Ingestible devices for long-term gastrointestinal residency: a review

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Abstract
Ingestible devices have been gaining attention from the medical community due to their noninvasive use in diagnostics and treatment of the gastrointestinal (GI) tract. However, their passive locomotion limits their GI residency period. Ingestible sensors residing in the GI tract are capable of providing continuous data, while long-acting ingestible drug delivery systems can reduce medication nonadherence. This paper presents a comprehensive overview of the state-of-the-art, long-term ingestible devices (LTIDs). Additionally, this review summarizes the current status of ingestible devices that persist in the GI tract for a prolonged period, as well as their inhabitance mechanisms and applications. Also included are relevant information about the GI structure and design considerations for understanding the significance and challenges associated with LTIDs. Finally, we discuss several potential applications of the LTIDs for therapeutic intervention in the GI tract and monitoring the physiology and pathophysiology of the GI tract for an extended period.

1. Introduction
Looking back to 1957, when the first-ever ingestible device was invented, it is evident how far the field of ingestible technology has matured. Back then, the device was known as endoradiosonde (radio pill) [1], which measured pressure, pH, and temperature in the gastrointestinal (GI) tract [2, 3]. In the 2000s, a wireless motility capsule (WMC) called SmartPill™ (SmartPill Corporation, Buffalo, NY, USA) was developed, approved, and commercialized to simultaneously measure pressure, pH, and temperature, which are the most important GI signals for diagnosing patients with slow gastric emptying [4]. Similarly, the concept of a video capsule endoscope (VCE) was developed in 1981, but it was not approved by the Food and Drug Administration (FDA) for commercial use until 2001 [5]. Since the start of the new century, miniaturization of electronic circuits [6] and powering methods [7], advancements in biomaterials [8], and innovation in drug delivery systems [9] have paved the way for researchers in the biomechanical sector to develop ingestible devices with a wide range of applications [10–12], including temperature sensing [13–15], pH monitoring [14, 15], motility sensing [2, 14], capsule endoscopy [16], biopsy [17], GI gas sensing [18], inflammation detection [19, 20], drug delivery [15, 21], and adherence monitoring [22, 23].

Despite many revolutionary advancements, there is still room for improvements and innovation in ingestible medical device research [24]. The movement of the ingestible devices inside the GI tract is passive, leading to incomplete endoscopy [25]. Moreover, most of the ingestible devices have a limited residency period in the GI tract. For example, both PillCam™ (VCE) and SmartPill™ (WMC) have a short transit time through the stomach and the intestine (less than 9 h) [26]. Due to its rapid transit through the GI tract, VCE, the most-used ingestible device, has a lower sensitivity than flexible endoscopy [27].

Researchers have developed several ingestible devices with inventive techniques for prolonging their residency periods inside the GI tract for the purposes of drug delivery, bariatric intervention, and biosensing. In this article, the ingestible device with a prolonged GI residency period is referred to as a long-term ingestible device (LTID) and is similar to implantable devices in function but is not placed surgically or
endoscopically. It has the following characteristics: (a) ingestible (i.e., orally administrable), (b) retentive in the GI tract for at least 24 h, and (c) either excretable with feces or dissolvable in the GI. Devices designed with all these characteristics are presented in table 1.

This article aims to present the current status of ingestible devices with an extended residency in the GI tract. First, we provide the anatomical and chemical characteristics of the GI tract that are pertinent to LTID function. We describe the mechanisms that enable existing LTIDs to stay in the GI tract for an extended period. Next, we provide the current applications of the LTIDs in drug delivery, obesity treatment, and biosensing. We then discuss the challenges and design considerations for LTIDs. We conclude our review with some potential applications for LTIDs to improve GI evaluation and chronic disease treatment.

2. The GI tract properties

The GI tract is a collection of hollow organs, including the mouth, esophagus, stomach, small intestine, large intestine, rectum, and anus, which digest food, absorb nutrients, and excrete the waste out of the body [44]. The other functions of the GI tract involve training the immune system [45], acting as a host for microbiomes [46], and communicating with the central nervous system [47]. Understanding the anatomical, physiological, and chemical properties of the GI tract is critical to overcoming the challenges of ingestible devices [48]. This section provides a description of the different organs of the GI tract (figure 1), which is essential in the development of an LTID.

2.1. Esophagus

The esophagus is the straight organ connecting the mouth to the stomach. It is tubular, 18–25 cm in length, and approximately 20 mm in diameter in the adult human [49], and it has a wall thickness of 4.7 mm (4.44–4.95 mm) when contracted and 2.11 mm (2.00–2.23 mm) when dilated [50]. Food passes through the esophagus in less than 10 s unless there is an esophageal disorder causing obstructions [51]. In normal conditions, the pH of the esophagus is between five and seven [52] but falls below four in the presence of gastroesophageal reflux disease (GERD) [66]. Many pathological markers such as motility disorder, cancer, and gastric fluid reflux can be identified in this region. As is the case with LTIDs taking up residence in any part of the GI, the obstruction must be considered when deploying an LTID to the esophagus. Therefore, the PillCam™ ESO was developed specifically to view the esophagus for a short duration. It provides data for diagnosing diseases like esophageal varices, GERD, Barrett’s esophagus, and esophageal cancer. Though the esophagus is affected by many gut disorders, drug delivery through the esophagus is an emerging field of research [67, 68]. A major challenge for esophageal device design could be the reduced area for food to pass through, which can cause considerable discomfort to the patients if the device is too large.

