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Review article

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Bioinspired oral delivery devices

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Abstract

Oral administration is a widespread and convenient drug delivery approach. However, oral delivery can be affected by the complex digestive tract environment, including irregular tissue morphology, the presence of digestive enzymes, mucus and mucosal barriers, and spatiotemporal variance in physiological parameters. These obstacles can prevent the oral delivery of many therapeutics. To overcome these challenges, oral delivery devices can be designed with bioinspired compositions, structures or functions to make more drugs available for oral administration. Various bioinspired oral delivery devices have been developed by harnessing biological materials and living microorganisms, or by imitating biological structures and functions. In this Review, we discuss the design and modification of bioinspired oral delivery devices, examining engineering strategies to target specific tissues and applications. We highlight how key bottlenecks in oral delivery can be addressed through bioinspired designs, concluding with an outlook on the remaining challenges towards the clinical translation of bioinspired oral delivery devices.

Sections

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Key points

- Biotic components produced by animals, plants and microbes, such as exosomes, pollen grains and bacterial spores, can be used for oral drug delivery and oral vaccination.
- Living microorganisms can be surface coated, encapsulated or genetically modified to allow oral delivery for the regulation of the intestinal environment, to maintain homeostasis or for disease treatment.
- Biological materials, such as polysaccharides, peptides, lipids and nucleic acids, including alginate, chitosan, gelatin, liposomes and DNA hydrogels, can improve the efficacy and efficiency of oral delivery devices.
- Bioinspired chemical components and physical structures can improve the tissue adhesion, permeation and adaption abilities of oral delivery devices.
- Bioinspired oral delivery devices targeting buccal, oesophageal, gastric and intestinal sites have been preclinically evaluated, and some have entered clinical trials.

Introduction

Oral delivery refers to the route of pharmaceutical absorption through the digestive tract for local or systemic therapy. Drug formulations are orally delivered to reach the buccal cavity[1], oesophagus[2], stomach[3] and intestine[4,5]. As one of the most common drug delivery methods, oral delivery offers a non-invasive, low-cost route of administration with high drug versatility and patient compliance[6,7] (Fig. 1a,b and Box 1). However, owing to the specific physicochemical features of the digestive tract, including the presence of digestive enzymes (for example, peptidase, lipase and amylase), cellular and mucus barriers, low pH of the stomach (pH 1–2), and varying pH values between the stomach and the intestine, drug absorption following oral delivery can be challenging, limiting drug bioavailability[8] (Fig. 1c). The bioavailability of orally delivered drugs can be improved by applying chemical modifications[9], absorption enhancers[10], enzyme inhibitors[11] or bioadhesive polymers[12,13]. In addition, carrier systems[14–17], such as nanoscale and microscale vehicles, have been explored. Although these strategies can improve oral drug delivery and absorption, adverse effects remain such as immunological stress, unpredictable pharmacodynamics, flora balance disturbance and low drug efficacy. Additionally, achieving optimal bioavailability remains difficult for oral drug formulations; in particular, the material composition and structural design of oral drug formulations need to be improved to increase bioavailability. Moreover, the implementation of specific features, such as spatiotemporal delivery of bioactive substances, remains difficult. The design of functional oral delivery devices that can adapt to the digestive tract environment, efficiently deliver drugs and control drug release profiles would make more categories of drugs available for oral delivery.

Inspiration and solutions for the design of oral drug delivery formulations can be drawn from nature; for example, microbes can produce protective shells or dormant bodies to maintain life activities and protect genetic material from environmental damage. Such features can be mimicked to engineer oral delivery devices that can withstand the harsh conditions of the digestive tract[18,19]. Climbing plants and animals, such as mussels, octopi and geckoes, possess adhesive abilities to achieve steady attachment to wet and dry surfaces[20–23]. The underlying mechanisms could be harnessed for the construction of adhesive oral delivery devices with intricate structural and chemical properties that result in strong tissue adhesion and prolonged drug action time[24–26]. Despite the tight mucosal barrier, intestinal pathogens can penetrate and disrupt intestinal barriers. This feature could be adapted to design oral delivery devices with penetration and insertion capabilities to improve drug efficacy[10,27]. Responsive and controlled drug delivery may also be achieved by imitating the interactions between the intestinal flora and the enteric epithelium[28]. Inspired by these biological phenomena, oral delivery devices are being developed with bionic designs in their physical, chemical and structural aspects.

Extracellular vesicles[29], pollen grains[30], microalgae[4], living microorganisms[31] and other biological materials[19,32] can be applied as oral delivery vehicles. For example, genetically engineered bacteria can be orally delivered to regulate brain functions through the gut–brain axis[33]. In addition, biological materials, extracted or synthesized by organisms[5,34], as well as bioinspired adhesion[24,26] and permeation structures[10,27] can improve oral delivery. Such bioinspired oral delivery systems can be fabricated by microfluidics to produce uniform microscale or nanoscale particles or capsules through intricate control of small amounts of fluids in microchannels[35] or by bio-printing[5,36]. Some devices have already shown promising results in preliminary in vivo experiments and phase I–IV clinical trials (Table 1).

In this Review, we discuss the bionic design of oral delivery devices that contain or imitate part of or an entire organism. We examine fabrication, in vivo fate and application requirements of naturally derived oral delivery devices based on biological ingredients or living organisms, and summarize design criteria to target these devices to specific tissues, including the oral cavity, oesophagus, stomach and intestine. Finally, we highlight technological challenges and provide an outlook on the clinical translation prospects of bioinspired oral delivery devices (Box 2).

