MEDICAL ROBOTS

Clearing away barriers to oral drug delivery

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Ingestible devices have the potential to clear away barriers to oral delivery of biologics to improve drug bioavailability.

Patients and physicians are likely to prefer oral delivery, which is painless, convenient, and easily self-administered compared with injections. However, several therapeutics, notably peptides and proteins including insulin and antibodies, must be administered by injection. This is because oral delivery presents multiple barriers to drug absorption in the gastrointestinal (GI) tract that are especially problematic for biologic drugs. In this issue of *Science Robotics*, Srinivasan *et al.* (*1*) present an orally ingestible robotic drug delivery device called RoboCap (robotic capsule), which overcomes critical GI barriers by clearing mucus from the intestinal wall and enhancing luminal mixing and drug absorption in the small intestine.

Drug absorption in the digestive tract is a highly regulated process, mediated by multiple barriers in the mouth, esophagus, stomach, and intestine. Those barriers include rapid transit through the GI tract, degradation by proteases, and poor absorption across epithelium covered by mucus. Multiple chemical/formulation-based approaches to overcome these barriers have been developed, but few have succeeded for biologics. Physical delivery methods, including robotic devices like RoboCap, use unique mechanisms that facilitate oral delivery of biologics (Fig. 1).

Some notable examples of delivery systems developed to overcome the mucus layer include MucoJet, which is a pill-sized, robotic device that was designed to overcome the mucosal barrier by rapidly jetting a liquid into the mouth's mucosa (*2*). In addition, EsoCap, which consists of a mucoadhesive drug-containing film that unrolls and adheres to the esophagus wall upon swallowing, can enable targeted drug administration to the esophageal mucosa (*3*). Another example that used a different approach is the self-orienting millimeter-scale applicator (SOMA): A pill with a retractable needle encapsulating drugs was designed to inject the therapeutics of interest directly into the stomach lining. It has been tested with insulin, monoclonal antibodies, and other drugs with absolute bioavailability up to 80% (*4*). In contrast, a number of oral biologic drugs administered by chemical formulations only achieve bioavailability in humans of less than 2% (*5*).

The relatively rapid transit time of a drug delivery system through the GI tract, usually within a day, limits availability of the drug. Bioadhesive and floating pills can prolong transit time only by several hours. To overcome this, one research group used a delivery system that is pill shaped when administered by mouth but is capable of unfolding into a star-shaped dosage form in the stomach. The star shape prevents the system from being passed through the pylorus of the stomach, thereby increasing its retention in the stomach for up to weeks, after which the system dissolves (*6*).

Drug delivery in the small intestine is limited by the epithelium, which is covered by a layer of mucus that provides transport barriers and by proteases that degrade drugs. Formulation-based approaches like chemical penetration enhancers, particulate carriers, and ionic liquids generally enable only modest improvements in the transport of biologics across these intestinal barriers (*7*).

Physical approaches, such as microneedles, can penetrate both intestinal mucus and epithelial barriers. The luminal unfolding microneedle injector (LUMI) pill was designed to automatically deploy small arrays of drug-loaded microneedles into the intestinal wall, where they dissolve and release their drug payload (*8*). A similar approach was used for the penetration of microneedles into intestinal mucosa from a capsule powered by a self-inflating balloon (RaniPill), which delivered a peptide drug (octreotide) with a bioavailability of 65% in a human clinical trial (*9*).

Unlike previous approaches, RoboCap improves oral absorption by using mechanical agitation of the intestinal surface to disrupt the mucus barrier and promote luminal mixing. RoboCap contains a vibrating motor controlled by battery-powered circuitry, activated by a pH-triggered switch, and assembled in a three-dimensionally printed capsule. Upon RoboCap reaching the small intestine, the pH of the intestinal fluid triggers dissolution of a membrane that subsequently closes a circuit to initiate the motor, resulting in the rotation and vibration of RoboCap against the luminal surface of the intestine. RoboCap was also designed with mucus-clearing studs and grooves that facilitate interaction with the intestinal wall. This mechanical action temporarily exposes the epithelial layer and increases drug absorption through the intestinal epithelium.

The mucus-clearing mechanism of RoboCap differs from previous mucus penetration approaches. For example, one such approach relied on mucus-penetrating nanoparticles with uncharged, hydrophilic surface properties achieved by PEGylation that avoided binding or entanglement with charged and hydrophobic domains of the mucin network (*10*). Another approach relied on disruption of the mucus layer using mucolytics, such as *N*-acetyl-L-cysteine, a compound that can make the mucus less viscous and sticky. Instead of relying on complex chemical formulations to modify mucus, RoboCap physically clears away the mucus barrier.

