rotates in a direction consistent with that of the magnetic field. Viscoelasticity of the internal organ and abdominal wall can be overcome by applying large magnetic force at the start of the operation. A large magnetic pulse is produced by generating a large electrical charge in a condenser which is passed to a coil that enables the robot to travel [34].

Wireless fluorescence capsule robot

White light endoscopy is the standard technique used for diagnosis of disease condition in the upper and lower part of the GI tract [35,36]. But it suffers from the drawback of low detection rate. Using the combination of White light Imaging, Fluorescence Imaging and Narrow Band Imaging a significant improvement has been observed and the detection rate has enhanced from 53% to 90% [36-39]. In fluorescence endoscopy, the fluorophore absorbs excitation energy of blue light and then re-emits some of that energy in the form of green light [40]. Endogenous fluorophores occur naturally within the human tissues that are used for autofluorescence endoscopy. Exogenous fluorophores can be introduced externally as labels to the biological system which are used in targeted fluorescence endoscopy. Concentration of endogenous fluorophores such as flavin adenine dinucleotide and other extracellular matrices such as collagen and elastin is 3 times lower in cancerous tissues than that in the normal tissues; thereby can be used for detection of cancer. Autofluorescence endoscopy avoids introduction of foreign material, eliminating risk of toxicity or other unwanted interaction with the biological system that are investigated [41]. In the targeted fluorescence endoscopy, the fluorescence response from the diseased tissue labeled with exogenous fluorophores is more than the surrounding healthy tissues which in turn increases detection probability and specificity of early stage abnormalities [40-43]. Antigen with labeled fluorescence preferentially binds to the tumour in the GI tract thus making the diseased area more visible through a fluorescence sensitive camera. This technique improves imaging resolution and enhances sensitivity [41,44-46].

Risks

Wireless Capsule Endoscopy is a safe procedure. The capsule is excreted out of the body by natural process. Capsule retention has been reported in less than 2% population. The term capsule retention is used when a capsule retains in the body for more than two weeks. Capsule retention has been observed in patients with GI disorders such as Crohn's disease, NSAID structures, intestinal adhesions, radiation enteritis and ulcerations. The longest period reported of capsule retention is 2.5 years. It does not cause any major problem due to small intestine obstruction. A low risk of skin irritation can occur because of the sensors. A person should not come near any high power electromagnetic field after ingestion of capsule [47,48].

Technical challenges

Limited size and energy budget are the two major constraints which limits the development of highly advanced and functional ingestible devices. Reduction in the size is one of the major challenges. The device should be small so that it can be easily swallowed. Attempts should be made to develop a capsule having diameter less than 1cm and length less than 3cm, so that it can easily pass through the digestive tract. Energy is another major requirement for ingestible medical devices. The space within the capsule is limited therefore accommodation of the components is a challenging task. Wireless communication through the human body is another major challenge for Wireless Capsule Endoscopy [49].

Other applications

pH monitoring

To examine certain critical areas in the GI tract, doctors mainly use WCE. For performing different diagnostic activities a sensing device is fixed in the WCE. This is mainly used in case of GERD, which requires longer pH monitoring. A capsule robot monitors pH and apparent opposition in an electrical current (impedance) of oesophagus. The capsule robot has great ability to differentiate between acidic and non acidic reflux [50]. Inside the capsule a magnet is placed or held onto the wall of the oesophagus internally. For capsule to adhere onto the oesophagus tract an internal locomotion technique can also be used.

For temperature monitoring

In the market, various types of temperature sensing capsule biosensors are available. One of them is Vitalsense, an ingestible temperature capsule. Prolonged monitoring of temperature is required as it travels through the GI tract. It sends four times transmissions per minute within 12-48 hour period [51]. There is another ingestible temperature sensor CorTemp which transfers the core body temperature as it passes through the GI tract. The capsule sends wireless signals which are recorded by CorTemp present outside on the body. The temperature sensor has a communication coil, quartz crystal, battery and circuit board. These are placed inside an epoxy shell. The magnetic flux generated by the frequency of vibrations of the crystal relative to the body temperature is responsible for transmission of low frequency signal to the data recorder [52].

For obesity treatment

Obesity is a medical condition in which excess body fat gets accumulated to an extent that it may have a negative effect on the health. It is caused by a combination of excessive food intake, lack of physical activity and genetic susceptibility.

