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Soft robot-enabled controlled release of oral drug formulations

Hao Huang,†[a] Yidan Lyu†[b] and Kewang Nan *[b]

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The creation of highly effective oral drug delivery systems (ODDSs) has long been the main objective of pharmaceutical research. Multidisciplinary efforts involving materials, electronics, control, and pharmaceutical sciences encourage the development of robot-enabled ODDSs. Compared with conventional rigid robots, soft robots potentially offer better mechanical compliance and biocompatibility with biological tissues, more versatile shape control and maneuverability, and multifunctionality. In this paper, we first describe and highlight the importance of manipulating drug release kinetics, *i.e.* pharmaceutical kinetics. We then introduce an overview of state-of-the-art soft robot-based ODDSs comprising resident, shape-programming, locomotive, and integrated soft robots. Finally, the challenges and outlook regarding future soft robot-based ODDS development are discussed.

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1 Introduction

Oral drug delivery systems (ODDSs) are the most prevalent and well-accepted methods of drug administration, with clear advantages such as being non-invasive, patient-friendly, low-cost, and easy to manufacture. ODDSs have accounted for more than half of all FDA-approved formulations.[1] ODDSs cover drugs from small molecules to macromolecules,[2] and potentially extend to biologics such as therapeutic bacteria[3,4] and mRNA-based therapeutics[5,6] for the treatment of life-threatening conditions and infectious diseases. However, further development of ODDSs is hindered by several fundamental limitations, one of the most critical being patient noncompliance, which refers to the failure to take prescribed medicine and discontinuity of the treatment process by the patient.[7] Patient noncompliance is a leading cause of medical waste. It is shown that noncompliant patients require three extra visits per year, resulting in a 20% increase in the annual medical bill. An estimated annual expenditure of up to 290 billion US dollars has been associated with the challenge of patient noncompliance in the U.S.[8]

Another significant limitation is the inability to sustain the pharmacokinetics of oral drug formulations over an extended length of time within the therapeutic window. When that happens, the medicine will not have a therapeutic effect below the lowest effective concentration, and side effects and intolerant toxicity will occur at concentrations that are too high. Most interventions to overcome the aforementioned shortcomings have been material-based, such as liposomes,[9–11] nanoparticles,[12–14] and hydrogels,[15–17] many of which have shown promising results in animal experiments. However, they encounter additional resistance during FDA approval due to potential toxicity and risks associated with introducing new compounds into the body.[18,19] Furthermore, a lack of entrapment efficiency, stability,[20] *in vivo* retention mechanism,[21] and easy manufacturing processes[22] pose additional barriers to clinical translation.

Oral drug development is further hampered by the complicated environment and anatomy of the gastrointestinal (GI) tract. Stomach acid and digestive enzymes cause the degradation of most substances, and are especially lethal to live probiotics and molecular drugs. In general, controlled release systems are usually designed with soluble materials that passively dissolve and release drug molecules overtime. However, variations in GI transit time and dietary habits introduce great variability among different patients. Furthermore, the thick mucus acts as a protection layer for deterring pathogen invasion, but at the same time slows absorption of drug molecules. As a result, ODDSs can be significantly beneficial if they can realize extended retention and controlled locomotion in the GI tract to avoid the harsh chemical environment and to ensure that a sufficient amount of drug molecules pass the physiological barriers.

For the above reasons, it is crucial to develop ODDSs that can simultaneously prevent chemical damage in the gastrointestinal tract, control release times and sites, modulate pharmacokinetic properties, and prolong drug efficacy. First utilized as temperature sensors and capsule endoscopes, ingestible robots can reach deep into the gastrointestinal tract to detect

[a] *College of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310058, China*
[b] *College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China. E-mail: knan@zju.edu.cn*
† These authors contributed equally to this paper.

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diseases and deliver therapeutics in an on-demand manner by leveraging real-time access to sensors and actuators. Ingestible robots have a variety of forms, such as capsules and micromotors, and have demonstrated delivery of a wide range of therapeutics, including small-molecule medications, protein drugs, genes, and even cells.[23,24] In addition, ingestible robots are capable of monitoring biological factors, detecting diseases, and performing surgeries.[25–27] Advances in wireless communication technology enable real-time data transmission to the outside of the body, potentially allowing for regulating *in vivo* release of medications using personal gadgets like mobile phones.[28–30]

A special class of ingestible drug delivery robots utilizes soft robotic substances such as magnetoactive soft materials, dielectric elastomers, and shape memory alloys and polymers, which are characterized by continuous deformation and better geometric maneuverability.[31–33] Soft robots integrate functions of actuation, sensing, movement, navigation, electronics, and power source into one compliant body. The soft actuators are at the center of this and convert various stimuli into either shape change or locomotion, therefore differentiating soft robots from conventional drug delivery devices. One advantage of soft robots suitable for biomedical applications is the ability to distribute forces uniformly over a larger contact surface. By establishing conformal contact with the target body parts, soft robots can potentially reduce the physical damage caused by relatively large force concentrations at specific contact points. Therefore, the stronger bio-interface and biocompatibility of soft materials makes soft robots safely engage and interact with humans. What is more exciting is that recently invented micro- and nanoscale soft robots can access constrained anatomic positions such as blood vessels, cardiac tissues, and even deep brain regions.[34–36]

In this review, we review the concepts and importance of pharmacokinetics, which justify the rationale for robot-based ODDSs. Then we introduce state-of-the-art soft robot-based ODDSs with multiple means of actuations, functions, and formulations, with special focuses on robotic systems targeting the GI tract. They include long-lasting resident soft robots to address the issue of non-compliance, shape-programming and locomotive robots controlled by external stimuli to deliver the drug to the desired areas, and integrated robots to realize oral delivery of macromolecules. Finally, the challenges and outlooks of soft robot-based ODDSs are presented.

2 Drug release kinetics

In this section, we present a brief introduction to drug release kinetics that informs the underlying logic for using robots in drug delivery. The basis for determining the dose and interval of drug administration is whether the drug can achieve a safe and effective concentration at its site of action, which is dynamically changed by the *in vivo* process of the drug. Therefore, it is of great significance to quantitatively study the processes (absorption, distribution, metabolism, and excretion) of drugs in organisms, *i.e.*, the study of pharmacokinetics.

To meet the needs of clinical medication or reduce medication frequency, people try to modify the drug release process. Modified-release dosage forms are pharmaceutical preparations designed for the purpose of controlling the release time process and/or the release location of drugs. Different approaches, including materials,[37,38] mechanical engineering,[39] electronics,[40] and others,[41] have been applied to the design and modification of drug delivery systems to provide more precise control of the drug release process. The process could be reflected by the drug release curve, which is generally expressed as a plot of plasma-drug concentration *versus* time. Appropriate delivery materials, routes and release mechanisms can give birth to a drug release curve that fits a specific disease, that is, drugs with required release kinetics can be obtained (Fig. 1A–C).

