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Review

Theranostic gastrointestinal residence systems

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THE BIGGER PICTURE Gastrointestinal (GI) residence systems have emerged as a promising area for the diagnosis and treatment of GI diseases. Compared with conventional drug pills and implantation systems, ingestible GI residence systems can be tailored to possess minimal invasiveness and multiple functionalities, therefore effectively addressing issues related to patient non-compliance, as well as monitoring and treating chronic diseases. A crucial aspect of GI residence systems is the *in vivo* retention time; numerous mechanisms are under development to extend device retention in various parts of the GI tract beyond the stomach. On the other hand, sensors, actuators, and electronics have been integrated into these systems to allow for multifunctional diagnosis and treatment. This review aims to provide an extensive overview of the mechanisms and applications of GI residence systems while presenting cutting-edge technologies to inspire the development of next-generation ingestible devices.

SUMMARY

Gastrointestinal (GI) residence systems that integrate functions such as sensing, stimulation, and drug delivery hold promise for intervening in and treating chronic GI conditions. However, extending device retention beyond 24 h remains challenging. In this review, we present current engineering approaches that extend GI retention across various spatiotemporal scales. We then summarize their applications in drug delivery, sensing, and stimulation within the GI tract that benefit from prolonged device residency. Finally, we outline emerging strategies that leverage breakthroughs in materials, mechanics, and robotics to enable the development of next-generation GI residence systems. This review aims to present a future of GI residence systems that enable long-term, autonomous, and closed-loop therapies and are thus indispensable in next-generation healthcare.

INTRODUCTION

Chronic gastrointestinal (GI) conditions, such as gastroesophageal reflux disease (GERD),[1] inflammatory bowel disease (IBD),[2] irritable bowel syndrome (IBS),[3] and colon cancers,[4] significantly affect human well-being, particularly that of aging populations[5] and outdoor enthusiasts who are frequently exposed to contaminated food and water.[6] For these vulnerable populations, theranostic systems that can stay in the GI tract for continuous monitoring and long-term intervention of GI diseases will significantly reduce risk and medical cost.[7] The requirement of GI retention time varies from disease to disease. For example, when properly diagnosed and treated, GERD can heal in less than a month depending on the severity of the case.[8] On the other hand, inflamed intestines can heal within 1 or 2 weeks with intravenous nutrition treatment, whereas Crohn's disease is a life-long disease that cannot be cured entirely.[9] However, the ability of systems to remain in the GI tract for extended periods is hindered by the challenging GI environment,[10] which includes factors such as the varying size of GI organs, a complex biochemical environment,[11] peristalsis, and rapid turnover of mucosal epithelium cells.[12] Clinical tools (e.g., endoclips) can stay on the GI mucosa for up to 26 months,[13] but these invasive approaches increase the risk of tissue perforation and infection. Therefore, developing proper GI residence systems that ensure extended retention and safety would be highly valued.

Systems with prolonged GI residence and minimal invasiveness were inspired by the discovery of bezoars in the GI tract.[14] Bezoars are masses of swallowed foreign material, often consisting of hair, fibers, or food remains. It was observed that larger bezoars tend to remain in the stomach, which led to the development of early artificial GI residence systems.[15] Pioneered by Cargill et al.,[16] these systems included ring and tetrahedron shapes with a diameter of at least 3.6 cm and

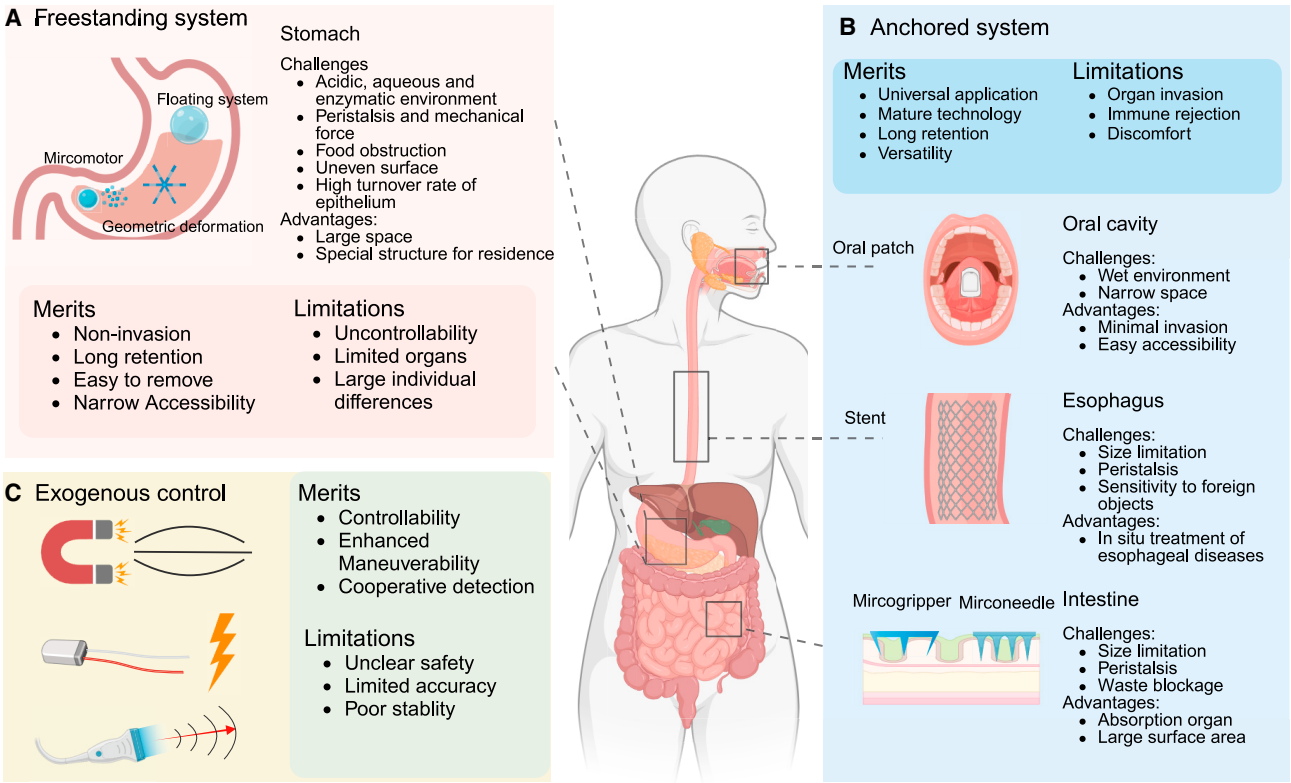

Figure 1. The mechanisms of GI residence systems and their merits and limitations

The corresponding GI regions with distinct challenges and advantages are also outlined.

(A) Freestanding system.

(B) Anchored system.

(C) Exogenous control.

achieved 100% retention over a 24-h period. Over time, GI residence systems have advanced significantly to incorporate components such as swellable hydrogels,[17] floating systems,[18] and gastric patches[19] with controlled-release formulations. These advancements primarily aim to enhance medication adherence, drug absorption, and bioavailability. Recently developed non-invasive gastric retentive systems that rely on structural unfolding[20,21] or volumetric swelling[22] mechanisms can reside in a human-scale stomach for several weeks, enabling sustained drug release, continuous temperature monitoring, and electrical stimulation. Meanwhile, many other mechanisms have been developed to extend the applicability of GI residence systems beyond the stomach.[23]

Whereas most other reviews focus on GI residence systems for targeted drug delivery primarily in the stomach,[24,25] our review expands the scope to include systems in the entire digestive tract, as well as functions beyond drug delivery, such as sensing and stimulation. In this review, we provide a comprehensive analysis of existing GI residence systems employed for drug delivery, sensing, and stimulation in the GI tract. We extensively examine the configurations of these systems and their applications. Additionally, we discuss commercially approved systems that have demonstrated both safety and prolonged human GI residence. Finally, we outline emerging materials, mechanics, and robotics strategies that aim to prolong GI residence and enhance functionality. These advancements lay the foundation for the development of next-generation GI residence systems.

CURRENT APPROACHES TO GI RESIDENCE

In this section, we first discuss the advancement of strategies for device retention in the digestive tract, categorized into three main mechanisms: freestanding, anchored, and exogenous control systems (Figure 1 and Table 1). Specifically, we focus on non-invasive approaches that allow for several hours of device retention in the GI tract while not interfering with patients' daily activities.

Freestanding systems

Freestanding systems are described as materials and devices that can move freely in a closed space, such as the stomach, while achieving long-term GI residence. These systems operate independently of organ and tissue support, thus causing minimized tissue damage and disruption to digestive functions. The stomach is the primary site for freestanding systems because of its spacious and enclosed geometric features (Figure 1A).