2.2. Stomach

The stomach is the digestive organ situated between the esophagus and the intestine. The functions of the stomach include storage, acid secretion, enzyme secretion, and GI motility [69]. The pylorus connects the intestine to the stomach and has a diameter that never exceeds 2.0 cm in humans and has a range of 1.3–2.0 cm [53]. In the average population, the gastric wall thickness is around 4–6 mm [54]. The stomach's width is 25 cm, and the distended volume of the human stomach can vary based on gender and age but not body weight [70]; its distended volume typically ranges between 2 to 4 l in adults [55]. Gastric transit time through the stomach may be instant (for liquid food) or to up to 6 h (for solid and fatty food) [56] and varies with meal composition [71], smoking [72], and gender [73]. For example, gastric emptying is quicker in smokers compared to nonsmokers and in males compared to females. Several fluids, ions, and enzymes are present in the stomach. The presence of hydrochloric acid produced by the gastric parietal cells and other chemicals in the stomach makes the gastric environment acidic (with the pH falling between 1 and 4.7 in the fasting state) [57]. For grinding and mixing food and passing it to the intestine, the stomach produces mechanical forces of 5–10 KPa, about 1000 cycles throughout the day [74]. Diseases like gastric cancer, gastritis, peptic ulcer, and gastroparesis are diagnosed through the stomach. The imbalance of pH in the stomach is a good indication of diseases like GERD. Due to the stomach's shape, the stomach is considered the easiest target for implanting a long-term ingestible medical device. As a storage component, the stomach controls the food intake, making it the only target for bariatric intervention using LTIDs.

2.3. Small intestine

The small intestine is the site of the GI tract’s most significant nutrient absorption. It has three parts: the duodenum, jejunum, and ileum. The intestine's shape is tubular. The average diameter of the intestine is 25 mm in adults [58], and the length of the intestine varies with height and has an average of 3–5 m [59]. The intestinal wall is thinner compared to the gastric wall (around 0.9–2 mm). The mucosa layer of the intestine
| Location      | Mechanism type      | Device name                        | Size                                      | Powering source | Residency period | Research progress | Applications                          | References |
|--------------|---------------------|-----------------------------------|-------------------------------------------|-----------------|-----------------|-------------------|----------------------------------------|------------|
| Stomach      | Hydrogels           | Ingestible hydrogel device        | Diameter 1 cm and length 3 cm 000" size capsule | Chemical        | 30 d            | Tested in pigs    | Biosensing and drug delivery           | [28]       |
|              |                     | Triggerable tough hydrogel        |                                           |                 |                 |                   |                                        |            |
|              |                     | Unfolding systems                |                                           |                 |                 |                   |                                        |            |
| Unfolding star structure | Foldable in size 000 gelatin capsule | Chemical | 2–4 weeks | Tested in pigs | Drug delivery | [30–32] |            |
|              |                     | Gastric resident electronics      |                                           |                 |                 |                   |                                        |            |
|              |                     | Unfolding ring                    |                                           |                 |                 |                   |                                        |            |
| Inflatable balloons | Wireless obesity treatment capsule | Length 157 mm and diameter 57 mm | Chemical and electric | On command exit | Prototype developed | Obesity treatment | [35]       |
|              | Swallowable sensing device | Length 25 mm and diameter 15 mm | Chemical and electric | On command exit | Prototype developed | Biosensing | [36]       |
|              | Wirelessly powered capsule robot | Length 80 mm and diameter 30 mm | Chemical and electric | On command exit | Prototype developed | Obesity treatment | [37]       |
|              | Magnetically actuated capsule endoscope | Length 27 mm and diameter 9.6 mm | Chemical and magnetic | On command exit | Tested in pigs | Obesity treatment | [38]       |
|              | EndoPil             | Length 35 mm and diameter 13 mm | Chemical and magnetic | On command exit | Tested in human | Obesity treatment | [39]       |
|              | Soft robots         | Shape programmable soft robot     | Length 40 mm and diameter 15 mm          | Magnetic        | On command exit | Prototype developed | Biosensing | [40]       |
| Small intestine | Tissue attachment | ICR                               | Length 37.5 mm and diameter 15 mm        | Electric        | 40–52 h         | Tested in pigs    | Drug delivery and biosensing           | [41]       |
|              |                     | Magnetic hydrogel                 | Radius 10 mm and thickness 1 mm          | Magnetic        | 7 d             | Tested in mouse   | Health monitoring and drug delivery    | [42]       |

