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Perspective

# Toward Next-Generation Ingestible Hydrogels

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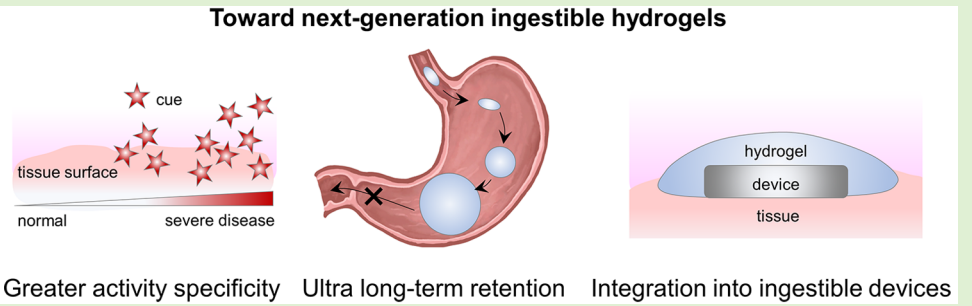


**ABSTRACT:** Ingestible hydrogels have long been used in food and therapeutic applications. Their polymeric composition endows these materials with programmable and dynamic properties to operate within the complex gastrointestinal tract. Recent advances have pushed the boundaries of hydrogel behavior and function; incorporating these features may enable new strategies to manage gastrointestinal and systemic diseases. In this perspective, we highlight some commercial ingestible hydrogel products to establish their current capabilities. We then discuss some recent advances of ingestible hydrogels that push these capabilities in the areas of tissue-specific activity, ultralong retention within the gastrointestinal tract, and incorporation into ingestible electronics and robots. Finally, we discuss some key considerations for translating ingestible macroscale hydrogels, which requires early consideration of *in vivo* models and regulation, safety, and manufacturing.



## INTRODUCTION

The need for advanced capabilities in the gastrointestinal tract (GIT), such as imaging and physiological sensing, has motivated the design of ingestible devices, capsule-scale electronics and/or mechanical systems capable of carrying out these complex tasks.[1−4] Such devices have impacted clinical care, simplifying gastrointestinal diagnostics and therapeutics. Capsule endoscopy devices such as the PillCam enable gastrointestinal imaging without the need for invasive endoscopic procedures. As the capsule navigates the GIT, images are transmitted to an externally worn recorder.[5] The SmartPill is able to sense multiple physiological signals (temperature, pH, and pressure), and is useful to measure gastrointestinal motility.[6] The RaniPill is able to spatially program delivery of biologics in the intestines. After dissolution of an enteric-coated outer capsule, the device inflates to facilitate alignment of a needle perpendicular to the intestinal wall.[7] To facilitate ingestion, these devices are of size 11 mm × 26 mm−11.6 mm × 32 mm and have transit times <9 h.[8,9]

Hydrogels, which are physically or chemically cross-linked polymeric networks comprising water, have emerged as attractive ingestible materials for biomedical applications.[10] Ingestible hydrogels have long been utilized in the food industry as they can be easily manufactured with biocompatible materials to create appealing foods, modulate food texture, and improve food shelf life.[11,12] Their established safety in the GIT has also made ingestible hydrogels attractive for several biomedical applications including weight loss and drug delivery.[13−15] Hydrogels and their polymer constituents can autonomously respond to their environment and play various roles as actuators, drug carriers, therapeutics, and sensors in a low-power manner.[16,17] Given their programmability, functionality, and dynamism, we believe that there are ample opportunities to expand the capabilities and performance of ingestible devices by leveraging hydrogels. While gastrointestinal hydrogels across length scales have been developed,[13] macroscale hydrogels, defined as technologies with a feature dimension on the millimeter or greater length scale, offer some key advantages. As examples, macroscale hydrogels are well-suited to engage with the large surface areas of the GIT, device functions can be spatially restricted through size exclusion, and stimuli-responsive hydrogels can rapidly

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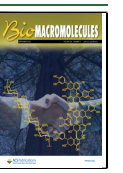





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Table 1. Commercially Available Ingestible Hydrogel Therapeutic Products[a]

| product name | category | primary polymers of hydrogel | FDA classification | refs |
|---|---|---|---|---|
| Acuform | drug delivery technology | poly(ethylene oxide) and hydroxypropylmethyl cellulose | N/A: pharmaceutical excipient | refs 23,24 |
| Actimask | taste-masking agent | gelatin | N/A: pharmaceutical excipient | ref 25 |
| Carafate | antiulcer agent | sucralfate | drug, prescription | refs 26,27 |
| Enterosgel | enterosorbent | polymethylsiloxane polyhydrate | device, Class IIa | ref 28 |
| Epitomee | weight-loss product | superabsorbent hydrogel particles (polymer not specified) | device, Class II | refs 29,30 |
| Esoxx | esophageal coating | poloxamer 407 | device, Class III | refs 31−33 |
| FiberCon | laxative | calcium polycarbophil | drug, over-the-counter | ref 34 |
| Gaviscon | antiacid and reflux suppressant | alginate | drug, over-the-counter | ref 35 |
| Gloup | dysphagia product | carrageenan | device, Class I | ref 36 |
| Phazix | dysphagia product | carrageenan | device, Class I | ref 37 |
| Plenity | weight-loss product | cellulose | device, Class II | ref 38 |

[a]Representative list of commercially available ingestible hydrogel products used in therapeutic applications. The column "Primary Polymers of Hydrogel" highlights the main polymers forming the crosslinked matrix, excluding other polymers and additives. The "FDA Classification" column specifies whether the product is determined as a drug, medical device, or falls into other regulatory categories, reflecting the level of oversight enforced by the FDA. For example, products like Acuform and Actimask are under general control and do not require approval as pharmaceutical excipients, although drugs containing them as inactive ingredients need to undergo FDA approval. For drug classifications, the table indicates whether they are prescription-based or over-the-counter, determined by the FDA based on safety and the need for supervision by licensed healthcare professionals. Devices are further classified into Class I (low risk), Class II (moderate risk), and Class III (high risk) based on regulatory controls necessary to ensure safety and efficacy.

respond to physiological conditions in a relevant length and time scale.

In this perspective, we first provide a brief history of the main commercial and clinical applications of ingestible macroscale hydrogels to establish some baseline features, and then highlight the advantages of macroscale hydrogels as gastrointestinal devices or device components through reports that push the boundaries of such features. Finally, we identify key challenges and considerations to the implementation and translation of gastrointestinal hydrogels, offering suggestions for how they can inform early stage research and development. Throughout this perspective, we direct the reader to key reviews that expand on relevant topics.

## A CONCISE HISTORY OF INGESTIBLE HYDROGELS

As gelatin hydrogels have long been used in food,[18] consumers are familiar with ingestible hydrogels. Hydrogels can uptake water via swelling and may be tailored with various bioresponsive properties,[19] which are more complex to program with metals and ceramics. Because hydrogels are soft and consist mostly of water, they are also biochemically and physically (e.g., soft edges) safe. Commercially, ingestible hydrogels have been used in the food and pharmaceutical industries, either as excipients or as standalone products. Here, we provide a brief overview of the current major applications of ingestible hydrogels, using some example commercial products that highlight hydrogel features (Table 1). For more examples of commercial hydrogels in the ingestible space and beyond, we direct the reader to these reviews.[20−22]