Table 1. Reported GI residence systems with *in vivo* validations

Approaches	Organ(s)	Longevity	Animal model(s)	References
Freestanding				
Geometric deformation	stomach	up to 30 days	Yorkshire pigs, rabbits	Kirtane et al.,[26] Hayward et al.,[27] Jin et al.[26–28]
Floating system	stomach	2–24 h	beagle dogs	Zhang et al.,[29] Praveen et al.[29,30]
Self-propelling systems	stomach, intestine	minutes to hours	mice	de Ávila et al.,[31] Zhang et al.[31,32]
Anchored				
Mucoadhesion	oral cavity, stomach, intestine	6–12 h	rats, mice	Gupta et al.,[33] Liu et al.[33,34]
Microstructure	stomach, intestine	4–24 h	rats, pigs	Ghosh et al.[35] and Zhang et al.[36]
Macrostructures	esophagus, stomach	varies (up to months to years)	Yorkshire pigs	Arafat et al.,[37] Babaee et al.[37,38]
Exogenous control				
Magnetic control	stomach, intestine	up to 7 days	mice	Liu et al.[23]
Electric control	stomach	varies (up to hours)	swine	Abramson et al.[39]
Photoacoustic control	stomach	up to hours	mice	Wu et al.[40]

Geometric deformation

The stomach serves as a spacious and resilient site for food storage and is characterized by a tight constriction known as the pylorus at its end. The diameter of the human pylorus typically ranges from 1.3 to 2.0 cm. Thus, GI retention systems relying on geometric deformation mechanisms are defined as systems that have a diameter greater than the pylorus when fully expanded/inflated/unfolded. The retention capabilities of devices with varying sizes, shapes, and flexibility were tested in the stomachs of fasting dogs.[15,16] Six different shapes were assessed for retention, and it was found that tetrahedrons and rings with overall dimensions greater than 2 cm exhibited over 91% retention during 24-h observation. Subsequently, systems and devices based on unfolding[41,42] and swelling[22] approaches were developed for oral ingestion. Initially compacted, these systems expand into predetermined sizes and geometries upon ingestion and reaching the stomach through elastic recoiling or water absorption. These devices have demonstrated gastric residence in Yorkshire pigs for at least 40 days and can support drug loading of up to 40% (w/w) for treating various GI conditions that require a sustained and high dosage.[41,42]

For safe elimination from the body, these devices can be constructed with bioresorbable materials, such as poly(lactic-co-glycolic acid) and polycaprolactone, with controllable dissolution rates. Alternatively, materials with optically[43] or chemically[22] triggered disintegration capabilities can be utilized for elimination purposes.

Floating systems

The human stomach usually maintains a resting volume of 25–50 mL and is rarely empty. Studies have shown that low-density, buoyant objects can stay in the stomach longer because of their tendency to be away from the gastroduodenal junction.[44] To exploit this observation, retention systems with air-filled floating chambers have been developed with materials such as popcorn, pop rice, and polystyrene.[45] Other approaches involve effervescent compounds, such as sodium bicarbonate, tartaric acid, and citric acid, which generate carbon dioxide in contact with gastric juice, providing buoyancy.[46] The average gastric retention time for these systems ranges from several hours to days depending on factors such as mechanisms, materials, device sizes, and physiological factors such as peristaltic ability and gastric juice volume.[47] A recently developed pufferfish-inspired ingestible hydrogel device made of superabsorbent hydrogel particles encapsulated with an anti-fatigue porous hydrogel membrane significantly extended the *in vivo* residence time of floating systems to weeks and can carry wireless, miniaturized sensors for continuous gastric temperature monitoring for a month.[22]

Self-propelling systems

Microorganisms, such as sperm and bacteria, employ specialized structures such as flagella and helical shapes for spontaneous movement in the reproductive or GI tract.[48] This natural movement strategy has served as an inspiration for the development of self-propelling systems. These include microcomputers, spiral microstructures, and other representative designs that utilize chemical or biological reactions, as well as their inherent structural characteristics, to generate propulsive forces. Consequently, these systems achieve prolonged transit times in the GI tract.

Self-propelling micromotors operate mainly through chemical or biohybrid propulsion mechanisms. Chemical micromotors, for instance, utilize hydrogen gas generated by the chemical reaction between magnesium and gastric acid for propulsion. A pioneer work by de Ávila et al.[31] proposed a therapeutic micromotor application to treat gastric bacterial infections in mouse models, facilitating targeted antibiotic delivery of clarithromycin. Similarly, Li et al.[49] demonstrated an enteric micromotor system capable of achieved accurate positioning and extended retention in the stomach of mice. Both studies utilized magnesium as a chemical promoter, showcasing promising efficacy for controlled and site-specific GI drug delivery. Another approach involves Janus particles, which are microspheres with two heterogeneous hemispheres of different chemical properties.[50] These particles can serve as micromotors through solute concentration gradient fields or electric potential gradient fields

generated by themselves. Particularly, metal-based micromotors demonstrated promising therapeutic efficacy for controlled and site-specific GI delivery.[49] However, their lifespan is relatively short: it ranges from tens of minutes to hours.

To extend the lifespan of micromotors, novel approaches have recently emerged to exploit the biohybrid propulsion mechanism by combining artificial materials with biological systems inspired by motile microorganisms such as sperm and bacteria.[51,52] These swimming micromotors leverage self-propulsion capabilities to navigate and perform tasks within body fluids. Sperm micromotors, for instance, utilize rapidly flapping flagella to enter narrow lumens and achieve targeted drug delivery.[51] Microalgae, on the other hand, are even faster swimmers with flapping speeds eight times faster than sperm.[53] Compared with metal-based micromotors, microalgae-based micromotors offer the advantage of a more robust driving force and longer lifespan, allowing them to remain active at a steady speed for over 12 h.[32] *In vivo* experiments have demonstrated that microalgae-based micromotors significantly improve distribution and enhance retention time in the intestine.[32] Furthermore, helical microalgae serve as excellent drug carriers capable of circumventing physiological barriers, thereby enhancing oral bioavailability and biocompatibility.[54]

Anchored systems

In contrast to freestanding systems, anchored systems exploit physical and chemical interactions between engineered materials and GI surfaces to achieve GI residence. Such systems can apply to other portions of the GI tract, especially those with tight constrictions, such as the esophagus and intestines (Figure 1B).

Mucoadhesion

Mucoadhesive materials consist of hydrophilic macromolecules, including natural polymers such as chitosan, sodium alginate, tragacanth, and gelatin, as well as synthetic polymers such as poly(acrylic acid) and synthetic polymethacrylate. These materials form physical and chemical bonds with the mucous membrane upon close contact and consolidation.[55] A collection of mechanisms contributes to mucoadhesion, including mechanical interlocking, electrostatics, adsorption, and fracture.[56]

Mucoadhesives have attracted significant interest in the pharmaceutical field because of their prolonged drug-delivery capabilities at various sites of action,[57] including the nasal cavity, the heart, the vaginal lumen, and different portions of the GI tract, such as the oral cavity, intestinal lumen, colon, and rectal lumen.[58] However, extending mucoadhesion in the GI tract beyond 6–12 h is a significant challenge primarily because of the rapid turnover of epithelial cells (~24 h).[59] Recent approaches attempted to address this challenge by utilizing *in situ* polymerization of dopamine with a native enzyme in the small intestine as the catalyst. This approach achieved mucoadhesive intestinal lining for around 24 h.[60]

Micro- and nanomaterials and devices are used to enhance interactions with GI surface mucosa and prolong GI residence. These systems have distinct physicochemical properties and higher surface-area-to-volume ratios, enabling efficient drug loading[61] and improved surface functionalization for mucoadhesive molecules.[62] Micro- and nanoscale carriers come in various forms, such as lipid nanoparticles, polymeric micro- and nanoparticles, polymer micelles, and micropatches.[63,64] These carriers achieve retention by being trapped in the outermost mucus layer of the digestive tract through steric or mucoadhesive forces. However, they are rapidly eliminated through mucociliary clearance within a few hours.[65] To enhance residence time and mucus and tissue penetration, mucus-penetrating particles (MPPs) have been developed.[66] MPPs have a mucus-inert surface and a sufficiently small particle size, allowing them to freely diffuse in deeper mucosal epithelial surfaces. This results in longer digestive retention, such as 12–24 h in the intestine and colorectum[66] and 36 h in the stomach.[67] Further research is needed for assessing *in vivo* toxicity and long-term biocompatibility, particularly regarding nanoparticle ingestion.