* Size 000 capsules has a length of 26.14 mm and diameter of 9.91 mm [43].
is also thinner than the stomach, making it a suitable drug absorption site [75]. The intestine contains some fluid and enzymes, such as pancreatic enzymes, bile acid, and mucus. The pH in the intestine reaches a neutral value after the acidic environment of the stomach. The pH is 6 in the duodenum and 7.4 in the terminal ileum [60]. The small intestine has two prominent motions: segmentation and peristalsis [76]. Segmentation mixes the food with digestive juices for nutrient and water absorption, and peristalsis moves the contents in the anal direction. Segmentation frequency is about 12 cycles per minute in the duodenum and 3 to 4 cycles per minute in the ileum [77]. The peristalsis has a wavelength of 10 cm and a velocity of 1 to 2 cm min⁻¹ [78]. Ingestible devices also experience contact pressure in the intestine due to muscle contraction and small lumen diameter. Terry et al measured the contact force exerted on a capsule by the small bowel using a migrating motor complex force sensor [79–82]. The contact force varied along with the location of the small bowel because of the diameter difference and was between 0.9 N cm⁻¹ and 2.9 N cm⁻¹ [82]. The transit time through the intestine is about 261 min (241–402 min) and varies with the food administrated [61]. VCEs designed for the small intestine identify inflammatory bowel disease, small bowel lesions, and small bowel tumors or cancers. Furthermore, the small intestine is a better target for drug delivery due to its absorption capabilities. For example, RaniPill® by Rani therapeutics is designed to deliver biological drugs in the small intestine, which protects the drug from the acidic environment of the stomach. However, drugs absorbed in the intestine will enter the liver and can be metabolized by liver enzymes, which may alter the drug and reduce efficacy [83].

2.4. Large intestine

The large intestine is the final organ in the GI tract and is divided into six sections: the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The large intestine functions include absorbing water and electrolytes, solidifying food to form feces, and propelling it towards the anus [62]. Vitamins are also produced and absorbed in the large intestine [84]. The shape of the large intestine is also tubular like the small intestine, but the average length and diameter are 150 cm [62] and 48 mm [58], respectively. When distended, the colonic wall thickness is between 0.2 and 2.5 mm, while in the contracted state, it can be up to 6 mm [63]. The pH in the caecum has a mean of 6.4, which rises to 7 in the left colon [64]. The motions present in the large colon are similar to the small intestine. A wide variety of bacteria present here (10¹² colony-forming unit/mL or higher in concentration), making it an excellent target for microbiome sensing [85]. The colon is also an optimal target for drug delivery [86]. Colonic transit time (CTT) is generally higher than gastric and small intestinal transit time and depends on fiber in the diet [87]. The mean CTT is 4 h with an upper limit of 84 h [65]. Ingestible devices are typically used for identifying

![Figure 1. The physical and chemical properties of the GI organs: esophagus [49–52]; stomach [53–57]; small intestine [58–61], and large intestine [58, 62, 63–65]. Created with BioRender.com.](image-url)
colonic diseases, such as inflammatory bowel disease, colorectal cancer, ulcerative colitis, colonic polyps, and more.

3. Mechanisms used in LTIDs

Ingestible devices require innovative techniques for achieving long-term residency in the GI tract. This section provides the existing GI residency mechanisms and their discharge methods from the body used in LTIDs. The mechanisms are divided into two types based on their residency location: (a) gastric residency mechanisms and (b) intestinal residency mechanisms. The residency mechanism of the esophagus is not discussed in this section as no existing literature provides such a mechanism. Although several long-term devices are implanted in the esophagus [88, 89] and colon [90, 91], they are implanted surgically or with a catheter/endoscope, not through oral administration.

3.1. Gastric residency mechanisms

When gastric residency for an ingestible device is considered, the key is to prevent its passage through the pylorus, which is generally obtained by some form of change in shape or size. Here, gastric residency mechanisms are categorized according to their retention mechanisms: (a) hydrogels, (b) unfolding systems, (c) inflatable balloons, and (d) soft robots.

3.1.1. Hydrogels

Hydrophilic gels (or hydrogels, for short) are crosslinked hydrophilic polymer chains that swell in the presence of water and have a wide range of biomedical applications due to their high biocompatibility [92]. As the hydrogels absorb water and swell, they can be used for GI residency [28, 29, 93–95]. For gastric residency, the hydrogels must swell to a greater volume before the start of gastric emptying and must have the ability to withstand the cyclic mechanical forces inside the stomach. One example of hydrogels for prolonging gastric residency is the ingestible hydrogel device by Liu et al. [28] (figure 2(a)). This ingestible hydrogel device used superabsorbent hydrogel particles (polyacrylic acid) encapsulated in an anti-fatigue porous hydrogel membrane of polyvinyl alcohol and freeze-thawed polyvinyl alcohol to make the device tough and fatigue-resistant. It had a high swelling ratio and speed, swelling to 100 times its original volume within 15 min. The device was tested by ingesting it into Yorkshire pigs, and it preserved its swollen shape for 9–29 d without passing through the pylorus. For the triggerable exit of the hydrogel from the GI tract, a calcium chloride solution was used to shrink the superabsorbent particles.