**Food and Food Technology.** One of the first written recipes of fish-derived jelly dates back to as early as the 10th century B.C., highlighting the longstanding prevalence of edible hydrogels.[18] Indeed, many foods are gels, such as yogurt, jam, and hard gummies.[12] In addition to being food themselves, hydrogel food technology has also been utilized to modify or augment food properties. Hydrogels have been applied for various purposes within food products, including: as fat replacers to reduce food fat and calorie content; encapsulation and protection of sensitive nutrients (e.g., vitamin precursors) to improve food shelf life; and modulation of nutrient and electrolyte delivery. Example products and applications include: intragastric pectin and alginate hydrogels are utilized as carbohydrate delivery vehicles to mitigate gastrointestinal symptoms in athletes (e.g., Maurten Gels);[39] and agar is included in foods (e.g., desserts) to mitigate dehydration and is a low-calorie additive.[40] An advantage of hydrogels in food technology is their similarity to the physicochemical properties of foods, which enables their ready incorporation into food while maintaining food physical and sensorial properties even at high temperatures required for cooking.[11,12,41−43] In fat replacement applications, consumer acceptance is critical but a complex function of multiple factors including mouthfeel, taste, texture, and appearance. Inclusion of hydrogel fat replacers may be tuned to impact these properties. As an example, modulation of gelatinized olive oil hydrogel content can result in reduced-fat meatballs with a comparable texture profile (e.g., hardness, springiness, cohesiveness, chewiness) to unmodified meatballs.[42]

**Drug Delivery.** Hydrogels are common excipients in oral drug formulations, where they are used to protect sensitive active pharmaceutical ingredients (APIs) from degradation, modulate pharmacokinetics, and program site-specific drug release. Common hydrogel excipients include hydroxypropylmethyl cellulose (HPMC), HPMC acetate succinate, poly(vinyl alcohol) (PVA), and poly(ethylene glycol) (PEG), which are used in everyday products such as Advil and Concerta. Pharmacokinetics have been modulated by tuning the GIT transit time of the formulation itself as well as the release rate of the API from the formulation. As described in prior reviews, there has been substantial interest in developing extended release formulations, which provide advantages in reducing patient pill burden and drug concentration fluctuations, and maintaining therapeutic drug concentrations for longer durations.[44−48] Here, we describe some example products that establish baseline characteristics of gastrointestinal hydrogel formulations, to motivate opportunities and areas for expansion.

Hydrogels have been utilized to modify pharmacokinetics by altering formulation physical properties, such as size and density, which in turn prolongs their transit through the GIT.[48] One area is through expansion and swelling to a size that


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mitigates passage through the pylorus (typically 13−17 mm),[49] prolonging gastric retention and thus drug release. Acuform comprises a proprietary polymeric matrix that rapidly swells (within 15 min) in the stomach to a diameter (18 mm) that is larger than that of the pylorus, and can remain intact within the stomach for 10−24 h.[50] This matrix has been utilized to maintain therapeutic drug concentration levels for medicines that require multiple daily administrations. As an example, a once-daily formulation of gabapentin utilizing Acuform, Gralise, achieves a comparable drug exposure as a three times-daily immediate-release formulation with reduced fluctuation.[51,52] Hydrogel flotation can also prolong therapeutic activity.[53,54] The Antiacid formulation Gaviscon comprises alginate, calcium carbonate, and sodium bicarbonate. Upon exposure to gastric fluid, the calcium carbonate dissolves and liberates calcium ions that cross-link alginate, forming a raft that floats on top of gastric fluid for up to 3 h. Thus, Gaviscon is able to provide prolonged acid reflux relief for longer durations (2−3 h v. ∼30 min) due to mechanical coverage of the gastric fluid and by acting as a depot for sustained Antiacid release.[35,55]

Mucoadhesion, defined as the adhesion of a surface to mucosal tissue,[56] has also been utilized to prolong pharmacokinetics and reduce the number of administrations. Polymers such as chitosan, alginate, HPMC, and cellulose can prolong transit through the GIT through interactions with mucosal proteins such as electrostatics and hydrogen bonds. To achieve mucoadhesion, such polymers are either incorporated directly into the hydrogel network or utilized as an exterior coating.[57,58] In a clinical trial, a once-daily extended release formulation of rifaximin performed comparably to a three times-daily formulation in reducing bacteria infection levels and alleviating gastrointestinal symptoms.[59] Its prolonged pharmacokinetics is likely due to inclusion of mucoadhesive polymers such as HPMC (the exact composition is proprietary); in sheep intestinal tissue, the formulation exhibited mucoadhesion for longer than 10 h.

In addition to prolonging formulation transit through the GIT, hydrogels or materials that form hydrogels *in vivo* offer strategies to control the rate and onset of drug release.[60] For example, for drugs that require faster onset, hydrogel capsules offer quick dissolution with the API already hydrated and dispersed. On the other hand, excipients like HPMC used in capsule formulations can control drug release by swelling *in vivo* and creating a polymeric mesh that APIs must diffuse through, hydrogel erosion, and/or polymer dissolution.[61,62] As an example, the drug pramipexole is used to manage Parkinson's disease symptoms. Efforts to develop an extended release formulation were challenging due to the high, pH-independent aqueous solubility of pramipexole. To overcome this limitation, a hydrogel formulation comprising HPMC, corn starch, and carbomer was utilized to control the rate of drug release. In a human bioavailability study, an extended release formulation of pramipexole taken once daily exhibited comparable 24 h drug area under the curve values as an immediate release formulation taken 3 times daily (91.7 v. 94.4 ng·h/mL).[63] Polymeric coatings can also control the site of drug release. Enteric polymers, which dissolve at alkaline pH, are used to program drug release in the alkaline environment of the intestines instead of the acidic gastric environment. Asacol is a formulation of mesalamine that is coated with the enteric polymer Eudragit for the treatment of ulcerative colitis.[64] In a clinical trial, 60% of patients treated with Asacol achieved remission, compared to 22% in the placebo group.[65]

**Other Therapeutic Applications.** In addition to modulating pharmacokinetics, hydrogel products have been developed that can improve the patient experience for orally administered drugs, which is expected to improve medication adherence and tolerability. Patients with dysphagia may skip or modify their medication due to hesitancy with solid medicines.[66] For these patients, the International Dysphagia Diet Standardisation Initiative provides a framework for the development and characterization of foods and drinks compatible with ingestion.[67] Hydrogels offer advantages in this space due to their tunability in flow, viscosity, and texture. Gel lubricants like carrageenan-based Gloup are intended to be applied onto drug capsules to make them easier to swallow.[36] Hydrogels such as Actimask are also used as taste masking agents in the form of capsule coatings or excipients in drug formulations to make medications more palatable.[25]

Other products utilize the mucoadhesive properties of certain hydrogel polymers to form therapeutic barriers. Several formulations for esophageal coatings, to protect against gastric fluid reflux, have been developed. As an example, Esoxx is a coating comprising hyaluronic acid and chondroitin sulfate, mixed with the bioadhesive polymer poloxamer 407 that mediates adhesion to the esophagus.[33,68] In clinical trials, Esoxx reduced symptoms associated with gastric reflux at a significantly greater rate compared to placebo (52.6% v. 32.1%). Given that Esoxx needs to be administered after every meal, the retention time of esophageal-adherent formulations is at least 2 h but likely shorter than 1 day.[31,69]

Leveraging their capability to swell in the GIT, cross-linked hydrogel products are used as bulk-forming laxatives. An example is calcium polycarbophil (FiberCon), which is poly(acrylic acid) cross-linked by divinyl glycol.[70] Swelling, cross-linked hydrogels that induce the sensation of satiety have also been developed for weight loss purposes. Plenity comprises superabsorbent biodegradable cross-linked hydrogel particles, made from cellulose and citric acid. Negative charges on the gel particles enable facile mixing with food by discouraging aggregation. Upon ingestion, the hydrogels increase substantially in volume within the stomach and small intestine to stimulate the sensation of fullness and decrease appetite. Once the hydrogels encounter the pH change in the colon, their cross-links are cleaved so that the absorbed water can be released and reabsorbed by the body.[38] In a clinical trial, Plenity administration resulted in significantly greater weight loss compared to placebo (6.4% v. 4.4%), with no safety risks.[71] Another weight-loss hydrogel device, Epitomee, is initially compact, but then rapidly expands into a triangular geometry that is 62 mm wide which mitigates its passage through the pylorus. The hydrogel comprises superabsorbent particles and a pH-sensitive envelope that promotes device disintegration at pH > 6.5, limiting its residence time in the stomach to several hours.[29,30] In a clinical trial, Epitomee administration significantly reduced body weight (6.6% reduction) compared to placebo (4.6%) in patients with a BMI of 27.0−40.0 kg/m$^2$, with no differences in adverse event rates between treatment and placebo.[72]