Microstructures

Researchers have discovered that parasites (e.g., thorny-headed worms) can adhere to the host's GI tract by using a barbed microstructure.[68] This has led to the creation of bio-inspired artificial microstructures that can grip onto the mucosa surfaces through external stimuli, such as magnetic fields and temperature changes.[69] For example, a thermally triggered microgripper, inspired by GI parasites, can autonomously latch onto mucosal tissue and retain its position in the GI tract of live animals for 24 h.[35] Cai et al.[70] designed magnesium-based micromotors that utilize suction-cup microparticles fabricated from hydrogel. These micromotors successfully combine the benefits of self-propulsion with the capability to adhere to the stomach's surface, thereby enhancing the effectiveness of treatment.[70]

Microneedles have been extensively used for transdermal drug delivery because they offer excellent penetration ability and minimal invasiveness. In the context of GI tract retention and drug release, biphasic cone-shaped microneedle arrays inspired by endoparasitic worms have been developed.[71] These microneedles feature swellable hydrogel tips that facilitate needle insertion and mechanical interlocking with intestinal tissue after swelling.[71] The soft microneedle tips allow for removal without significant tissue damage or inflammation. Although the potential and advantages of microneedle technology are evident, certain challenges remain, including precise dosage control and the safety of matrix materials.

Macrostructures

Stents were some of the earliest GI residence systems used for treating GI obstructions and perforations.[72] They rely on passive structural interlocking through expansion and clamping. Originally rigid and cylindrical, stents required extensive endoluminal dilation before placement, leading to a short retention time of 1 week and an increased risk of tissue damage, misplacement, and migration.[73] The invention of self-expandable metallic stents (SEMSs) eliminated the need for dilation, allowing for compressed insertion.[73] SEMSs can be inserted into smaller lumens, extending retention times to up to 3 months.[74]

Recent developments of GI retentive stents have exploited drug-eluting,[37] radioactive,[75] and biodegradable[76] features for active disease interventions, brachytherapy, and non-surgical removal. For example, a kirigami-inspired stent platform integrated with a soft actuator is capable of injecting drug depots deep into the GI mucosa.[38] The resultant sustained and targeted drug release is ideal for the treatment of esophageal and

intestinal diseases. Additionally, integrating wirelessly powered electronic components into a deformable stent allows for the delivery of continuous electrical stimulation to the lower esophageal sphincter, enabling non-invasive therapy.[77]

Other related approaches exploit wearables or implants, such as mouthguards,[78] tooth enamel,[79] and artificial anal sphincters,[80] as hosts for smaller functional devices within the GI tract. When the host device remains intact and durable, this approach can result in remarkably long retention times, ranging from months to years.[81] A clear limitation is that these systems can be applied to only superficial portions of the GI tract.

Exogenous control

Both passive approaches mentioned above can achieve relatively long-term GI residence, but they lack active control of the location and duration. To address this, reserachers have developed various strategies that utilize external energy fields, such as magnetic fields,[23] electric fields,[82] and near-infrared (NIR) light irradiation,[40] for the remote manipulation of navigation and retention of devices within the GI tract (Figure 1C).

Magnetic field

The principle of magnetic-field manipulation of objects hinges on the magnetic force. Precise control over the object's motion and position can be achieved through regulation of the strength and direction of the magnetic field.[83] Static magnetic fields are considered safe for the human body[84] and therefore are used widely to manipulate small-scale magnetic devices by guiding them through blood vessels or the digestive tract for localized drug delivery, biopsy, and sensing.[85] Static magnetic fields offer advantages of high sensitivity and easy operation.[84] Certain structures with embedded magnetic materials can deform in response to these fields, enabling smart control within the GI tract. For instance, an origami-inspired, magnetic hydrogel-based ingestible device can be magnetically navigated and deployed at specific locations on the gastric mucosa and then expand up to ten times its initial area for gastric ulcer treatment.[86] Recent advancements in ingestible magnetic robotics allow retention in the intestine by attaching a magnet to the abdominal skin, facilitating macromolecule delivery, GI bleeding detection, and on-demand removal using the natural peristalsis movement of the intestine.[23] Additionally, the combination of magnetic nanomaterials enables magnetic-field-controlled navigation and targeted release of microneedles and micromotors.[36] The limitation of a magnetic field controlling retention lies in its dependence on the presence of specific magnetic properties or components in the object or subject, whose safety implications remain uncertain.[87]

Electric field

The mucosa layer, a critical component of biological tissues, predominantly comprises cationic proteins, thereby exhibiting a positive charge. Capitalizing on these inherent electrostatic characteristics, hydrogel systems with anionic polymers can be ingeniously designed to foster rapid electrostatic attraction between the oppositely charged cationic and anionic components.[88] A recent study showed that an ~10-V electric field can induce long-lasting adhesion between the mucosa and hydrogel by electroadhesion.[82] Remarkably, the adhesion achieved through electroadhesion can be reversed by the application of an opposite electric field of the same magnitude.[82] Furthermore, the potential for reversible electroadhesion has been demonstrated through the use of a polymeric diode structure at a low voltage of 1 V.[89] This recent discovery implies the possibility of safe and on-demand long-term retention on mucosal surfaces. Although remote power technology has reached a high level of maturity, unresolved power consumption issues persist, demanding attention.[90] As this technology remains in its nascent stages, its safety and effectiveness require further comprehensive investigation.[91]

Photoacoustic control

The photoacoustic control of objects is based on the photoacoustic effect, which involves the generation of acoustic waves due to the absorption of light by a material.[92] When the material is exposed to pulsed laser light, it absorbs the light energy, causing localized heating and rapid expansion. This sudden expansion creates pressure waves that propagate as acoustic waves through the surrounding medium. By precisely modulating the intensity and timing of the laser pulses, it is possible to manipulate the motion and behavior of the object.[93] Photoacoustic technologies, commonly used for imaging purposes, are now being employed for controlling GI residence systems in the GI tract. By integrating photoacoustic computed tomography, real-time monitoring of ingestible micromotors in the intestines can be achieved with high spatial resolution, enabling precise *in vivo* on-demand control. For instance, NIR light can remotely activate gas generation from drug-loaded microdevices coated with magnesium. This approach allows for remotely controlled propulsion within the GI tract because NIR light can penetrate tissues up to a depth of 7 cm.[40] Nevertheless, the development of photoacoustic control is still in its infancy and necessitates extensive research across multiple facets. The essential improvement of its penetration performance hinges on resolving organizational barriers. Additionally, the precision and stability of photoacoustic control needs further improvement.[94]

In section "current approaches to GI residence," we summarized the different mechanisms of GI residence systems, including macro- and micro-scale systems. These mechanisms enable not only passive but also active retention. Comparatively, macro-scale residence systems tend to exhibit a longer residence time, yet their safety necessitates further verification because of their large volumes. On the other hand, achieving a stay of more than a week with micro-scale residence systems proves challenging. Additionally, some invasive resident systems require careful selection to suit specific scenarios and prevent potential organ damage.

APPLICATIONS OF GI RESIDENCE SYSTEMS

Advancements in system integration technology have facilitated the inclusion of diverse functions in GI residence systems, such as drug depots, sensors, imaging systems, and actuators. This integration enables sustained drug release, physiological monitoring, capsule endoscopy, tissue stimulation, and more.[95] These multifunctional GI residence systems hold promise in addressing challenges related to drug non-compliance and chronic GI monitoring.[96]

Table 2. Commercial products and clinical trials of GI residence systems

Residency systems	Organ	Longevity	Clinical impact	Clinical stage	Clinical trial number
OraMoist	oral cavity	4 h	xerostomia	commercial product[98]	N/A
Striant SR	oral cavity	12 h	male hypogonadism	commercial product, FDA approved in 2003[99]	N/A
WallFlex	esophagus	12 months	benign biliary strictures	commercial product, FDA approved in 2009[100]	N/A
Ultraflex	esophagus	12 months	esophageal obstruction	commercial product[101]	N/A
Gabapentin extended release tablet	stomach	5–7 h	vasomotor symptoms	phase III	NCT01080300
Soctec capsule	stomach	12 h	N/A	early phase I	NCT02335515
Accordion pill	stomach	up to 12 h	insomnia	phase II	NCT01277107
Accordion pill	stomach	up to 12 h	Parkinson's disease	phase II	NCT02605434
Gabapentin extended release system	stomach	12–24 h	vasomotor symptoms	phase III	NCT00777023
Gabapentin	stomach	12–24 h	epilepsy	phase III	NCT00335933
Atom gas capsule	stomach	24 h	GI disorders	phase I[102]	N/A
Abilify MyCity	stomach	7 days	depression	FDA approved in 2017[103]	N/A
Gastric-retentive capsule	stomach	up to 7 days	Alzheimer's disease	early phase I	NCT03468543
Stellate pill	stomach	up to 7 days	schizophrenia	early phase I	NCT04567524
Stellate pill	stomach	up to 9 days	Alzheimer's disease	early phase I	NCT03711825
Extended release capsule	stomach	up to 9 days	N/A	early phase I	NCT03718390
Extended release capsule	stomach	up to 9 days	Alzheimer's disease	early phase I	NCT03711825
Long-acting oral LYN-005	stomach	up to 5 weeks	schizophrenia	phase III	NCT05779241
Self-expandable metal stent	stomach	10 months	stage IV gastric cancer	observational study	NCT04599179
SmartPill	intestine	3–5 days	GI motility disorders	FDA approved in 2006[104]	N/A
RaniPill	intestine	4 h	acromegaly	phase I	NCT03798912
GRDF furosemide	small intestine	up to 12 h	edema	phase I	NCT01887379

To date, several minimally invasive GI residence systems are currently undergoing clinical trials, offering potential improvements in patient adherence and treatment options for chronic conditions (Table 2). US Food and Drug Administration (FDA)-approved devices, such as the TransPyloric Shuttle and the EndoBarrier,[97] are being increasingly utilized and studied for their effectiveness in treating obesity. Ingestible GI residence electronics with real-time, programmable monitoring and electroceuticals over an extensive period represent yet another area of future development.[95] In this section, we discuss residence systems used in different portions of the GI tract (oral cavity, esophagus, stomach, and intestines) for different applications (drug delivery, sensing, and stimulation).