3.1.2. Unfolding systems

For gastric retention, an unfolding system can be tucked into a pharmaceutical carrier (gelatin capsule), which dissolves in the gastric environment and unfolds into a shape with a span greater than the diameter of the pylorus. Researchers developed several gastro-retentive doses by using unfolding systems in the past century [96]. One recent development in the unfolding system is the unfolding star structure [30–32](figure 2(b)). This structure had a core made of elastomeric material and six arms connected to it, giving it a stellate structure. The elastomeric core provides the structure and flexibility for folding the system into a capsule form, while the arms give the structure rigidity. The unfolding force depends on the elastomeric core and is designed to be greater than 1.5 N (the maximum gastric antrum force) to resist folding in the stomach. In vivo studies with pigs, this structure could persist in the gastric environment for up to 30 d [32]. Zhang et al developed a pH-responsive foldable ring, made of poly(acryloyl 6-aminocaproic acid) and poly(methacrylic acid-co-ethyl acrylate), for gastric residency and achieved gastric retention of 4–7 d in pigs [34]. Another example of an unfolding structure in the stomach is the 3D-printed gastric resident electronics (GRE) for remote diagnostics and automated therapeutics (figure 3) [33]. The device had a capsule-shaped body with two arms made of biocompatible poly-L-lactic acid connected to the capsule body with thermoplastic (polyurethane). The arms unfold in the gastric juice with a span of 48 mm. The device attained gastric residency for 36 d and maintained wireless communication with the outside for 15 d. All of the systems mentioned above disintegrated over time, enabling safe passage through the GI tract.

3.1.3. Inflatable balloon

Another method for achieving gastric residency is incorporating an inflatable balloon in the ingestible device [35–39, 97]. The ingestible device with a balloon is first swallowed, and the balloon is inflated inside the stomach through a chemical reaction producing CO₂ for attaining gastric residency. Once inflated, the system can stay in the stomach for an extended period unless the balloon is deflated (figure 2(c)). Kencana et al developed a volume controllable ingestible capsule robot that used acetic acid and sodium bicarbonate for CO₂ production, and the process was operated by an onboard actuator controlled by an external signal [35].
Figure 2. Gastric residency mechanism. (a) Hydrogel (reproduced from [28], CC BY 4.0), (b) unfolding systems (from [30], Reprinted with permission from AAAS), (c) inflatable balloon (© [2016] IEEE. Reprinted, with permission, from [36]) and (d) soft robot (© [2012] IEEE. Reprinted, with permission, from [40]).

Figure 3. GRE with unfoldable arms for gastric residency including a drug delivery module and integrated electronics and a power system for communication and control. Reproduced from [33], CC BY 4.0, © 2019 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.
Another example of an inflatable balloon mechanism was developed by Yan et al., in which the mechanism is inflated by a wireless communication system outside the body [37]. The receiver present in the capsule robot triggers the controller, which drives the microactuator to initiate the chemical reaction to produce CO\textsubscript{2} for inflating the balloon. For removing the capsule from the stomach, the actuator releases the CO\textsubscript{2} from the balloon to the stomach enabling natural excretion of the capsule robot. Nakamura et al. also used the same reaction for producing CO\textsubscript{2} in their device, but it was divided into two sections, one containing the acid and the other containing the sodium, separated by gelatin and edible glue [36]. The glue and gelatin melted in the gastric juice and internal temperature, allowing the mixing of the chemicals for inflating the balloon. For removing the device from the stomach, the balloon was deflated using wireless communication from outside of the body, which triggered the actuation of a needle to penetrate the balloon and release the CO\textsubscript{2}. If used for biosensing, the device would consist of a deflation module, a memory microcontroller unit, a wireless communication module and power supply, a rechargeable battery, and a sensor that could supposedly increase the dimensions. Do et al. further simplified the mechanism by using a magnetic actuation system with an external magnetic field to open the inflation valve (figure 4) [38, 39, 97, 98]. The external magnetic field also controlled the deflation valve for removing the device from the stomach after treatment.

### 3.1.4. Soft robots

Soft robots adapt to their environment through easily deformable material, which could be used for long-term retention in the GI tract. A semi-implantable, shape-programmable soft capsule robot was developed with a bistable mechanism: an initial cylindrical shape for oral administration and a spherical shape for gastric retention (figure 2(d)) [40, 99]. The robot has two tiny internal permanent magnets, and a permanent external magnet is used for inducing the transformation between the two states. The robot exits the body by going back to its cylindrical form. The structure of this robot is provided in figure 5.

### 3.2. Intestinal residency mechanisms

Unlike the stomach, the change in shape is not as helpful for the ingestible devices for intestinal residency as the intestine's shape is uniform, and the peristaltic force moves it forward towards the colon. For safe passage of food through the intestine, long-term intestinal resident devices cannot cause obstruction.

Intestinal retention has already been solved by parasites living in the intestine. Poulin et al. found a similarity in the attachment mechanism used by parasites [100]. They reported that most parasites use suction and an anchor or hook present in their mouth to cling to the intestinal wall. Based on this observation, Xie et al. developed a tissue attachment mechanism (TAM), a device for long-term attachment to the GI wall [101], and Sarker et al. later optimized the mechanism by varying the design parameters [102]. This device was designed to be used with capsule robots for deploying biosensors or payloads for drug delivery. They tested their device on two pigs. X-ray images taken every day for 6 d on the 2nd pig showed no
change in location for the device. Tissue collected from the intestine after euthanizing the pigs showed no noticeable trauma to the tissue. Later, the TAM was added to a biosensor implantation capsule robot (ICR) (figure 6) [41]. The ICR had a capsule body with circuits and batteries to control the TAM separation from the capsule in the GI tract. The capsule left the GI tract, and the TAM remained attached to the intestinal wall. Upon deploying the TAM with the ICR, the maximum attachment duration was between 40 and 52 h. Due to the proof-of-concept size not being in the swallowable range, the ICR was placed inside the small intestine by laparotomy, though future versions are expected to be swallowable.