Naturally derived oral delivery devices

Biotic components[37] and living organisms[31] can be harnessed or mimicked for the construction of oral delivery devices. Some biotic components can be directly acquired from organisms without or with little intervention; for example, animal exosomes[29], plant pollen grains[30], microbial cell walls and bacterial extracellular vesicles[32]. Such biological components, and in particular plant pollen grains and bacteria, exist in large quantities, thereby enabling the large-scale manufacturing of naturally derived oral delivery devices. Biotic components often have a large specific surface area, core–shell structures, resistance to harsh environments, high mobility, and cell affinity and, thus, they can promote drug encapsulation, gastrointestinal (GI) permeation and drug absorption[19,29]. Moreover, some biotic components or living organisms can react to the surrounding environment, providing cues for targeted, localized and on-demand drug delivery[38].

Biotic components

Biotic components produced by animals, plants or microbes can have therapeutic effects[39] or can be used to encapsulate, protect and deliver drugs[29–32]. Their uneven surfaces or cell membrane-analogous structures contribute to GI adhesion and permeation, improving drug bioavailability. For example, extracellular vesicles[40], such as exosomes[29], are nano-sized bilayer phospholipid vesicles that can be derived from

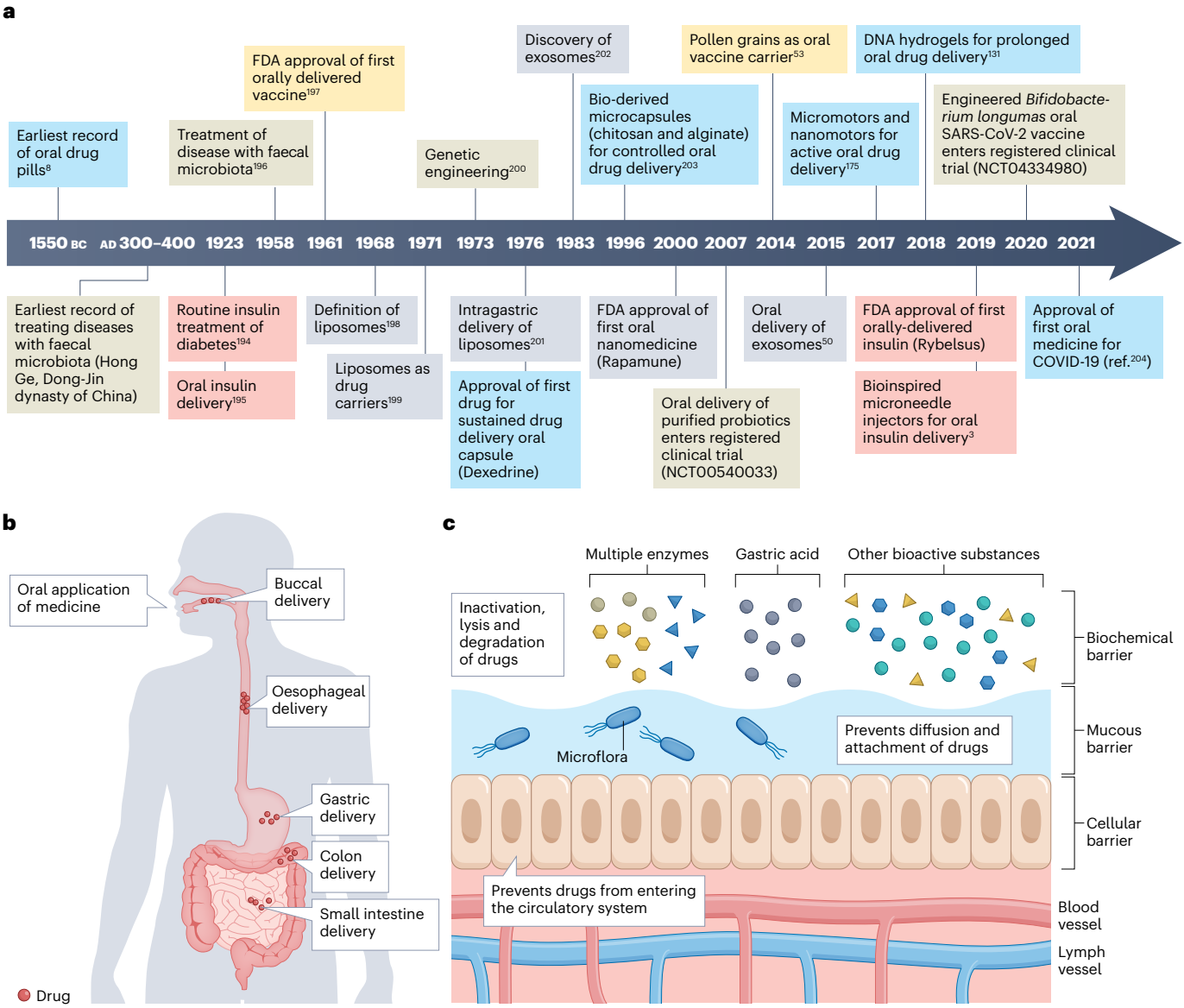

Fig. 1 | Oral drug delivery. a, Timeline of key advances in oral administration and bioinspired oral delivery device development (first FDA-approved sustained drug delivery oral capsule (Dexedrine), first FDA-approved oral nanomedicine (Rapamune) and first FDA-approved orally delivered insulin (Rybelsus)). **b**, Delivery sites of oral drugs include the oral cavity, oesophagus, stomach and intestine. **c**, Oral delivery faces three main barriers. Multiple digestive enzymes (such as pepsin, trypsin, lipase and amylase), gastric acid (pH 1–2 in the stomach), and the presence of living and bioactive substances constitute the biochemical barrier. Mucus coats the digestive tract (mucous barrier), and epithelial cells and their tight junctions form the cellular barrier. The biochemical barrier can destroy drug molecules and cause drug inactivation. The mucous barrier restricts drug permeation and can trap drug molecules. The cellular barrier inhibits drug absorption from the gut lumen into the blood[194–204].

animal cells. Biotic components can also be extracted from plant sources; for example, pollen grains[30], spores[41], leaf materials[42] (including fresh leaf fragments and lyophilized leaves) and plant cell-derived extracellular vesicles[40]. Moreover, bacterial ghosts[43], fungal cell walls[37], microalgae shells[4], bacterial spores[19] and bacterial outer membrane vesicles (OMVs)[32] can be obtained from microorganisms (Table 2). With surface or internal modifications, these biotic components enable the targeting of different parts of the GI tract as well as responsiveness to environmental stimuli[18,41].

