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A REVIEW ON ROBOTIC CAPSULE FOR DRUG DELIVERY TO THE GASTROINTESTINAL TRACT

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Abstract: Increasing development in healthcare systems and availability of efficient miniaturize components or systems that are economics 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.

Index Terms - Capsule drug; delivery; technology; innovation; digestive; gastrointestinal; capsule endoscopy

I. INTRODUCTION

A small bowel endoscopy is urgently required in order to reduce the discomfort of invasive gastrointestinal (GI) testing.[1] It has encouraged unique partnerships. These have changed how GI endoscopy is often done [2,3].Over twenty years have passed since the invention of capsule technology. It has taken a while and a pandemic for capsule endoscopy (CE) to establish itself as a leader in other fields, despite the fact that it has become the primary method for studying the SB [4]. Esophageal [5] and colon cancer are the results of a variety of adaptations and evolutions. [6] capsules. Despite the quick development of artificial intelligence (AI) in computing and electronics (CE), the time of a single device for a comprehensive, pan-enteric examination is still rather far off. However, it appears likely that one CE may eventually offer not only photos but also on-the-spot diagnosis and treatment. A number of conditions must be met for this to occur, including external capsule control, motility, precise localisation, anda durable and dependable power source.The size and construction of the commercially available SB capsules vary depending on the manufacturer, but they all adhere to the same fundamental ideas. They typically weigh between 3 and4.5g and measure about 26 11 mm [7]. White-light emitting diodes, a lens with a macro and high-speed photographic capability, a recorder or data transmitter, and an internal battery are all housed in one small housing. This design has undergone modifications that allow for magnetic control and longer battery life. Unfortunately, the size is sacrificed for these enhancements. For instance, colon capsule devices, like the PillCamTM COLON2 (Medtronic, Minneapolis, MN, USA), are a little bit longer and need a second camera head. Improvements like these have created fascinating opportunities and the possibility of The goal of this comprehensive review is to provide an in-depth look at capsule driven drug delivery systems for gastrointestinal tract, beginning with early prototypes and concluding with the devices currently available.

Direct Drug Delivery Systems -

Drug Delivery Systems (DDSs) have also been developed for other target areas[8]. However, due to the intricate anatomy and physiologic conditions of the gastrointestinal tract, there are several challenges that must be addressed. For example, a drug releasing mechanism and anchoring system must be in place in the target area. This is why there are a number of micro-echotronic systems. The status of these capsules falls into the following categories: - Prototype - Patent - Concept - Commercial. This overview will focus mainly on the commercial category.

Releasing Mechanisms-

DDS have either passive or active mechanisms of release. Passive mechanisms involve the chemical being exposed to the gastrointestinal tract at the time of an external trigger, such as pH or temperature. Active mechanisms, on the other hand, involve the drug being actively expelled at the time of remote activation. The primary benefit of active mechanisms of release is greater control of DD.