Ghosh et al developed a similar intestinal mechanism inspired by living organisms [91]. The mechanism consisted of a multi-clawed gripper with microtips that grab the mucosal tissue for prolonged residency. The gripper was 250 µm wide when open and 150 µm when closed. The grippers were made of thick, stiff segments and residually stressed bilayer hinges with a thermosensitive wax layer on top. When the wax coating softened at body temperature, which occurs when thermal equilibrium is attained in the body, the microtips fold and attach to the GI wall and deliver drugs for 24 h. Though retainable, this mechanism is not considered an LTID because it was designed to be implanted with a catheter through the anus for colonic drug delivery and is not ingestible.

Liu et al developed an ingestible magnetic hydrogel device that can adhere to the intestinal wall through an external wearable magnet [42]. The device was fabricated by incorporating microparticles of neodymium-iron-boron magnets into a polyvinyl alcohol hydrogel matrix. The magnetic particles were coated with a nanolayer of silica shell to protect them from corrosion in the hydrated environment of GI. The size of the magnetic hydrogel device was only 10 mm in radius and 1 mm in thickness to leave enough room for food passage. The wearable magnet (radius 25.4 mm, thickness 12.7 mm) used for enabling GI retention of the magnetic hydrogel was placed 15 mm apart from the ingestible magnetic hydrogel device. The device attained GI retention of 7 d in a mouse.

Mucoadhesives have been used in drug delivery systems for prolonging drug absorption in the intestine [103]. Nevertheless, long-term adhesion can hinder the passage of food and chyme if the device is too large.
To address this, Lee et al developed a dual-sided device with an omniphobic side to enable repulsion of the food and fluid stream and an opposite mucoadhesive side to allow attachment to the GI mucosa by the mucoadhesive side [104]. The device used carbopol polymer for mucoadhesion and cellulose acetate for its omniphobic properties. This device can be tuned with drugs for prolonged drug delivery; however, the adhesion duration of this device was not evaluated in vivo.

Several other devices are developed for the controlled movement of capsule endoscopes in the GI tract [78]. Some of these devices contained actuation systems with retaining mechanisms that enable them to stop at a particular location for better visualization and can also be used for targeted drug delivery or biopsy. For stopping at a specific location, the devices used attachment mechanisms for clinging to the intestinal mucosa [105–107]. Even though these mechanisms attached to the intestinal wall for controlled movement in the GI tract, they were not designed nor evaluated for long-term intestinal residency. As a result, these are not considered LTIDs.

4. Functions of existing LTIDs

Ingestible devices that reside in the GI tract offer a wide variety of applications. This section discusses the functions of existing LTIDs in drug delivery, obesity treatment, and biosensing.

4.1. Drug delivery

Many factors contribute to the prescribed treatment after diagnosis of a disease, and the lack of adherence to the prescribed drug dosage is one of them [108]. The adherence to medication lowers with the frequency and complexity of the dose regimen [109]. Long resident drug delivery systems can improve adherence by reducing dose frequency. Prolonging the residency of the drug delivery system in the GI tract enhances absorption and bioavailability of the drug [110].

Oral administration of ivermectin (IVM), a well-known drug for treating infections caused by different parasites [111], can kill mosquitoes after they have bitten an infected person, which reduces the chance of transmission to a healthy person [112]. Frequent administration of this drug could reduce malaria transmission, and repeated use does not cause any significant harm to the person [113]. Bellinger et al developed an LTID, a single-dose oral delivery system that delivered an IVM formulation for up to 14 d in a swine model [30]. The unfolding star structure discussed in section 3.1.2 was used for gastric residency, and the IVM was put into a polymer matrix (PCL) for controlled drug release. Compared to stromectol (commercial name for IVM), which was only effective for 2 d, their formulation (60% PCL, 20% IVM, and 24% P407) showed a better concentration over 14 d (figure 7(a)). Bellinger et al also created a mathematical model to validate that their gastric resident formulation could reduce malaria prevalence via mass drug administration.

Taking a combination of antiretroviral drugs has been proven efficient for managing HIV [114]. It requires patients to follow drug doses precisely and daily. Kirtane et al developed an ingestible gastric resident drug delivery system that delivered three different antiretrovirals—dolutegravir, cabotegravir, and rilpivirine—for a week in a pig with a single administration using the same unfolding star structure discussed in section 3.1.2 (figure 7(b)) [31]. The drugs were loaded in three types of polymer matrices (polyether, polyanhydrides, and polyester) according to the recommended daily dose for achieving different release rates.