RoboCap was found to be capable of increasing intestinal absorption of small peptides (vancomycin and insulin). However, biologics often have higher molecular weight and hydrophilicity, making it a

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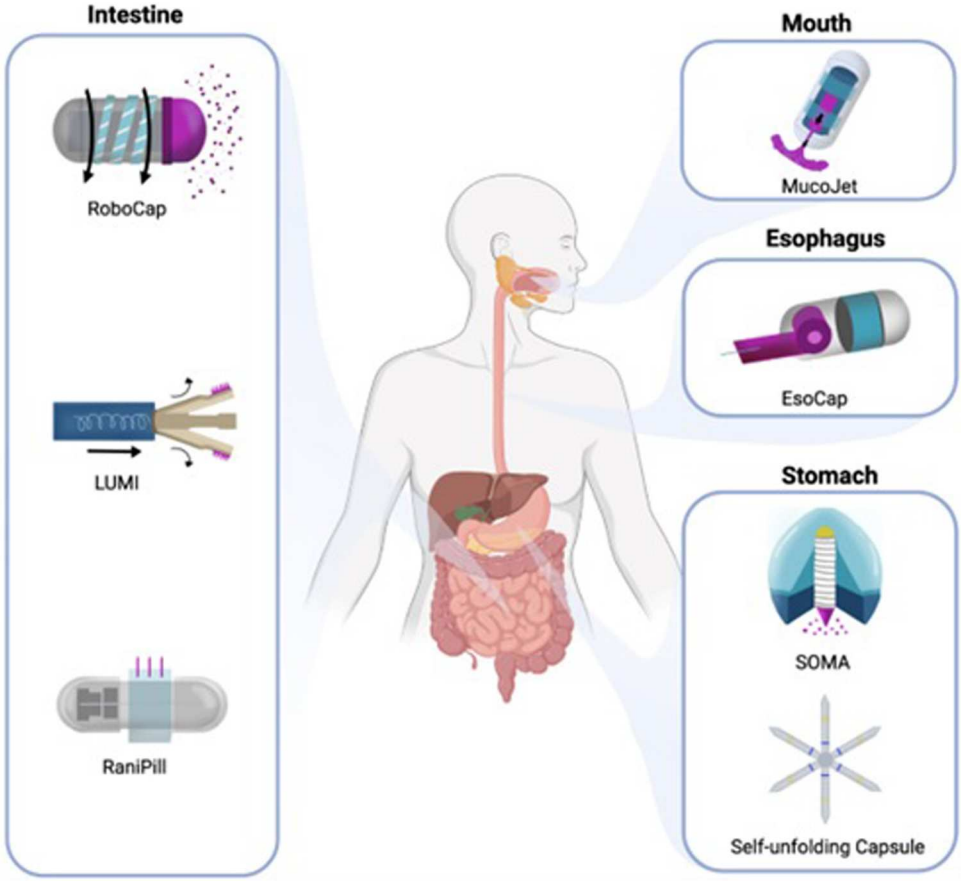

Fig. 1. Ingestible devices designed to clear away barriers to oral delivery of biologics. Delivery systems for targeting the intestine include RoboCap, which was designed to clear the mucus barrier in the small intestine by mechanical agitation. Others include LUMI, which was designed to overcome intestinal barriers by microneedle autoinjection, and RaniPill, which was developed to use microneedles powered by a self-inflating balloon for intestinal injection. MucoJet was developed to target the mouth, and it uses a jet of liquid containing drugs that can penetrate the buccal mucosa. EsoCap was designed to target the esophagus, and it relies on unrolling a mucoadhesive film that adheres to the walls of esophagus. For the stomach, SOMA was designed to automatically self-orient and inject drugs across the stomach lining. A self-unfolding capsule was also designed to target the stomach by expanding in size to increase retention time for drug release.

challenge to facilitate their transport across the epithelium, such that mucus clearing may not be enough. Mucus clearing could be combined with other methods that increase epithelial permeability to further increase bioavailability, especially for macromolecules.

In addition, biologics and other drugs released into the intestine often suffer from enzymatic degradation, which RoboCap does not directly address. This may necessitate the addition of enzyme inhibitors in some cases.

As we look to the future, oral delivery of biologics is both highly desirable and extremely challenging. It is largely accomplished today using chemical formulations but is generally limited to small synthetic molecules. Physical approaches, sometimes involving robotic elements, offer new capabilities with real potential to improve oral delivery. However, these approaches often require devices that are complex, costly, and limited to small sizes that can be passed safely through the GI tract and include batteries or electronics that could raise environmental concerns when disposed into the sewage system.

Advances in oral delivery of biologics will require technology developers to create drug delivery systems that are not only safe and effective but also simple to operate, reliable, manufacturable, and cost-effective. It will also require clinicians, patients, and pharmaceutical companies to accept new delivery systems that are unfamiliar. Together, we can clear away the barriers to oral drug delivery.

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