

A Smart Pill That Can Sense, Sample, and Treat

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Ingestible electronics will deliver drugs and take biopsies

Photo-illustration by Edmon de Haro

One day soon, a doctor might prescribe a pill that doesn't just deliver medicine but also reports back on what it finds inside you—and then takes actions based on its findings.

Instead of scheduling an endoscopy or CT scan, you'd swallow an electronic capsule smaller than a multivitamin. As it travels through your digestive system, it could check tissue health, look for cancerous changes, and send data to your doctor. It could even release drugs exactly where they're needed or snip a tiny biopsy sample before passing harmlessly out of your body.

This dream of a do-it-all pill is driving a surge of research into ingestible electronics: smart capsules designed to monitor and even treat disease from inside the gastrointestinal (GI) tract. The stakes are high. GI diseases affect tens of millions of people worldwide, including such ailments as inflammatory bowel disease, celiac disease, and small intestinal bacterial overgrowth. Diagnosis often involves a frustrating maze of blood tests, imaging, and invasive endoscopy. Treatments, meanwhile, can bring serious side effects because drugs affect the whole body, not just the troubled gut.

If capsules could handle much of that work—streamlining diagnosis, delivering targeted therapies, and sparing patients repeated invasive procedures—they could transform care. Over the past 20 years, researchers have built a growing tool kit of ingestible devices, some already in clinical use. These capsule-shaped devices typically contain sensors, circuitry, a power source, and sometimes a communication module, all enclosed in a biocompatible shell. But the next leap forward is still in development: autonomous capsules that can both sense and act, releasing a drug or taking a tissue sample.

WHAT SMART CAPSULES CAN DO

Ingestible electronic capsules use miniaturized sensors and actuators to monitor the gut, deliver medication, and collect biological samples.

That's the challenge that our lab—the MEMS Sensors and Actuators Laboratory (MSAL) at the University of Maryland, College Park—is tackling. Drawing on decades of advances in microelectromechanical systems (MEMS), we're building swallowable devices that integrate sensors, actuators, and wireless links in packages that are small and safe enough for patients. The hurdles are considerable: power, miniaturization, biocompatibility, and reliability, to name a few. But the potential payoff will be a new era of personalized and minimally invasive medicine, delivered by something as simple as a pill you can swallow at home.

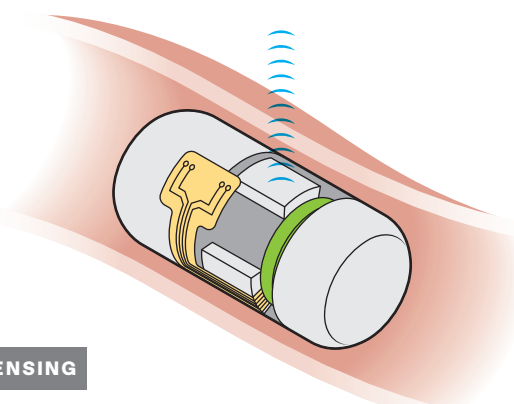
The idea of a smart capsule has been around since the late 1950s, when researchers first experimented with swallowable devices to record temperature, gastric pH, or pressure inside the digestive tract. At the time, it seemed closer to science fiction than clinical reality, bolstered by pop-culture visions like the 1966 film *Fantastic Voyage*, where miniaturized doctors travel inside the human body to treat a blood clot.

For decades, though, the mainstay of GI diagnostics was endoscopy: a camera on a flexible tube, threaded down the throat or up through the colon. These procedures are quite invasive and require patients to be sedated, which increases both the risk of complications and procedural costs. What's more, it's difficult for endoscopes to safely traverse the circuitous pathway of the small intestine. The situation changed in the early 2000s, when video-capsule endoscopy arrived. The best-known product, PillCam, looks like a large vitamin but contains a camera, LEDs, and a transmitter. As it passes through the gut, it beams images and videos to a wearable device.