As hydrogels swell, they can also uptake molecules from their surroundings. Enterosgel is an intestinal adsorbent, or enterosorbent, that uses this capability to remove toxins like bacterial products and bile salts from the GIT to treat irritable bowel syndrome with diarrhea. Composed of porous


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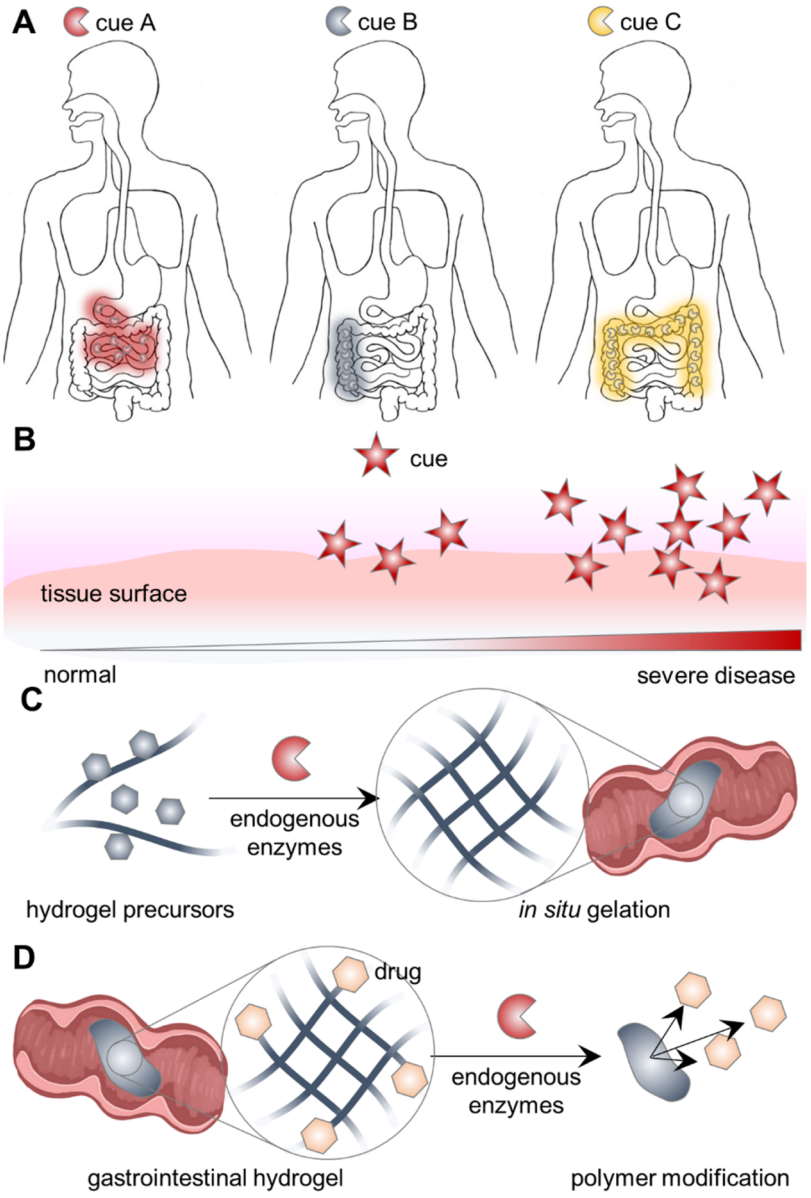


**Figure 1.** Ingestible hydrogels with greater specificity in formation and activity. By leveraging biological cues such as enzymes or reactive oxygen species, ingestible hydrogels may be engineered to have greater spatial specificity in their formation and activity. (A) Anatomical differences in the abundance of biological cues may be leveraged to program hydrogel specificity in locations where such cues are enriched. Reproduced or adapted with permission from ref 199 National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Accessed 2025−05−08. (B) Even within tissues, certain cues may vary spatially and temporally depending on disease state, and may only be present during severe disease. Disease presentation within tissue may be spatially heterogeneous, and may undergo cycles of remission and relapse. (C) Such cues may be leveraged to induce hydrogel formation at controlled sites to form localized drug depots or therapeutic barriers. Shown here is an example of hydrogel polymer and monomer precursors undergoing catalyzed polymerization and cross-linking *in vivo*. (D) In addition to bond formation, biological cues may be leveraged for bond breaking to, for example, degrade linkers and release drug at specific sites or during disease.

polymethylsiloxane polyhydrate microparticles linked into a larger hydrogel, Enterosgel can adsorb both hydrophilic and hydrophobic compounds and features multiscale porosity with micro-, meso-, and macropores spanning 2−100 nm in diameter. Intriguingly, Enterosgel demonstrates improved sorption capability for substances with higher molecular weights, which may be advantageous for removing large bacterial toxins without interfering with the pharmacological action of coadministered small molecule drugs.[28] In a clinical trial, Enterosgel significantly improved stool consistency, abdominal pain, and stool frequency and urgency, with 60% of patients reporting satisfactory symptom relief.[73]

## ■ ADVANCES IN INGESTIBLE HYDROGEL FEATURES

Recent advances have expanded how ingestible hydrogels behave in the GIT, to transform their role from passive carriers to materials that are active, in terms of formation, degradation, and actuation, in response to biological or user cues. We see the following as critical examples that expand the application space of ingestible hydrogels.

**Leveraging Endogenous Cues to Program Greater Specificity within the GIT.** Current commercial products utilize mucoadhesion or physical changes to prolong retention with the GIT, or leverage physiological pH changes to program drug release. As discussed in the previous section, these


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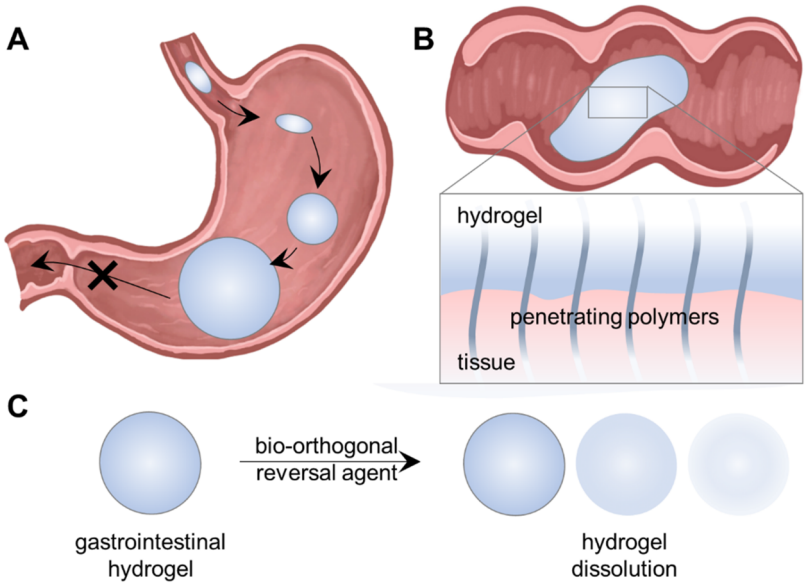