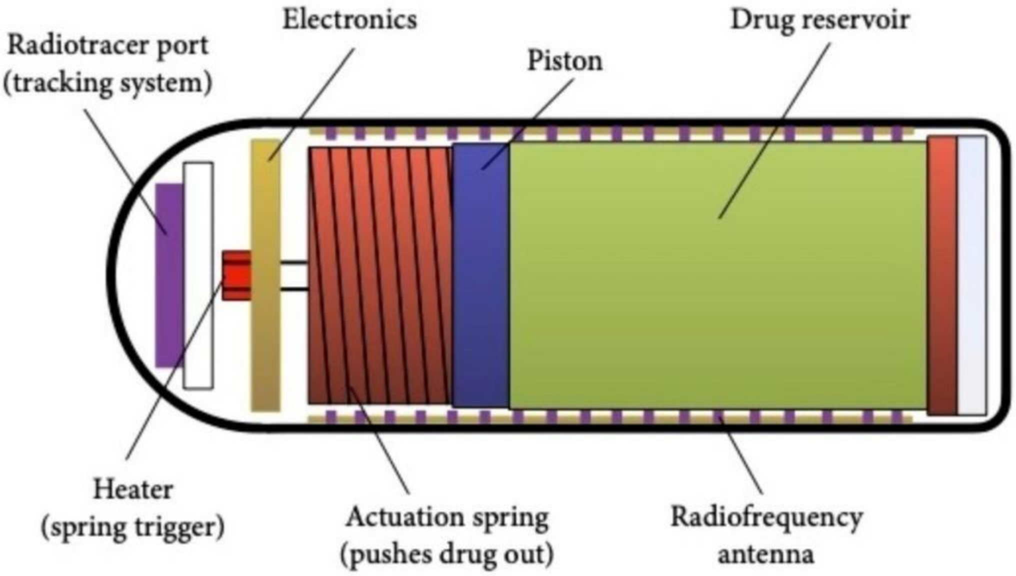
Passive Release Mechanisms-

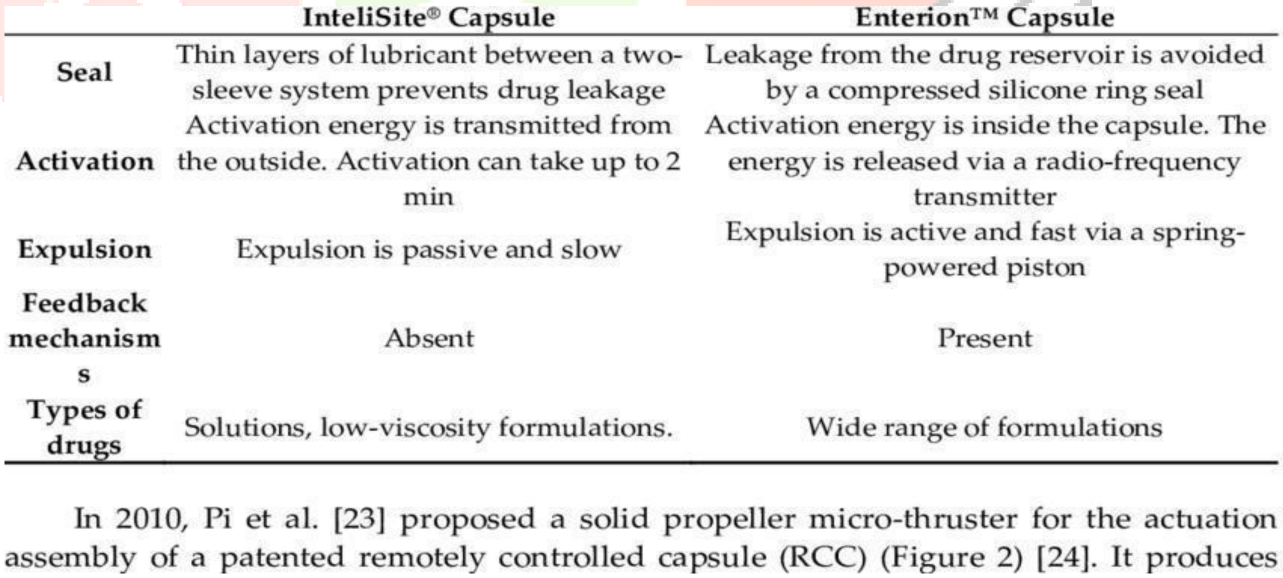
The high-frequency (HF) capsule [9], created in Germany in the 1980s, serves as the first example in this discipline. In this technique, a radiofrequency generator outside the body heats and melts a thread, causing it to pierce a latex balloon carrying the chemical with a released needle [10].Similarly, InteliSite® (Scintipharma Inc., Lexington, KY, USA) makes use of a similar technique. A spring mechanism in the capsule's inner cage is activated by heat from an external radiofrequency signal to push the reservoir's contents (0.8 mL capacity) through the outer shell [11]. The magnetic active agent release system (MAARS) (Mathesy GmbH, Jena, Germany) is another illustration of a passive mechanism. The carrier capsule is made up of two magnetic components that are joined together and medication [12]. More recently, the RaniPillTM (Rani Therapeutics, San Jose, CA, USA) investigated another releasing method. A robotic autoinjector and a self- inflating balloon are embedded in a capsule made of hydroxypropyl methylcellulose that is protected from dissolving in the stomach's acid by an enteric coating. The coating melts as the pill reaches the SB (higher pH), expanding the balloon. When the balloon is inflated, a dissolvable needle is made visible, enabling drug administration through the intestinal wall. [13]. This technique was primarily created for use with chronically unwell patients who needed frequent intramuscular or subcutaneous injections. Furthermore, these methods have been proposed for drugs like octreotide, TNF inhibitors, parathormone, or insulin. Although attractive, these systems have drawbacks. The content may leak if the outer shell's sealing is imperfect, the activation may fail due to interposed tissues weakening the electromagnetic signal, and the site targeting prior to release may not be accurate or practical (for instance, the InteliSite® capsule relies on gamma scintigraphy). Active systems were later created to address these constraints.

Active Release Mechanisms-

The Medimetrics (Eindhoven, Netherlands) single-use electronic IntelliCap® gadget is made up of a cap (which holds 0.3 mL of liquid medication), a microcontroller, a battery, pH and temperature sensors, an RF transmitter, and a pump[14]. A laptop can be used to manually manage drug delivery, or the drug can be pre-programmed to release at a certain location in the GI tract. With wireless data transfer,the device keeps track of local temperatures, pH, and resident times along the GI tract. This enables automatic drug release with placement based on pH and temperature, which correlates well with scintigraphy. [15]. Additionally, depending on the therapeutic or research goal, the screw-pump release mechanism can be employed for fluids, pastes, or suspensions in a customized way [16,17]. A gas-producing cell and a receiver system were included in the capsule-shaped device Groening and Bensmann presented in 2009 [18]. A polypropylene cylinder (14.5 x 6.7 mm) with a 4.8 mm long piston separating the drug reservoir and the gas-producing cell serves as the body of the capsule. Oxprenolol hydrochloride (0.7 g/mL) is an aqueous solution that is present in the drug reservoir in 0.17 mL and is discharged through a 0.6 mm borehole in the rubber form sealing. The 3.5 7.8 mm (size 3) gas-producing cell from Simatec, Herzogenbuchsee, Switzerland, is bonded to the cylinder. The electric circuit, which includes a tiny coil, an SMD trim condenser, two SMD Skottky diodes, and a MOSFET transistor, is installed close to the gas- producing cell. This device has a 1 hour activation period for releasing the dose, and only 16% of the capsule volume is needed for the loaded medicine. The magnetically actuated soft capsule endoscope (MASCE) makes use of magnetic activation methods as well. When turned on, these two permanent magnets compress a soft material. Consequently, the medication might be released from a