Today, capsule endoscopy is a routine tool in gastroenterology; ingestible devices can measure acidity, temperature, or gas concentrations. And researchers are pushing further, with experimental prototypes that deliver drugs or analyze the microbiome. For example, teams from Tufts University, in Massachusetts, and Purdue University, in Indiana, are working on devices with dissolvable coatings and mechanisms to collect samples of liquid for studies of the intestinal microbiome.

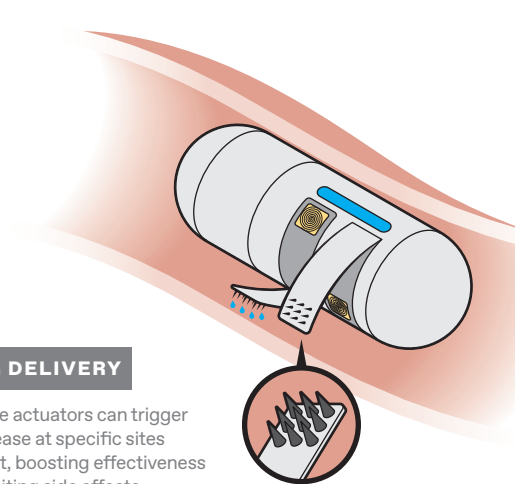
Still, all those devices are passive. They activate on a timer or by exposure to the neutral pH of the intestines, but they