**Figure 2.** Ultra long-term retention in the gastrointestinal tract. Ultra long-term (weeks to months) gastrointestinal hydrogels could enable new strategies for drug delivery, and to monitor local (gastrointestinal) and systemic health and disease. (A) By rapidly swelling to a diameter that exceeds that of the pylorus, hydrogels have been reported to reside within the stomach for up to 30 days. (B) However, similar strategies are challenging to apply to the intestines due to risk of obstruction. A potential strategy is to utilize mucoadhesion, leveraging advances in electroadhesion and penetration enhancers to better drive polymer-tissue interactions and promote adhesion and retention. (C) For long-resident hydrogels, reversibility should be considered in the event of an emergency, to facilitate hydrogel dissolution and removal. Such strategies should be bio-orthogonal to minimize the risk of premature reversal.

methods have generally been effective in esophageal and gastric-resident systems. The intestines are an important target organ due to the need to treat diseases of the intestines such as inflammatory bowel disease (IBD) and cancer. However, implementing such systems in the intestines remains challenging due to the following: size-changing systems risk obstruction of the intestines; mucoadhesion is a nonspecific phenomenon; and the wide pH fluctuations within and between individuals.[58,60] Researchers have thus utilized alternative cues to facilitate defined drug activity within the GIT, by leveraging bioresponsive materials. While spatial specificity can also be achieved by local administration (e.g., endoscopic delivery[74,75]) or external control (e.g., with magnetic fields[76,77]), ingestible chemistries that are responsive to endogenous stimuli could simplify administration and reduce reliance on costly infrastructure or highly trained operators (Figure 1). Moreover, use of multiple magnets presents potential risks of gastrointestinal obstruction or perforation.[78]

Researchers have engineered gelation strategies that are triggered by tissue-specific cues for programmed hydrogel activity in the intestines. These hydrogels have been utilized as tissue barriers against absorption for weight loss applications, and for local delivery of therapeutics to reduce off-target effects. Endogenous enzymes are attractive cues to drive *in situ* hydrogel formation due to their rapid and tissue-localized activity. Li et al. leveraged the enzyme catalase to trigger in situ polymerization of dopamine in the intestines. Catalase activity was found to be higher in the duodenum and jejunum of the small intestine compared to the rest of the GIT. This finding was used to drive *in situ* dopamine polymerization of therapeutic films with multiple uses, to reduce glucose absorption, and to achieve intestinal localization of therapeutic enzymes and drugs.[79] Kinetic studies demonstrated that the films persisted for at least 6 h *in vivo* in porcine intestines, but not longer than 24 h.

Disease-associated tissue properties may also be leveraged to drive even greater specificity within tissues, especially with diseases that are spatially inhomogeneous. During IBD, the local environment presents with mucosal thinning, which makes the underlying epithelium susceptible to bacteria invasion. Zhang et al. functionalized hyaluronic acid with thiols, rendering them responsive to cross-linking by reduction. Here, the hyaluronic acid-thiol undergoes cross-linking with itself and mucus due to reactive oxygen species (ROS) present during disease, forming a therapeutic barrier that mitigates bacterial invasion and improves gastrointestinal recovery.[80] While hydrogels were observed within inflamed mice colons for as long as 8 h postadministration, their persistence is likely shorter than 24 h as therapeutic studies were performed with daily administrations.

In addition to formation of therapeutic hydrogels, endogenous cues may be leveraged to trigger bond-breaking and release of conjugated therapeutics. During IBD, inflamed intestinal epithelium acquires a cationic charge due to mucosal depletion and local accumulation of positively charged proteins. To drive intestinal localization during inflammation, Zhang et al. developed anionic hydrogels comprising ascorbyl palmitate. When administered in mice, these hydrogels exhibited greater intestinal retention, for at least 12 h, in animals with colitis compared to normal animals, and were able to mitigate intestinal colitis when loaded with drug. Drug release was achieved through hydrolysis, mediated by esterases that are upregulated during disease; the retention ability of the hydrogel increased the drug area under the curve 3−5-fold (depending on the disease model) compared to free drug.[81] Other bioresponsive materials that have been described include ROS- and hyaluronidase-cleavable hyaluronic acid for triggered release in the inflamed colon,[82,83] as well as


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azoreductase-sensitive hydrogels for microbiome-triggered release in the colon.[84,85]

While these *in situ*-forming hydrogels can achieve disease- and tissue-specific activity, the resulting hydrogel film typically persists for ∼1 day, requiring frequent (daily) administration. Many GIT diseases are chronic; thus, expanding the duration of these materials could be impactful in their management. Moving forward, materials may be designed with constituents that utilize multiple and orthogonal coupling chemistries (e.g., covalent, electrostatics; see the following section). Another open area is augmenting the mechanical properties of the resulting hydrogel films. Gastrointestinal bleeding requires hemostatic agents that can withstand and resist blood flow, which may overcome the mechanical integrity of thin films that polymerize *in situ*. Hydrogels have been developed that undergo rapid (within 5 s) cross-linking to staunch GIT bleeding but require endoscopic application.[86−89] Autonomous hemostats, capable of localizing to the bleed site and applying a mechanically tough hemostat in a noncompressible setting,[90] could enable rapid, point-of-care deployment. Such strategies could potentially combine preformed hydrogels within capsules that are opened by cues associated with bleeding (e.g., proteases[91]), or by developing hydrogels that cross-link *in situ* in response to bleeding.[92,93] Beyond therapeutics, tissue-specific hydrogels could expand opportunities for physiological sensing, diagnostics, and basic science. Hydrogels incorporating chemical and microbial sensors have been developed,[77,94,95] and incorporating similar sensors in ingestible *in situ*-cross-linking systems could facilitate operator-free and chronic monitoring of defined tissue regions.

**Enabling Ultra Long-Term Gastrointestinal Retention.** Current commercial formulations exhibit gastric retention times of approximately 1 day. Hydrogels capable of ultralong retention in the GIT, on the order of weeks to months, could enable new strategies to chronically deliver drugs or monitor physiological signals.[8] For drug delivery applications, gastrointestinal drug depots could improve health outcomes by increasing patient medication adherence through reduced dosing frequency, as well as minimize fluctuation of drug concentrations.[51,52,96] While there are long-acting injectable and implantable drug delivery products capable of drug release over 6 months, patients tend to prefer oral administration over other routes, motivating the need for long-acting ingestible drug delivery systems.[97] In addition to drug delivery, long-term retention within the GIT could enable continuous health monitoring, which is difficult with current, single point-in-time assessments in the clinic.[8,98] As demonstrated with commercially available hydrogels, their capacity to swell and respond to stimuli makes them promising materials for programming GIT retention (Figure 2). We are excited about the opportunity for the field to push these properties even further to enable ultra long-term retention in a safe and ingestible format.

Within the gastric cavity, one strategy to achieve long-term retention is through confinement via volumetric expansion: such devices leverage the expansive capacity of the stomach to expand to a size that prevents hydrogel passage through the 2 cm-wide pylorus.[49] Indeed, bariatric balloons, which can be filled with 450−600 mL saline corresponding to a sphere of diameter ∼10 cm, can be safely retained in the stomach for up to 12 months.[99] However, long-term retention of hydrogels in the stomach is challenging because of their inherently lower strength compared to other materials, such as metals. Researchers can learn from recent progress on imbuing hydrogels with enhanced mechanical properties. Liu et al. developed an ingestible device comprising a porous PVA hydrogel membrane that encapsulates superabsorbent poly(acrylic acid) particles. By undergoing freeze−thawing cycles, nanocrystalline domains were introduced into the PVA membrane in order to enhance its fatigue resistance under cyclic loads. The superabsorbent particles enabled the devices to rapidly swell in the stomach of live pigs, reaching a final volume of ∼50 $cm^3$ corresponding to a sphere of diameter ∼4.6 cm within 1 h, and achieving gastric residence for up to 30 days.[100] A complication with relying on swelling for volumetric expansion is that hydrogel mechanical properties tend to weaken after swelling.[101] To address this issue, Jin et al. developed a double network hydrogel in which the first polyacrylamide network swells immediately upon ingestion, whereas the second network, comprising chitosan and alginate, forms over time in the acidic gastric fluid. In simulated gastric fluid, these hydrogels swelled to a size (>12.8 mm) larger than the diameter of the human pylorus within 50 min, and continued to swell over 2 h. Increasing the content of chitosan and alginate from 2% to 6% reduced the hydrogel swelling ratio from 1258.1% to 1035.9% but increased the compressive stress at 60% strain from 45.6 to 93.8 kPa, after 30 days exposure to simulated gastric fluid. These tough hydrogels were retained in rabbit stomachs for 16 days.[102]