0.17 mL internal chamber [19].The ability to administer the medication in various doses at a set rate is this system's key benefit. The EnterionTM capsule (Phaeton Research, Nottingham, UK) likewise uses a magnetic-field-driven mechanism (Figure 1). This 32 x 11 mm capsule has a 1 mL reservoir within, as well as a spring mechanism that may be opened by a magnetic impulse. The capsule's piston quickly releases the medication after being opened by an internal heating element [2o]. Comparative data between this system's features and those of the InteliSite® capsule can be found in Table 1.





	InteliSite® Capsule	Enterion™ Capsule
Seal	Thin layers of lubricant between a two-sleeve system prevents drug leakage	Leakage from the drug reservoir is avoided by a compressed silicone ring seal
Activation	Activation energy is transmitted from the outside. Activation can take up to 2 min	Activation energy is inside the capsule. The energy is released via a radio-frequency transmitter
Expulsion	Expulsion is passive and slow	Expulsion is active and fast via a spring-powered piston
Feedback mechanisms	Absent	Present
Types of drugs	Solutions, low-viscosity formulations.	Wide range of formulations

In 2010, Pi et al. [23] proposed a solid propeller micro-thruster for the actuation assembly of a patented remotely controlled capsule (RCC) (Figure 2) [24]. It produces

Figure 1.Schematic drawing of the Enterion capsule

- DESIGN-

Robotic capsules are utilized for drug delivery in both therapy and diagnosis.

The components of the capsule robot change in accordance with how it is intendedto be used.

Capsule robots for endoscopy

Disorders of various areas of the GI tract are diagnosed using a wireless capsule endoscope (WCE). Depending on the organ it is utilized for, the capsule endoscope has various properties. You swallow a tiny cameo that is roughly the size of a large vitamin pill during a capsule endoscopy procedure. Like

The colon, small intestine, esophagus, and stomach can all be examined using a capsule endoscopy. It is swallowed like any other capsule and passes from the mouth to the stomach through the esophagus.

In general, a capsule endoscopy is very safe

- CAPSULE ENDOSCOPE FOR OESOPHAGUS-

Due to the ingested substance's extremely quick (10s) transit time via the oesophagus, a dual camera system and faster image capturing speed are needed. The PillCam ESO marked capsule has a frame rate of 14 frames per ssecon[21,22].

Figure 2 : Capsule endoscopy for Oesophagus Capsule endoscope for stomac

The use of floating capsules is necessary. A propeller is utilized to offer 3D steerable locomotion the ability. The advertised capsule, PillCam ESO 2, features an 18 frames per second frame rate [23,24].

The gelatin coating on the RoboCap deteriorates after it enters the stomach, and a pH-sensitive membrane breaks as it enters the small intestine due to the pH change. By closing an electrical circuit inside the capsule, this activates the RoboCap

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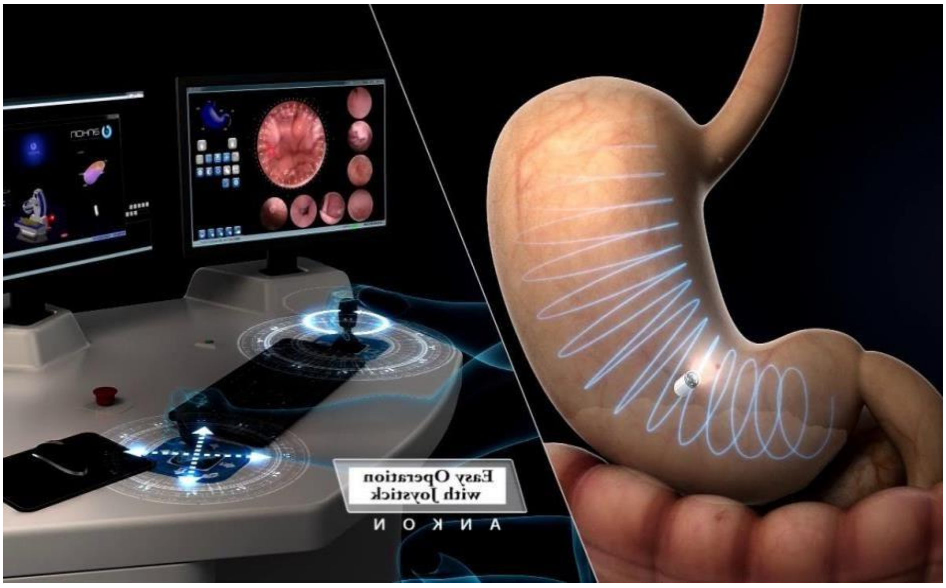

