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Smart ingestible devices: Orally delivering macromolecules and beyond

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Oral administration of macromolecule drugs is traditionally challenging due to the harsh environment these drugs navigate through the gastrointestinal tract and the resultant low blood adsorption. Recently, a series of work has demonstrated the use of smart ingestible devices comprising an intricate design of a drug-loaded vehicle that can adjust direction and accurately pierce into tissue wall, thus delivering macromolecule drugs with high efficiency.

Bioactive macromolecules, such as antibodies and peptides, have emerged as one of the most promising therapeutic agents that can revolutionize methods of disease treatment. Delivery of biomacromolecules is crucial yet challenging due to their intrinsic susceptibility to biodegradation. Among all the delivery routes, oral delivery offers a non-invasive and patient-preferable strategy. However, orally administered biomacromolecules suffer from extreme conditions in the gastrointestinal (GI) tract including harsh pH, a richness in protease, a mucus layer, and cellular junction, which together result in limited bloodstream adsorption.[1,2] Although preclinical strategies have been proposed to circumvent these restrictions, including the use of intestinal absorption enhancers, enzymatic degradation inhibitors, mucoadhesive polymers, and various forms of nanocarriers, the currently achieved bioavailability of biomacromolecule drugs is still far from satisfactory.[3] Therefore, novel systems for safe and efficient oral delivery of biomacromolecules are highly desired.

In recent years, substantial progress has been demonstrated in oral delivery of biomacromolecule drugs based on microcarriers, such as microparticles, micromotors, and microneedle devices. In particular, smart ingestible devices that consist of a variety of the above functional units can execute multiple instructions programmatically after being delivered to the target site, which has attracted extensive attention since being proposed. A research group led by Traverso and Langer from the Massachusetts Institute of Technology (MIT) reported in February 2019 in *Science* a leopard-tortoise-inspired oral insulin capsule containing a compressed insulin millipost, also called a self-orienting millimeter-scale applicator (SOMA) (Figure 1A).[4] Upon reaching the patient's stomach, the capsule could reorient automatically and inject the millipost into the stomach wall, releasing insulin at a controlled rate into the bloodstream. In addition to stomach delivery, they made another breakthrough in oral delivery of insulin to the wall of the small intestine. Writing in October of the same year in *Nature Medicine*, they developed a capsule called luminal unfolding microneedle injector (LUMI) (Figure 1B).[5] The capsule had a polymer shell that could survive in the acid environment in stomach. Upon reaching the small intestine, the capsule ruptured due to the rise in pH and ejected three folding arms inside. Each folding arm had a microneedle array that, with the force of actuation, penetrated the small intestinal mucosa and released the insulin or other macromolecule drugs. Despite the fact that the SOMA and LUMI capsules could function well as they demonstrated, there remained some essential limitations, including low dose capacity (300–700 μg per pill), low absolute bioavailability (10% or less), and the requirement of enduring the degradative-enzyme-filled GI fluid before drug injection.

To solve these issues, the same team recently presented a new version of a SOMA in *Nature Biotechnology* by redesigning the actuation and delivery systems (Figure 1C).[6] The new pill, called liquid-injecting SOMA (L-SOMA), upgraded the drug loading capacity to 4 mg and enabled liquid formulations of bioavailable drugs into gastric submucosa. It consisted of a liquid drug, an injection needle, and a plunger that could squeeze the liquid out of the capsule. The needle and plunger were locked in place by pellets made from isomalt. As the pill entered the moist environment of the stomach, the pellets began to dissolve, thrusting the needle into the stomach wall, while the plunger squeezed the liquid drug into the bloodstream. Once the liquid drug was fully released, the plunger pulled the needle back into the pill, which was eventually expelled through the digestive tract. To assess the efficacy, they used the system to deliver four commonly used injectable drugs, including recombinant human insulin, GLP-1 analogs, adalimumab, and epinephrine, and studies their efficacies through an *in vivo* swine model. Insulin, inactivated GLP-1, or

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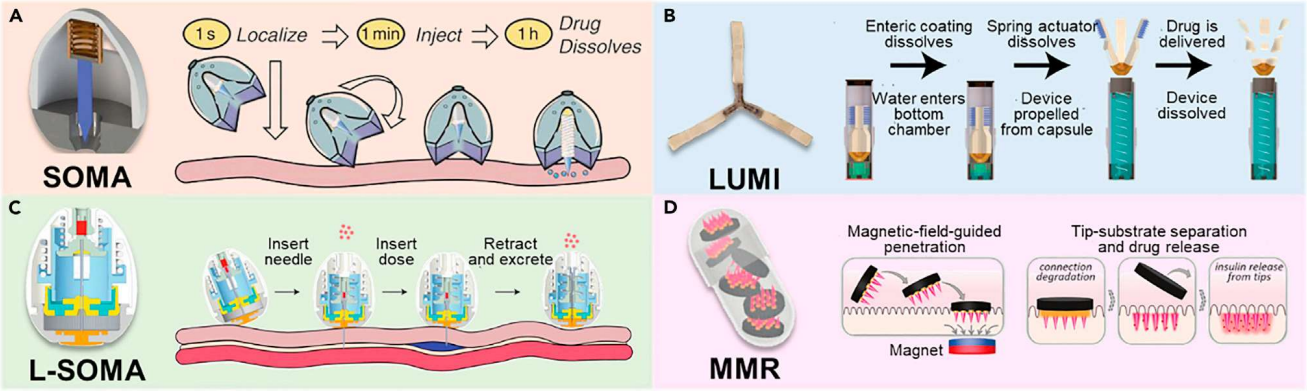