In addition to swelling, shape change could be another avenue to program geometries that are initially ingestible and capable of GI retention. While shape-changing gastrointestinal devices, which typically comprise thermoset polymers or metals, have been reported,[103−105] such behavior in ingestible hydrogels remain to be established. Various strategies to induce shape-change in hydrogels have been developed, and include temperature change, acidic pH, light irradiation, and environmental salt composition (e.g., salt concentration).[106−109] For example, Löwenberg et al. developed a gelatin-based hydrogel that in water, adopts a smaller geometry due to gelatin chain condensation into helices. The presence of chaotropes such as $MgCl_2$ disrupts helix formation, resulting in a random coil structure that "unfurls" the hydrogel to a larger geometry.[110] Similar hydrogels could potentially be programmed for gastric retention by adopting an initially smaller geometry in water, to facilitate ingestion, but then unfurling into a wider geometry to mitigate gastric passage by leveraging environmental salts. However, additional work is needed to characterize the mechanical performance of such shape-changing hydrogels, as well as their performance across a range of conditions within the chemically complex GIT.

Whether ingestible hydrogels are capable of gastric retention beyond a month remains an open question. As the field continues to push the boundaries of retention time in the stomach, more explicit benchmarks for mechanical property requirements would be beneficial so that researchers can iterate quickly in the development phase without needing to rely on costly large animal models for validation. One example of a useful benchtop test for geometry- or size-based retentive devices involves compressing a device within a funnel whose outlet matches the dimensions of the pylorus. Previous work has demonstrated that devices requiring 3 N of force or greater to pass through the funnel were likely to be gastric-resident *in vivo*.[105,111]

In regions of the GIT outside the stomach, such as the intestines and esophagus, long-term retention strategies that do


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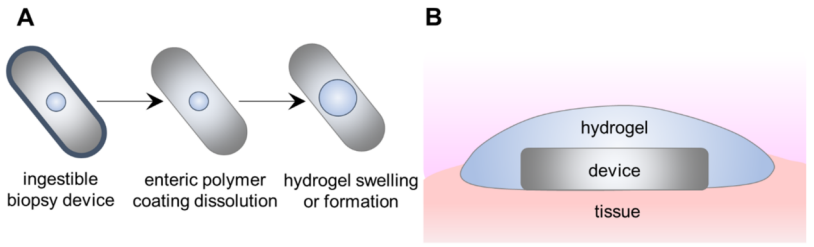


**Figure 3.** Hydrogels integrated into ingestible devices. As part of ingestible electronics, hydrogels can confer low-power device functionality. (A) Hydrogels incorporated into ingestible devices can enable battery-less bacteria biopsy in the gastrointestinal tract. Dissolution of an enteric polymer coating triggers hydrogel activity either by swelling or polymerization and cross-linking, leading to bacteria capture in a solid matrix that can be retrieved after passage through the gastrointestinal tract. (B) By acting as a bioadhesive patch, hydrogels can augment the performance and lifetime of ingestible sensors and stimulators through intimate contact with gastrointestinal tissue.

not rely on volumetric expansion are needed to prevent obstruction. While not yet demonstrated *in vivo* in GI regions outside the stomach, we believe hydrogel-based adhesives are well-suited to meet this goal.[112] A major challenge with adhesion in the GIT is that the surface mucosa undergoes a relatively high rate of cellular turnover, with these estimated cell lifespans: stomach, 13 days; small intestine, 5.3 days; and colon, 3.4 days.[113,114] For long-term retention, adhesive devices should ideally penetrate through these high-turnover surface layers. One strategy involves coupling adhesive hydrogels with penetration enhancers like sodium dodecyl sulfate, which can increase hydrogel adhesion to *ex vivo* porcine skin by 3- to 50-fold depending on enhancer concentration compared to no-enhancer controls. Validation with gastrointestinal tissues is still needed.[115] Electroadhesion is another approach, wherein application of an electric field drives adhesion between cationic polymers and anionic proteins within the slow-turnover epithelial layer of the mucosa.[116] In a recent study, electroadhesion enabled hydrogel retention on the mucosal surface of the gastric cavity for 11−30 days in pigs; in contrast, control hydrogels adhered to the gastric mucosa by EDC/NHS chemistry were cleared within 2 days.[117] To realize such approaches in an ingestible format, more research is needed on tetherless methods of applying an electric field.

Finally, an important consideration for long-resident hydrogels is reversibility: controlled deswelling or degradation of the hydrogel. This feature is critical for emergency settings, such as gastrointestinal blockage or an allergic reaction, or when the therapeutic course is completed. While biodegradable chemistries (e.g., hydrolyzable esters, pH-sensitive chemistries) may be incorporated to enable passive degradation and clearance of long-residing hydrogels, these are typically challenging to control due to the variations of the gastrointestinal environment. Thus, on-demand reversibility typically utilizes reversible chemistries that are orthogonal to biological processes. In one example, Raman et al. developed hydrogel networks that were cross-linked with *ortho*-nitrobenzyl-containing linkers, which is cleavable by blue light (365−405 nm) that can be applied with an LED-functionalized endoscope or ingestible capsule. Whereas control balloons exhibited swelling, test balloons exposed to blue light for 30 min decreased in size after 6 h in live porcine stomachs, indicating successful *in vivo* reversal of the light-cleavable linker.[118] Hydrogels can also be reversed with biocompatible chemicals that may be ingested on-demand. To form mechanically tough yet reversible hydrogels, Liu et al. developed double-network hydrogels comprising alginate and polyacrylamide networks, the latter of which was cross-linked with a disulfide-containing linker. These polymer networks were selected because they are reversible by EDTA and glutathione via calcium chelation and disulfide reduction, respectively. Exposure of hydrogels to 40 mM EDTA and 20 mM glutathione reduced hydrogel compressive stress from 373 to 5.6 kPa after 2 h, indicating hydrogel dissolution. In live porcine stomachs, hydrogels exposed to administered reversal agents (0.5 L of 40 mM EDTA and 20 mM glutathione) degraded and dissolved after 1 h, whereas untriggered hydrogels resided in the stomach for up to 8 days.[119]

Achieving safe and robust reversibility of ingested hydrogels can be challenging due to the wide environmental changes of the GIT across various sites as well as between normal and disease states. Indeed, the GIT is constantly secreting fluids and proteins, which complicate efforts to maintain defined chemical conditions for reversal. For hydrogels within the stomach, this may be mitigated by timing of administration: fasting results in reduced gastric fluid volume (45 mL) compared to feeding (>600 mL),[120] or coadministration of generally recognized as safe antacids to mitigate stomach acidity. Leveraging the large volume of the stomach (1−1.5 L), we recently utilized dilution as a strategy to better control the gastric chemical environment through administration of large (200 mL) volumes compatible with ingestion.[121] For reversal strategies that utilize chemicals and bond breakage, the safety of the reversal agent, degraded materials, and any potential byproducts must be understood and characterized, not only for host tissue but also for the microbiome.[122] Functional groups that result from cleavage (e.g., thiols) might render new interactions with the GIT.[119,123] Moreover, the hydrogel and its degradation products may be modified by the disease environment and the microbiome; for example, during certain diseases, the colon exhibits unusually acidic pH (as low as 2.3) that may alter materials physicochemical properties.[124]