2.1 Uncontrolled release kinetics

Generic oral drugs such as regular tablets, granules, and capsules are normal-release formulations, meaning that the drug is routinely released in its normal state in the GI tract after oral administration. The limitations of these formulations are evident in that they are expelled from the body at a relatively rapid rate and the drug concentration levels are therefore not well maintained within the therapeutic window. After a single dose, the drug will be rapidly metabolized, manifested as a rapid increase in the plasma drug concentration *versus* time curve, followed by an immediate exponential decline (Fig. 1A). The limited time between the lowest effective concentration and the lowest toxic concentration is not sufficient to produce a significant therapeutic effect. Although multiple or increased doses may seem to compensate for this deficiency, they may cause plasma drug concentrations to fluctuate outside the treatment window (Fig. 1D), and higher dosing frequency may also lead to poor patient compliance.[42] Therefore, a more controlled release process dosage form is urgently needed to provide a stable drug concentration level over an extended period to enhance the therapeutic efficacy.

Apart from the rate of drug release, the control of timing and location is also of great concern. The timing of the onset of some diseases is closely linked to biological rhythms and the treatment of such diseases requires the use of "chronotherapy".[43] By controlling the timing of drug release, biorhythms and medical treatments can be reconciled to provide maximum health benefits and minimal harm to the patient. Besides, conventional oral drugs have difficulty reaching the middle and back end of the digestive tract because they are often subject to unfavorable GI environments. This calls for the development of new formulations that can avoid GI tract damage and target specific sites. In summary, it is important to develop oral drug delivery systems that can avoid GI tract damage, accurately control drug release, reduce the dosing frequency, and prolong drug efficacy.

2.2 Controlled release kinetics

Various approaches have been sought to solve the problems of conventional dosage forms. With the development of material science, controlled drug delivery systems have become one of the most promising areas in medical research. Depending on

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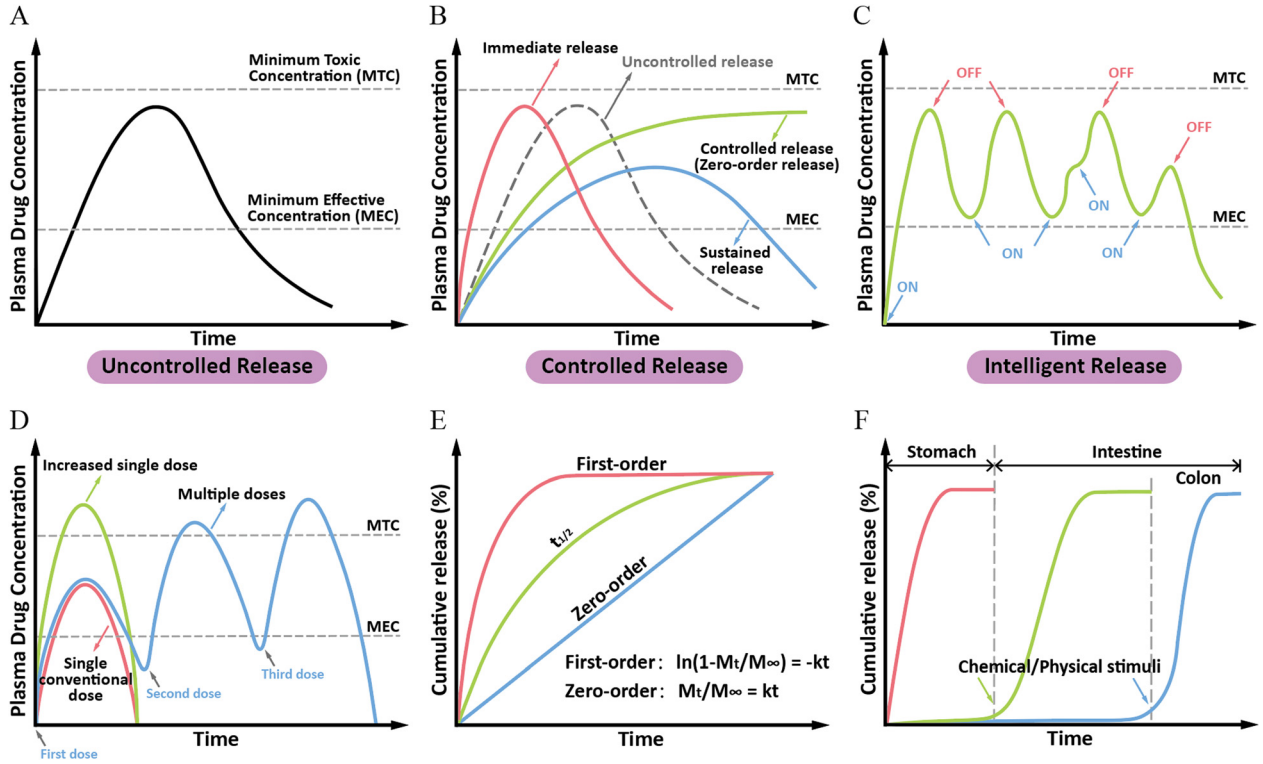

Fig. 1 Pharmacokinetic curves. Plasma drug levels of (A) uncontrolled release, (B) controlled release, and (C) intelligent release. (D) Fluctuations in plasma drug concentrations caused by multiple or increased doses. (E) *In vitro* drug release curves and rate equations. (F) Pharmacokinetic curves of site-controlled release.

the controlled factors, controlled release systems can be classified as rate-controlled, time-controlled, and site-controlled release.

Rate-controlled release. Oral rate-controlled formulations include immediate-release, sustained-release, and controlled-release dosage forms (Fig. 1B). Oral immediate-release dosage forms generally refer to solid formulations that disintegrate and release rapidly after oral administration and can be absorbed rapidly through mucous membranes, including oral immediate-release tablets, self-emulsifying drug release systems, effervescent tablets, *etc.*[44] The key to the prescription design of most immediate-release dosage forms is the addition of disintegrating agents to promote disintegration through capillary or swelling action. Although immediate-release dosage forms have the advantages of rapid onset of action, adequate absorption, and low intestinal residues, the field of sustained and controlled-release dosage forms is much more explorable. The difference between sustained release and controlled release is that the former is released at a non-constant rate that varies over time, which is reflected in the pharmacokinetics as first-order kinetics, while the latter is characterized by a constant rate of release (or near-constant rate) independent of the drug concentration, *i.e.*, zero-order release (Fig. 1E). The main advantages of sustained and controlled-release dosage forms are the reduction of the number of doses and the smoothing of blood concentrations, which are particularly suitable for drugs with long therapeutic cycles and low therapeutic indices, and can provide better therapeutic effects while reducing drug toxicities. There are two main types of material-based sustained and controlled release formulations: skeletal and reservoir-based, which rely on blocking materials that disperse the drug[38] and polymeric coatings that encase the drug to regulate drug release,[45] respectively. The release rate can be regulated by precisely designing the dissolution time of the barrier layer and coating layer. Microparticles, microcapsules, and microspheres can also be used as carriers to optimize the release kinetics of drugs.[46] Their current limitations are: (i) the flexibility of dose adjustment in clinical applications is still low, and treatment cannot be stopped immediately; (ii) they are often designed based on population pharmacokinetic parameters of healthy populations, and it is difficult to flexibly adjust the drug delivery regimen when pharmacokinetic parameters are altered by disease states; and (iii) technical defects can make the drug release rate not meet the design requirements, or even risk sudden drug release and produce side effects.