Drug delivery

Oral cavity

Mucoadhesive patches are a heavily researched approach for creating residence systems in the oral cavity. Existing as monolayered or bilayered tablets, films, and wafers, these patches have an average retention time of 5–6 h.[47] There are several commercially available products based on mucoadhesive technology. Oramoist, for example, is used to treat dry mouth (xerostomia) and can adhere to the roof of the mouth for up to 4 h.[98] Striant uses saliva to adhere to the buccal mucosa for 12 h and deliver testosterone.[99] Compeed, which treats cold sores, employs an adhesive film that is placed on the affected area. The drawback of Compeed is that it lacks disintegrating ingredients and must be physically removed after use.[105]

Moreover, mucoadhesive hydrogels, nanoparticles, and microneedle arrays have been utilized to enhance drug retention within the buccal mucosa and circumvent its function as a barrier to macromolecule absorption. The sustained, ingestion-based administration of insulin and other peptide drugs is particularly intriguing because it offers the prospect of reduced dosage frequencies and enhanced patient adherence in comparison with needle-based injections. For example, Chen et al.[106] utilized self-assembled liposomes with electrospun fibers to achieve prolonged buccal cavity retention. Another method for insulin delivery involves the use of nanoparticles to enhance the protection and delivery of macromolecules to the buccal mucosa. Patil and Devarajan[107] prepared insulin-loaded alginic acid nanoparticles by using a nanoprecipitation process, which showed a rapid initial release followed by a slow release over 12 h. Microneedle patches present an alternative strategy for macromolecule release. Caffarel-Salvador et al.[108] developed a drug-loaded microneedle patch capable of delivering 1 mg of insulin to the buccal cavity of swine.

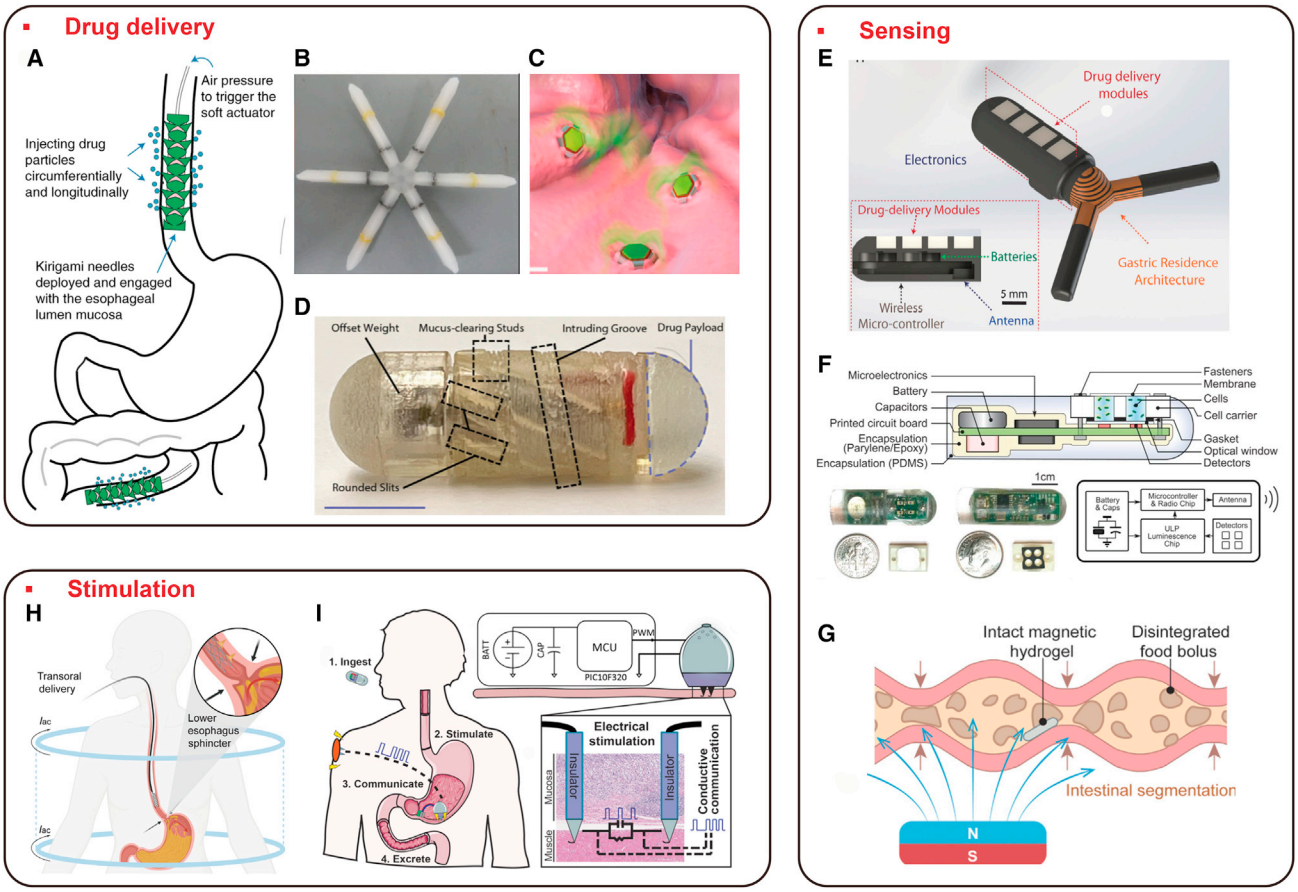

Figure 2. Applications of GI residence systems

(A) Kirigami-inspired stents for drug delivery. Reprinted with permission from Babaee et al.[38] Copyright 2021 Springer Nature.

(B) The design of a star-shaped gastric residence system. Reprinted with permission from Bellinger et al.[20] Copyright 2016 AAAS.

(C) Microgrippers latching onto the mucosal tissue for drug release. Reprinted with permission from Ghosh et al.[35] Copyright 2020 AAAS.

(D) Robocap: a mucus-clearing capsule robot. Reprinted with permission from Srinivasan et al.[114] Copyright 2022, AAAS.

(E) Wireless gastric resident sensor. Reprinted with permission Kong et al.[115] Copyright 2019 Wiley-VCH.

(F) Bacterial-electronic capsule capable of communicating with external devices for detecting GI health. Reprinted with permission from Mimee et al.[59] Copyright 2018 AAAS.

(G) Magnetic hydrogel for intestinal residence and diagnosis. Reprinted with permission from Liu et al.[23] Copyright 2021 Wiley-VCH.

(H) Wireless esophageal stent for stimulation of the sphincter. Reprinted with permission from Zhang et al.[77] Copyright 2023 AAAS.

(I) Gastric electronic stimulation system. Reprinted with permission from Abramson et al.[39] Copyright 2020 AAAS.

Esophagus

Esophageal stents, established technologies with an average residence time of 3 months,[109] are promising residence systems for long-term drug delivery. Examples include modified stents with crack propagation[110] or those using thermoresponsive materials[111] to regulate drug release. Additionally, biodegradable materials present a promising avenue for eliminating the need for stent retrieval.[112] Biodegradable stents have demonstrated a lifespan of up to 6 weeks during *in vivo* testing in rabbits.[112]

The deployment of active devices that utilize thermo- or bioresponsive materials facilitates the noninvasive delivery and retrieval of devices designed for extended residence. Babaee et al.[113] have developed two distinct esophageal deployment devices.[113] The first device uses thermoresponsive metamaterials that trigger device degradation when warm water is consumed. *In vivo* testing in pigs confirmed the successful deployment and retrieval of this device.[113] The second design consists of a kirigami-based stent, where the drug-loaded, denticle-like needles enable submucosal injections through robust radial expansion. *In vivo* experiments in swine showed that the needles could penetrate >1 mm into the submucosa tissue without causing perforations, and the drugs were released over a week[38] (Figure 2A).

Mucoadhesive polymers can provide sustained contact with the esophageal mucosa like those commonly applied to the oral cavity, enabling retention for up to 5 h. For instance, Antonino et al.[116] developed a gelling, thermally reversible mucoadhesive that encapsulates budesonide to treat inflammatory diseases.[116] *In vitro* testing showed 4 h of mucosal retention, whereas *in vivo* studies in a murine model indicated successful

treatment of intestinal mucositis. Moreover, Modi et al.[117] prepared chitosan-based nanoparticles by using the ionic gelation method. They optimized the ratios of polymer to drug and polymer to cross-linking agent to achieve 5 h of retention in both the esophagus and stomach during *ex vivo* testing.