**Integration into Ingestible Electronic and Robotic Devices.** Ingestible electronic and robotic devices have the potential to render GI medicine more convenient, effective, and widely accessible through autonomous and closed-loop function.[1,2,125,126] Generally, electronics enable sensing, feedback, recording, stimulation, and control of other device components. For diagnostic purposes, ingestible electronics and robotics systems may replace traditional clinical tools like endoscopy, which are relatively invasive and often require sedation. As an example, ingestible devices such as the PillCam are used in the clinic to identify lesions and characterize gastric motility disorders. For therapeutic applications, electronics are useful for applications like on-demand drug delivery, neuromodulation, and medication monitoring.[2,127,128] Indeed,


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Biomacromolecules 2025, 26, 5497−5513

ingestible electrical stimulators have been demonstrated to enhance or inhibit appetite by modulating the production of the hunger hormone ghrelin.[129,130] Meanwhile, hydrogels have been utilized to improve the performance of bioelectronics in other regions of the body, such as the heart, brain, and skin. Uses include: maintaining intimate contact of strain sensors with dynamic tissues, mitigating foreign body responses in long-term tissue interfaces, and conducting bioelectric signals.[131−133]

Similarly, as part of ingestible devices, hydrogels have significant potential to augment the functionality of ingestible electronic and robotic devices due to their low-power, programmable responsivity and ability to provide a soft, hydrated interface between rigid device components and soft biological tissues (Figure 3). Their low-power functionality is an advantage, as ingestible devices have limited space and thus constraints on power supply. Thus, incorporation of hydrogel components can reduce or mitigate the need for batteries, which may pose safety issues.[1,134] In the long term, we envision that the advantages of hydrogels described in the previous sections can also be leveraged toward next-generation devices like region-specific, autonomously targeted robotic tools and long-term retention of electronic sensors for management of chronic GI diseases.

Ingestible robotic devices may augment or even eliminate the need for a clinician to operate tools within the GIT, paving the way for the ultimate vision of a "surgeon-in-a-pill."[135] Chen et al. developed an automated microbiome biopsy device contained within an enteric-coated capsule. Upon capsule dissolution in the alkaline intestine, the poly(ethylene glycol) diacrylate, iron chloride, and ascorbic acid powder dissolves and automatically undergoes rapid (∼1 min) radical polymerization, trapping gut bacteria in a solid matrix that can be retrieved after device passage through the GIT.[136] Here, incorporation of a hydrogel enables "sensing" (dissolution in intestinal fluid) and "response" (rapid *in situ* polymerization and capture of bacteria) without the need for electronics or battery power. In similar applications, after dissolution of an enteric-coated capsule or inlet, superabsorbent hydrogels within the collection chamber swell with sample fluid and seal the inlets, preventing further fluid exchange. In a benchtop setting, sampling rate was found to depend on media viscosity, varying from 20 min in water to 30 min in porcine small intestine slurry. Upon testing in dogs, the devices exhibited a transit time varying 24−60 h.[134] In another design, hydrogels undergo a critical swelling height at pH > 6, opening a collection inlet which automatically closes afterward to restrict sample collection within the intestines.[137]

The described examples have featured device activation in response to hydrogel hydration, which is a nonspecific stimulus. Future work in this area should explore hydrogel chemistries that actuate in response to a wider range of endogenous or exogenous stimuli in order to increase specificity of sampling. For example, while enteric coatings have been utilized in microbiome sampling applications; there is overlap in the pH values of the duodenum (pH 4−6), jejunum (pH 5−7), and ileum (pH 7−8) which all have segment-specific microbiota.[138] Incorporation of chemistries that are specific to additional stimuli (e.g., enzymes) may help to improve specificity of sampling.

Additionally, similar stimuli-responsive behaviors could be used to design actuators for soft robots to replace surgical tasks like grasping and sealing. Overall, the intersection between ingestible devices, soft robots, and hydrogels remains relatively underexplored. One major challenge is the fact that hydrogels typically do not generate sufficient mechanical force to perform operations like cutting, lifting, or combining tissues. To overcome this limitation, researchers may be able to harness recent advances that have led to dramatic improvements in the actuation stress and power achievable in hydrogels, such as leveraging turgor pressure or elastic prestrain.[139,140] Another remaining challenge is the use of hydrogels in applications requiring rapid activation of hydrogel activity. Indeed, hydrogels may take at least 1 h to respond (e.g., swell, shrink, or dissolve) to their environment. By leveraging environmental enzymes, we see opportunities in expediting hydrogel responsivity, for example via enzymatic degradation of exterior capsules, or to trigger hydrogel formation.[79,141] Heat-sensitive materials have also been utilized for rapid activity (as quickly as 5 min) upon exposure to physiological temperature; this strategy has been utilized to achieve gastrointestinal residency of hydrogels via mechanical gripping.[104,142]

Beyond capsule-based form factors, hydrogels have been utilized as patches to increase the surface area and time of engagement with gastrointestinal tissue. This is critical for the performance of ingestible electronics, as intimate contact with mucosal surfaces enables efficient therapeutic stimulation and high-fidelity sensing of electrophysiological signals.[143] By utilizing electroadhesive hydrogels to interface impedance sensors to the small intestine mucosa in a porcine model, Ying et al. reported a reduction in relative error in both amplitude (from 39.4 to 3.2%) and phase (from 1.6 to 0.48%) at 1 kHz, compared to untethered sensors.[117] Sensors immobilized by electroadhesion were reported to remain adherent for >1 h *in vivo*. Thus, coupling ingestible sensors with bioadhesive hydrogels can augment sensor precision in an easily implementable manner. Other approaches for hydrogel bioadhesion have also been described. In another approach, an ingestible origami hydrogel patch unfolds into a patch after wetting. The hydrogel contained an embedded magnet, which enabled it to be guided and localized with external magnets.[144] Expanding on this approach, hydrogels have been coated with EDC/NHS-functionalized chitosan to adhere electronics to the stomach wall via covalent bond formation with tissue. These patches included a magnet to facilitate correct orientation of the functionalized surface toward tissue via an external magnet, enabling ingestible electronics retention on the stomach for at least 2 days and electrical stimulation of gastric cells to secrete hormones.[145] Thus, by incorporating various modes of hydrogel adhesion (covalent, electroadhesion, magnetic immobilization), different time scales of device-tissue interactions can be achieved to augment device function.

Hydrogels with electrically conductive properties may further improve electronic signal transfer at the device-tissue interface. Several conductive hydrogels have been developed for wearable and implantable applications using hydrophilic conjugated polymers, which possess an alternating double-bond structure that enables them, when doped, to transmit electrical charges across their macromolecular backbone. In addition to being more flexible than traditional conductive materials, conjugated polymer hydrogels also exhibit mixed ionic and electronic conductivity, which enables them to be highly effective at transducing ionic biological signals into electrical signals that can be processed downstream by conventional circuitry.[146] For example, a hydrogel made from the conjugated polymer system poly(3,4-ethylenedioxythio-


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Biomacromolecules 2025, 26, 5497−5513