Time-controlled release. Since some disease episodes exhibit changes in physiological and pathological rhythms, there is a need for formulations that can release drugs quantitatively in response to physiological or pathological changes.[43] Time-controlled formulations, also known as responsive pulsatile drug delivery formulations, include both externally regulated and self-regulated forms. Material-based time-controlled drug release systems are generally limited to the self-regulated type

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and mainly include osmotic pump type, coated type, and pulse plug capsules. The design principle of the osmotic pump type system is to form a tablet core of drug and osmolar active substance, and the digestive solution can penetrate through the micro-pores of the outer coating membrane thus prompting the core to swell until it breaks the membrane and eventually produces a pulse effect.[47] Coated pulse release formulations use the coating layer to block the release of the drug from the core, and the blocking time is determined by the composition and thickness of the coating layer.[48] Capsules, on the other hand, can also be designed for pulsatile drug release through expansion, dissolution, or enzymatic degradation types of shell.[49] Time-controlled formulations can release the drug at regular intervals based on the rhythmic characteristics of the human body, potentially avoiding the drug tolerance that occurs with slow-release formulations and further separating drug efficacy from toxicity. One significant disadvantage of these formulations, however, is that their one-time release profile does not meet the treatment requirements for chronic diseases.

Site-controlled release. Orally orientated drug release systems can deliver a drug to a specific site in the GI tract, and a variety of modalities have been used to achieve this (Fig. 1F). Gastrically targeted drug release formulations can achieve retention in the stomach by swelling or floating of materials such as gels. Small intestinal or colonic localized drug release systems usually utilize pH-responsive delivery vehicles such as hydrogels, nanoparticles, enteric capsules, *etc*.[50] In general, these drug delivery systems often keep relatively stable in the stomach and release with the increase of pH. Alternatively, time-controlled formulations can be designed for localized drug release depending on gastric emptying time and intestinal transit time.[51] Flora-dependent drug release systems can achieve site-specific drug release through materials that can be degraded by enzymes produced by specific intestinal flora.[52] Pressure-controlled drug release systems[53] can be controlled to rupture under the pressure of intestinal peristalsis to achieve site-specific localization such as colonic colonization. Targeted drug release can be used for local treatment, which can improve efficacy and reduce systemic adverse effects. It can also improve drug deactivation or incomplete absorption due to the influence of the gastrointestinal environment. However, relying solely on the material to achieve localized release still presents challenges for long-term therapy.

2.3 Intelligent release kinetics

Although material-based drug delivery systems can respond to both endogenous and exogenous stimuli, they still have less precise control over the spatiotemporal distribution of drugs. With advances in electronics and materials engineering, on-demand and intelligent delivery techniques have been developed. These methods use external stimuli, including electrical,[40] magnetic,[54,55] optical,[56] and ultrasonic stimulation,[57,58] to control the precise release of drugs according to specific physiological properties and requirements.

Digital and electronic-based drug delivery systems can achieve pulsed drug release by utilizing external and wireless physical energy sources. This means that the system can provide dynamic control of the full process of release, and the precision of this control can be reflected in more complex release profiles (Fig. 1C). The optimized release profile facilitates better adaptation to the patient's physiological rhythms and promises to enable the regulation of drug release according to the temporal differences in the drug's *in vivo* process. In addition to ''chronotherapy'', the intelligent drug delivery system is also suitable for multiple dosing of a single implant.[57] Furthermore, the introduction of sensing capabilities into the system has the potential to achieve fully automated drug delivery, *i.e.*, a closed-loop feedback regulation system. For example, if a device for real-time sensing of blood indicators (*e.g.*, blood glucose) is added to an existing oral gastrointestinal drug delivery system,[54] a timely and responsive release of the payload may be achieved, with the idealized result being the maintenance of blood glucose stability. Intelligent drug release systems have greatly advanced the field of targeted and remotely controlled drug delivery. The long-term *in vivo* residence of low-cost and highly functional drug delivery systems can undoubtedly have far-reaching implications for public health.

3 Soft robot-based drug delivery systems

Oral drug delivery is a sophisticated multi-step process involving drug loading, transportation, positioning, and release. Once ingested, the GI environment further complicates each step like operating in a black box. The main advantage of robot-based ODDSs is to introduce quantitative, precise control over each step through human interventions, sensors, and closed-loop algorithms. This section outlines some of the design ideas and implementations that exploit robots as a means to overcome the complex GI conditions and improve the drug delivery outcomes. The functional design of the soft robots and the corresponding materials are also summarized (Table 1).

3.1 Resident drug delivery robots

Patient noncompliance has long been a problem that is easily neglected. Scientists have proposed several approaches to deliver medications to patients continuously using implantable or wearable devices that require surgery. In contrast, a gastric-resident robot that can be administered orally may be a more suitable solution. Because of their elastic nature, some soft materials can be compressed and unfolded in response to environmental changes, which provides a basis for the development of soft robots. Zhang *et al.*[59] first described an enteric elastomer made from a special supramolecular polymer gel sensitive to changeable pH (Fig. 2A). This material remained elastic under acidic conditions and would dissolve under neutral conditions. Thus, combined with polycaprolactone, the material was used as a key component in making an annular gastric retentive robot. *In vivo* experiments demonstrated the

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Table 1 Design mechanisms and materials for representative ingestible soft robots

Type	Design mechanism	Materials or designs	Ref.
Residence	Swelling-enabled hydrogel	Sodium polyacrylate homopolymers	67
		Alginate and polyacrylamide	98
		Glycol chitosan	66
		Hydroxyethyl cellulose and sodium carboxymethyl cellulose	65
	Unfolding system	Elastollan 1185A10	61–63
		Polyurethane filaments	99
		Poly(acryloyl 6-aminocaproic acid) and poly(methacrylic acid-*co*-ethyl acrylate)	59
	Tissue adhesion	Silicon nanoparticle	100
		Dopamine	82
Deformation	Shape memory alloy	Polydimethylsiloxane and neodymium-iron-boron	75
		EMG 1200 dry magnetic nanoparticles	73
	Shape memory polymer	Biolefin	71
		Agarose hydrogel	72
		Thermoplastic polyurethane	63
Locomotion	Magnetic drive	Neodymium-iron-boron	76
		Neodymium-iron-boron and PVA	80
		Fe_3O_4 magnetic nanoparticles	101
	Self-oriented system	Gravitational action	86 and 87
	Micro-motors	Magnesium	70
		Algae motors	84

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stability of the elastomer in the stomach, and that the disintegration of the elastomer into small rigid elements in the intestine allowed safe passage without obstruction.