Figure 3: capsule endoscope for Stomach

A cutting-edge device called the Stomach Capsule System combines magnetic control with creative and sophisticated software to enable medical professionals remote robotic control over the capsule that is inside the human body. An operator from a control panel or remote console can use NaviCam® to guide the minimally invasive treatment in real-time in five dimensions (two rotational and three translational planes).The NaviCam® Stomach System was demonstrated to be a safe way to visualize the gastric mucosa by remote magnetic manipulation without the requirement for intubation or sedation in a significant, prospective, multicenter blinded research.2The ER environment is one of the settings where the NaviCam® Stomach System can be used in clinics and hospitals.The natural motility and gravity of the digestive tract, especially the stomach, are what drive traditional capsule endoscopy. Complete viewing of the gastrointestinal cavity has hitherto been impossible due to these restrictio

- CAPSULE ENDOSCOPE FOR SMALL INTESTINE-

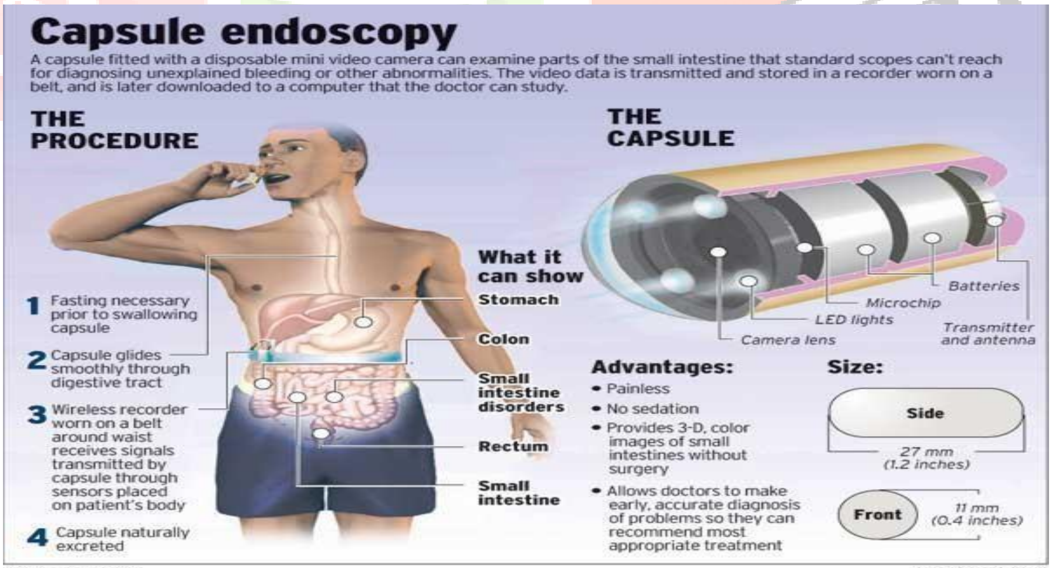

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Figure 3 : Capsule endoscope for small intestine

Capsule travels through the small intestine by peristaltic movement.

Locomotion that is active is possible. A strong battery backup is necessary if the capsule is meant to detect symptoms in the small intestine for a prolonged period of time. PillCam SB2 is the advertised product, and its frame rate is 2 frames per second. PillCam SB, OMOM, Endocapsule, and MicroCam Capsule are more brands of marketed capsule endoscopes [21].

CAPSULE ENDOSCOPE FOR LARGE INTESTINE-

Active movement is required to examine the whole surface area of the internalintestinal wall due to the huge diameter of the big intestine. Comparatively speaking to other capsule endoscopes, capsules can be longer in length. PillCam colon is the brand-named capsule, and its frame rate is 4-35 frames/s [22].

Components [27]

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
  iv) illumination, and
  v) modality.
- Receiver-transmitter

FABRICATION[28]-

The biggest difficulty in creating a capsule robot is fitting multiple components into a limited space. To perform tasks including vision, movement, telemetry, biocompatibility, localization, sensors, power source, and other interventional systems, a capsule endoscope is made up of many parts. Dependingon the intended usage, some of these elements may be present.