Stomach

Gastric retention drug-delivery systems provide a solution to medication nonadherence and the degradation of drugs due to first-pass metabolism. Over the past decade, various types of retention approaches have been developed to achieve long-term gastric residence. Geometric conformation devices, employing a star-shaped configuration that is released upon degradation of the capsule casing, have demonstrated retention for up to 42 days in pigs[20] (Figure 2B).

Simultaneously, hydrogels have been incorporated in diverse ways to improve gastric residence. Swelling hydrogels, such as superporous hydrogel[118] and blank-slate hydrogel (polyethylene glycol diacrylate [PEDGA]),[119] fall under the geometric conformation category because they inhibit passage through the pylorus until the hydrogel degrades. Swelling hydrogels within the stomach have also been utilized for drug delivery, tissue engineering, and bacterial interventions.[120] Furthermore, light-triggerable hydrogels have been developed to interface with inflatable balloons and stents, enabling biocompatible triggering of device degradation.[43] Floating devices, created with hydrogels with a lower density than gastric fluid, have been designed in tablet or capsule shapes through 3D printing.[121] Charoenying et al.,[121,122] Fu et al.,[123] and Shin et al.[124] achieved retention times of up to 10, 72, and 12 h, respectively, in animal models. Lastly, bioadhesive hydrogels have been incorporated into mucoadhesive technology to achieve gastric residence for up to 48 h.[125] Combining mucoadhesion with magnetic-field navigation allows for the controllable deployment of these devices to their target locations with greater accuracy.

Intestine

Drug delivery to the small intestine is a highly researched area because it offers the potential for enhanced absorption of macromolecules. Expanding devices, similar to those used in the stomach, are some of the major platforms adopted for small-intestine drug delivery. These devices enable prolonged retention, inhibiting their continued flow through the intestines. Ghosh et al. and Abramson et al. have separately reported swellable microneedle devices[35,42] designed for targeted drug delivery in the small intestine (Figure 2C). Thermally responsive shape-changing microdevices for solid-formulation drugs[126] and the effect of shape in the administration of nanowire-coated microparticles in the intestines have also been studied.[71]

In addition, a polydopamine-based mucoadhesive platform offers an alternative approach to drug delivery. This platform allows direct contact with the intestinal mucosa without the risk of obstruction. The polydopamine-based platform has successfully demonstrated applications in the attenuation of radiation-induced syndrome,[127] luminal coating,[128] and synthetic epithelial linings of the intestine.[60]

The integration of potential systems with resident systems holds promising implications for improving application prospects. An example of such an innovation is the drug-delivery robot Robocap, developed by Srinivasan et al.[114] This robotic pill can effectively remove mucus layers and deliver drug payloads to the small intestine through turbulent motion, thereby enhancing drug absorption. However, a limiting factor hindering its widespread application is its relatively short residence time within the intestines (Figure 2D).

Sensing

Oral cavity

Compared with drug patches, electronic devices have rigid components and occupy more space, requiring different strategies for long-term retention in the oral cavity. These strategies include replacing bulky battery components with wireless radio frequency power, adopting flexible and miniaturized sensors and electrical connections, and utilizing existing wearable and implantable devices as hosts and substrates. Ciui et al.[78] described a printed electrochemical sensor for detecting (carboxymethyl)lysine in saliva.[78] They fabricated the sensor by using a screen-printing technology on a flexible foil substrate, and it remained stable for over 30 days with only a 4.62% sensitivity decay.

Furthermore, Arakawa et al.[129] combined a mouthguard with a glucose sensor by using a cellulose acetate membrane to monitor salivary glucose levels. *In vivo* testing demonstrated successful measurements of glucose in human saliva, suggesting a noninvasive platform for managing diabetes. Additionally, sensors in ultraflexible forms have been directly interfaced with tissues, such as tooth enamel, to enable intimate contact and high signal fidelity. Mannoor et al.[79] developed a graphene-based wireless sensor that prints graphene onto water-soluble silk, allowing for the bio-transfer of graphene nanosensors onto tooth enamel.

Esophagus

Because of the increased load of electronic devices, surgical implantation is necessary to ensure device stability without obstruction or migration. Currently, stent devices are being utilized as platforms for monitoring the esophageal environment. These stents, composed of novel metamaterials,[130] integrate nanogenerators and wireless sensor chips for self-powering and self-sensing capabilities.[49] Prolonged residence times of up to 1 month have been documented.[130] To minimize invasiveness, catheters are employed for insertion and precise positioning of the devices, enabling accurate placement with reduced surgical intervention. pH sensing is commonly used to monitor GERD, which occurs when acidic stomach juices or fluids back up into the esophagus.[131] Existing tools for this purpose include multichannel intraluminal impedance (MII) and pH-sensing capsules, but they can cause discomfort and have limited sensitivity ranges. Cao et al.[131] successfully designed and developed an implantable pH sensor that operates wirelessly and surpassed the performance of a commercially available capsule device in porcine models. The accurate measurement of temperature is of paramount importance in cardiac surgery. Garner et al.[132] developed a device composed of heat-responsive biomaterials for temperature monitoring during catheter ablation of the left atrium.

Stomach

Monitoring gastric waves offers a better understanding of the gastric environment and can lead to improved diagnosis of gastric disorders. One of the most common methods for noninvasive gastric sensing involves device expansion to inhibit

passage through the pylorus without obstructing the flow of chyme to the intestines. Liu et al.[23] reported on a swelling hydrogel device with an embedded temperature sensor that swells up to 100 times in volume, enabling 9–29 days of temperature monitoring in the stomach of a Yorkshire pig model. Kong et al.[115] developed a star-shaped device capable of temperature sensing. This device, used for controllable stimulation in the GI tract, achieved 36 days of residence and 15 days of wireless communication in a porcine model (Figure 2E). Furthermore, the convergence of biological engineering and semiconductor electronics presents promising avenues for revolutionizing the domains of health and disease diagnosis, management, and monitoring. Mimee et al.[59] introduced a novel oral microbial electronic device that employs probiotics and possesses the ability to detect heme and identify instances of bleeding in the porcine stomach.[59] Subsequent detection results can be obtained via external wireless devices, such as smartphones. Notably, the device operates on low power and can run for an impressive 1.5 months when fully charged. As a result, when combined with GI residence systems, it enables long-term wireless monitoring of gastric bleeding (Figure 2F).

Another approach to achieving long-term residence for sensors deployed in the stomach is through magnetic-field-enabled anchoring and expansion. Zhou and Alici[133] reported a magnetically driven anchoring system utilizing magnetic springs for remotely controlling wireless capsule endoscopy. Kaan et al.[134] developed an ingestible inflated balloon capsule for treating obesity; it embeds a magnetic sensor to confirm that the device has reached the stomach for safe inflation.

Intestines

One area of extensive research for intestinal resident sensors is focused on reducing the discomfort and invasiveness of colonoscopies and other rectal monitoring procedures. The introduction of robotic or self-propelling navigation techniques can facilitate easier completion of these procedures. Chen et al.[135] demonstrated a pneumatically actuated endoscopic device for inspecting the large intestine. Martin et al.[136] proposed a tethered magnetic capsule for endoluminal inspection. Atallah et al.[137] and Seah et al.[138] also reported on the comparison and utilization of commercially available robotic platforms for colon navigation. Another heavily researched topic in the field of intestinal sensors is the detection of lower GI bleeding. Liu et al.[23] developed a small-intestinal device based on magnetic nanoparticle-enriched hydrogels to detect heme. This device has been reported to be retained successfully in the small intestine for up to 7 days (Figure 2G).

Overall, current diagnostic systems capable of chronically tracking physiological signals in the GI tract open a paradigm for the early detection of GI conditions. One step closer, more focus could be on developing novel sensing techniques that enable the detection of versatile disease biomarkers in the GI tract, including gas, protein, DNA, and RNA biomarkers associated with peptic ulcers, inflammation, and GI cancers.[139]

Stimulation

Oral cavity

Similar to sensors, stimulators can be integrated into mouthguards to enable long-term intraoral electrostimulation. Strietzel et al.[81] reported on the integration of stimulation electrodes into mouthguards for sustained electroceuticals of the oral cavity. This device consists of an electronic circuit that the patient can activate and deactivate by using an infrared remote control. The electrodes provide direct electrical stimulation to the oral mucosa in the mandibular third molar area, near the lingual nerve. The device remained stable throughout a multi-stage, multi-month study, demonstrating that daily use of this device alleviated complications of xerostomia.