Based on the achievement above, Bellinger *et al.*[60] developed a star-shaped gastric-resident robot that facilitated the sustained release of drugs (Fig. 2B). The robot was composed of an elastomeric core linked with six drug-loaded arms. The elastic core enabled the star-shaped body to fold into a capsule shape and rebound into an open star when the capsule is disassembled. The property of flexibility provided elastic flexion to adapt to the unstructured environment while allowing all other components to maintain their shape. The main component of the six drug-loaded arms was the PCL polymer matrix, which was linked by pH-dependent copolymers that could remain tough in the stomach and degrade in the intestines. The elaborate design of the material and structure gave the robot the right stiffness to hold a specific shape for a long time without causing tissue damage or food blockage. According to the *in vitro* release experiment, a dose of one capsule could release ivermectin sustainably from the PCL matrix for 14 days in simulated gastric fluid. The release rate of the drugs could be adjusted by changing the ratio between the drug content and the polymer matrix. *In vivo* in swine, the robotic formation could achieve a prolonged residence time and provide a therapeutic effect for up to 10 to 14 days. From these characteristics, it was evident that the robot could avoid the defects of short drug half-life, reduce the frequency of drug administration, and improve patient compliance. Similarly, a few star-shaped gastric-resident robots were developed for the continuous delivery of contraceptives and meloxicam, and the treatment of HIV antiretrovirals.[61,62]

In addition to pH sensing, shape-programmed matter reactive to the temperature of the body has been selected. Babaee *et al.*[63] created a compressed robotic capsule (Fig. 2C) that entered the stomach through the esophagus and deployed into a fenestrated spherical shape by temperature sensing. It consisted of flexible elastic hinges and drug-carrying polymer matrix arms, which were linked by thermosensitive linkers. The elastic hinges endowed the robot with deformability. When exposed to warm water, the rigidity of the linkers would be greatly reduced, and the drug release arm would be disassembled into small portions so that it could be discharged from the body without causing a blockage. As the *in vitro* and *in vivo* experiments showed, the robot retained within the stomach without any damage and continued to release therapeutic agents for 14 days, reducing the maximum plasma drug concentration prominently. This type of robot capable of long-term drug delivery provided a new platform for the therapy of chronic diseases. In the same article, another thermosensitive robot was mentioned prepared to be employed for drug delivery in combination with microneedles.

The maximum drug loading capacity of the drug delivery robots described in these articles above generally does not exceed 500 mg. To obtain a higher drug loading capacity, Verma *et al.*[64] developed a gastric-resident gram-level loading system taking a superelastic nitinol wire as the main body, which coated drug-matrix pills were strung on (Fig. 2D). It was administered through the nasal cavity. After entering the stomach, a cylindrical coil was formed to stay and continue the administration. After the drug release, the robot could be retrieved *via* the nasogastric route. *In vitro* experiments were performed with isoniazid, ethambutol, pyrazinamide, moxifloxacin, and rifampicin as model drugs. *In vitro* release curves showed that the drugs could be released continuously for up to 30 days, and several curves had been consistent with the zero-order release. Furthermore, the release rate could be optimized by modifying the wire length and the tablet matrix. In their experiments, a total of 10 g of doxycycline hyclate was loaded into the system and administered to swine. The results showed

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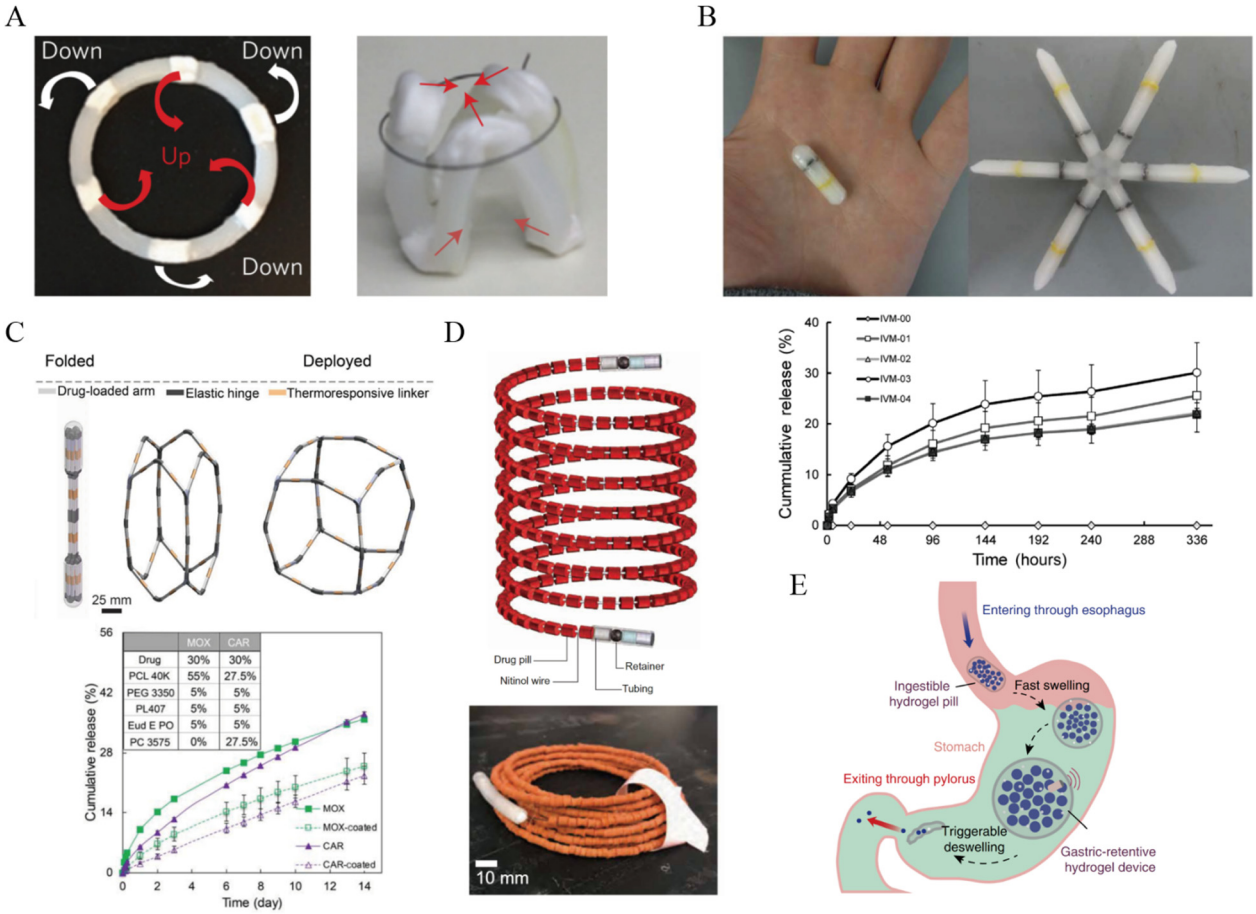