SENSING

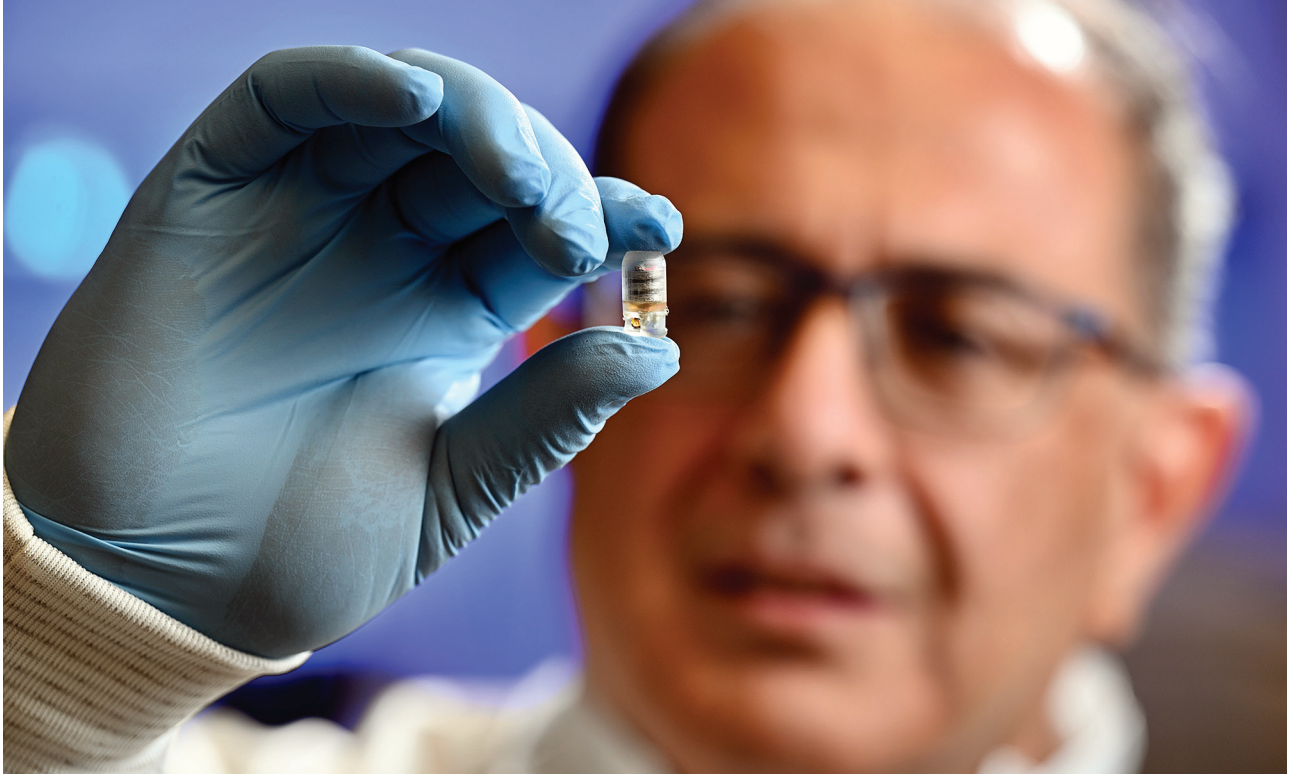


Embedded sensors can probe the gut—for example, measuring the bioimpedance of the intestinal lining to detect disease—and transmit the data wirelessly.

DRUG DELIVERY



Miniature actuators can trigger drug release at specific sites in the gut, boosting effectiveness while limiting side effects.



don't adapt to conditions in real time. The next step requires capsules that can sense biomarkers, make decisions, and trigger specific actions—moving from clever hardware to truly autonomous “smart pills.” That’s where our work comes in.

Since 2017, MSAL has been pushing ingestible devices forward with the goal of making an immediate impact in health care. The group built on the MEMS community’s legacy in microfabrication, sensors, and system integration, while taking advantage of new tools like 3D printing and materials like biocompatible polymers. Those advances have made it possible to prototype faster and shrink devices smaller, sparking a wave of innovation in wearables, implants, and now ingestibles. Today, MSAL is collaborating with engineers, physicians, and data scientists to move these cap-

One of the authors (Ghodssi) holds a miniaturized drug-delivery capsule that’s designed to release medication at specific sites in the gastrointestinal tract.

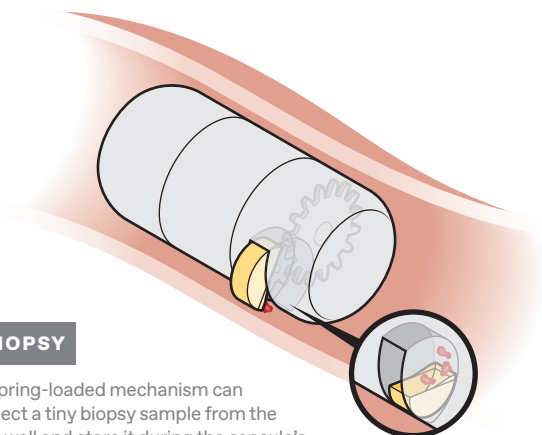
sules from lab benches to pharmaceutical trials.

As a first step, back in 2017, we set out to design sensor-carrying capsules that could reliably reach the small intestine and indicate when they reached it. Another challenge was that sensors that work well on the benchtop can falter inside the gut, where shifting pH, moisture, digestive enzymes, and low-oxygen conditions can degrade typical sensing components.

Our earliest prototype adapted MEMS sensing technology to detect abnormal enzyme levels in the duodenum that are linked to pancreatic function. The sensor and its associated electronics were enclosed in a biocompatible, 3D-printed shell coated with polymers that dissolved only at certain pH levels. This strategy could one day be used to detect biomarkers in secretions from the pancreas to detect early-stage cancer.

That first effort with a passive device taught us the fundamentals of capsule design and opened the door to new applications. Since then, we’ve developed sensors that can track biomarkers such as the gas hydrogen sulfide, neurotransmitters such as serotonin and dopamine, and bioimpedance—a measure of how easily ions pass through intestinal tissue—to shed light on the gut microbiome, inflammation, and disease progression. In parallel, we’ve worked on more-active devices: capsule-based tools for controlled drug release and tissue biopsy, using low-power actuators to trigger precise mechanical movements inside the gut.