Extracellular vesicles from animal sources. Extracellular vesicles are nano-sized bilayer phospholipid vesicles secreted by cells for information transfer and intercellular communication[44]. The four major types of extracellular vesicles are exosomes, microvesicles, apoptotic bodies and virus-like particles. Exosomes have a size range of 30–200 nm and a specific endocytosis–fusion–secretion biogenesis pathway. Briefly, this process starts with inward growth of the plasma membrane, followed by internalization of cellular substances, maturation of membrane vesicles and fusion of the plasma membrane, resulting in exosomes

that are released from the cell. Exosomes contain various biomolecules, such as proteins, nucleic acids, lipids and polysaccharides, can be produced by almost all cell types, and exist widely in biofluids and excreta, including blood, saliva, breast milk, faeces and urine[44,45]. Thus, exosomes can be easily acquired and purified by various techniques, including ultracentrifugation and tangential flow filtration, on a large scale. Exosomes can transport cargo across plasma and cell membranes, acting as drug carriers[46]. Moreover, exosomes can circulate in the blood for up to a few hours, contributing to the high bioavailability of loaded drugs; for example, chemotherapeutic agents delivered in exosomes in mouse models[29,47].

Exosomes are being explored as natural oral delivery vehicles (Fig. 2a). Drugs can be loaded into exosomes either by directly incorporating drugs into purified exosomes or by pre-loading drugs in parental cells, followed by the secretion of drug-carrying exosomes[29,44]. Various exosome-based oral drug delivery devices have been developed, including intestinal cell-derived[45], T cell-derived[48], stem cell-derived[49] and milk exosomes[50]. However, the application of exosomes faces the challenges of unclear in vivo mechanisms and heterogeneity as well as unwanted content, the complete removal of which is difficult. Fluorescence tracer technologies are used to understand the fate of exosomes after oral administration. For example, fluorescently labelled milk exosomes can enter the circulation system of mice and are distributed in different organs, including the GI tract, liver, kidney and spleen[51]. After about 48 h, the exosomes become undetectable in these organs, indicating body clearance[51].

Plant-derived biotic components. Plant-derived biotic components mainly include pollen grains, spores, leaf materials and extracellular vesicles. Pollen grains are robust microscopic objects that accommodate and protect plant gametes and associated proteins. Because of their resistant shells, pollen grains have a high tolerance to mechanical force, high temperatures and extreme chemical conditions such as acids, alkalis, enzymes and organic solvents[52]. These features help them withstand the harsh gastric environment and to serve as oral delivery devices[52–55]. In addition, pollen grains have irregular surface morphologies and show strong mucosal adhesion, leading to longer GI retention time and higher drug bioavailability in comparison to similarly sized synthetic delivery vehicles with a smooth surface[53]. Pollens are either totally or partly digested in the GI tract and excreted, depending on their chemical nature and the integrity of the pollen wall[54,55]. To remove the inherent allergic substances in the cavity of pollen grains and to load drugs, a sequence of chemical treatments is applied, including strong acids, strong bases and organic solvents[30] (Fig. 2b), creating open apertures on pollen shells through which drugs can be loaded. Secondary modification or wrapping of the pollen shell with functional materials can prevent drug leakage and the influx of gastric fluids. For example, coating pollen vehicles with zein inhibited drug degradation in simulated gastric fluids and induced drug release in simulated intestinal fluids[56]; drug loading of these modified pollens reached 90.49 ± 1.19 mg/g (nobiletin nanoparticles per gram of pollen), and drug release was less than 10% in simulated gastric fluids after 2 h and nearly 100% in simulated intestinal fluids after 48 h. Pollen grains also have the capacity to activate the innate immune system and enhance immune responses; thus, allergen-free ragweed pollen grains can serve as adjuvants and oral vaccine carriers[57].

Spores are produced by many plants as carriers of genetic material for reproduction. Similar to pollen grains, spores consist of protective capsules with a large internal chamber and a monodisperse structure. Spores could serve as oral delivery vehicles with high biocompatibility[58]; for example, unmodified spores and those modified with biomaterials, such as alginate and cellulose, can carry drugs for oral delivery and modifications with biomaterials can help to tune the drug release profile[39,58]. Moreover, plants can be genetically engineered to express therapeutic proteins for oral delivery. For example, foreign genes can be integrated into chloroplast genomes to produce functional proteins at high levels, including growth factors[59], insulin analogues[42], antimicrobial peptides[60] and vaccine antigens[61]. Oral administration of leaf materials that contain such engineered chloroplasts leads to the release of functional proteins with therapeutic effects. Similarly, rice can be engineered to produce recombinant human lactoferrin, which is biologically active and stable, as demonstrated by antimicrobial experiments against enteropathogenic *Escherichia coli* and