Fig. 2 Soft robotic strategies to achieve gastrointestinal retention. (A) An enteric elastomer made of a special supramolecular polymer gel sensitive to changeable pH. (B) A deployable star-shaped gastric-resident robot that can realize sustained release for two weeks, and its cumulative release curve. (C) A compressed drug delivery capsule that can deploy into a fenestrated spherical shape by sensing changing temperature, and *in vitro* release curve. (D) A rope-shaped soft robot that can load gram-level drugs and be administrated through the nasal cavity. (E) An ingestible hydrogel device that can swell to dozens of times its original volume to remain in the stomach. Panel A is reproduced with permission from Springer Nature. Panel B is reproduced with permission from AAAS. Panel C is adapted with permission from AAAS. Panel D is reproduced with permission from AAAS. Panel E is reproduced with permission from Springer Nature.

that the gastric-resident system was retained in the stomach for 28 days without damage and was retrieved safely. During this period, the levels of the model drug could be detected for at least 28 days. Among the advantages of the robot were its success in increasing drug loading, reducing the frequency of administration, increasing the types of therapeutic agents and diseases to which it can be applied, and improving patient compliance.

However, the retrieval of soft robots is another issue that needs to be better addressed. Contrary to rigid parts, hydrogels are considered to be a kind of multifunctional material with the property of superior mechanical compliance and biocompatibility. For example, swollen hydrogels with sustained drug release formulations have been used for extended ODDSs in the stomach.[65,66] Liu *et al.*[67] invented an ingestible hydrogel robot that was made of super absorbent hydrogel particles wrapped in an anti-fatigue porous hydrogel membrane (Fig. 2E). It could be ingested as a small pill and swelled into a soft ball that would lie in the stomach. The researchers proved that the hydrogel robot could stay in the stomach for up to 29 days and had wide potential applications in drug delivery and biological sensors.

3.2 Shape-programmed and locomotive drug delivery robots

A lot of soft robots are composed of special materials generally including dielectric elastomer (DE), shape memory alloy (SMA), and shape memory polymerization (SMP). These materials can change into three-dimensional, self-folded, or self-assembled structures, in response to exogenous stimuli without the need for manual control. One of the most promising approaches to control robotic motion is based on external magnetic fields, which have shown good performance due to ease of operation and manipulation.[68] In particular, magnetoactive soft materials have made remarkable progress in their design and fabrication, with the capability of shape programming and locomotion.[69] Some new materials can even achieve autonomous movement without any external energy.[70] Integrating the above technologies, soft robots can deliver orally-administered therapeutics

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to the location of interest, showing great potential for biomedical applications.

Origami robots offer great opportunities for *in vivo* surgery and therapeutics. Miyashita *et al.*[71] designed two types of origami robots called the battery remover and the drug deliverer, that could fold up and spread out in the stomach. The multifunctional miniature robots they designed could provide effective clinical intervention for patients with gastrointestinal damage caused by accidental ingestion of button batteries. The first robot, the battery remover, took the form of an ice capsule containing a magnet. After it was swallowed by the patient, the ice capsule melted in the stomach, and the device was driven by a controlled magnetic field to the location of the battery. It then magnetically attracted the battery and dislocated it from the inflammatory site. After the battery was removed, the drug deliverer with biodegradable composite sheets, including the drug layer, was sent to the stomach and landed on the inflammation site, releasing drugs through the degradation of the robot. The whole process of removal and repair done by origami-based robots provided new ideas for the treatment of gastrointestinal diseases. d'Argentre *et al.*[72] fabricated a deployable hydrogel patch and plug robot to treat gastric ulcers. The robot was constituted of shape memory agarose hydrogel and an embedded magnet at the center. The hydrogel could remain rigid and compress into a pill shape when dried, and when ingested, it could expand several times by hydration. The magnet made the robot controlled by a coil system and localized with the assistance of three hall-effect sensors to the ulcer location. A strong magnetic field was then used to fix it on the diseased site as a plug or patch to cure the ulcer.

The advancement of soft robots is greatly inspired by biomimetics. Living organisms in nature provide creative design concepts for soft robots. Joyee *et al.*[73] designed and fabricated a multi-material multiscale soft robot with versatile utilization. The robot was made from three parts, a deflected segmented body, anterior legs, and posterior legs. The segmented body allowed the robot to alter the direction of movement. Both legs were composed of smart materials with the characteristic of the preprogrammed magnet, which provided the possibility of magnetic actuation. Inspired by arthropods that have tapered and wrinkled hairy setae, a hierarchical surface structure was designed to cover the footpad of the robot to achieve locomotion in complex or wet surface environments such as the stomach. Furthermore, some functional sections, including grippers and drug reservoirs, could integrate with the forefoot and hindfoot. The *in vitro* simulation experiment on the pig stomach showed efficient movement and flexibility of the robot, demonstrating great potential in drug delivery.