Like all new medical devices and treatments, ingestible electronics face many hurdles before they reach patients—from earning physician trust and insurance approval to demonstrating clear benefits, safety, and reliability. Packaging is a particular focus, as the capsules must be easy to swallow yet durable enough to survive stomach acid. The field is steadily proving safety and reliability, progressing from proof of concept in tissue, through the different stages



BIOPSY

A spring-loaded mechanism can collect a tiny biopsy sample from the gut wall and store it during the capsule’s passage through the digestive system.

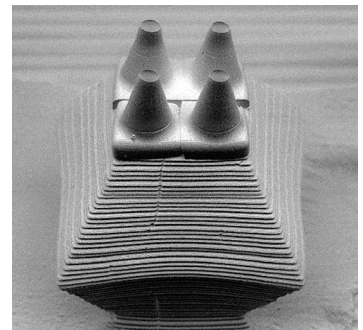
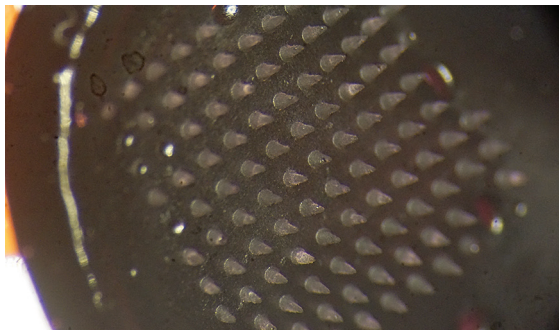
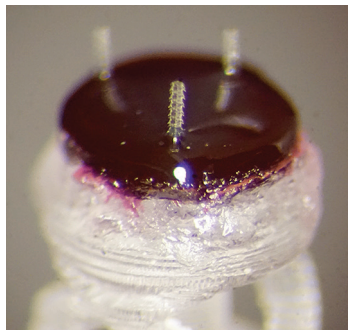
of animal studies, and eventually to human trials. Every stage provides evidence that reassures doctors and patients—for example, showing that ingesting a properly packaged tiny battery is safe, and that a capsule's wireless signals, far weaker than those of a cellphone, pose no health risk as they pass through the gut.

The gastrointestinal tract is packed with clues about health and disease, but much of it remains out of reach of standard diagnostic tools. Ingestible capsules offer a way in, providing direct access to the small intestine and colon. Yet in many cases, the concentrations of chemical biomarkers can be too low to detect reliably in early stages of a disease, which makes the engineering challenge formidable. What's more, the gut's corrosive, enzyme-rich environment can foul sensors in multiple ways, interfering with measurements and adding noise to the data.

Take, for example, inflammatory bowel disease, for which there is no standard clinical test. Rather than searching for a scarce biomarker molecule, our team focused on a physical change: the permeability of the gut lining, which is a key factor in the disease. We designed capsules that measure the intestinal tissue's bioimpedance by sending tiny currents across electrodes and recording how the tissue resists or conducts those currents at different frequencies (a technique called impedance spectroscopy). To make the electrodes suitable for in vivo use, we coated them with a thin, conductive, biocompatible polymer that reduces electrical noise and keeps stable contact with the gut wall. The capsule finishes its job by transmitting its data wirelessly to our computers.

In our lab tests, the capsule performed impressively, delivering clean impedance readouts from excised pig tissue even when the sample was in motion. In our animal studies, it detected shifts in permeability triggered by calcium chelators, compounds that pry open the tight junctions between intestinal cells. These results suggest that ingestible bioimpedance capsules could one day give clinicians a direct, minimally invasive window into gut-barrier function and inflammation. We believe that ingestible diagnostics can serve as powerful tools—catching disease earlier, confirming whether treatments are working, and establishing a baseline for gut health.