Box 1

Clinically approved oral delivery strategies

FDA-approved oral drug formulations include troches or lozenges, oral solutions, suspensions, capsules, conventional tablets, effervescent tablets, coated tablets, chewable tablets, dispersible tablets and extended-release formulations[205]. Troches or lozenges are compressed tablets that slowly dissolve in the oral cavity and produce local effects for up to hours in the mouth and pharynx. Oral solutions belong to liquid pharmaceutical forms and sometimes contain Chinese medicine decoctions. Suspensions are non-uniform liquid formulations composed of insoluble, solid drug particles in dispersion media. Capsules are solid formulations prepared by sealing drugs and auxiliary materials inside hollow hard or soft capsule walls. Conventional tablets are fabricated by compacting drugs and excipients into uncoated tablets. Effervescent tablets typically contain sodium bicarbonate and organic acids, which generate carbon dioxide bubbles, leading to their rapid disintegration following exposure to water. Coated tablets, such as sugar-coated, film-coated and enteric-coated tablets, are conventional tablets modified with a functional coating on the surface. Chewable tablets are taken by swallowing after chewing in the mouth. Dispersible tablets rapidly disintegrate and disperse evenly in water; they can be orally administered with water, sucked in the mouth or swallowed. Extended-release formulations can deliver drugs in a sustainable manner, thus reducing the administration frequency and ensuring more stable effects than other tablet formulations. Among the 50 new drugs approved by the FDA in 2021, there are 24 oral drugs, of which 7 are capsules (for example, Tavneos, Fotivda and Exkivity), 15 are tablets (for example, Verquvo, Tepmetko, Ponvory and Brexafemme), 1 is an extended-release formulation (Qelbree) and 1 is an oral solution (Livmarli)[206]. Biological materials, such as gelatin and lactose, are often used as pharmaceutical adjuvants in the clinic; however, only a few bioinspired materials or devices have been approved by the FDA as oral delivery devices thus far, for example, Plenity, approved for weight management in the treatment of obesity (Plenity establishment registration and device listing).

Table 1 | Selected clinical trials of bioinspired oral delivery devices

Bionic elements	Dosage forms	Applications	Status	Clinical trial identifiers[a]
Biotic components				
Fruit exosomes	Tablet (curcumin conjugated to exosomes)	Colon cancer	Phase I	NCT01294072
Bacillus subtilis spore extract	Capsule	COVID-19	Not applicable	NCT05158855
Nanovesicles delivered from *Citrus limon* (*Linnaeus*) juice	Spray-dried formulation of citraVes	Metabolic syndrome	Not applicable	NCT04698447
Herbal components (*Fructus Cannabis*, *Radix et Rhizoma Rhei*, *Radix Paeoniae Alba*, *Semen Armeniacae Amarum*, *Fructus Aurantii Immaturus*, *Cortex Magnoliae Officinalis*)	Granule solution	Constipation; gastrointestinal disorders	Phase II	NCT01695850
Alga *Dunaliella bardawil*	Capsules containing the alga powder	Retinitis pigmentosa	Phase II, phase III	NCT01680510
		Psoriasis	Phase III	NCT01628081
Living organisms				
Engineered *Bacillus subtilis*	Capsule (1×10^{10} CFU of *Bacillus subtilis* spore)	COVID-19-related pneumonia	Not applicable	NCT05239923; NCT05057923
Lactobacillus acidophilus and *Bifidobacterium infantis*	Liquid (2.5×10^{8} CFU of each strain)	Nosocomial infection; necrotizing enterocolitis	Phase III	NCT01340469
Lactobacillus salivarius PS2	Powder (10^{9} CFU)	Mastitis	Phase I, phase II	NCT01505361
Multi-strain probiotics (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus lactis* W58)	Powder ($\geq2.5\times10^{9}$ CFU)	Parkinson disease; anxiety	Phase II	NCT03968133
Bifidobacterium longum, *Lactobacillus acidophilus* and *Enterococcus faecalis*	Solution ($>0.5\times10^{7}$ CFU)	Disorder of stomach function and feeding problems in paediatrics	Phase IV	NCT02060084
Lactobacillus rhamnosus	Capsule (10^{10} CFU)	Glucose intolerance	Phase III	NCT01436448
Saccharomyces boulardii	Capsule (*Saccharomyces boulardii* 250 µg)	Irritable bowel syndrome	Phase IV	NCT04627337
Lactobacillus rhamnosus GG	Capsule (10^{10} CFU)	Post-traumatic stress disorder	Phase II	NCT04150380
Lactic acid bacteria (*Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* ssp. *paracasei* 19, *Lactobacillus plantarum* 2362)	Granule solution	Colorectal neoplasms	Not applicable	NCT01479907
Streptococcus salivarius K12	Fast melt powder (10^{9} CFU)	Healthy adults (to evaluate the colonization efficacy of the probiotic bacterium from the formulation)	Not applicable	NCT05367518
Biological materials with medicinal functions				
Polysaccharides (β-glucan, inulin, pectin, starch)	Granule solution	Colorectal neoplasms	Not applicable	NCT01479907
Starch, pectin	Confection (adding starch or pectin for prolonged or intermitted release, respectively)	Healthy adults (to study the ingredients from black raspberry confection in preventing oral cancer)	Phase I	NCT01961869
Lipids	Methotrexate-loaded, cholesterol-rich lipid nanoparticles	Anti-inflammation efficacy and safety for atherosclerosis and stable coronary artery disease	Phase II, phase III	NCT04616872

Not applicable is used to describe trials without FDA-defined phases. CFU, colony-forming unit. [a]Clinical trial identifiers currently listed on ClinicalTrials.gov.

uptake experiments in Caco-2 cells as well as by in vitro digestion using sequential treatment by porcine pepsin and pancreatin[62].

Plant-derived extracellular vesicles have the advantages of biosafety, easy accessibility and the capability of promoting absorption. Particularly, extracellular vesicles derived from edible or medicinal plants, such as acerola (*Malpighia emarginata* DC), can provide additional medical values[40]. For example, extracellular vesicles from grapes or grapefruit can participate in GI epithelial renewal and stimulate the anti-inflammatory capacity of intestinal macrophages[63].

Microbial sources. Bacterial ghosts, fungal cell walls, microalgae shells, bacterial spores and bacterial OMVs can be obtained from microorganisms and applied as oral delivery devices. Bacterial ghosts are microscale capsules that remain when bacterial cell content is removed through lysis or chemical processing[43]. The hollow bacterial ghost can be loaded with drug formulations through physical or chemical interactions[64]. Bacterial ghosts preserve the surface structure, immunogenicity and adhesiveness of the original bacteria, which enables them to serve as carriers for vaccine delivery[65]. Although their immunogenic property benefits vaccine delivery, it can trigger the expression of pro-inflammatory cytokines and stimulate humoral and cellular immunity. In addition, their heterogeneity and unclear in vivo mechanisms restrict clinical application.