Oral administration is the most accepted by women among the methods available for contraceptive delivery. However, continuous use is essential for preventing pregnancy [115]. Moreover, discontinuous use of oral contraceptives can cause other side effects. Kirtane et al developed a once-a-month oral contraceptive and tested it in swine models using the same unfolding mechanism (figure 7(c)) [32]. The contraceptive drug (levonorgestrel) was loaded in polydimethylsiloxane-based polymer matrices for sustained release. Although the plasma concentration was achieved in the pigs, more studies need to be done to evaluate its efficacy as birth control.

Hydrogels have been used for the controlled release of drugs in vivo. Lumefantrine, an antiparasitic drug, was loaded inside hydrogels, and a constant blood concentration was maintained for 4 d by a single administration [28]. The GRE discussed in section 3.1.2 was integrated with a controlled release formulation of doxycycline (figure 7(d)) and contraceptive (figure 7(e)) in a hydrophobic, biodegradable PCL matrix–delivered drug for 7 d in a swine model [33]. Compared to the delayed-release tablet of the same weight, the controlled release formulation lasted 3 d longer. The contraceptive also had a noticeable concentration for 7 d.

4.2. Obesity treatment

Obesity is one of the major underlying causes of death globally. The percentage of obese people in the US alone was 42.4% in 2017–2018, rising from 30.5% since 1999–2000 [116]. With the rise of morbidly obese
people, bariatric surgery, which reduces the stomach's size, has become popular in the US as it does not require any dietary restriction or lifestyle change. Even though the complication and mortality rates are relatively low (4% and 0.1%, respectively), the surgery cost is high, and it permanently modifies the stomach anatomy [117]. Implanting an intragastric balloon (IGB) in the stomach is a less complicated method for weight loss as it does not permanently change the size of the stomach. While IGB is safe and efficient in weight management for obese people [118], it requires a catheter or an endoscope or surgery for insertion.
and removal by a physician. As a result, for noninvasive placement of IGB, several ingestible devices have been developed for obesity treatment in the last decade. PURETECH developed an ingestible pill named Plenity® for weight loss that is approved by the FDA for commercial use and made with superabsorbent hydrogel particles that disintegrate inside the stomach and swell to 100 times its weight by absorbing water. Besides commercial products, some literature also suggests using ingestible gastric resident systems for obesity treatment with an inflatible balloon [35, 37–39, 97, 98]. One of the ingestible IGBs was tested in a pig of 37.8 kg and induced a weight loss of 1.5 kg in a week [98]. Figure 7(f) shows an IGB with a magnetic inflatible system.

4.3. Biosensing
Monitoring the vital signs, body temperature, heart rate, and respiratory rate helps detect underlying medical conditions. The GRE and ingestible hydrogel devices were integrated with temperature sensors. The ingestible hydrogel device was integrated with a temperature sensor (DST nanoRF-T, Star-Oddi) and recorded the stomach temperature for 29 d [28]. The temperature recorded from the sensor showed distinct fluctuations in core body temperature throughout the day with the change of day–night and food intake in the pig (figure 7(g)). Similarly, GRE recorded the core body temperature for a week (figure 7(h)) and maintained communication with a cell phone via Bluetooth connection [33]. The magnetic hydrogel device was able to identify GI bleeding in rats by incorporating heme-sensing bacteria in the device [42].

5. Current challenges and future directions
Ingestible devices, in general, face several challenges to fulfill their functions in the GI tract. Many factors should be considered while designing ingestible medical devices. LTIDs, in particular, will require additional features to sustain extended residency in the GI tract. This section delves into the plausible challenges that could hinder the development of an ingestible device with long-term goals and provides some existing solutions to overcome them.

5.1. Size limitation
A challenge for developing any ingestible device is the size limitation of the swallowable capsule. When choosing the size, two critical considerations are: is it in the swallowable range, and will it cause an obstruction? The PillCam™ has dimensions of 26 mm × 13 mm and has several integrated components, like a powering unit, a communication unit, and a sensing unit. For LTIDs, the swallowable device also needs to include a long-term residency mechanism that might increase its size. In most in vivo pilot studies, the LTIDs were placed endoscopically or through surgery as the size exceeded the swallowable limits due to the presence of multiple circuits, sensors, and batteries. Miniaturization of electronic circuits and remote powering could help reduce the size of LTIDs [6]. For drug delivery systems, as the largest available swallowable capsule size is 000 (length 26.14 mm and diameter 9.91 mm), the volume for housing drugs is limited to 1.37 ml. As some drugs require higher doses (i.e. higher drug volume) for achieving plasma concentration [113], a long-term ingestible drug delivery system might not be suitable for high-volume drugs.