Microneedle designs for drug-delivery capsules have evolved over the years. An early prototype [left] used microneedle anchors to hold a capsule in place. Later designs adopted molded microneedle arrays [center] for more uniform fabrication. The most recent version [right] integrates hollow microinjector needles, allowing more precise and controllable drug delivery.



Targeted drug delivery is one of the most compelling applications for ingestible capsules. Many drugs for GI conditions—such as biologics for inflammatory bowel disease—can cause serious side effects that limit both dosage and duration of treatment. A promising alternative is delivering a drug directly to the diseased tissue. This localized approach boosts the drug's concentration at the target site while reducing its spread throughout the body, which improves effectiveness and minimizes side effects. The challenge is engineering a device that can both recognize diseased tissue and deliver medication quickly and precisely.

With other labs making great progress on the sensing side, we've devoted our energy to designing devices that can deliver the medicine. We've developed miniature actuators—tiny moving parts—that meet strict criteria for use inside the body: low power, small size, biocompatibility, and long shelf life.

Some of our designs use soft and flexible polymer “cantilevers” with attached microneedle systems that pop out from the capsule with enough force to release a drug, but without harming the intestinal tissue. While hollow microneedles can directly inject drugs into the intestinal lining, we've also demonstrated prototypes that use the microneedles for anchoring drug payloads, allowing the capsule to release a larger dose of medication that dissolves at an exact location over time.

In other experimental designs, we had the microneedles themselves dissolve after injecting a drug. In still others, we used microscale 3D printing to tailor the structure of the microneedles and control how quickly a drug is released—providing either a slow and sustained dose or a fast delivery. With this 3D printing, we created rigid microneedles that penetrate the mucosal lining and gradually diffuse the drug into the tissue, and soft microneedles that compress when the cantilever pushes them against the tissue, forcing the drug out all at once.

Tissue sampling remains the gold standard diagnostic tool in gastroenterology, offering insights far beyond what doctors can glean from visual inspection or blood tests. Capsules hold unique promise here: They can travel the full length of the GI tract, potentially enabling more frequent and affordable biopsies than traditional procedures. But the engineering hurdles are substantial. To collect a sample, a device must generate significant mechanical force to cut through the tough, elastic muscle of the intestines—while staying small enough to swallow.

FROM LEFT: UNIVERSITY OF MARYLAND/WILEY; UNIVERSITY OF MARYLAND/ACS

Different strategies have been explored to solve this problem. Torsion springs can store large amounts of energy but are difficult to fit inside a tiny capsule. Electrically driven mechanisms may demand more power than current capsule batteries can provide. Magnetic actuation is another option, but it requires bulky external equipment and precise tracking of the capsule inside the body.

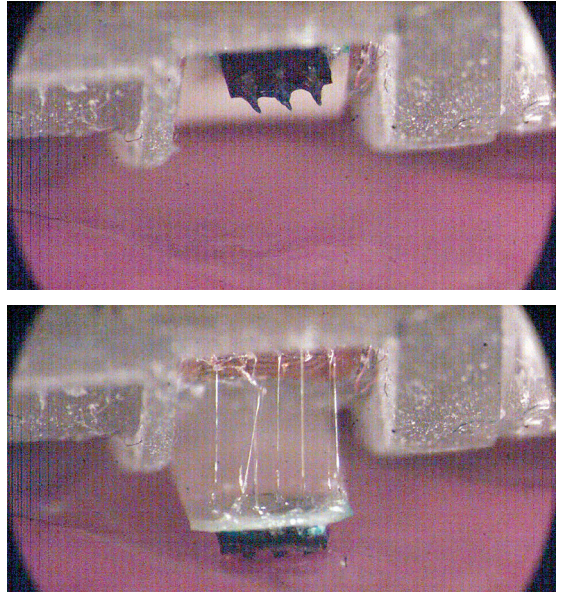
Our group has developed a low-power biopsy system that builds on the torsion-spring approach. We compress a spring and use adhesive to “latch” it closed within the capsule, then attach a microheater to the latch. When we wirelessly send current to the device, the microheater melts the adhesive on the latch, triggering the spring. We’ve experimented with tissue-collection tools, integrating a bladed scraper or a biopsy punch (a cylindrical cutting tool) with our spring-activated mechanisms; either of those tools can cut and collect tissue from the intestinal lining. With advanced 3D printing methods like direct laser writing, we can put fine, microscale edges on these miniature cutting tools that make it easier for them to penetrate the intestinal lining.

