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Gulp! Electronics Down the Hatch

Prachi Patel

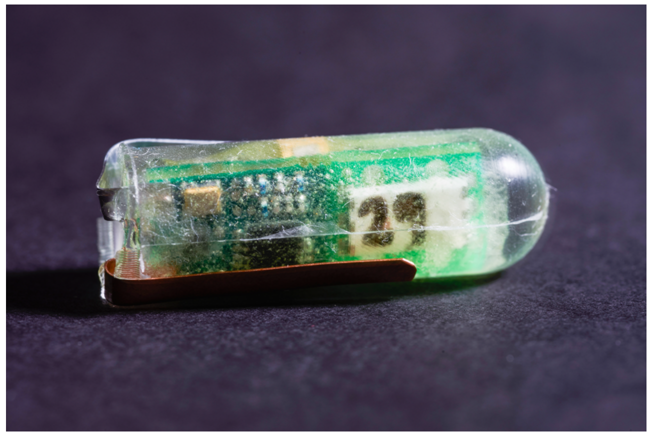
Appetite is growing for sensors that can be swallowed.

In the 1966 movie *Fantastic Voyage*, a shrunken submarine called Proteus is injected into a scientist's body so the vessel's crew can operate on his brain. That may be science fiction, but tiny devices that can monitor health have already become reality. Battery-powered, swallowable cameras in the shape of a large pill have been on the market since 2001. About a dozen companies make such capsules to take pictures of the esophagus, small intestine, and colon as the capsules move through the gastrointestinal tract—offering a less invasive alternative to endoscopies and colonoscopies. And in 2012, the U.S. Food & Drug Administration cleared for human use a silicon chip the size of a grain of sand that can be embedded in pharmaceutical pills to monitor whether patients are taking prescribed drugs as they should.

But ingestibles could do much more than just snap pictures and tattle on patients who skip their meds. Engineers envision gadgets that travel through the digestive tract to detect the first faint markers of bacterial infections, cancer, and hard-to-diagnose disorders like irritable bowel syndrome. Or, such swallowable devices could manage chronic diseases like diabetes by sensing glucose and delivering insulin. They could also drop drugs exactly where and when they are needed in the gut, making therapies safer and more effective.

Today's pill cameras are large and rigid, use batteries made of toxic materials, and are designed to pass out of the body in a day or two via the digestive process. But tomorrow's ingestible sensors will need to reside longer in the body, do their job unnoticed, and then ideally disintegrate into benign materials. To achieve those goals, engineers need tough, biocompatible materials to make unobtrusive devices that are small and easy to swallow. And they need to power these sensors with nontoxic, long-lasting batteries.

"The GI tract is one of the most heterogeneous and harsh environments in the body", says C. Giovanni Traverso, a gastroenterologist and biomedical engineer at MIT. Its pH can vary from 1 to 7; it's wet; it harbors hundreds of bacterial species; and on a given day it can be full of a huge range of substances depending on a person's diet. "That poses a lot of material constraints", he says. The good news is that the GI tract has an "incredible capacity" to tolerate a range of materials and objects, Traverso adds. Thanks to new materials and chemistries, materials scientists and engineers are now getting closer to practical ingestible devices that are small, safe, easy to use, and long-lasting.



This ingestible battery relies on stomach acid to complete its circuit. It offers a way to power ingestible devices that could monitor health within the GI tract. Credit: Diemut Strebe.

A Gut Feeling

The market for smart ingestible electronics will be worth almost US $680 million by 2022, according to the research firm MarketsandMarkets. The key drivers are the need for monitoring patients in real time, assuring medication adherence, monitoring chronic diseases, and offering patients the option for accurate, less invasive diagnosis tests, says research analyst Rahul Kumar.

By catching diseases early, swallowable devices could help cut healthcare costs associated with disease complications and improve quality of life, says Traverso. "They offer an unobtrusive mode for sensing a broad range of analytes from the body", he says, compared to a more intrusive blood test. And an internal sensor could catch gastrointestinal bleeding, for example, earlier than any other method, allowing for early intervention and avoiding catastrophe, he says.

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Ingestible sensors would give doctors direct, real-time access to the complex chemistry present in the GI tract while it is operating normally with food and liquid in it, something not currently possible via standard tests like stool studies or endoscopies. Such sensors could probe the gut's proteins, electrolytes, enzymes, hormones, and metabolites—plus the trillions of bacterial cells that influence many aspects of human health. In the stomach, imbalances in the levels of gastric acids, digestive enzymes, hormones, and more can indicate disorders, whether ulcers, inflammation, or cancer. Short-chain fatty acids in the colon are a signature of its health. The small intestine carries a similar complex mixture. Makers of ingestible sensors want to dig into this trove of information.