Yeast cell wall particles can be obtained after a sequence of treatments using alkali, acid and organic solvents[37,66]. The resultant yeast capsules can entrap chemicals or nanoparticles and deliver drugs to target sites. In addition, the microalgae *Spirulina platensis* can be loaded with drugs and used for oral delivery[4]. *S. platensis* can protect drugs in the stomach and, owing to its helical structure, can reside and degrade in the intestinal villi, thus contributing to prolonged drug release[18].

Bacterial spores are dormant bacterial cells that can resist adverse external environments, allowing bacteria to survive. Under favourable environmental conditions (for example, adequate temperature and humidity and neutral pH), spores germinate and bacteria restart the vegetative replication mode. Small molecules can be anchored to the surface of spores, triggering the self-assembly of spores into nanoparticles following spore germination[67]. For example, *Bacillus coagulans* spores have been modified with deoxycholic acid and chemotherapeutic drugs (doxorubicin and sorafenib)[19] (Fig. 2c). When reaching the intestine, the spores germinate and autonomously produce nanoparticles by in situ self-assembly of the spore protein coat, drugs and deoxycholic acid, achieving a nanoparticle production efficiency of 86.8% ± 1.8% in vitro and 73.5% ± 1.2% in a rat intestinal perfusion model. The nanoparticles then enter the circulation through transepithelial absorption, with a 61.4% uptake rate by Caco-2 cells in vitro and a 39.8% ± 1.2% absorption rate in a rat intestinal loop model, indicating the responsiveness and targeting capabilities of such oral delivery devices.

Bacteria can secret nanoscale OMVs to intracellularly transfer bioactive molecules. Composed of biocompatible lipid bilayers, OMVs can carry various cargos, including lipophilic and hydrophilic cargos, micromolecules and macromolecules, as well as stable and unstable bioactive compounds[32]. The cargo is protected inside OMVs and can be released within the intestine. OMVs can overcome the intestinal epithelial barrier by transmigrating through epithelial cells using a paracellular pathway[32,68]. Thus, owing to their biocompatibility, versatility, protective effect and intestinal absorption ability, OMVs are being explored for oral drug delivery. For example, 5-fluorouracil-loaded mesoporous silica nanoparticles were camouflaged in *E. coli* OMVs. The drug-loaded OMVs were then orally administered to treat colon cancer in BALB/c nude mice[69]. Similarly, OMVs derived from *L. rhamnosus* GG were shown to modulate gut microbiota and reduce inflammation in a mouse model of colitis[70]. The post-administration fate of *Bacteroides thetaiotaomicron* OMVs was evaluated by fluorescence tracing in C57BL/6 mice. Interestingly, OMVs were shown to mainly concentrate in the GI tract (small intestine > caecum > stomach > colon) and to also accumulate in other systemic organs, with most OMVs accumulating in the liver[68].

Living microorganisms

Probiotics are health-beneficial, active microorganisms colonizing the intestinal tract. Probiotics can also serve as therapeutic agents, regulating the intestinal environment and maintaining homeostasis[71].

Box 2

Translational considerations

To achieve regulatory approval and, thus, clinical translation of bioinspired oral delivery devices, uniform and standardized fabrication and manufacturing steps need to be established. Current laboratory-scale fabrication processes often involve cell and microbe cultivation, which harbour the risk of biological contamination. In addition, oral delivery vehicle production often suffers from batch-to-batch variation. Source acquisition, raw material processing, quality control, product preservation and waste disposal need to be streamlined and adapted to industrial production conditions. The production costs of bioinspired oral delivery devices should also be considered. The processing of biological materials or living organisms usually requires aseptic conditions, and the production of nanoscale and microscale structures requires high-precision microfabrication equipment and multistep processing, which are costly. Simplified, highly integrated or automatic techniques, such as microfluidics, are needed to reduce costs without sacrificing quality. In addition, authoritative evaluation and regulation standards are required for each type of bioinspired oral delivery device. For example, although regulatory requirements are available for genetic engineering tools from the FDA, the International Conference on Harmonization and the National Institutes of Health (NIH guidelines for research involving recombinant or synthetic nucleic acid molecules; Guidance for industry: design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products; Guidance for industry and food and drug administration staff: applying human factors and usability engineering to medical devices; and S6(R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals), specific guidelines for engineered microorganisms for oral delivery have not yet been established, complicating regulatory approval.

Moreover, clinical trials are not keeping up with the development of new bioinspired oral delivery devices. For example, although phase I clinical trials were performed in 2006 to study the oral delivery of probiotics (*Lactobacillus rhamnosus* GG)[207] and genetically engineered bacteria (transgenic *Lactococcus lactis* expressing human IL-10)[208], only a few clinical trials (for example, NCT01680510 and NCT01628081) have been conducted on new bionic devices, for example, animal cell-derived exosomes, algae and editable injection capsules (Table 1). Importantly, the preclinical performance of newly developed devices should be compared to similar, clinically available products. For example, the advantages and limitations of bioinspired oral insulin capsules should be validated against clinically used insulin injection devices in terms of blood glucose control and user compliance to improve the new technology and demonstrate clinical necessity.