Compared with capsule-sized robots, millimeter-scale soft robots have been designed to achieve broader biomedical applications by smaller size and better manipulability. The magnetoactive soft material is an emerging intelligent and multifunctional soft polymeric composite with the advantages of remote actuation, shape manipulation, and fast response, which has great application prospects in minor soft robots.[74] Inspired by scallop opening and closing, Chen *et al.*[75] fabricated a magnetically actuated untethered robot for drug delivery (Fig. 3A). Through 3D-patterned continuum magnetization systematic methodology developed by themselves, the robot could roll on the complex surface of the stomach, and grab and release drugs on the sites of damage. Zhang *et al.*[76] proposed a three-dimensional micromachining method to achieve programmable deformation of soft magnetic materials (Fig. 3B). Based on this method, they made a small-scale hollow spherical robot

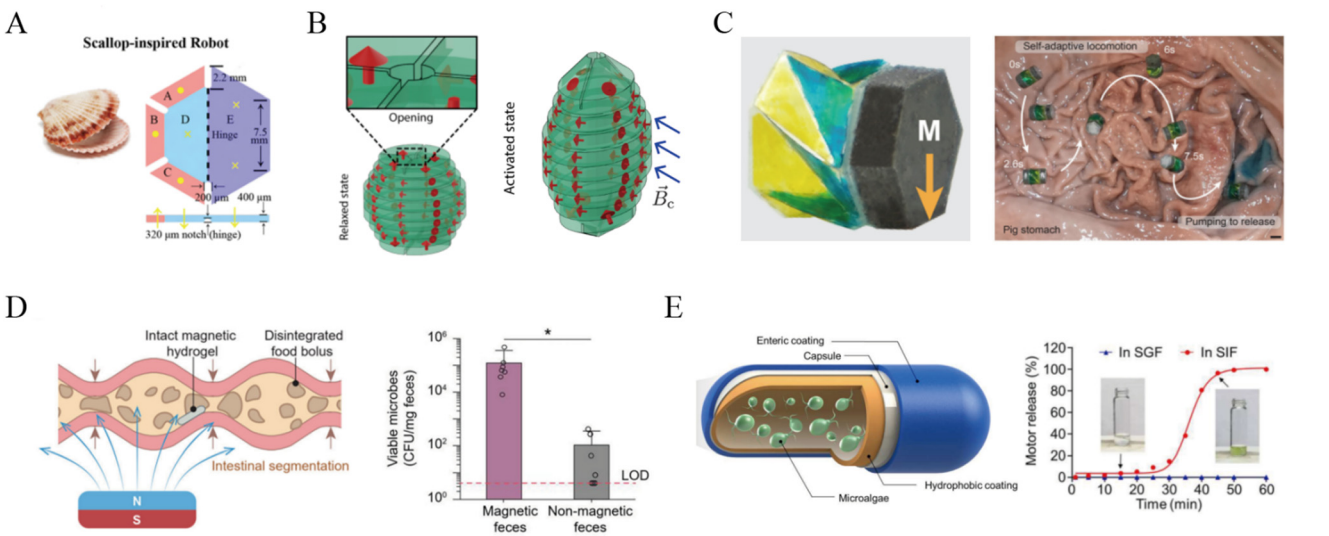

Fig. 3 Shape-programmed and locomotive drug delivery robots controlled by external magnetic stimulation. (A) A magnetically actuated untethered robot inspired by scallops. (B) A small-scale hollow spherical robot capable of programmable deformation. (C) An amphibious origami millirobot that can release the drug by changing the state of folding and unfolding. (D) A magnetic hydrogel to increase the probiotics colonization. (E) A capsule loaded with algal micro-motors to improve drug distribution and prolong drug residence time in the GI tract. Panel A is reproduced with permission from American Chemical Society. Panel B is reproduced with permission from AAAS. Panel C is reproduced with permission from Springer Nature. Panel D is reproduced with permission from Wiley-VCH GmbH. Panel E is reproduced with permission from AAAS.

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that could deform under magnetic actuation. The *in vitro* gastric simulation experiment manifested that the drug-loaded robot could roll along the surface, release the medicine at the target position, and then leave for retrieval under complex conditions. An amphibious origami millirobot was proposed by Ze *et al.*[77] The shape of the robot was a triangulated hollow cylinder providing convenience for rolling, jumping, and spinning to suit various environments (Fig. 3C). Meanwhile, the robot changed the state of folding and unfolding as a pump to release drugs or cargo. To validate its application potential, the robot was used to deliver drugs in a pig stomach filled with viscous liquid, where the robot exhibited controlled locomotion and release. Recently, a growing number of studies have shown that the gut microbiota is strongly associated with physiological characteristics such as vitality and fatigue, as well as diseases such as colorectal cancer and inflammatory bowel disease. Probiotics are regarded as beneficial microbes to treat various diseases.[78] With the development of synthetic biology, engineered microorganisms have been used to carry drug molecules.[79] However, microorganisms cannot survive under gastric acid, and another factor limiting progress in this area is the difficulty of microbial colonization of the gastrointestinal tract. Hydrogels are a good choice for delivering live probiotic drugs because of the moist environment they provide, their soft surface, and their good biocompatibility. Liu *et al.*[80] mixed magnetic particles and living bacteria in the hydrogel to fabricate a resident robot of the magnetic hydrogel (Fig. 3D). The hydrogel robot had a certain degree of rigidity, which ensured its structural stability during peristalsis in the gastrointestinal tract, while the soft surface of the robot would not damage the tissue. The localization and residence of the magnetic hydrogel in the gastrointestinal tract could be realized by wearing an external magnet, which was verified in a mouse model *in vivo*. Furthermore, some types of hydrogel are designed to be sensitive to physical and chemical signals. For example, light can be taken as a dynamic trigger to degrade hydrogels to release drugs, enabling remote control of drug release.[81] Recently, a novel hydrogel, which could form epithelial linings and yield strong tissue adhesion under the function of catalase, was developed.[82] These findings substantiate great potential for hydrogels as robot-based ODDSs.

For some organs, millimeter-scale robots are still relatively oversized. Moreover, the robots described above need external magnetic field power, which increases the difficulty of future applications. Initially obtaining inspiration from myosin and kinesin utilizing chemical energy to locomote, scientists have paid great attention to studying micromotors due to their tiny size and spontaneous motion properties. Additionally, micromotors can propel themselves to hard-to-reach locations, facilitating drug delivery and other biomedical applications.[83] However, most micromotors have a short life in the gastric fluid, resulting in rapid retention and poor drug absorption. Zhang *et al.*[84] reported a capsule robot that loaded algae-based micromotors with good cell compatibility and adaptability (Fig. 3E). The microalgae could beat the flagella on both sides to swim in different aqueous environments. Competing with Mg-based micromotors, microalgae had a stronger driving force and a longer life span, improving the distribution of micro-motors and prolonging the retention time of a model drug. To decrease the damage of gastric acid for micromotors, a protective capsule, constituted by a pH-sensitive outer layer and hydrophobic inner layer, was developed. This capsule robot would have many potential applications, for example, therapeutic agents could be linked to algal micromotors *via* chemical clicks, making oral delivery of drugs to the intestinal tract feasible.

3.3 Integrated drug delivery robots

Developments in pharmacy have also placed greater demands on drug delivery systems. Robots have integrated functional components, including injectors, vibrators, and electronic devices, to perform more sophisticated functions and handle more complex conditions. Above all, soft materials are regarded as indispensable parts to devise a swallowable robot. Their softness and flexibility allow the robots to adapt to the complex environment inside the body without causing damage to the surface of the esophagus and gastrointestinal tract. Furthermore, elastic materials have the latent capability to act as minor actuators.