Some ingestibles, such as the PillCam by Given Imaging, owned by Medtronic, can already sense temperature, pressure, and pH. But this and other gut cameras are the size of large vitamin pills, have rigid polycarbonate casings, and use silver oxide coin batteries that can be toxic and would be a disaster if released into the gut. They are not exactly easy pills to swallow.

The PillCam, by Given Imaging, is a little over an inch long. In addition to taking pictures as it moves through the GI tract, it senses temperature, pressure, and pH. Credit: Medtronic.

To be widely acceptable to patients, ingestibles need to be smaller softer, nontoxic, biocompatible, and able to safely pass through the GI tract, says Christopher J. Bettinger, a professor of materials science and engineering and biomedical engineering at Carnegie Mellon University. The sensors, controllers, and transmitters in edible electronics can be made of the typical materials used in conventional electronics. Think silicon microchips, iron magnets, tiny quartz crystals, and copper wires—materials that don't sound edible but actually are benign in the body in small amounts. Since 90% of a device's mass is its batteries and packaging, he says, making those components safer and easier to ingest would go a long way toward making devices more practical.

A Smart Pill To Swallow

"I initially thought it wouldn't be possible", says George Savage, cofounder and chief medical officer at Proteus Digital Health, recalling when in 2001 his cofounder Andrew Thompson first suggested putting a simple computer inside pharmaceutical pills. But Savage and Thompson did just that. They made a tiny 1-mm^2 silicon chip that can be embedded in a pill to detect its ingestion. The goal is to help patients stick to prescription regimens, something an estimated 40–50% of patients don't do. The silicon fleck, which carries a unique identification code for that pill, is coated with thin films of cuprous chloride on one side and magnesium on the other that act as electrodes.

Instead of relying on a traditional battery, the chip is powered by stomach juice. When the pill dissolves in the stomach, the electrodes contact gastric acid, creating a path for electron flow and forming a battery cell. The cell generates 1–10 milliwatts of power in the five minutes before the electrodes get consumed by the stomach acid—enough power for the silicon chip to transmit its code to a receiver patch stuck on the person's torso that records which pill was taken and when. "After that, the sensor just becomes an inert particle of sand that transits into the intestine along with food", Savage says.

Although the FDA cleared the chip alone for human use in 2012, Proteus and Tokyo-based Otsuka Pharmaceuticals are now seeking FDA approval to embed the sensor in Abilify, an antipsychotic drug made by Otsuka to treat symptoms of schizophrenia and bipolar disorder.

Gut Power Punch

Current pills are designed to pass through the GI tract in a day. Traverso wants to make devices that stay in the stomach for days, even weeks, to deliver drugs or sense chemicals, and then break down to exit the body. To work toward this goal, he and his colleagues have made new hydrogels that are highly elastic so they can be compressed into easily ingestible pills, yet tough enough to withstand the stomach's harsh acidic environment and squeezing forces.

One such gel is made of poly(acryloyl 6-aminocaproic acid) and poly(methacrylic acid-*co*-ethyl acrylate). It degrades over a period of days in gastric fluid, but dissolves within hours in the neutral pH of the intestines. The team has made ring- and star-shaped devices composed of rigid, drug-infused polycaprolactone (PCL) segments joined together by the gel. Tested in pigs, the elastic devices begin folded up within a capsule, then expand within minutes in the animals' stomachs to reach their full size of just over 2 cm, so they don't pass through the stomach's 2-cm-wide exit. After delivering drugs for 5 days, the slightly disintegrated devices can leave the stomach and enter the intestine, where the gel dissolves completely, leaving small PCL pieces that pass out of the body.

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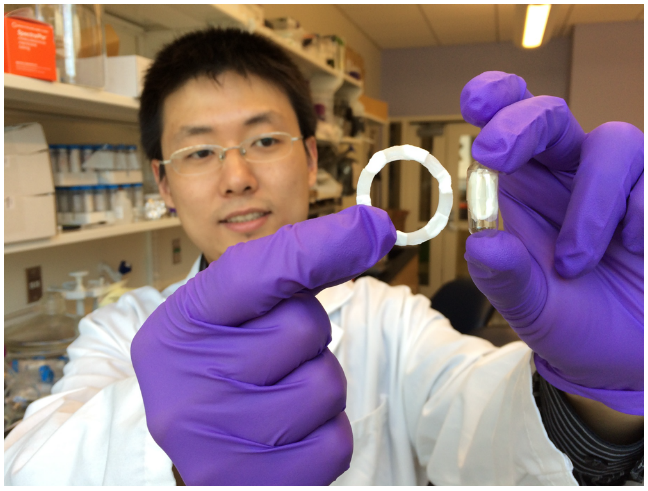

This drug-carrying device begins folded up in a swallowable capsule. Once in the stomach it remains for days or weeks delivering a drug. After becoming partially degraded, it passes out of the body. Courtesy Langer Lab.