Table 2 | Biotic components as naturally derived oral delivery devices

Components	Applied sites	Advantages	Disadvantages	Refs.
Animal sources				
Exosomes	Intestine	Carrying and transporting molecules across plasma membranes; easy acquisition and large-scale production; improving drug bioavailability and biosafety	Heterogeneity and individual variation; require special purification; unclear in vivo mechanisms	29,44–46,48–50
Plant sources				
Pollen grains	Intestine	Tolerance to gastric environments; high mucosal adhesion; easy integration with other materials; potential as oral vaccine carriers; easy extraction	Heterogeneity; require additional physical and/or chemical treatments to remove inner substances; require further modification to avoid leakage of loaded drugs	30,52,53,56,57
Spores	Intestine; stomach	Biocompatibility; protective ability; able to carry drugs; easy extraction	Heterogeneity; require additional physical and/or chemical treatments	41,58
Leaf materials	Intestine	Versatility; large-scale production; easy extraction	Safety issues concerning genetically modified drugs	42
Extracellular vesicles	Intestine	Biosafety; promote drug absorption; easy extraction	Heterogeneity; require special purification; unclear in vivo mechanisms	40
Microbial sources				
Bacterial ghosts	Intestine	Drug-loading ability; high drug bioavailability; potential as oral vaccine carriers; easy extraction	Heterogeneity; immunogenicity; unclear in vivo mechanisms; varying stability	43,64,65
Yeast cell wall particles	Intestine	Protective ability; drug-loading ability; high drug bioavailability; easy extraction	Unclear in vivo mechanisms; require additional physical and/or chemical treatments	37,66
Microalgae	Intestine	Protective ability; biodegradability; drug-loading ability; intestinal aggregation ability; long retention time; easy extraction	Unclear in vivo mechanisms; remain inadequately investigated	4,18
Bacterial spores	Intestine	Protective ability; responsiveness to environments; easy integration with other materials; easy extraction	Unclear in vivo mechanisms; possible toxicity	19,67
Bacterial outer membrane vesicles	Intestine	Biocompatibility; versatility; drug-loading ability; protective ability; promoting drug absorption; easy extraction	Heterogeneity; require special purification; complex composition and possible biotoxicity; unclear in vivo mechanisms	32,68,70

They can be genetically modified to express therapeutic and functional molecules, allowing in situ drug production and targeted drug delivery[72]. To design living microorganism-based oral drug delivery vehicles, various technologies have been developed, including microbial and cell cultivation[28,73], biological surface modification[74], gene editing[75] and microencapsulation[76]. The post-administration fate of living microorganisms differs between strains and doses[77], and bioluminescence imaging can be applied to study the dynamic changes of microorganism distribution in vivo. For example, engineered *E. coli* accumulates in the mouse caecum 2 h after administration and moves to the colon 12 h after administration[78].

Surface modification and coating. Living microorganisms can be coated with protective and nutrient substances to support their survival and improve their functions[79,80] (Fig. 3a). For example, bacterial spore coats with high resistance against acidic and enzyme-rich conditions can be anchored on probiotics[81] to allow them to pass through the harsh environment in the stomach and to supply nutrients for their growth and colonization in the intestine. Some gut probiotics require specific living conditions such as a strict anaerobic environment. In this case, surface modification is a protective strategy against oxygen toxicity. For example, metal–phenolic networks have been non-covalently attached to prokaryotes, such as *Bacteroides thetaiotaomicron*, to protect them from oxygen exposure and other manufacturing conditions, paving the way for the application of anaerobic probiotics in oral delivery[74].

Functional materials can also be attached to the surface of living microorganisms to impart specific properties such as responsiveness, adhesiveness and antioxidant activity. For example, pH-responsive Eudragit L100 and muco-adhesive tannic acid have been applied to *E. coli*[82]. The Eudragit L100 layer stays intact at pH 2–5, shielding *E. coli* from acidic conditions in the stomach of mice. The layer dissociates at pH > 6 in the intestine, exposing the tannic acid-coated bacteria to the intestinal mucosal epithelial layer and allowing bacterial adherence. Similarly, *Lactobacillus* species can be coated with phenolic compounds to provide resistance against acidic conditions, tissue adhesion and oxidation inhibition[83]. The gastric tolerance of these coated probiotics and their adhesion to Caco-2 cells, serving as an in vitro intestinal epithelial model, have been determined to be approximately 1.4 and 0.6 times higher than those of bare probiotics, respectively. Moreover, modifying living organisms with functional molecules can add therapeutic functions and improve treatment efficiency. For example, *Saccharomyces cerevisiae* modified with alcohol dehydrogenase-encapsulating metal–organic framework nanoparticles have been applied for the treatment of colorectal cancer[84]. After oral administration in mice, the modified *S. cerevisiae* targets tumour-associated macrophages and accumulates in hypoxic tumour sites, where *S. cerevisiae* produces ethanol, which is subsequently converted to

acetaldehyde by dehydrogenase, inducing tumour cell apoptosis and macrophage polarization to an anti-tumour phenotype, eventually resulting in tumour inhibition.

Microencapsulation. Microspheres or microcapsules containing microorganisms of the same or different species can be fabricated for oral delivery. These biohybrid microparticles can regulate the GI microenvironment, improve GI functions and treat disease[85,86]. Biohybrid microparticles that contain cells or living microorganisms can be fabricated by microfluidics. For example, a multi-strain cocktail therapy has been developed by encapsulating three faecal bacteria strains (*Escherichia*, *Bacillus* and *Enterobacter*) into polydopamine (PDA)–alginate microspheres to form a micro-ecosystem[76] (Fig. 3b). The *Escherichia* strain converts urea to ammonia, the *Bacillus* strain converts creatinine to ammonia, and the *Enterobacter* strain converts ammonia to amino acids. Therefore, such a micro-ecosystem can eliminate nitrogenous waste products and aid kidney functions[76]. Oral administration of this micro-ecosystem showed satisfactory outcomes in maintaining blood creatinine and urea levels in a pig kidney failure model, indicating potential clinical value.