As a result, integrated robots have made a breakthrough in the field of macromolecular delivery. Macromolecular drugs, such as insulin and other monoclonal antibodies, are regarded as the most efficient way to treat various diseases, including diabetes and cancer. However, macromolecular drugs are not suitable for presence in the gastrointestinal tract due to the threat of multiple proteases and the variable acidic environment, as well as the obstruction of penetration by the thick mucus layer.[85] Therefore, macromolecular drugs have long been administered by hypodermic injection. Compared to subcutaneous injection, oral administration is considered to be non-invasive, and thus patient compliance is better. There are several robots developed to inject macromolecules into the gastrointestinal tract, which is minimally invasive and painless. A self-orienting millimeter-scale applicator (SOMA),[86] getting inspiration from a leopard tortoise, was designed to inject spontaneously insulin-loaded milliposts into the intestine (Fig. 4A). The shape of SOMA consisted of a low center of mass and a high curvature upper shell that enabled the robot to localize and orient the surface of the stomach passively. Meanwhile, the streamlined design with a high curvature shell made it easier to reduce the external resistance. Then, the actuator was considered seriously to ensure that the milliposts would not impale the tissue. A time-delayed actuator, whose energy source was from a soft spring with a tiny volume, was adopted to inject with minimal damage. Sucrose and isomaltose were used as hydration-dependent actuators to achieve millisecond actuation. When SOMA was given to pigs, it could achieve the same effect as subcutaneous injection, and no physiological abnormality or tissue damage was found. However, the weakness of this generation of SOMA was the low drug load, resulting in low bioavailability. To increase the drug loading, the next generation of SOMA called L-SOMA was created, using liquid injection[87] (Fig. 4B). Compared with solid formulations, liquid drugs presented advantages in terms of increased

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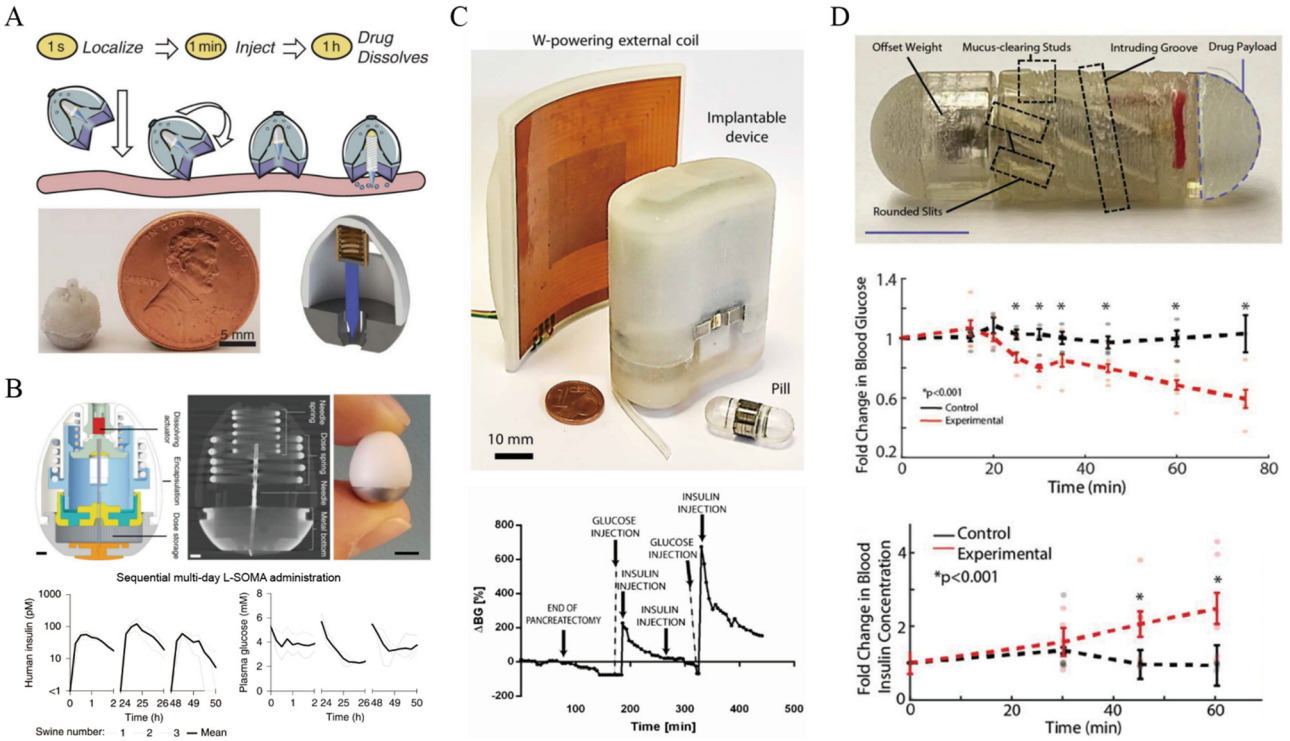

Fig. 4 Integrated drug delivery robots containing soft materials. (A) The process of injecting macromolecules using a self-orienting millimeter-scale applicator (SOMA), and a cross-sectional view of SOMA. (B) The structure and appearance of L-SOMA using liquid injection, as well as the profiles of changes in insulin concentration and blood glucose levels *in vivo* after administration. (C) An implantable system for storing and delivering macromolecules that can be refilled by ingestible capsules, and glucose profiles in *in vivo* trials. (D) A robot called RoboCap that can remove the mucus layer to enhance the absorption of the drug, and graphs of changes in blood glucose and insulin levels after drug administration. Panel A is reproduced with permission from AAAS. Panel B is reproduced with permission from Springer Nature. Panel C is reproduced with permission from AAAS. Panel D is reproduced with permission from AAAS.

surface area for drug-tissue interactions, which could accelerate the pharmacokinetics and pharmacodynamics of the drug. To achieve better liquid injection, a two-stage spring actuation system was used, compressed by pellets and fixed on top of the robot. When the actuator dissolved, the first-stage spring would push the needle into the tissue, forcing the second spring to push down the plunger, and the liquid drug was then injected through the needle into the submucosa. In this way, the drug could enter the deep gastric submucosa. L-SOMA could load monoclonal antibodies, proteins, and small molecules with an increased drug loading capacity of 5–10 times that of the original drug. In the *in vivo* experiment in pigs, insulin bioavailability of up to 80% has been proved, much higher than previously reported data. Furthermore, the SOMA robot was applied to mRNA delivery with the potential to transform therapeutic nucleic acid delivery routes.[88]