5.2. Materials
In the United States, the FDA does not normally regulate specific materials for implantable medical devices; instead, it evaluates the complete architecture [119]. The biocompatibility of a material is considered while designing a medical device, meaning that the chemical stability (pH in the GI tract), mechanical properties, and intrinsic toxicity of materials are generally assessed while designing an ingestible device. Typically, ingestible medical devices are transient, which decreases the risk of chronic toxicity and biofouling. However, LTIDs possess the risk of both toxic reactions and fouling. According to the guidance for ‘generally recognized as safe’, 370 substances are considered safe for use in food. Some inorganic components like zinc oxides, silica, copper, and iron, and some polymers like gelatin, cellulose, and various derivatives of poly(l-lactide-coglycolide) are included in the guidance [120], which can be modified for use in ingestible devices. However, the long-term effect of several biomaterials is unknown. Fouling of the material can be one possible barrier for long-term use, which can be minimized by applying a non-fouling surface layer over the LTIDs [121]. Zwitterionic polymer compositions have been shown to have excellent fouling resistance [122]. Hydrogels also demonstrate promising non-fouling properties [123]. Moreover, nonionic hydrophilic materials and amphilphilic materials show good non-fouling properties. Rigid biocompatible polymers could be used as a shell material for the LTIDs to protect the electric components inside of them.
5.3. Long-term powering of electrical components

Powering the electronic components is one of the major design challenges for ingestible devices, mainly due to size limitations, battery life, and the potential risk to patients. For long-term monitoring of the vital signs, LTIDs might require a powering component that continuously collects, receives, and transmits data to a receiver outside the body for several days. Ingestible devices can be powered through three techniques: in-house batteries, remote powering, and energy harvesting [124]. For confinement in a swallowable capsule, a coin or button-type battery is the most fitting choice. Even though Li-ion batteries have higher power density, they are not approved for clinical use because they can increase gastric juice pH [125]. Commercial VCEs use silver oxide batteries that generate 20 mW of power and function for eight hours [126].

Biodegradable and biocompatible batteries can replace traditional batteries. A biodegradable paper-based Mg–MoO3 battery (2 cm × 2 cm × 0.5 cm) can generate 1.6 V for 13 d [127]. SmartPill™ (WMC) has a transmitter providing data at 434 MHz with a minimum battery life of 5 d [128]. Remote energy transferring techniques, such as ultrasound, electromagnetic waves, and light, can solve battery toxicity and size limitation problems and have the potential to be used in LTIDs [129]. To avoid the leaking of toxic substances into the GI tract and facilitate more space in the capsule, RF System Lab developed a wireless powering system for a capsule endoscope called Norika [130]. External powering, however, requires external components such as wearable devices. Besides battery and wireless powering, using the human body’s resources for harvesting energy could also reduce the short battery life burden. An in vivo galvanic cell using Zn/Cu electrodes measured and transmitted temperature data from the GI tract to a receiver outside of the body for 6.1 d on average [131]. However, the size of this energy harvesting ingestible system is 40 mm × 12 mm, which is above the swallowable range but can be minimized using a smart circuit design. A piezoelectric nanogenerator generates electric power from a minuscule amount of deformation and vibration and can be used in ingestible devices by gathering energy from GI forces [132]. Other energy harvesting approaches, such as using body heat [133], can also be helpful in LTIDs.

5.4. Communication

Some LTIDs may need to maintain prolonged communication for real-time data sharing (e.g. temperature, pressure, pH, vital signs) outside the body, which could be conveyed to external equipment for analysis or treatment assistance. It may also need a communication system for performing a task, such as activating a mechanism on command signals. However, not all LTIDs require communication components, such as controlled release drug delivery for chronic diseases [30–32], but could be helpful in optional drug release (e.g. migraine patients). Generally, ingestible devices communicate through wireless RF telemetry, which typically comprises a transmitter or a receiver or a transceiver and an antenna. The antenna size must be at least one-fourth of the wavelength. As a result, RF signals with lower wavelengths (i.e. higher frequency) require a smaller antenna. However, higher frequency suffers from higher attenuation and scattering in the human body leading to a larger loss due to power absorption [134]. The RF signal attenuation is mainly due to the presence of water in the human body. Li et al used water as a medium for simulating the RF signal’s attenuation of 2.45 GHz [135]. They found that the attenuation is affected by the relative position of the receiver to the body. Both far-field and near-field RF technology are used in ingestible devices. Though far-field RF requires larger antennas than near-field RF, one key benefit is that they are omnidirectional while near-field can only transmit data in specific directions, which is generally solved using multiple receivers worn around the body. For miniaturizing the antenna size, Kim et al used an outer wall loop antenna connected to a high-speed, high-efficiency transceiver system transmitting data at 20 Mbps through a 500 MHz RF channel and only occupied 1 mm² of capsule area [136]. Miniaturized flexible antennas can also be used in LTIDs for dealing with space limitations [137]. For long-term use, low-power transceiver designs with high data rates and small antennas are needed. Using human body communication technology is another way of maintaining communication with the outside [138]. This technology is used in MiroCam™ for transferring data. It uses two gold electrodes for transmitting data and an array of electrodes attached to the human skin to receive data in which the human body works as an electronic conductor [139].