The surface of the tongue is another advantageous location for an electrical stimulator interface in the oral cavity because of its direct access to sensory neurons, making it suitable for treating neurological disorders. Conlon et al.[140] tested the concept of bimodal neuromodulation by combining auditory stimulation with electrostimulation of the tongue for the treatment of tinnitus. A 32-site tongue surface electrode array, known as a tongue-tip, played an essential role in this process.

Esophagus

As for sensing devices, stimulation of the esophagus requires surgery to securely place the device and establish intimate contact between the electrodes and nerve-containing tissues. Proton-pump inhibitors are commonly used to treat GERD, but up to 40% of patients can experience incomplete symptom control with this treatment.[141] An alternative approach for GERD treatment is long-term stimulation of the lower esophageal sphincter (LES), which has demonstrated safe and effective results. Because of the large area required for the stimulation device, accurate implantation through invasive surgery is necessary. Ganz et al.[141] attempted another approach for GERD treatment, where they used a magnetic device to augment the LES. Magnetic attraction between neodymium iron boride beads restored the esophageal sphincter's resistance to normal. Although this device required laparoscopic implantation, it showed positive results in treating GERD in human volunteers.

Recently, a wirelessly powered electronic stent was developed for applying electric stimulation to the esophagus[77] (Figure 2H). This stent, made of soft materials with deformable properties, can adapt to the narrow environment of the esophagus. Additionally, the remote charging function enables long-term residence. Furthermore, electrical stimulation of the esophagus is utilized for targeted temperature management after cardiac arrest. The esophageal cooling device circulates temperature-controlled water through a silicone heat exchanger connected to an external heat exchanger console. Although this device requires a semi-invasive procedure for implantation, it has shown positive results in temperature cooling for patients suffering from cardiac arrest.[142]

Stomach

Although research is increasingly focused on noninvasive oral delivery of retentive devices, surgical implantation is still the dominant approach for gastric stimulators to modulate electrophysiological activity. Deb et al.[143] reported the deployment of a wireless gastric stimulator via endoscopic insertion to treat refractory gastroparesis. Wang et al.[144] developed an implantable miniature wireless system for treating functional GI disorders. Additionally, Alighaleh et al.[145] proposed a gastric pacing device that requires surgery to address slow-wave abnormalities.

Recently emerged GI residence technologies attempt to improve noninvasiveness of gastric stimulation and convert it into a completely ingestible process. Abramson et al.[39] applied device expansion technology combined with micro-electronic systems to retain residence in the stomach while stimulating the gastric wall for gastric motility disorders (Figure 2I). Inspired by *Moloch horridus*, Ramadi et al.[146] developed a fluid-wicking capsule that possesses a surface capable of displacing fluid. This innovative capsule demonstrates rapid fluid absorption and local stimulation of mucosal tissue, thus modulating the activity of orexigenic GI hormones.

Intestines

Because of the increased area requirements, stimulation devices face numerous challenges when it comes to their residence in the intestines, leading to poor performance in *in vivo* trials. Among the current approaches, the combination of magnetic nanoparticles and wearable magnetic devices shows the most promise for prolonged intestinal residence and stimulation. Yu et al.[147] designed a wearable magnet device for controlling the movement of enterically coated magnetic nanoparticles. Additionally, a commercially available device known as Endobarrier is an FDA-approved device that can be delivered to patients endoscopically and is used for treating obesity by lowering nutrient absorption in the small intestine.[148]

In section "applications of GI residence systems," we examined GI residence systems utilized in various segments of the GI tract by catering to distinct applications. Although certain applications have already been integrated into peoples' lives, others remain in the clinical trial phase, and several are in their early developmental stages. Regardless, the GI tract plays a pivotal role in affecting human health and quality of life, making safety the paramount concern in the application of GI residence systems. The exploration of more suitable technologies to surmount the structural complexity of organs represents a crucial next step.

DESIGN RATIONALE FOR FUTURE GI RESIDENCE SYSTEMS

Despite recent efforts and progresses outlined in the previous section, retaining minimally invasive devices in the GI tract for longer than 24 h remains a daunting task in general because of various physiological and pathological barriers in the GI environment (Box 1 and Table 3). In this section, we discuss recent materials, structures, and robotics advancements that could offer potential solutions to overcome these hurdles toward next-generation long-term and multifunctional GI residence systems.

Materials approaches

Mechanical matching

Digestive tissues possess elastic moduli between tens and hundreds of kilopascals (e.g., 120–150 kPa for the colon and stomach).[160] Certain tissues, such as the esophagus, duodenum, stomach, and colon, experience ongoing peristalsis and deformation as a result of food-induced forces. Yet, conventional retentive devices—often composed of metals, silicon, ceramics, or plastic—exhibit mechanical rigidity and higher moduli.[22] This mechanical mismatch can cause debonding or delamination during peristalsis[160] (Figure 3A). In addition, stiffer retentive systems with a Young's modulus over 100 GPa, such as metal-based hooked structures,[39] risk tissue perforation and inflammation, potentially compromising long-term retention. Consequently, a thorough understanding and appropriate consideration of tissue-specific properties are essential for optimal retention performance and clinical outcomes.

Future digestive retention systems should possess mechanical properties, such as stretchability and flexibility, to accommodate dynamic forces from tissues, resist fractures, and ideally match the mechanical behavior of various retentive tissues. Two potential design strategies can be considered. The first involves retention systems with self-adaptive moduli that adjust to the mechanical properties of the adhered digestive tissues. This could minimize debonding and improve retention capabilities. For example, muscle-inspired hydrogel polymers that grow and remodel in response to their mechanical environment could be ideal for constructing retentive films, needles, or hooks.[165]

Living tissues are characterized by their non-linear elastic properties, displaying both viscoelastic and viscoplastic behaviors.[161] (Figure 3B). The second strategy capitalizes on the viscoplastic properties of stretchable organic materials to design morphing electronics for neuromodulation in growing tissues.[166] These growth-adaptive features might better withstand repeated organ movements. Other considerations include using metamaterials such as kirigami film, which has demonstrated enhanced adhesion on skin,[167] and unconventional polymer network architectures, such as bottlebrush polymer networks, that exhibit extraordinarily low shear moduli and tissue-like stress-strain relations in solvent-free states.[168]

Long-term forces originating from peristalsis, estimated at ~1,000 cycles per day of 5–10 kPa in the stomach,[169] and repeated food-induced shear forces and pressure challenge retention performance.[170] Current retentive systems rarely consider bonding failure because of fatigue of the retentive matrix after multiple cycles. Therefore, fatigue resistance is an important factor in designing long-term adhesion and injection matrices for digestive retention systems lasting more than a week.

Hydrogel bioadhesives

Commercial tissue adhesives, such as cyanoacrylate, fibrin glue, and polyethylene-glycol-based adhesives, could be potential candidates for long-term digestive retention,[171] but they present issues with cytotoxicity, wet-surface incompatibility, and mechanical mismatch with dynamic digestive organs.[172] These issues can lead to mechanical stress, tissue damage, and inflammation during prolonged retention.

Mechanically robust and stretchable hydrogel bioadhesives have been engineered to secure biomedical devices, enabling long-term retentive sensing, stimulation, and wound sealing.[173] The elastic moduli of these hydrogel matrices can be tuned to match target tissues' elastic modulus through the adjustment of polymer chemistry, molecular weight, and cross-linking density.[174] In addition, ideal bioadhesive characteristics, such as conductivity,[175] anti-swelling,[172] biocompatibility,[176] controllable degradability,[177] and anti-fatigue,[178] have been utilized for both *in vitro* and *in vivo* applications, holding promise for next-generation long-term digestive retention systems.

Box 1. GI physiological and pathological properties

The GI tract consists of various organs responsible for digestion, absorption, and elimination. Each organ has specific properties that make device retention challenging without surgical intervention. Understanding these characteristics is crucial in addressing the challenges associated with device retention in the GI tract.

ORAL CAVITY

The oral cavity, characterized by a well-defined shape formed by the lips, cheeks, and soft and hard palates, has an average surface area > 200 cm^2.[149] The buccal mucosa lining, usually flat and stationary, acts as an adhesive interface for drugs and provides insights into a patient's well-being through metabolite levels.[150] With its easy accessibility and direct access to the GI tract, the oral cavity is a promising site for noninvasive device retention in the digestive tract. However, the continuous secretion of water and saliva by the salivary glands poses a challenge by lubricating the oral cavity and weakening adhesive mechanisms that rely on the surface.[151]

ESOPHAGUS

The esophagus is a vertical muscular tube with striated muscle in the upper part and smooth muscle in the lower part. It measures 18–25 cm in length and around 20 mm in diameter. Food and liquid pass through the esophagus in just a few seconds, aided by peristalsis. The esophagus has specific structural characteristics that prevent obstruction and potential complications. Obstruction in the esophagus can cause severe complications and breathing difficulties. In addition, the esophagus is highly sensitive to foreign objects, requiring careful material selection for GI systems.[152] Therefore, deploying residency systems in the esophagus is challenging because of its unique properties. Current device retention in the esophagus, lasting up to 3 months,[109] primarily involves semi-invasive or invasive approaches that require surgeries.

