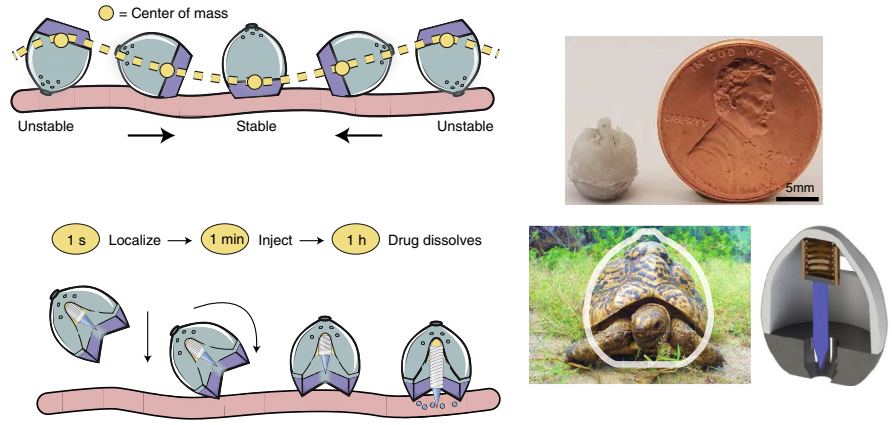
DRUG DELIVERY

To the stomach and beyond



Credit: Adapted with permission from Abramson, A. et al. *Science* **363**, 611–615 (2019), AAAS

Having to swallow a pill can sometimes be unpleasant, but getting an injection almost always is. For individuals living with a disease that requires frequent injections, such as diabetes, this represents more than a brief discomfort. Oral formulation of biologics, such as antibodies or insulin, however, remains an unsolved challenge. A recent paper by Abramson et al. (*Science* https://doi.org/10.1126/science.aau2277, 2019) presents a small, ingestible capsule that sits upright in the stomach and injects insulin through the mucosa.

Proteins traveling through the gastrointestinal tract encounter many hurdles before they can reach the systemic circulation. Hazardous pH, proteases, mucus and cellular barriers make it all but impossible for biologics to reach the blood intact. Efforts to protect proteins using approaches such as nanocarriers have made inroads, but the ability to reach meaningful systemic protein concentrations following oral delivery has been elusive.

The goal of Abramson et al. was to engineer an ingestible capsule that rights itself every time it reaches the bottom of the stomach. Once there, it would inject its cargo through the stomach's mucosa, deep enough to reach systemically but making a puncture small enough to prevent tissue damage and perforation.

To achieve this, the scientists took inspiration from the roly-poly wobble toy, which has a shape and weight distribution that enables it to return to the preferred upright position, and also from the leopard tortoise, which in addition to this has an edge that prevents it from easily tipping over. "If you want to give an injection, you need a controlled and guided interaction between the object and the mucosa. And that needs to happen every time, reliably," says Giovanni Traverso, an assistant professor at Harvard Medical School who, together with Robert Langer at the Massachusetts Institute of Technology, was a senior author on the study.

Using a combination of polycaprolactone and stainless steel to achieve the desired center of mass and shape, the bioengineers created a pea-sized capsule they call a SOMA (for self-orienting millimeter-scale applicator). They load insulin as cargo but, instead of delivering it as a liquid as is normally done, formulate it as a solid (with and without excipient) to increase the amount of protein that can be packaged. This solid protein tip is connected to a biodegradable shaft, creating a 'millipost' that measures 7 millimeters in length. The millipost is held in place by a stainless steel spring, and sucrose is used as its actuator. When exposed to humidity, the sucrose dissolves, releasing the compressed spring and injecting the millipost into the tissue.

When tested in pigs, SOMAs in the stomach delivered insulin systemically in a matter of minutes, lowering blood glucose. The puncture holes made are small, and delivery using springs with almost twice the force of those in SOMAs does not perforate the tissue. As far as the researchers measure, the SOMA and its components are not toxic to cultured cells or to pigs.

"The approach is a breakthrough," says María José Alonso, a professor of biopharmaceutics and pharmaceutical technology at the University of Santiago de Compostela in Spain. "It's classically been assumed that the stomach is a place for digestion, not a place of absorption of drugs. The stomach was thought of as an obstacle." While previous oral delivery approaches had focused on the intestine, Abramson et al. chose the stomach because it is one of the most robust tissues in the gastrointestinal tract. Also, Traverso explains that there is substantially greater variability in the time it takes for a capsule to travel from the mouth to the intestine as compared to the stomach.

A limitation of SOMAs is that they work only in animals that are fasted. Alonso is not surprised, pointing out that "there would be a lot of variability depending on how much food there is in the stomach." But she points out that there are many drugs that are administered in the fasting state, including antibodies. Although the authors have not yet tested chronic drug administration using SOMAs, Traverso says that a once-daily dose (as soon as the individual wakes up) is their goal as they continue to develop the approach for clinical use. Although this would not solve diabetes patients' injection problem, this clever strategy may be the kickoff to exciting new developments in oral delivery. ❐

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