Table 2. Gastrointestinal Tract Dimensions and pH across Organisms[a]

| feature | humans | pigs | dogs | rats | mice |
|---|---|---|---|---|---|
| esophagus length | 25 cm ref 160 | 40 cm ref 167 | 27 cm ref 168 | 9 cm ref 169 | 1.5−2 cm ref 170 |
| esophagus diameter | 25 mm ref 160 | 25 mm ref 171 | 20 mm ref 172 | 2−3 mm ref 173 | 2 mm ref 174 |
| stomach capacity | 1−1.6 L ref 160 | 6−8 L ref 160 | 1 L ref 160 | 3.4 mL ref 175 | 0.4 mL ref 175 |
| stomach pH | fed: pH 4.3−5.4 fasted: pH 1.4−2.1 ref 160 | fed: pH 4.4 fasted: pH 1.7−3.4 refs 176,177 | fasted: 1.5 fed: 2.1 ref 160 | fed: pH 3.2 fasted: pH 3.9 ref 175 | fed: pH 3.0 fasted: pH 4.0 ref 175 |
| pylorus diameter | 13−17 mm ref 49 | 14−18 cm ref 178 | 12.8 mm ref 179 | ∼2−3 mm ref 180 | ∼250 $\mu$m ref 180 |
| small intestine length | 6.25 m ref 160 | 15−22 m ref 181 | 2.25−2.9 m ref 160 | 1.02−1.49 m ref 160 | 0.50−0.55 m ref 181 |
| small intestine pH | pH 5−7 ref 160 | pH 6.1−6.7 ref 176 | pH 6.2−7.5 ref 160 | pH 5.0−6.1 ref 175 | pH 4.7−5.0 ref 175 |
| colon length | 1.5 m ref 160 | 4−6 m ref 156 | 0.25 m ref 160 | 0.09−0.110 m ref 160 | 0.05−0.14 m refs 182,183 |
| colon pH | pH 5.5−7 ref 160 | pH 6.1−6.6 ref 176 | pH 6.5 ref 160 | pH 5.5−6.6 ref 175 | pH 4.4−5.0 ref 175 |
| total gastrointestinal tract transit time | 10−73 h ref 184 | 50−262 h refs 155,185 | 13−28 h ref 179 | 10−20 h ref 186 | 6−7 h ref 182 |

[a]Comparison of gastrointestinal physiology across humans and various animal models.

phene):polystyrenesulfonate (PEDOT:PSS) was integrated into an ingestible patch for electrostimulation of the gut to improve the quality of the tissue-electrode interface.[145] Though not yet explored in the GIT, novel conductive hydrogels have recently been developed with *in situ*-forming and stimuli-responsive capabilities.[147,148] By harnessing both features, we envision that hydrogels may be able to, for example, form conformally along tissue at disease sites (e.g., by leveraging disease-upregulated enzymes) but not normal tissue, for pathophysiology monitoring, or undergo programmed disassembly in response to biological processes. Moving forward, we believe these materials can be leveraged to create next-generation electronic ingestibles that combine high signal quality with tissue specificity and programmable retention.

## TRANSLATIONAL CHALLENGES FOR NEXT-GENERATION INGESTIBLE HYDROGELS

Translation of next-generation ingestible hydrogels will require engineers to carefully select preclinical models, demonstrate sufficient safety and efficacy to meet regulatory requirements, and address constraints related to manufacturing, storage, and distribution. Awareness of such downstream considerations during the early phases of research can increase the likelihood of translational success. Here, we give a brief overview of major translational challenges and how they might inform early stage materials selection and experimental design.

**Testing in Appropriate *Ex Vivo* and *In Vivo* Models.** As hydrogels transit through the GIT, they are exposed to a wide range of physiological conditions including mechanical forces, acidic and alkaline pH, and fluid compositions. Patient factors such as age, sex, and disease history may impact GI motility and thus, exposure times to these conditions. For example, the global prevalence of diabetes is increasing (from 9.3% in 2019 to ∼11% by 2045), and patients commonly (e.g., 47% in the DCCT-EDIC cohort) experience delayed gastric emptying, or gastroparesis.[149,150] pH levels in the GIT are often impacted by disease state, as is the case for patients with IBD where colonic pH can be highly acidic (pH 2.3).[124,151] Ashiru et al. found that a 0.75 g dose of PEG 400 increased the oral bioavailability of ranitidine by 63% in male, but not female, subjects.[152] In sum, ingestible hydrogels are subject to complex *in vivo* environments that exhibit interpatient variability, which may impact their properties and function. However, they can be tuned to be resilient and withstand these challenges: in disease states where hydrogels may be subject to prolonged acidic pH, careful selection and tuning of polymers with the appropriate $pK_a$ and drug linker chemistries can enable spatiotemporal control of hydrogel activity. As hydrogel polymers may inadvertently act as drug excipients, selection and design of nonbiodegradable, high-molecular weight polymers may limit their modification of drug pharmacokinetics.[152] Preclinical testing in appropriate models is thus critical for technology iteration and validation. In addition to animal models, benchtop models have utility in testing device features and toxicity, particularly in earlier stages of technology development. Here, we discuss some examples and advantages of such models in order of increasing complexity.

Initial experiments with *ex vivo* tissue and biofluids such as blood, urine, and gastric fluids may be valuable to down-select and test designs on the benchtop prior to *in vivo* experiments. In this context, pigs are an attractive source as their size means that large amounts of tissue can typically be sourced for high-throughput experimentation. Tissues may be available from vendors, local abattoirs, and local veterinary and medical schools. While human-derived tissue is potentially available through clinical organizations and collaborators, their sourcing may not be as predictable or reliable and thus may be reserved for late-stage validation. Testing apparatuses that approximate the shape and scale of GI tissues have also been used to test device features.[105,153]

Rodent models are routinely used in biomedical research, but are of limited utility in macroscale device development due to incompatibilities in GI size scale and anatomy (Table 2). Compared to that of humans, rodent GITs are significantly smaller, exhibit different pH values, and pass ingested materials quicker. These differences may result in inaccurate safety concerns. For example, in our work with gastric *in situ*-cross-linking hydrogels, hydrogels formed in pig stomachs safely passed through the GIT, whereas hydrogels formed in rats were much larger than the rat pylorus.[121] Rodent models still have utility in device development through toxicity testing of new device constituents. In our work with triggerable, disassembling gastric devices, we tested the toxicity of eutectic gallium indium in rodents.[154] In this context, rodent models present several advantages: their manageability and relatively low costs enables multiple treatment groups (e.g., control, low dose, medium dose, high dose) to be tested simultaneously. Moreover, there are established methods and tools to safely


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Biomacromolecules 2025, 26, 5497−5513

restrain and orally gavage animals in a rapid manner. We see rodent models as important for early stage assessments of the biochemical safety of device components; however, testing of complete device function would likely require large animal subjects.

For macroscale ingestible device development, large animal pigs and beagles are particularly attractive models over rodents due to the similarity of their GI physiology compared with humans (Table 2). These similarities have been described in-depth in other reviews.[155−160] Notably, humans and pigs have similar microbiomes: 96% of human microbiome functional pathways are also found in pigs.[161] Dog microbiomes are closer to that of humans than pigs.[162] Beagle dogs are utilized in drug development, and can be predictive of the effects of food and formulation on pharmacokinetics.[163−165] Notably, experiments with such animals come with unique considerations. Large animals are challenging to procure and maintain due to their resource needs: they require large housing facilities and veterinarian oversight, resulting in a substantial cost for each animal. Moreover, experiments with dog models may not be viewed favorably by the public,[166] and some institutions do not allow experimentation on dogs (e.g., MIT). As such, these models may not be as accessible as rodents. Other avenues exist to support working with large animals without requiring substantial infrastructure, such as working with contract research organizations. Sufficient demand and resources could be pooled to motivate the creation of large animal cores (*e.g.*, University of North Carolina School of Medicine). Local medical and veterinary schools may utilize pigs for training purposes, and could be an accessible source for procuring tissues or *in vivo* experiments.