In July, Traverso and his colleagues reported hydrogels that can remain intact until triggered to break down and pass out of the body. This would be useful for making devices that deliver drugs for a precise amount of time or that can be removed in case of an obstruction or adverse reaction. These new gels consist of alginate and polyacrylamide networks cross-linked by ionic calcium and disulfide bonds. The bonds can be broken by ethylenediaminetetraacetic acid or glutathione, which are used as medical supplements and food additives, so they are easy and safe to administer when needed to clear the device.

To address the question of power, Traverso and Bettinger take a similar approach to Proteus Digital Health, making use of stomach acid to complete an electrochemical circuit. Traverso and his partners have made a battery cell with zinc and copper electrodes linked by stomach juice as the electrolyte. In tests on pigs, the device generated enough power in the GI tract over 6 days to power a temperature sensor and to wirelessly transmit the data to a receiver two meters away.

Bettinger's battery has a manganese oxide anode and a cathode made of melanin, the pigment that colors hair and skin. Melanin comes from cuttlefish ink sacs and is cheap at $100 per kilogram. Lab tests of these electrodes provide 5 milliwatts of power for 20 h. Bettinger aims for a final form in which the materials are jelly rolled like in a typical AA battery, then encapsulated in gelatin and other FDA-approved polymers.

Nanoengineer Joseph Wang and his colleagues at the University of California, San Diego have taken the term edible sensors to a whole new level by making sensors entirely out of food materials. They made edible carbon paste from a mix of activated charcoal and corn oil or olive oil, and added enzyme-rich mushroom or horseradish tissues as biocatalysts. Then they packed the paste into hollow food items like penne pasta, green beans, candy, and cheese. The simple sensors could detect uric acid, ascorbic acid, and dopamine in artificial saliva, gastric juice, and intestinal fluid respectively, since the enzymes trigger a small spike in current when they react with the target chemicals.

Living Sensors

In an approach that sidesteps batteries altogether, Timothy K. Lu, a professor of biological and electrical engineering at MIT, is working on sensors that harness living cells. He hacks their genetic circuits so that they can detect specific molecules and respond by glowing a certain color, making them "living sensors". The color change could be detected in stool. The idea is to package them into capsules that could be ingested; once in the gut these sensors wouldn't require a power source. "We've already shown that bacteria can sense antibiotics, sugars, carbohydrates, heavy metals, inflammation, and can also sense certain molecules made by pathogenic bacteria", Lu says.

Keeping the bacteria safe, happy, and alive in the gut is key. So he infuses them along with nutrients into tough, stretchable and biocompatible hydrogels made in mechanical engineer Xuanhe Zhao's lab, also at MIT. By engineering both the bacteria and the hydrogel, such living sensors could be designed to stay in the gut for days, weeks, and even longer, he says.

In June, Lu's group started trials of bacterial ammonia sensors in patients with a disorder that makes their liver produce high ammonia levels. He is also combining the bacterial sensors with a silicon device that transmits a wireless signal when the cells sense a chemical of interest and glow.

Stay on target

Some gut problems would be best addressed by ingestible devices that could home in on a particular site in the gut and arrive just where they are needed. Wang and his colleagues have made and tested in mice tube-shaped microscopic motors of a biocompatible poly(3,4-ethylenedioxythiophene) polymer filled with zinc, which reacts with hydrogen inside the body to produce bubbles that propel it like a rocket. The motors swim to the stomach lining and deliver cargo, tests show.

In other work by Wang's group, the researchers have coated the rockets, which can be swallowed as a suspension, with a methacrylate-based polymer that withstands gastric acid but dissolves in neutral intestinal fluid. by changing the

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coating's thickness, the researchers can control how far the motor travels in the GI tract before it propels itself into the intestinal lining.

Bettinger believes that the next generation of smart ingestible electronics will start simply. "The first application will likely be a drug delivery device with a very simple circuit to deliver a high-value drug that has low oral bioavailability", he says.

Yet pioneers of new materials and chemistries for ingestible devices know that they face complex regulatory, insurance, and adoption hurdles. "We have demonstrated safety and performance", says Proteus's Savage, but now the company needs to get the word out to health providers to get them to use the technology it in their clinics. "The challenge now is very much on the ground."

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