6. Potential application of LTIDs

Long residency of an ingestible device in the GI tract could enable applications such as long-term monitoring for diagnosing chronic diseases, drug delivery for several days or weeks, knowledge of microbiome behavior, and temperature and pH sensing. In this section, we discuss the potential application of LTIDs in both monitoring and treatment.
6.1. Continuous core body temperature monitoring
The rise in core body temperature (temperature within the pulmonary artery [140]) is the body’s response to infection or inflammation. Both endogenous and exogenous factors influence body temperature variability throughout the day [141, 142]. The exogenous factors mainly hinder the original or core body temperature from showing up externally [143]. Among the many methods for measuring body temperature [144], rectal temperature reflects the core body temperature the most accurately [145]. However, this method is uncomfortable and inconvenient for patients and lags behind rapidly increasing or decreasing core body temperature due to poor blood flow to the rectum [146]. In contrast, the ingestible temperature sensor can measure the core body temperature without causing any discomfort. An ingestible core body temperature sensor can be a valuable tool for the early detection of disease. Long-term core body temperature sensors can also prevent death by accidental hypothermia among elderly patients, where symptoms do not always correlate with the core temperature. Implanted an ingestible temperature sensor inside patients in the emergency unit or in a coma can detect a sudden change in the core body temperature and notify the medical personnel through wireless communication, reducing the necessity for measuring the temperature with an external means. Prolonged temperature sensing with ingestible devices could also indirectly measure early immune response to infection and physiological changes.

6.2. Microbiome behavior monitoring
The microbiome influences immune development, controls the properties of the mucus layer, promotes the development of lymphoid structures, modulates immune cell differentiation, regulates the production of immune mediators, and regulates host physiology [147]. Microbes contribute to the behavior of the human not only physiologically but also psychologically. Understanding the connection between the microbiome and human health, both physical and mental, can provide novel insights into many human behaviors and diseases, which will require long-term microbiome monitoring. Though it is very challenging with the current technology available to create an ingestible device to identify the microbiome present in the GI tract [148], researchers have already developed a device that indicates their behavior in the gut [18]. Using the device mentioned above with a long-term residency mechanism or manufacturing the device with a long-term residency component could provide researchers with more insight into the microbiome behavior of the GI tract and dysbiosis. Furthermore, one intuitive question is whether the change in the gut microbiome causes the disease or the other way around. Understanding how diet influences gut microbiota, how gut microbiota influences the diet, and how they impact the gut health of an individual could be a prospective research field. Implanted an ingestible sensor in the GI for a prolonged period could help the researcher understand the microbiome behavior.

6.3. Drug delivery
Long-term drug delivery systems have already demonstrated promising results to improve HIV, malaria, and oral contraception adherence. Similar mechanisms can be used in patients suffering from chronic diseases that require daily doses (e.g. diabetes, arthritis). Medication complexity is the most common reason for nonadherence among elderly patients with chronic kidney disease [149]. Elderly patients and patients with a psychiatric disorder (e.g. Alzheimer’s) can benefit from clinic-assisted once-a-month oral drug delivery as studies have shown that they have many difficulties following daily oral doses and have less care available [150]. Daily abdominal insulin injection for management of type 2 diabetes also hinders the patient’s compliance with the medication [151]. They are reluctant to inject insulin due to fear of needles [152], which is one reason for nonadherence among the patients. Long-term oral delivery of insulin can help with the management of type 2 diabetes or similar chronic diseases.

6.4. Replacement for wearable sensors
Wearable sensing technology (e.g. smartwatches or fitness trackers) has been in wide demand for mobile health diagnosis due to the popularization of personalized health concepts and concerns surrounding physical health [153]. The wearable sensors can measure vital signs, such as heart rate, respiratory rate, and temperature through the skin, which are crucial for diagnostics. However, they are only useful in physical sensing and not in chemical sensing and could cause skin irritations [154]. Skin temperature also does not reflect the actual core body temperature. LTIDs with Bluetooth connections can also monitor vital signs through the GI tract [155] and create a noninvasive remote monitoring platform. LTIDs can also measure the pH profile continuously for early diagnosis of GERD.

6.5. Insights into unknown diseases and their pathogenesis
The etiologies behind many GI-related disorders, for example, Crohn’s disease, ulcerative colitis, Menetrier disease, and many more, are still unknown. Monitoring the genetically susceptible group for such diseases
could provide researchers with more insights into the underlying conditions causing disease. LTIDs could provide researchers with continuous data from the GI tract and help them identify the underlying conditions.

7. Conclusion

Due to the prevalence of GI disorders and the demand for precise and noninvasive monitoring, capsule endoscopes have garnered a reputation for creating a noninvasive diagnostic and treatment platform in the last 2 decades. There have been many remarkable improvements in VCEs since the 1st FDA approval in 2001, especially in imaging technology and sensing technology with ingestible sensors. However, there has not been much improvement in locomotion, localization, residency, and lifetime. In this review article, we discussed the residency aspect of the ingestible devices. We provided several mechanisms for LTIDs and discussed their current and potential applications. We also discussed the associated challenges and design considerations for LTIDs. An important consideration is that most of the devices discussed in this article are either conceptual or tested in porcine models. The anatomy of the GI tract of a pig is different from that of a human [156]. As the primary goal behind medical device research is commercialization and clinical transition, more trials are needed with larger animals followed by human trials.

In summary, LTIDs can create a noninvasive monitoring and therapeutic platform for several days, which could help early diagnostics of disease, mobile health monitoring, extended drug delivery, obesity treatment, and many more applications. For better clinical evaluation or long-term treatment through the GI tract, further research is needed to place ingestible devices in the GI tract for a prolonged period.

Data availability statement

No new data were created or analyzed in this study.

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