The SOMA robot offers an oral alternative to subcutaneous injection as a platform that can be used for multi-drug delivery. However, such a robot cannot remain in the body for continuous drug delivery and is therefore not suitable for the long-term treatment of chronic diseases. Fortunately, there is great potential for emerging implantable robots to address clinical challenges and they are already well-established in a wide range of applications. Taking diabetes as an example, an implantable system can perform intraperitoneal delivery of drugs to effectively treat type 1 diabetes. However, such an implantable system typically requires the attachment of an intraperitoneal catheter to an external reservoir or pump, a process that is highly susceptible to complications such as infection and blockage. To solve the problem of drug shortage and simplify the drug-filling process, Iacovacci *et al.*[89] described a fully implantable robotic device that could be refilled with ingestible magnetic pills carrying the drug (Fig. 4C). The refilled device would then act as a programmable microinfusion system for precise intraperitoneal drug delivery. Initially, the drug-loaded capsule reached the position of the implanted robot through the peristalsis of the gastrointestinal tract and was fixed by magnetic attraction. Then, a thin needle stuck out of the robot, penetrated the capsule, and transferred the drug from the capsule to the reservoir. Once the insulin in the capsule was utilized, the needle would retract. Then the capsule was discharged naturally after passing through the small intestine and colon rectum. The insulin pump could slowly release insulin to manage the glucose level. It is worth mentioning that the tube was in direct contact with the liquid and human tissues, so a medical-grade silicone tube was chosen to deliver liquid insulin with the benefit of flexibility and biocompatibility. The use of electronic components in the robot enables remote

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communication and wireless battery recharging needs for extended power. This robot has made great progress in intraperitoneal drug delivery, simplifying the drug delivery process and extending the service life of implant devices.

In general, the larger the molecular weight of a drug, the less likely it is to be absorbed into the intestinal cells. The presence of mucus, mucosa and enterocytes creates multiple layers of obstruction to drug absorption. Among them, the mucus barrier is the first layer that blocks the drug because its thickness and viscosity properties reduce the interaction between drugs and small enteric cells. To overcome this barrier, Srinivasan *et al.*[90] reported a capsule robot called RoboCap, which could remove the mucus layer to enhance absorption (Fig. 4D). The capsule robot was coated with soft gelatin material to avoid damage to the esophagus. After the robot entered the stomach, the coating was degraded by gastric acid and the exposed capsule consisted of three main parts: the offset weight, the vibrator, and the drug payload. When entering the intestines, the acid solution would trigger the actuator to switch on the RoboCap. The capsule robot could vibrate and rotate assisted by the centripetal force caused by the offset weight. Multiple surface features were designed to efficiently clear the mucous membrane. Besides, a helical groove was selected for the outer robotic body because the shape could accelerate the rotation rate. And studs were present in the recesses of the spiral groove to suck up and remove mucus as well. Along with rotation and mucus cleaning, the drug was dissolved and the particles were deposited on the surface of the mucosa. Results from animal experiments showed that employing robotic work to deliver insulin orally could significantly reduce blood glucose levels. The RoboCap robot offered a viable alternative to subcutaneous injections and facilitated the development of new therapies for diseases such as diabetes.

4 Outlook

Maintaining drug plasma levels within the therapeutic window is crucial to enhancing the efficacy of treatment. Conventional drug formulations are discharged from the body in a relatively short time and the drug concentration is not well maintained at the treatment level. Routine, repeated administration is a common method that causes fluctuation in plasma drug concentration and is prone to non-compliance problems. Furthermore, some drugs such as insulin and hormones are not optimized at constant plasma concentrations. With the requirement of personal treatment and chronotherapy, on-demand administration will be the future trend. Various release curves are regulated for different drugs to achieve maximum drug effectiveness and meet diverse needs.

Robotic ODDSs have been considered the next hotspot in pharmaceutical research. Among them, soft robots have attracted extensive research interest. The property of softness makes soft robots the first choice for the oral administration of drugs with minimal damage. The flexibility and controllability make it possible for soft robots to overcome the harsh conditions of the GI tract. In addition, some have miniaturized structures that can traverse unstructured and narrow spaces, which show great potential in specific site-controlled drug delivery. However, soft robots for ODDSs still have many shortcomings. First, the excessive flexibility of soft materials brings difficulties to precise control of geometries and locomotion. And the uneven surface of the stomach, peristalsis of the gastrointestinal tract, and sticky food also hinder precise manipulation. Therefore, the development of a more accurate navigation, locomotion, localization, and intelligent control system is equally important. Second, soft robots face the same problem as other ingestible devices, which is the size limitation. It is necessary to consider whether the robot can be swallowed without causing blockage and tissue perforation. Besides, the addition of functional parts further restricts the space for drug loading, limiting the delivery of high doses of drugs.[91] Third, manufacturing costs should be considered in designing these devices, as integrating multifunctional parts will undoubtedly increase costs and they are prone to malfunction and high maintenance costs.[92]

Most of the mentioned ingestible drug delivery robots are still conceptualized without extensive animal data. For a long time, the FDA has had strict requirements on oral drugs and ingestible devices. In particular, the biocompatibility, toxicity, and chemical stability of the manufactured materials need to be given high priority for overcoming the challenges in the dynamic and complex gastrointestinal environment. Future research in large animals such as dogs and pigs should serve as necessary iterations for optimizing soft robots as ODDSs before conducting human trials. This new form of drug administration also puts forward new standards for medication and nursing. For example, ODDSs and disease detection robots have huge market potential in stock farming of large animals.[93] The design and safety requirements for such robots are not as high as those applied to humans, but they are easier to implement and can produce huge economic benefits.

Still, the direction of development for oral drug delivery robots is human-oriented. Meeting the diverse needs of people is the goal of future ODDSs. Robotic ODDSs with integrated navigation, positioning, diagnosis, and treatment functionality make recycling possible and meaningful. These gastric resident, on-demand ODDSs may be the best answer to solving patient noncompliance.[94] Non-drug-based electronic devices also provide new forms of disease treatment.[95–97] Combining the latest wireless technology, users can realize real-time interaction with robots and deploy a responsive medication that reports disease status in real-time, coupled with remote control or automated treatment. Such intelligent ODDSs with sensory feedback can lead to intelligent closed-loop drug delivery for treating acute and chronic diseases, and take health management to the next level.

Author contributions

H. Huang and Y. Lyu contributed equally to this work. H. Huang, Y. Lyu, and K. Nan conceived this work, designed the figures, and

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organized the outline of the manuscript. K. Nan supervised this work. All authors contributed to the discussion and writing of this manuscript.

Conflicts of interest

There are no conflicts to declare.

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