STOMACH

The stomach is a hollow, J-shaped organ with a maximum volume of 2–4 L. It contains two sphincters: the cardiac sphincter connecting to the esophagus and the pyloric sphincter connecting to the duodenum. With gastric juice of pH < 2 and digestive enzymes denaturing macromolecules, the stomach is vital for chemical digestion.[153] It exhibits a unique peristaltic motion called the "mixing wave," which has a mechanical force of ~2 N for thousands of cycles[154] and softens and mixes food with digestive fluid. However, the stomach's aqueous, acidic, and enzymatic environment poses challenges for synthetic materials used in residency systems, requiring careful consideration of material selection and mechanical resistance. The constant secretion of an aqueous mucus layer and the folds and wrinkles of the stomach's surface further complicate device adhesion and mechanical interactions.[155] Retentive devices in the stomach must overcome these challenges to maintain retention, avoid pylorus blockage, and enable monitoring and drug absorption,[154] given its role as a transit station between the esophagus and the small intestine.

INTESTINES

The intestines consist of the small intestine (3–5 m long, 2.5–3 cm in diameter) and the large intestine (1.5 m long, 7 cm in diameter).[156] Their continuous structure allows for sufficient interaction with a food bolus and unidirectional flow toward waste elimination. However, this configuration increases the risk of foreign-body obstruction, which can lead to complications such as diarrhea, infection, and peritonitis.[157] In addition, ingestible electronics and insoluble devices, such as wireless capsule endoscopy, have a higher chance of abnormal retention in patients with enteropathies. Therefore, the FDA sets strict guidelines for the size and shape of ingestible tablets and capsules (<22 mm).

Peristalsis poses another challenge for device retention with varying contraction frequencies along the digestive tract (duodenum, 12 per minute; colon, 2–10 per hour[158]). The constant force generated by peristalsis makes long-term retention difficult.[159] Nonetheless, intestinal retentive devices offer opportunities for enhanced drug absorption and noninvasive endoscopic navigation, considering their role in nutrient and water absorption.

Despite these advancements, bioadhesives have rarely been used on the epithelial layer of digestive tracts because of the complex environment. A recent breakthrough using *in situ* pH-independent and ultrafast polymerization of hydrogels based on a thiourea-catechol reaction has demonstrated potential for improving bioadhesion. In this approach, hydrogels remained attached to ulcer sites in the stomach for at least 48 h, facilitating ulcer healing through inflammation suppression, promotion of re-epithelialization, and stimulation of angiogenesis.[125]

Innovative strategies for enhancing the effectiveness of hydrogel bioadhesives in long-term digestive retention could consider four potential approaches. The first could involve designing retentive hydrogel bioadhesives with biomimetic micro- and nanotopologies that can bond directly to epithelial cells by repelling digestive mucus layers[162] (Figure 3C). For instance,

Table 3. Characteristics and challenges of different sections of the GI tract

GI tract section	Key characteristics	Challenges
Oral cavity	- average surface area > 200 cm^2 - shape defined by lips, cheeks, and soft and hard palates - buccal mucosa ranges in thickness from 50–450 μm	- presence of water and saliva weakens adhesive mechanism - constant secretion of saliva
Esophagus	- vertical muscular tube composed of striated and smooth muscle - length: 18–25 cm - diameter: about 20 mm	- obstruction can cause dyspnea and severe complications - sensitivity to foreign objects - limited options for device retention
Stomach	- vertical, hollow, J-shaped organ - maximum volume: 2–4 L - gastric juice of pH < 2 - mechanical force during peristalsis: 2 N	- aqueous, acidic, and enzymatic environments harm synthetic materials - folds and wrinkles in the mucosa hinder traditional patch adhesives - constant secretion of aqueous mucus layer
Intestine	- continuous tubular structure - composed of small intestine and large intestine - small intestine length: 3–5 m - diameter: 2.5–3 cm	- foreign-body obstruction risk - peristalsis contractions that tend to purge foreign objects

microneedle-structured hydrogel bioadhesives could extend digestive retention through mechanical interlocking and covalent bonding while reducing tissue inflammation rates.[179]

The second strategy is the utilization of long-chain bridging polymers, such as chitosan, to form topological, physical, and covalent adhesion between the hydrogel matrix and epithelial cells via mucoadhesive diffusion and interpenetration.[180] A recent study of ultrasound-enhanced tissue adhesive could enhance digestive retention by bridging polymer diffusion and mechanical interlocking without chemical bonding.[181]

The third promising approach involves targeting bonding to specific digestive mucosal tissues and cells with slower turnover rates[60] (e.g., epithelial cells turn over approximately every 4–5 days[182]). A recent study demonstrated the extended residence time (at least 48 h) of nanodrugs in the small intestine by employing polydopamine-coated nanodrugs to enhance penetration of the mucus barrier and maintain drug concentration.[127]

The last approach could leverage certain microbes that can robustly attach to human tissues through the redistribution of charged groups. Recent studies have demonstrated the possibility of cell-specific *in situ* polymerization of polyaniline conductive polymers in the rat brain with adeno-associated virus (AAV) vectors. This approach established robust interfaces between electrodes and specific cellular membranes for electrical recording and stimulations.[183] Consequently, hydrogel bioadhesives could serve as an ideal platform for microbial proliferation and selective bonding to digestive mucosal tissues and cells that have slow turnover rates. This could potentially enable a renewable adhesive system, thus ensuring extended digestive retention.

Bioinspired structures

Bioinspired, miniaturized mechanical anchoring systems employ a minimally invasive approach to secure themselves to the mucosal surface, thus facilitating the retention of devices. For instance, needle electrodes with hooked[39] or barbed[184] tips can effectively penetrate to tissue depths of approximately 1 mm within the mucosal layer. The design of a biphasic cone-shaped microneedle array, inspired by endoparasitic worms, includes swellable hydrogel tips that facilitate both needle insertion and mechanical interlocking with skin and intestinal tissue[71] (Figure 3D). Soft microneedle tips allow for removal without causing significant damage or inflammation to the tissue. The application of mucoadhesives to these microneedle tips can attain an extended duration of retention within the mucosal environment. This outcome arises from the synergistic interplay of mechanical interlocking and covalent bonding mechanisms.[179] However, their long-term stability and the potential risks of tissue perforation require further evaluation.

Animals such as the remora, octopus, and gecko[185] possess unique body features that enable adhesion under wet and slippery conditions. These features can serve as inspiration for developing adhesive mechanisms for devices in hydrated mucosal environments. For example, soft robotic devices inspired by the suction discs of the remora have demonstrated reversible adhesion to both natural and synthetic wet surfaces.[186] Compared with untreated film materials, soft materials patterned with microscopic suckers inspired by octopus arms[162] or micropillars inspired by gecko setae[187] have shown enhanced and long-term adhesion to wet tissues, causing negligible tissue inflammation. These materials can be further functionalized with adhesive chemicals, such as mussel adhesive-based coatings, to target long-term digestive mucosal use.[160]

Robotic approach

The complex environment of the GI tract presents challenges for residence systems to function effectively and consistently. Advances in robotic technology show promise for expanding the possibilities of ingestible residence systems. Two FDA-approved, ingestible robots, Proteus and Etect-Rx, have demonstrated the feasibility of using ingestible robots to monitor drug adherence.[188] By combining the strengths of a variety of materials and integrating multifunctionality, such as actuation, movement, navigation, and electronics, into a single, compact body, robotic approaches can reach deep into the narrow GI tract to perform drug delivery, surgery, and physiological monitoring.[11]

