DRUG DELIVERY

Pills give patients a shot inside the stomach

Capsules that internally inject insulin and other medicines could do away with daily jabs

By **Robert F. Service**

In 1922, a 14-year-old boy in Toronto, Canada, received the first injection of insulin to treat life-threatening diabetes. The same year, researchers began to test oral insulin formulations, hoping to relieve people with diabetes of daily shots. That effort failed, as have dozens of similar attempts. But realistic hope for oral insulin may finally be here. Researchers report in this issue of *Science* that they've engineered a capsule that, once ingested, pokes a tiny hole in the lining of the stomach to deliver insulin or other so-called biologic medicines that can't be taken by mouth.

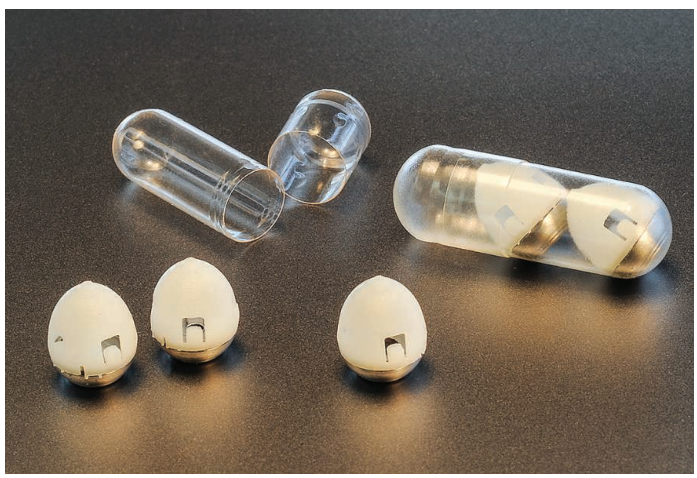
Other research groups and companies have also made recent progress in delivering once-injected medicines orally, raising hopes that for many patients, painful injections may become a thing of the past. "This field is really at an exciting stage," says Samir Mitragotri, a biomedical engineer at Harvard University. "I think it's going to completely transform how patients take drugs."

Optimism has surged before. But the harsh environment of the stomach and intestine has thwarted many attempts to deliver complex, delicate drugs by mouth. "There are a lot of dead bodies in this space," says Mir Imran, CEO of Rani Therapeutics, a San Jose, California, company working to commercialize oral biologics. "People keep trying because it's such an important area."

Unlike traditional pharmaceuticals, which are small molecules that the digestive tract easily absorbs, biologics are typically proteins: large, unwieldy molecules produced by microbes or other living cells. Biologics, which include seven of the 10 top selling drugs by sales in the United States, are more likely to hit a target molecule in the body without side effects because of their large size. But they're also more liable to degrade in the stomach or be blocked from entering the bloodstream by thick layers of mucus and tightly packed epithelial cells that line the stomach and gut. Getting past these defenses "is honestly one of the biggest challenges and holy grails in drug development," says Carlo Giovanni Traverso, a gastroenterologist and bioengineer at Harvard Medical School in Boston and the Massachusetts Institute of Technology (MIT) in Cambridge.

In recent years, pharmaceutical companies have encapsulated several small proteins, called peptides, in chemicals called permeation enhancers that promote absorption by the small intestine. But most permeation enhancers allow less than 1% of peptides to cross into the bloodstream.

Mitragotri's team at Harvard is trying to improve on the approach. He and his colleagues reported in 2018 in the *Proceedings of the National Academy of Sciences* that they encapsulated insulin in a liquid that has the consistency of honey. When the capsule dissolves in the small intestine, the viscous liquid gloms onto the lining and briefly disrupts the lipid membrane of the cells on the surface, allowing the insulin or other drugs to be absorbed. Last week, Mitragotri and his colleagues formed a biotech company to commercialize the technology. Similarly, Oramed Pharmaceuticals, a Jerusalem-based biotech company, is testing insulin capsules containing components that shield the protein from digestive acids and enzymes and promote its absorption in the small intestine.



These pills were engineered to drive a tiny needle into the stomach lining.

PHOTO: FELICE FRANKEL

Traverso, with Robert Langer, a drug delivery expert at MIT, and their colleagues turned instead to engineering. They developed a hollow pill with one flattened end. The shape, along with the capsule's center of mass near the flat end, ensures that the pill rights itself in the stomach, with its flat surface facing the stomach lining. Just inside the pill's flat end, which is made of sugar, sits a tiny tensed spring topped with a needle made from solid insulin. In the moist stomach, the sugar begins to dissolve, eventually allowing the spring to poke the insulin needle into the outer stomach layer, where it dissolves and enters the bloodstream.

In rats and pigs, the pill could deliver essentially the same insulin levels into the blood as a subcutaneous injection. And histology studies showed no signs of lasting damage from daily internal needle punctures.

"It's a very smart design," says Edith Mathiowitz, a biomedical engineer at Brown University. However, she adds, the team needs to ensure that creating even tiny perforations in the stomach doesn't pose long-term health problems for patients, and that undesirable proteins or bacteria can't wiggle their way in alongside the insulin.

Rani Therapeutics is banking on similar ingenuity. Instead of a spring, Rani's pills use a chemical reaction set off by the small intestine's pH to generate carbon dioxide that inflates a tiny balloon. The balloon presses a needle packed with the drug through the intestinal lining. Although it has not published papers on its pills, Rani has completed more than 100 animal studies. In an initial safety study of pills without needles or drugs, people reported no awareness of the device's balloon as it inflated, Imran says. This year, he adds, the company plans its first clinical trials of pills loaded with octreotide, a biologic that treats acromegaly, a dangerous enlargement of the face, hands, and feet.

It could take years for any of these technologies to complete safety and efficacy studies. But because the engineered pills are intended to work with existing drugs, they could spread rapidly if approved, realizing a century-old goal—and the hopes of countless patients. ■

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