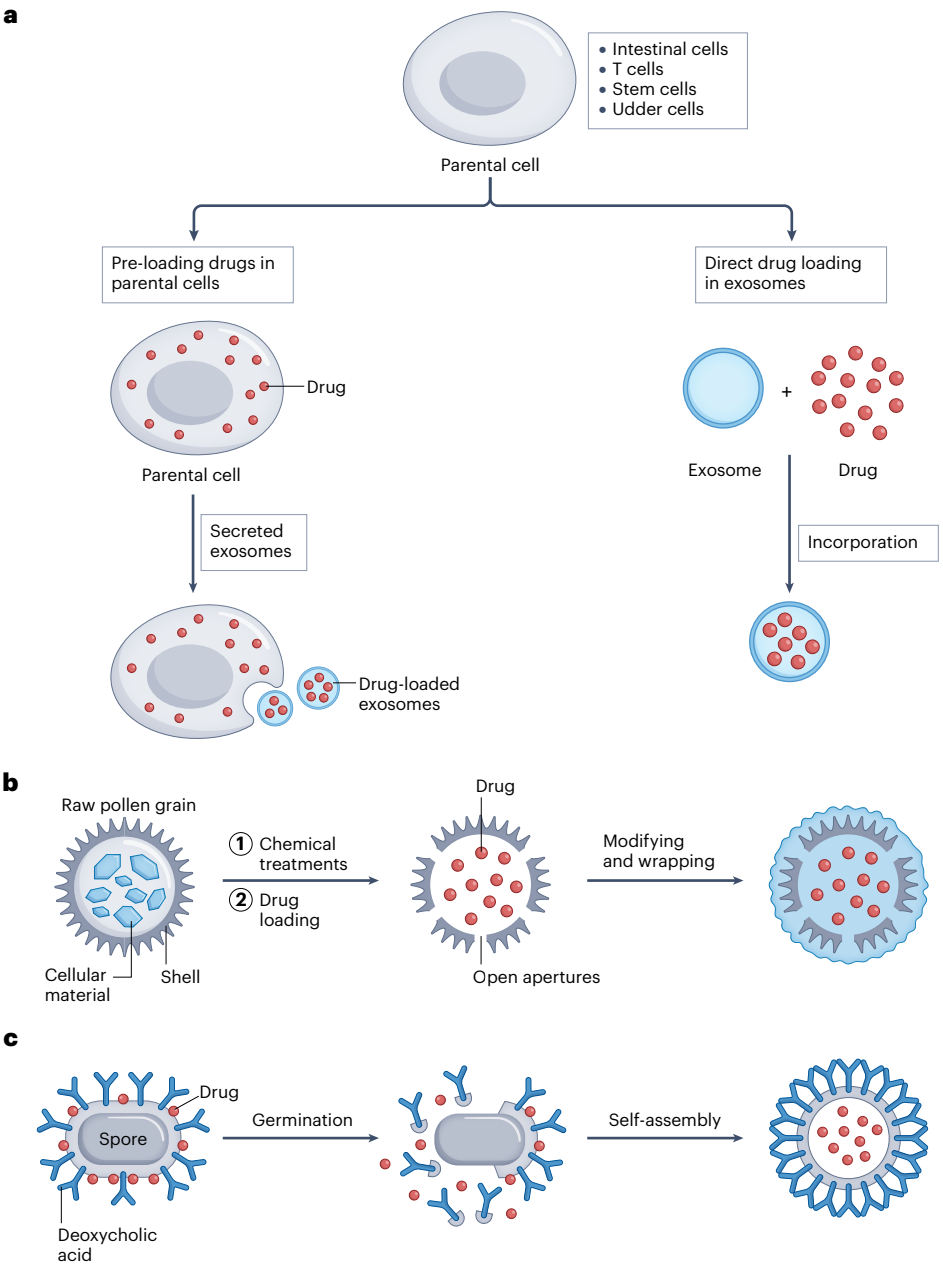

Fig. 2 | Biotic components for oral delivery. a, Exosomes can be derived from intestinal cells, T cells, stem cells and udder cells. Drugs can be pre-loaded in parental cells or incorporated into purified exosomes. **b**, To use pollen grains as oral delivery devices, they need to undergo chemical treatments to remove cellular material, followed by drug loading and, possibly, secondary modification or wrapping. **c**, By attaching small-molecule drugs and deoxycholic acid to bacterial spores, they can self-assemble into nanoparticles after spore germination, enabling oral delivery.

Genetic engineering. Genetic engineering can improve the safety of microorganisms and provide additional functions such as regulation of the GI microbiota[31,72]. Genetically engineered microorganisms can be programmed to colonize, proliferate and release therapeutic products in specific target environments, thus improving drug efficacy and reducing side effects[28]. Owing to their capacity to self-replicate and constantly express bioactive substances, sustained drug release can be achieved with small doses[87]. Thus, transfecting microorganisms with functional genes can allow the development of platforms for controlled and responsive delivery[88].

Genetically engineered microorganisms can act as live factories to produce therapeutic bioactive molecules[33,89] (Fig. 3c). Various tools and approaches have been explored for genome editing[75], including for microorganisms intended for oral delivery devices. For example, lactic acid bacteria, including *Lactobacillus* species and *Lactococcus* species, are part of the gut microbiota and, owing to their beneficial effects on health, are often used in health-care and food products. These bacteria can be genetically engineered as oral delivery devices; for example, *Lactobacillus paracasei* has been engineered to express angiotensin (a peptide hormone) to treat diabetic retinopathy in mouse models[87], and *Lactococcus lactis* has been designed to produce the neurotransmitter γ-aminobutyric acid to treat Parkinson disease in mice[33]. Engineered *E. coli* has been used to produce tumour necrosis factor to treat 4T1 breast tumour-bearing mice[88]. Gene editing methods have also been applied to FDA-approved edible spirulina to encode protein biopharmaceuticals with high precision. Spirulina was engineered to produce different types of therapeutic proteins, such as antibody fragments, hormones and cytokines, and an antibody as a therapeutic agent, the safety and pharmacokinetics of which were tested in a phase I clinical trial (NCT04098263)[72].