VISION-

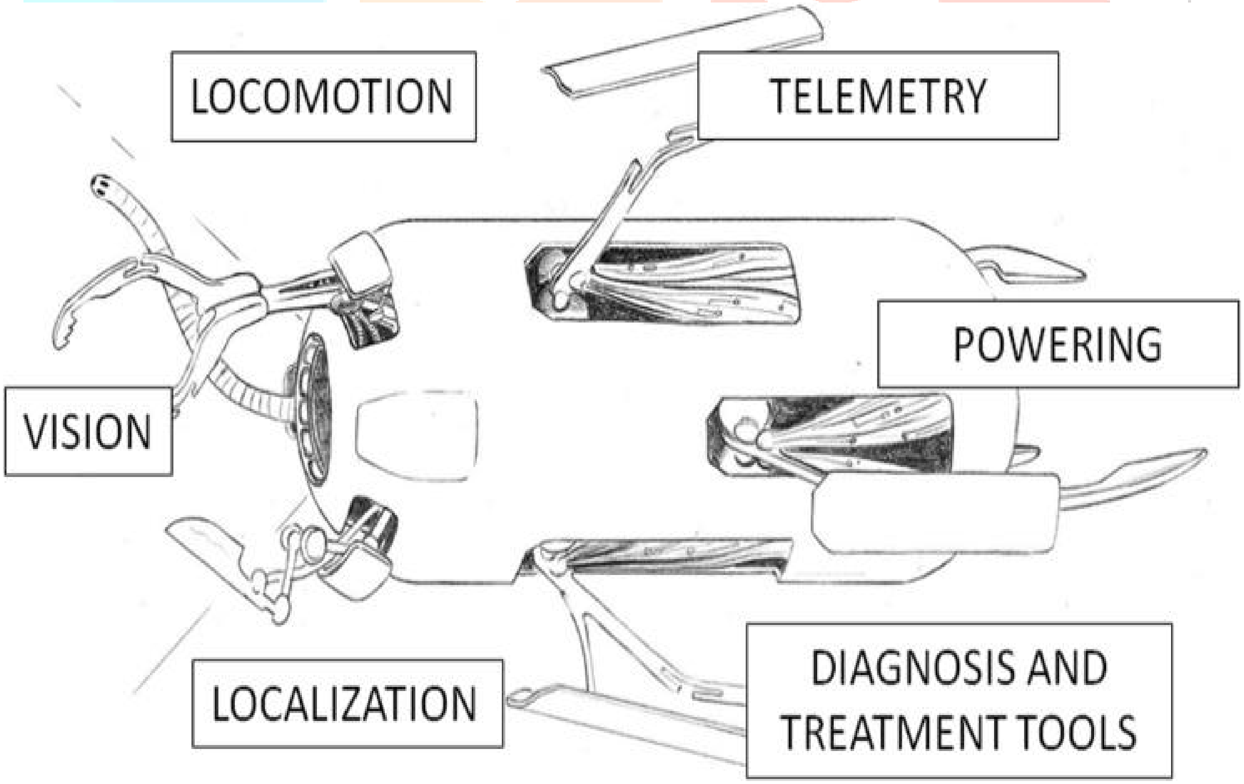
Of course, the primary goal of a CE is to capture photos of the inside anatomy. As a result, when building these systems, imaging capabilities— including modality, sensor characteristics, and illumination—must be taken into account.[29,30] Many different solutions with a wide range of capabilities have been suggested. These will be taken into account in this section: Field-of-view (FoV), sensor resolution, sensor position, and

- *Locomotion-*

Designing a robotic endoscopic capsule requires careful consideration oflocomotion, which is an essential component. Depending on whether they move ina regulated or uncontrolled way, WCEs can be either active or passive. The market is now dominated by passive locomotion (such as PillCam® WCEs). Active locomotion is still mostly a research topic, but it has a lot of potential because it would let the doctor move the tool for accurate targeting. However, technical integration is the fundamental problem. Due to limitations on actuation size and power, it is challenging to integrate a locomotion module within a swallowable capsule. For instance, a legged capsule device consumes roughly 400 mW of power just from the motors, necessitating the incorporation of a large and capacitance battery.[31]There are two major methods for implementing active locomotion in an endoscopic swallowable capsule: the first involves embedding a miniature locomotion system (or systems) inside; the second requires an external approach; and the third involves external locomotion. The latter method frequently makes use of magnetic field sources.

- *Internal locomotion-*

The most important solutions to the literature's investigation of various internal locomotion approaches will be discussed and provided here.Tortora et al. created an intriguing active capsule device for gastroscopy.[32] Four independent,miniature propellers driven by DC brushed motors are used by the robotic capsule that resembles a submarine. These propellers are located in the back of the capsuleand are wirelessly controlled to ensure 3D navigation of the capsule inside a stomach filled with water. De Falco et al. have created a more sophisticated version of this capsule that has a camera module.[33] Flagellar or flap-based swimming mechanisms are other potential bio-inspired strategies for moving through a water-filled stomach cavity. 34, 35] A soft-tethered gastroscopic capsule



and water jets from a multichannel external water distribution system are used toposition the camera capsule in Caprara et al.'s recently developed novel method for stomach inspection. [36]