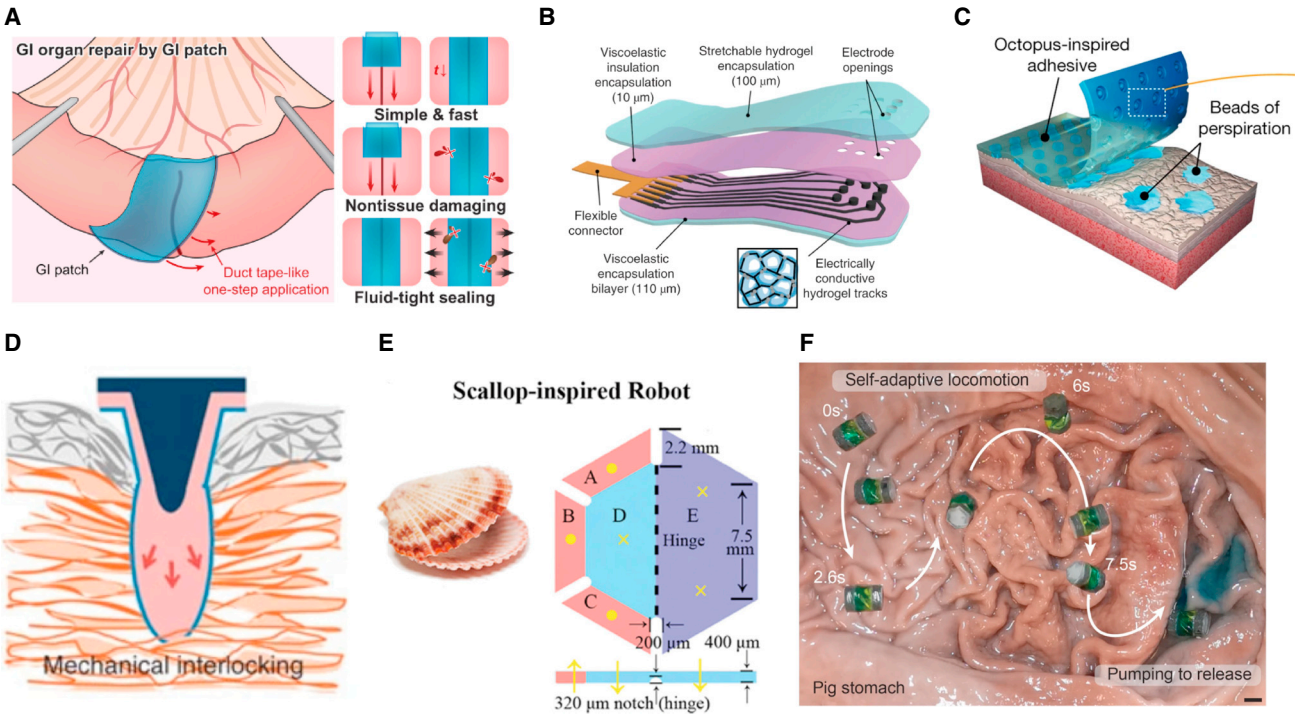

Figure 3. Recent progress in materials, structures, and robotics for extending GI residence

(A) A bioadhesive hydrogel patch for wet environments and repair of GI organs. Reprinted with permission from Wu et al.[160] Copyright 2022 AAAS.

(B) Schematic of a hydrogel containing a viscoelastic electrode array and matching the surface of tissue. Reprinted with permission from Tringides.[161] Copyright 2021 Springer Nature.

(C) Schematic illustration showing the wet-tolerant adhesive patch inspired by an octopus. Reprinted with permission from Baik et al.[162] Copyright 2017 Springer Nature.

(D) Mechanism diagram of a swellable microneedle interlocking with tissue. Reprinted with permission from Yang et al.[71] Copyright 2013 Springer Nature.

(E) Structure of a scallop-inspired soft robot. Reprinted with permission from Chen et al.[163] Copyright 2020 American Chemical Society.

(F) Potential application of a magnet-controlled amphibious origami millirobot with the ability of self-adaptive locomotion. Reprinted with permission from Ze et al.[164] Copyright 2022 Springer Nature.

Additionally, soft robots excel in adapting to their surroundings by utilizing highly flexible materials, enabling them to withstand the demanding conditions within the GI tract for extended periods of time. For example, some biomimetic robots employ deflected, segmented bodies for multidirectional movement, anterior and posterior legs with setae to move on wet surfaces, and a gripper for drug delivery.[189] Zhang et al.[190] made a small-scale hollow spherical robot by using a 3D micromachining method to achieve programmed deformation, realizing the adaption to the environment of the stomach.[190] These robots are powered by magnetic polymer composites with programmable properties and can be controlled to crawl and stop on the surface of the stomach.[189] Compared witih other methods, robotic approaches emphasize controllability and multifunctionality, making them an attractive option for biomedical applications.

The field of robotics has seen significant advancements with the development of 4D printing, which combines different actuation systems and leverages 3D printing technology to expand its possibilities.[191] This innovative technique enables the creation of 3D objects that can undergo transformative changes in their physical properties, including shape, density, elasticity, and electromagnetic characteristics, in response to specific stimuli, such as magnetic control.[86] One remarkable application of 4D printing is its integration with soft robotics, where robots constructed from easily deformable materials can be remotely controlled to execute a wide range of mechanical movements, including expansion, rotation, jumping, and bending. Notably, Chen et al.[163] demonstrated the design of a shell-inspired soft robot capable of controlled opening and closing actions, resembling a firm grasp similar to that of a hand, on the surface of GI organs, with the potential for long-term residence (Figure 3E).

The potential of these soft robots for long-term retention within the GI tract is evident. By combining the principles of structural engineering and remote-control systems, small-scale robots exhibit omnidirectional locomotion and amphibious movement, showcasing their ability to facilitate fixed-point drug release and *in vitro* diagnoses without limitations on size or flexibility[164] (Figure 3F). These groundbreaking designs offer compelling solutions for resident systems to effectively withstand the harsh conditions present within the GI tract. Furthermore, the capability to fabricate intricate, small-scale robots by using diverse materials, structures, and magnetic properties provides the flexibility to tailor these robots to meet the specific requirements encountered within the GI tract.[192]

In section "design rationale for future GI residence systems," we have summarized insights derived from the latest research on materials, bioinspired structures, and soft robots, all of which hold promise for shaping the future of safer, more durable GI residence systems. As we navigate the complexities of the GI environment and explore innovative solutions to overcome its challenges, the prospects of groundbreaking advancements in GI residence systems become increasingly evident. By integrating more functional components, residence systems are likely to evolve into a controllable "space station" within the GI tract.

CONCLUSION AND OUTLOOK

Minimally invasive, multifunctional GI residence systems are being developed as platforms to address the complexity and longevity of GI disorders. They enable continuous monitoring, real-time diagnosis, and sustained drug release over extended periods. Although some systems have already been commercialized, their retention durations and *in vivo* stability need further improvement in comparison with existing implantation systems. Further robust evaluations in animal models and/or clinical trials need to assess material compatibility, toxicity, size limitations, structural congruence, safety, precision of the control system, and real-world effectiveness.

Further research is needed for understanding the dynamic relationship between GI residence systems and the changing characteristics of the GI tract. Considering variations in digestive tract properties among different species is crucial to justifying the effectiveness of long-term retention systems. Tissue-specific requirements for mucoadhesives, for example, vary significantly, leading to discrepancies between studies. Challenges arise from model-dependent variations, such as rats' resistance to intra-abdominal infection and rabbits' susceptibility to post-surgical adhesions. These challenges hinder accurate prediction of clinical performance and successful technology translation.[193]

Standard approaches to evaluating these GI residence systems involve endoscopy, X-ray, and ultrasound. New techniques should be developed for more spatial precision with long-term tracking ability beyond clinical settings. Sharma et al.[194] employed a proficient planar electromagnetic coil to produce a 3D magnetic field gradient within the GI field of view.[194] Employing distinct magnetic-field sizes to encode each spatial point allowed the coil to achieve 3D positioning of the GI residence system. This system exhibits the potential for quantitative assessment of navigation and precise targeting. In a similar vein, Gleich et al.[195] devised magneto-mechanical resonator (MMR) sensors with heightened signal strength, thereby accomplishing miniaturization of sensing technology, resulting in a linear size one to two times smaller than that of the prevailing LC resonator technology.[195] Moreover, the detection range of MMR sensors extends up to 25 cm, which surpasses the approximately 5-cm range offered by current sensors.[196]

The pathological condition of digestive tissues is another critical factor because it can alter their physical and chemical properties and the immune response to retentive systems.[172,193] Inflammatory colitis and colon cancer, for instance, can significantly affect material adhesion strength. In inflamed colitic tissues, a dextran- and dendrimer-based material exhibited 60% less adhesive strength than healthy tissues. Conversely, the same adhesive demonstrated stronger adhesion to tumors than healthy tissue, possibly as a result of changes in collagen levels.[197]

Future development of GI residence systems should embrace multiple disciplines and benefit from advancements in various other engineering fields. The convergence of information science, electronic engineering, and biomedical technology revolutionizes medical care by offering intelligent and individualized treatment options and streamlined medical management.[115] The integration of residence systems with electronic sensors enables continuous monitoring of patients' physiological signals, providing valuable data for personalized treatment plans. Real-time feedback-driven automated drug release can be achieved through drug-delivery modules, creating a closed-loop system that integrates detection, diagnosis, and treatment.[198,199] Wireless transmission systems, such as Bluetooth and WiFi, enable remote communication with residence systems via common electronic devices, decentralizing medical resources to improve healthcare access.[11,139] Overall, residency systems serve as a minimally invasive platform that empowers remote and information-based medical diagnosis and treatment by combining technology with human expertise to enhance patient outcomes and overall quality of life.

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AUTHOR CONTRIBUTIONS

B.Y., H.H., and K.N. drafted the manuscript. Z.G. and K.N. supervised the project. All authors contributed to the review and editing of the manuscript.

DECLARATION OF INTERESTS

Z.G. is the co-founder of Zenomics Inc., ZCapsule Inc., and μZen Inc.

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