**Ingestible Hydrogel Chemistry.** Here, we describe remaining challenges in ingestible hydrogel chemistry and potential solutions, with a focus on synthesis, biofouling, and microbiome impacts. Currently, most ingestible hydrogels utilize natural polymers or synthetic polymers made using free radical polymerizations. An advantage of synthetic polymers is the ability to expand and control the types of physicochemical properties that can be realized in ingestible systems. Ideally, synthesis of hydrogel precursors can be performed at scale with minimal organic solvents and toxic catalysts (e.g., copper) to streamline purification and minimize toxicity concerns. Here, researchers can leverage polymerization techniques that are enzyme-catalyzed (e.g., horseradish peroxidase, glucose oxidase, pyranose oxidase) in aqueous solutions.[187]

Another challenge is biofouling, particularly for hydrogels designed for long-term retention in the GIT. The ingress of complex gastrointestinal fluids and materials into ingestible hydrogels may cause accelerated degradation. At the same time, hydrogels require water to, for example, maintain geometry and mechanical properties. Various approaches have been reported to mitigate fouling of surfaces within the GIT. Lee et al. developed a multilayer adhesive in which the outermost layer was fluorinated and lubricated with biocompatible perfluorocarbon liquid to render an omniphobic surface. This coating prolonged gastrointestinal adhesion in an *ex vivo* setting when the adhesive was challenged with mock food (10 min), whereas control adhesives lost retention within 7 s.[188] In another example, Shimamoto et al. functionalized the tip of endoscopes with 2-hydroxyethyl methacrylate hydrogels, and evaluated their capacity to mitigate fouling during endoscopic procedures in pigs. Application of the hydrogel to the endoscope reduced fouling and improved visual contrast.[189] However, whether these strategies are durable at longer timespans in the GIT remains to be tested.

Finally, more research should consider the impacts of hydrogels and their degradation products on the microbiome. As an example, Ishibashi et al. demonstrated that oral administration of PEG 400 and PEG 4000 altered the microbiome in rodents. Moreover, administration of 40% PEG 400 reduced weight gain in a rodent model of high fat diet-induced obesity without affecting food intake.[190] Similarly, Ariaee et al. demonstrated that inulin with 27 repeat units (inulin 27), but not inulin 7 or inulin 14, decreased weight gain in a rodent model of high fat diet-induced obesity.[191] Together, these studies underscore the importance of studying the impact of hydrogel polymer physicochemical properties on the microbiome.

**Regulatory and Safety Considerations.** The regulatory classification of a new medical product determines the specific safety and efficacy milestones it needs to clear for approval. In the United States, designation of a product as a drug or device determines which center at the FDA will regulate the product. This designation has significant implications for toxicity testing requirements, manufacturing requirements, clinical trial design, and postmarket requirements. Because the FDA defines a drug as a substance whose primary intended purpose involves chemical or pharmacological interaction with the body, many ingestible hydrogels are likely to be regulated as devices.[38] For example, Plenity was originally approved through a de novo pathway (for low to medium risk devices with no predicates) and required a prescription, but was later approved for over-the-counter use via a 510(k) pathway, which offered a faster, cheaper regulatory approval process.[192] On average, it takes 150 days for approval via the 510(k) pathways and 356 days by the de novo pathway.[193] However, it is important to emphasize that the distinction between a drug and a device is not always clear, especially for hydrogels designed to respond to and interact with physiological signals, and early collaboration with the FDA can be useful to help define regulatory strategy.

Regardless of their classification, new hydrogels designed with materials that have already been used in FDA-approved products can increase the likelihood of obtaining satisfactory safety and toxicity profiles. Researchers are encouraged to consult the generally recognized as safe (GRAS) list and the FDA's inactive ingredients database, which lists all approved excipients and their approved concentrations and routes of administration.

**Manufacturing, Storage, and Distribution.** Material choices during the early research and design stages of a new hydrogel technology can significantly impact its manufacturability down the line. Supply needs can vary by orders of magnitude as a product moves from Phase 1 through Phase 3 to commercialization, depending on the indication. Availability of raw materials can become a roadblock depending on the scale and supply chain of existing polymer suppliers. Fabrication methods must also be consistent with current good manufacturing processes (cGMP). Manufacturing processes may impose constraints on hydrogel properties; for instance, additive manufacturing methods often require that gel-forming inks exhibit specific rheological characteristics like a yield stress and thixotropy. Early stage characterization of materials that have been processed by scalable production methods may also be important to ensure comparable performance to prototypes, as certain manufacturing methods may cause structural alterations like bond cleavage or cross-


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Biomacromolecules 2025, 26, 5497−5513

linking.[55,194] Additionally, it is important to minimize batch-to-batch variation, which may be more challenging for natural polymers depending on their source, whereas synthetic polymers may be more reproducible in their synthesis.

Reproducible sterilization methods are also needed for ingestible devices to obtain regulatory approval and clinical translation. Hydrogels can be rendered sterile either by manufacturing them using sterile manufacturing techniques or by performing terminal (at the end of production) sterilization, which can either be in the form of physical (e.g., heat, ionizing radiation, plasma) or chemical (e.g., alcohols, peroxides) processing of the final product.[195] Aseptic techniques require that all components involved in product manufacturing be sterilized separately, and that manufacturing occurs within highly controlled environments. Meanwhile, terminal sterilization options for hydrogels are limited to ones that do not cause polymers to decompose or degrade to the point of impacting critical performance attributes. The presence of water within hydrogels may limit their shelf life, since water can accelerate chemical reactions that break bonds and change material properties, especially for products meant to be biodegradable within the GIT. In general, sterilization strategies should be validated by monitoring their impact on key material properties defined for the target application, such as rheological, surface, cargo-releasing, and load-bearing capabilities.

Storage stability must also be considered during development. For applications in the developing world, resilience against high temperature and humidity is especially critical, as inconsistent cold-chain infrastructure may result in prolonged exposure to storage temperatures as high as 42 °C and relative humidity as high as 88%.[196] These conditions may destabilize or alter hydrogels through multiple mechanisms, including evaporation, phase transitions, water uptake leading to swelling, oxidation, and degradation. To tackle these challenges, methods such as reversible chemistries or water immobilization within the polymer network may help to improve therapeutic and hydrogel stability across a range of storage conditions.[197,198]

## CONCLUSIONS AND OUTLOOK

The mechanical properties, hydrophilicity, tunability, and responsiveness of hydrogels offer tremendous opportunities for ingestible, hydrogel-based technologies to transform medical care. Long-term therapeutic devices that can target specific regions of the GIT would reduce dosing frequency, which improves medication compliance, while reducing off-target effects and optimizing absorption of encapsulated APIs. In this perspective, we highlighted various ways that hydrogels can form in defined regions beyond the stomach, exhibit gastric residency, and improve the performance of ingestible electronics and robots. Whereas typical ingestible devices pass through the GIT in <9 h, hydrogels can exhibit gastric retention for up to 30 days. Beyond the stomach, hydrogels can be programmed to form rapidly (<5 s) and specifically in the small intestines. As part of ingestible bioelectronics, hydrogels can offer a low-power way for rapid (∼1 min) microbiome sampling or as a way to adhere bioelectronic devices to specific GI tissue. However, the field still has work to do to endow additional properties to ingestible hydrogels, such as having hydrogels persist for >24 h in the intestines or >30 days in the stomach. Collectively, there are now a suite of strategies to spatiotemporally control hydrogel activity in the GIT.

This field of ingestible hydrogels is especially promising because there has been clear precedence for their commercial and clinical acceptance. While challenges remain toward realizing the next-generation features highlighted in this perspective, we believe that many of these are solvable through interdisciplinary efforts that consider gastrointestinal biology alongside cutting-edge advances in hydrogel engineering. We described how patient and disease factors may cause variations in GI transit time and chemical composition that alter hydrogel performance. To study these variables, ingestible hydrogels should ideally be studied in GITs and environments that emulate the biology and size scale as that of humans. We provided a perspective on the advantages of various models: while porcine and dog are attractive models, they present challenges in access, cost, and infrastructure. In this regard, *ex vivo* tissues and fluids may be useful to iterate on materials prior to involved *in vivo* studies. To leverage these resources, researchers could consider machine learning approaches to study and optimize the interactions between hydrogel properties and *ex vivo* materials, to develop robust hydrogels with predictable *in vivo* behavior. Finally, we encourage researchers to inform themselves about downstream development, regulatory, manufacturing, and storage needs, even during the early stages of ideation and experimentation, as these can inform strategic selection of materials and processes that enhance the likelihood of eventual translational success.

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### Notes

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