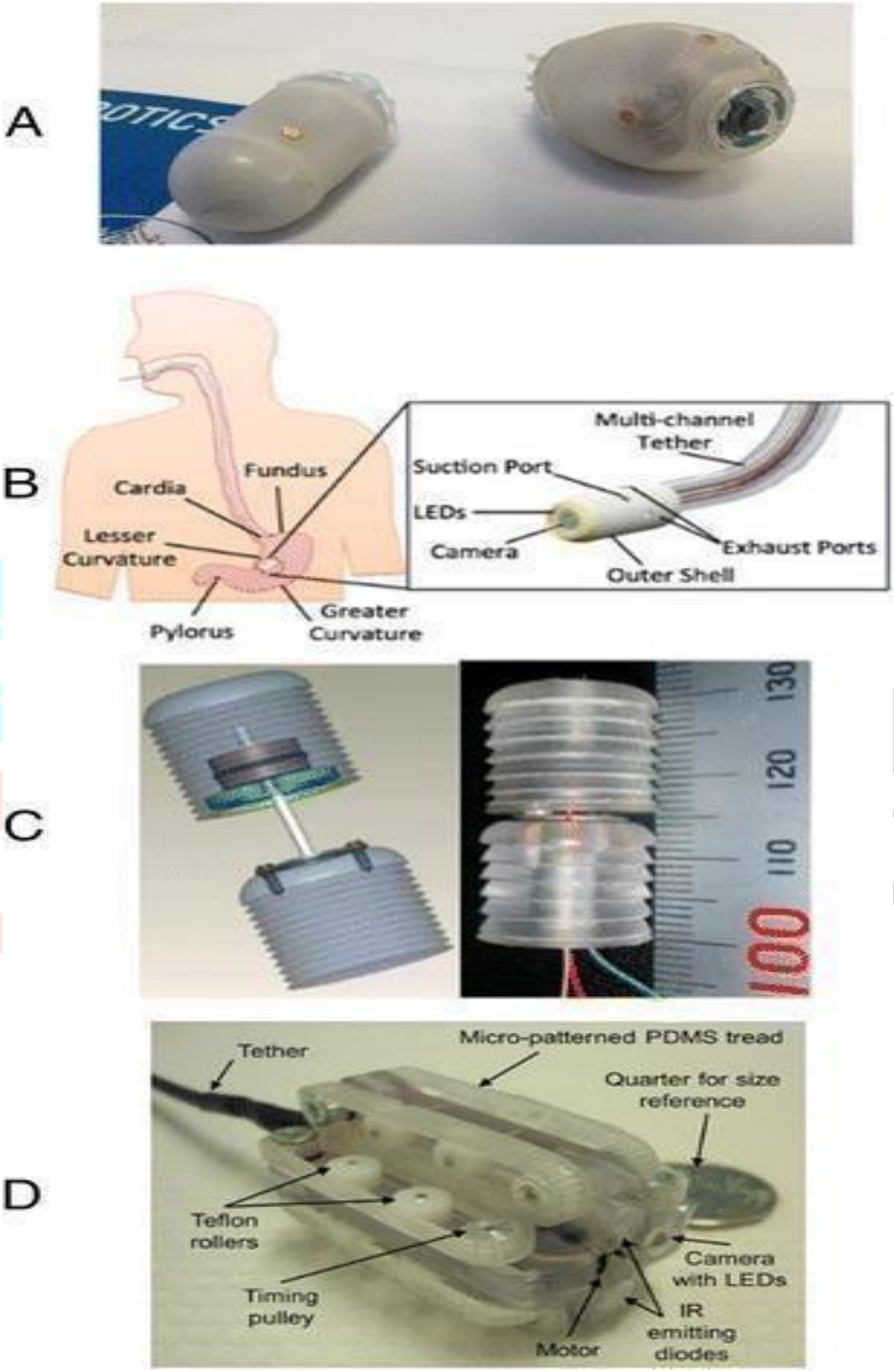


Figure 5: Internal locomotion platform of Robotic capsule

A number of internal locomotion-based techniques have been created to target both the big and small bowels as well as the entire gut. Although internal locomotion has many benefits, such as local tissue distension (i.e., no insufflation is needed for accurate lumen visualization), it also has a significant disadvantage: the excessive internal encumbrance required to achieve the size of an ingestible capsule (e.g., due to the presence of actuators, transmission mechanisms, and high-capacity power modules).

- EXTERNAL LOCOMOTION-

When using permanent magnets or electromagnets for external locomotion, external field sources interact with magnetic internal components that are embedded inside the capsule to provide navigation and steering. Because the external technique relies on a small-integrated magnetic field source, most often apermanent magnet, there are no on-board actuators, mechanisms, or batteries.[37,38]