Figure 1. Schematic illustration of four smart ingestible devices
(A) Self-orienting millimeter-scale applicator (SOMA).[4]
(B) Luminal unfolding microneedle injector (LUMI).[5]
(C) Liquid-injecting SOMA (L-SOMA).[6]
(D) Magnetic-controlled microneedle robotic (MMR).[7]

epinephrine with L-SOMA administration could be observed in the serum within 15 min, and the plasma exposure time for adalimumab was 1 h. The swine dosed with insulin immediately developed hypoglycemia, and the adalimumab-dosed or inactivated-GLP-1-dosed swine experienced measurable plasma drug levels for at least 3 days, in a way consistent with the half-lives of the drugs. A total of 28 of 31 L-SOMA-treated swine showed a positive rate of systemic absorption (over 90%). Overall, based on the L-SOMA macromolecule drug delivery system, maximum drug plasma concentrations similar to standard subcutaneous injections could be achieved in 30 min and absolute bioavailability of up to 80% could be achieved in a few hours.

Instead of relying on an injecting system for the insertion of drug-loaded milliposts or microneedles, Zhao and colleagues, from Nanjing University, reported an intelligent magnetic-controlled microneedle robotic (MMR) device for oral macromolecule delivery (Figure 1D).[7] Writing in *Advanced Materials*, they introduced a microneedle robot comprising drug-loaded tips, separable connections, and a magnetic substrate. The MMR could be taken orally with the aid of commercial enteric capsules, and it could be released as it entered the small intestine. With the presence of its polarized magnetic substrate, the tips of the MMR could be reoriented to the wall of the small intestine, overcoming obstacles, inserting into tissue, and delivering encapsulated bioactive substances under a specific magnetic field. In addition, after the degradation of the separable connections, the tips could be left in the tissue and continuously release drugs; the magnetic substrate could be excreted safely. An *in vivo* test in a diabetic minipig model showed that the insulin-loaded MMRs could be induced by magnet and penetrate the intestinal mucosa with a depth of 500 μm under magnet control. Then the blood glucose level in the treated minipigs was found to fall back to normal within about 2 h. Additionally, when treating the diabetic minipig with MMRs after oral glucose administration, the blood glucose level slightly increased and quickly recovered to the normoglycemia state. This study extended the design of oral macromolecule delivery devices by coupling with external fields.

Overall, to improve the oral absorption efficiency of biomacromolecules, a large amount of research based on smart ingestible devices has been proposed in recent years, which has greatly promoted the development of this field. The general design principle for these devices comprises two approaches. One is to encapsulate the macromolecule drugs within a vehicle to transport them to the target site of the GI tract. The other is, through structural design of the vehicle, and in some of the cases, with the aid of remote control such as a magnet, for built-in drug-loaded vehicles to adjust direction and accurately pierce into the tissue wall, thus delivering the drug. As the drug is gradually released into the bloodstream, the vehicle automatically separates from the GI tract through degradation and is eventually absorbed or excreted from the body. Note that such design enables physical insertion of milliposts or microneedles for drug delivery, thereby surpassing the conventional diffusion process and achieving a higher blood adsorption efficiency. Compared with simple oral administration formulations, these smart ingestible devices point out the research direction for efficient oral delivery of biological macromolecules such as proteins, peptides, and vaccines.[8] While considering their applications in future clinical therapy,

there are several other issues that need to be further addressed. First, due to the structural complexity of the devices, further optimization to completely avoid digestive tract obstruction and other risks should be taken into consideration. Second, sufficient clinical trials are needed to assess their safety, their efficacy, and any possible adverse reactions in humans before these devices are ready to enter the commercial market. Third, it is conceivable that beyond delivering macromolecules, therapeutic cells (e.g., stem cells, probiotics, etc.) could be delivered precisely to target sites in the GI tract by direct encapsulation in smart ingestible devices during the manufacturing process, avoiding damage by complex physiological environments.[9,10] These living cargos should maintain viability after long-term storage and the vehicle should have enough cell capacity to execute potent therapeutic performances. Although challenges lie ahead, we believe that rapid advances in material science, robotics, and the drug industry could boost the development of smart ingestible devices for oral delivery of biomacromolecules and beyond, which would bring great hope to countless patients.

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