Storing and protecting the sample until the capsule naturally passes through the body is a major challenge, requiring both preservation of the sample and resealing the capsule to prevent contamination. In one of our designs, residual tension in the spring keeps the bladed scraper rotating, pulling the sample into the capsule and effectively closing a hatch that seals it inside.

Looking ahead, we expect to see the first clinical applications emerge in early-stage screening. Capsules that can detect electrochemical, bioimpedance, or visual signals could help doctors make sense of symptoms like vague abdominal pain by revealing inflammation, gut permeability, tumors, or bacterial overgrowth. They could also be adapted to screen for GI cancers. This need is pressing: The American Cancer Society reports that as of 2021, 41 percent of eligible U.S. adults were not up to date on colorectal cancer screening. What’s more, effective screening tools don’t yet exist for some diseases, such as small bowel adenocarcinoma. Capsule technology could make screening less invasive and more accessible.

Of course, ingestible capsules carry risks. The standard hazards of endoscopy still apply, such as the possibility of bleeding and perforation, and capsules introduce new complications. For example, if a capsule gets stuck in its passage through the GI tract, it could cause bowel obstruction and require endoscopic retrieval or even surgery. And concerns that are specific to ingestibles, including the biocompatibility of materials, reliable encapsulation of electronics, and safe battery operation, all demand rigorous testing before clinical use.

Powering these capsules is a key challenge that must be solved on the path to the clinic. Most capsule endoscopes today rely on coin-cell batteries, typically silver oxide, which offer a safe and energy-dense source but often occupy 30 to 50 percent of the capsule’s volume. So researchers have investigated alternatives, from wireless power transfer to energy-harvesting systems. At the State University of New York at Binghamton, one team is exploring microbial fuel cells that generate electricity from



Stills from a high-speed video show how a capsule deploys microneedles to deliver drugs into intestinal tissue.

probiotic bacteria interacting with nutrients in the gut. At MIT, researchers used the gastric fluids of a pig’s stomach to power a simple battery. In our own lab, we are exploring piezoelectric and electrochemical approaches to harvesting energy throughout the GI tract.

The next steps for our team are pragmatic ones: working with gastroenterologists and animal-science experts to put capsule prototypes through rigorous in vivo studies, then refining them for real-world use. That means shrinking the electronics, cutting power consumption, and integrating multiple functions into a single multimodal device that can sense, sample, and deliver treatments in one pass. Ultimately, any candidate capsule will require regulatory approval for clinical use, which in turn demands rigorous proof of safety and clinical effectiveness for a specific medical application.

The broader vision is transformative. Swallowable capsules could bring diagnostics and treatment out of the hospital and into patients’ homes. Whereas procedures with endoscopes require anesthesia, patients could take ingestible electronics easily and routinely. Consider, for example, patients with inflammatory bowel disease who live with an elevated risk of cancer; a smart capsule could perform yearly cancer checks, while also delivering medication directly wherever necessary.

Over time, we expect these systems to evolve into semi-autonomous tools: identifying lesions, performing targeted biopsies, and perhaps even analyzing samples and applying treatment in place. Achieving that vision will require advances at the very edge of microelectronics, materials science, and biomedical engineering, bringing together capabilities that once seemed impossible to combine in something the size of a pill. These devices hint at a future in which the boundary between biology and technology dissolves, and where miniature machines travel inside the body to heal us from within. ■