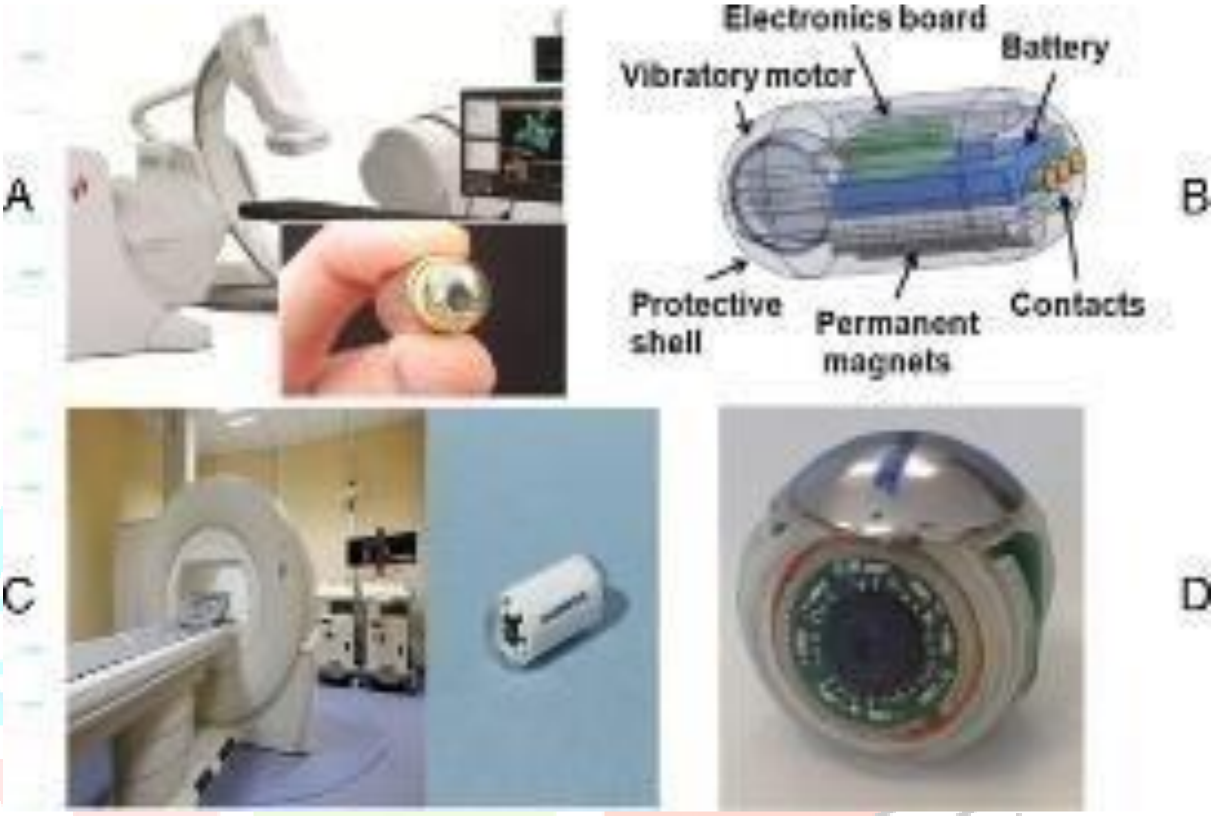


Figure 6: External locomotion platform of Robotic capsule

- TELEMETRY-

A key aspect of WCE technology is data transmission and reception. High-resolution imaging needs a telemetry system with a high data rate. The telemetry subsystem is frequently a bottleneck in capsule design due to physical restrictions and technology limitations of wireless communication[39]. Robotic endoscopic capsules can communicate by radiofrequency transmission, through the human body, or by integrating a data storage device, eliminating wireless connectivity. The human body is used as a conductive media in human body communication technology. Although it uses more skin-based sensor electrodes than RF communication, it uses less electricity.[40]Wireless capsules that communicate by radiofrequency are appealing due of their effective transmission through the skin's layers. This is especially true for transmission at low frequencies (UHF-433 ISM and below).[41] Low frequency transmission,

however, necessitates substantial electrical components. Given Imaging's capsules have a Zarlink transceiver and have a 2.7 Mb/s 403–434 MHz transmission rate.[42] The creation of impulse radio ultra-wideband antennas (IR-UWB) for WCE is the subject of some of its latest research. [43,44] A CMOS system with a superetherodyne receiver and an ON-OFF keying modulation is given.[45] We talk about a low power transmitter that operates in the ISM 434 MHz band.[46] It has a 0.13 mm CMOS architecture and uses 1.88 mW of power.

BIOCOMPATIBILITY-

The created device needs to be able to function within the body. The WCE’spackaging should be simple to swallow, biocompatible, safe, and inert to stomach acid and intestinal flora. For an optical dome, the shell should be transparent. The majority of capsule housing is made of polycarbonate material.

LOCALIZATION-

Locating the lesions in the GI tract, choosing a course of treatment for the future, and giving feedback on capsule motion (in the event of active locomotion) all depend on the position and orientation of the capsule. This makes a precise localization system essential for WCE.[47] Different localization techniques are used by commercially marketed WCEs, for example Given Imaging patented a localization technique in 2013 based on a single electromagnetic sensor coil, while Intromedic’s localization technique makes use of electric potential values.