For obesity treatment there are traditional balloon robots that operate by incorporation and removal of balloons in the stomach with the help of endoscopes. But with this patients get complications such as nausea and sickness. An ingestible weight management capsule is a new application [49]. A new capsule was developed in which the balloon is attached to the capsule robot [52,53]. It operates by wireless powering and communication system which is placed into the capsule and the module is outside the body. The capsule is swallowed and moves to the stomach by peristaltic motion. For the inflation process, a wireless communication board (sender) outside sends inflation signals to the receiver in the capsule. The receiver then triggers the controller and a microactuator is driven such that it rotates the needle which breaks the chemical containers. Acetic acid solution then flows out and enters the balloon where it reacts with sodium bicarbonate present in the balloon and produces carbon dioxide. The carbon dioxide gas causes inflation of the balloon and fills a certain space in the stomach. This induces a feeling of satiety and thus reduces the food intake. For the deflation process, the sender inputs a deflection signal to the receiver which triggers the actuator to rotate backwards such that the deflation passage on a particular part of deflation module is opened and carbon dioxide is released into the stomach from the balloon. After deflation the capsule is evacuated into the large intestine and excreted naturally [53].

For surgical treatment

A capsule robot is used in surgical operations, a novel endoscopic capsule proposed by Valdastri., *et al*. It has dimensions of 12.8mm x 33.5mm. This novel endoscopic capsule has four permanent magnets which on interaction with an external magnet enables movement of the capsule from one place to another. A nitinol clip is located at the top which is released when the signal is received. As the capsule can clip the iatrogenic bleeding, it can perform multifunctional tasks like diagnosis and treatment [54].

For patch release [55]

A wireless robotic capsule for releasing bioadhesive patches in the gastrointestinal tract is designed, fabricated and preliminarily tested. The deployment of a bioadhesive patch onto ex vivo porcine tissue is accomplished and the patch adhesion strength verified. The main application of the prototype is the deployment of anchoring patches for miniature robotic modules to be operated in the targeted anatomical domain. A 15 x 25 mm^2 Patch Supporting Plate (PSP) is then designed. The PSP is fully encapsulated within the capsule case and a release mechanism is designed for its ejection, also exploiting two Ejectable Shells (ES). A mechanism for patch release is as follows:

1. An elastic preloading is designed for PSP holding prior to release
2. PSP release is associated with a remotely activated triggering mechanism; and
3. Patch deployment onto the tissue is achieved by synchronizing PSP lift with a suitable displacement of the ES.

Scope

In case of the hardware, future work will aim to include additional microprocessors, sensors, actuator modules and wireless transceivers that implement different communication protocols and carrier frequencies [56]. Advanced studies need to be conducted to estimate performance of available capsule robots when the dosage form is changed. Moreover, the material to fabricate the drug reservoir has a scope for future work. Reducing capsule size is a major challenge and aim of future development of a capsule robot. Multidimensional diagnostic capability to a capsule endoscope can be imparted by incorporation of biosensors for pH, temperature and oxygen level monitoring. There is a need to develop a capsule robot which has ability to diagnose diseases as well as treat them *in situ*. Further miniaturization of the components can lead to the development of capsule nanobots that can travel through the systemic blood circulation and treat disorders. Capsule robots should have the ability to release the drug in rapid as well as in sustained manner. The efficacy of the drugs delivered via capsule robots need to be proven as compared to the existing drug delivery systems [57]. Future work should also focus on developing a capsule robot which is affordable and can benefit all classes of patients.

Conclusion

The capsule endoscopy is a non invasive method for diagnosis and treatment of GI disorders. In future WCE can replace both diagnostic and interventional flexible endoscopies by providing additional functionalities such as body tissue/fluid sampling and drug delivery. Capsule robots can be developed for targeted drug delivery. Controlled drug delivery can be achieved by controlling the drug release depending on receiving wireless signals externally. Capsule robots can be developed to perform multifunction of diagnosis and treatment at a time. Capsule robots can find huge applications in chemotherapy to kill only the cancerous cells. Capsule robots are the future of diagnostic and therapeutic field.

Conflict of Interest

There is no conflict of interest.

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