[49] Capturing pictures from the capsule is one of the approaches utilized for localization; anatomical landmarks are used to identify each section of the GI tract.[50] An image-based tracking technique was put out by Spyrou et al. using algorithms for 3D reconstruction based on the registration of successive frames. [51]Instead, a number of research teams have concentrated on localization methods based on electromagnetic waves and magnetic fields. Human tissue can conduct low-frequency magnetic signals without any attenuation. Additionally, magnetic sensors can detect the capsule even when they are not in direct line of sight [52].[53]The size of the permanent magnet is constrained by the dimensions of the capsule, which also limits the accuracy of the results, and precision reduces if a ferromagnetic tool is accidently placed into the workspace.[55] Additionally, ifa magnetic actuation technique is used, it’s feasible that the magnetic localization system could be interfered with unintentionally.Based on a triangulation method, Salerno et al. devised a localization system that is compatible with external magnetic locomotion. To find the capsule in the GI tract, it makes use of an original on-board tri-axial magnetic sensor. Position errors of 14 mm along the X axis, 11 mm along the Y axis, and 19 mm along the Z axis were reported. X and Y are in the plane of the abdomen.Salerno et al.’s online localization system, which operates at 20 Hz and incorporates a 3D Hall sensor, 3D accelerometer, and pre- calculated magnetic field maps characterizing the external-source magnetic field, was also developed[56]. When the external magnet and localization module are 120 mm apart, the authors reported a position inaccuracy of less than 10 mm.Magnetic manipulation is compatible with the localization approach put out by Di Natali et al. [57,58]. It is a real-time detection method that makes use of numerous sensors and a predicted magnetic field map. Within a 15 cm radius spherical workspace, the suggested technique demonstrated position detection errors of less than 5 mm and angular errors of less than 19°. A Jacobian-based iterative technique for magnetic localization in robotic capsule endoscopy was put out by the same authors. Since the overall refresh rate was 7 ms, closed-loop control techniques for magnetic manipulation were able to run at rates higher than 100 Hz. In cylindrical coordinates, the average localization error was less than 7 mm in the radial and axial components and less than 5° in the azimuthal component. [59]These technologies are combined with electromagnetic wave techniques. In both outdoor and indoor settings, radio frequency has been routinelyutilized to locate objects with an accuracy of hundreds of millimeters.[60] This localization technique was incorporated into the PillCam®SB system by Given Imaging Inc. The strength of the signals the capsule emits is measured by eight sensors that are implanted in the upper abdomen. The highest position error is 114 mm, with a 37.7 mm average inaccuracy.[61]Other strategies that are currently employed in the clinical procedure are suggested by medical practices. The use of medical imaging is one of these strategies. It is also possible to use X-rays to follow an object, such as an endoscopic capsule inserted into the digestive system.[62] The Enterion capsule, a form of medication delivery capsule, is positioned in real time using the gamma scintigraphy technology.[63]Dumoulin et al. suggested using an MRI scanner to track interventional devices in real time. [64]

❖ SENSOR-

The area that the traveling capsule images depends on where the sensor and lens are located. The majority of image sensors are installed at the tip of the capsule since most devices are built with an anticipated travel direction in the longaxis of the capsule. More recently, multi-camera capsules with the potential to capture forward- and backward-looking images, such PillCam®, have been created.UGI and colon 2 capsules. Lens design may also provide comparable effects.[65] A single sensor could be utilized to generate a multi-view image whilemaintaining a compact device footprint, in particular, microlens arrays or lenticular lens arrays, which have been proven in laparoscopic surgery[66]. The use of a side viewing sensor has also been investigated in various configurations because facing ahead isn't always the clinically best option.[67] With side viewing capabilities, it may be possible to map the entire lumen around the capsule and assure continuous monitoring, which can be crucial for mapping algorithms.Powering Due to size restrictions and high power-consuming components like LEDs, power management is a significant difficulty in WCE.[68] Silver oxide button batteries are typically used to power capsules. Up to three of them can run continuously for 15 hours.[69] Thin film batteries and lithium ion polymer batteries are viable alternatives to increase power density and minimize battery size.[70] There have also been studies into wireless power transfer. Since it is non-invasive and non-ionizing, RF power transfer is especially well suited for medical equipment.[71] We show an inductive power system with a 300 mW output operating at 1 MHz.[72] In is a demonstration of a portable magnetic power transmission device.[73] The system's energy conversion efficiency on a pig during testing was 2.8%. It introduces a wireless charging system that uses induction.[74] It has a power output of up to 1 W and can recharge a VARTA CP 1254 battery in 20 minutes. In [75] A FEM simulation is used to compare analytically simple solenoids, pairs of solenoids, double-layer solenoids, segmented solenoids, and Helmholtz power transmission coils (PTCs). It demonstrates the highest power transfer capability of the segmented solenoid PTC.

❖ CONCLUSION-

A non-invasive technique for GI problem diagnosis and treatment is capsule endoscopy. WCE may eventually replace both diagnostic and flexible endoscopies for interventional use by adding features like medication delivery and body fluid/tissue sampling. Robotic capsules can be created to administer drugs tospecific areas. By managing the medication release in response to receiving wireless signals from outside, controlled drug delivery can be achieved. Robots in capsule form may one day perform multiple tasks, including diagnosis and treatment. To selectively target malignant cells during chemotherapy, capsule robots can be quite useful. The future of the diagnostic and therapeutic fields belongs to capsule robots.

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