In addition to in situ fabrication of therapeutic molecules, genetically engineered microorganisms can achieve precise control of drug delivery. Synthetic biology tools can be applied to incorporate stimulus-sensitive promoters and genes of interest to create genetic circuits[33,88]. Proteins of interest are thus expressed and exert functions only when the specific stimulus is applied. For example, a timing circuit can be introduced into the microbial genome[90] (Fig. 3d), causing the bacteria to lyse and simultaneously release bioactive molecules once their density reaches a specific threshold. Following lysis of the population, a small amount of bacteria survives to rebuild the group, reproduce and prepare for the next cycle of lysis, contributing to the periodic release of molecules.

Living microorganisms could also play an important role in disease diagnosis and treatment by harnessing their inherent biological functions and enhancing them with genetic engineering. For example, the principle of colony competition has been employed to resist bacterial pathogens. *Lactobacillus* probiotics can be engineered to excrete *Listeria* adhesion protein (LAP) on their cell surface. Such modified probiotics can be applied to treat pathogenic *Listeria* by competitively occupying LAP receptors[91] (Fig. 3e). This process can repair intestinal barrier function, restore intestinal immune homeostasis and prevent *Listeria* infection in infected mouse models[91]. Additionally, bacteria can be genetically transformed to express enzymatic reporters as signalling molecules[92]. Such orally administered bacteria colonize target site environments and produce enzymatic reporters. These enzymes then catalyze substrates to produce colourimetric, fluorescent or luminescent signals as readouts in faeces or urine specimens. Based on this strategy, integrated therapeutic and diagnostic systems could be established[93].

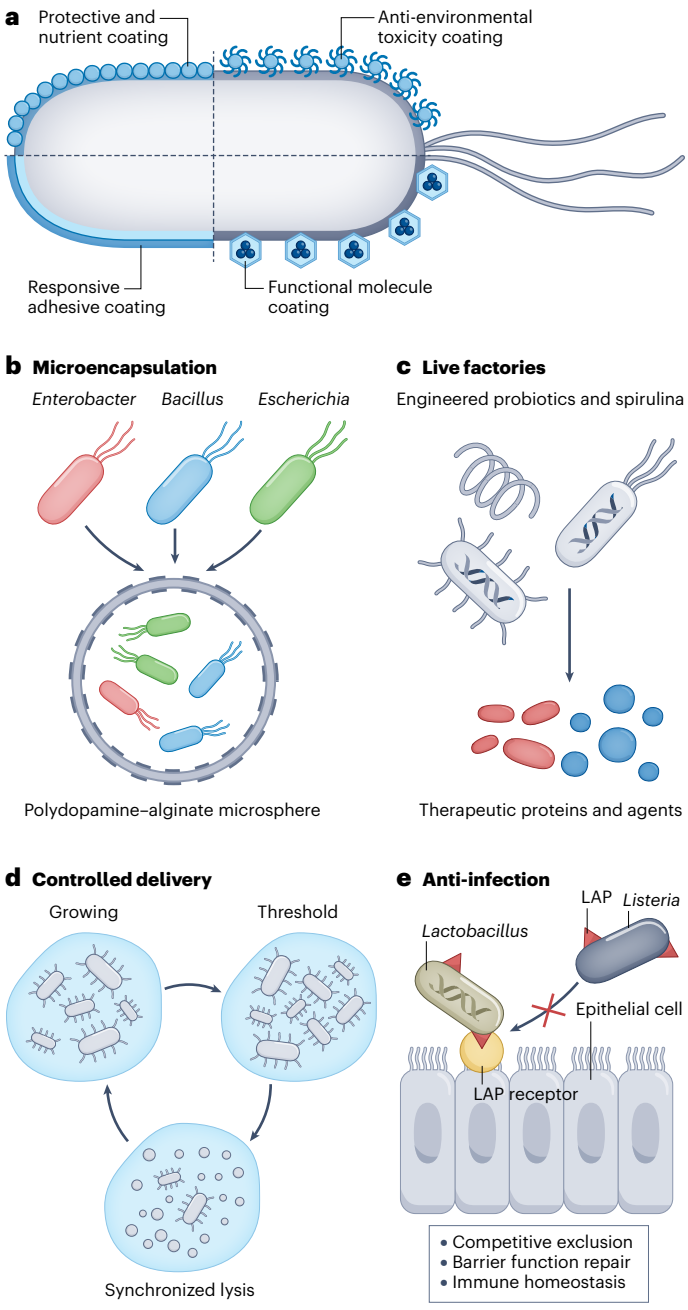

Fig. 3 | Living organisms for oral delivery. a, The surface of living organisms, such as bacteria, can be modified and coated to protect them from the environment in the digestive system, to allow nutrient supply, to add responsive or adhesive abilities, or to include functional molecules. **b**, *Escherichia*, *Bacillus* and *Enterobacter* can be encapsulated in polydopamine–alginate microspheres to engineer a micro-ecosystem. **c**, Engineered microorganisms, such as probiotics and spirulina, can serve as live factories to produce therapeutic proteins and agents. **d**, Controlled drug delivery can be achieved by introducing a timing circuit to engineered bacteria. Once the bacteria population grows to a threshold, synchronized lysis is initiated and simultaneous release of the inner bioactive molecules begins. **e**, Engineered *Lactobacillus* probiotics express *Listeria* adhesion protein (LAP) to competitively occupy LAP receptors, mitigate *Listeria* infection, repair intestinal barrier function and restore immune homeostasis.

Bioinspired oral delivery

Biological materials, including polysaccharides[94], peptides[95], lipids[96] and nucleic acids[34], can be used to fabricate oral delivery devices and to improve their biocompatibility and drug delivery efficiency. Alternatively, synthetic oral delivery devices can be designed with bioinspired architectures, such as hooks[24] and suction cups[97], or modified with functional molecules or chemical moieties such as catechol groups[98] and cell-penetrating peptides[10]. However, such bioinspired oral delivery devices have mainly been tested in preclinical experiments thus far.

Biological materials

Biological materials intended for oral drug delivery have to meet several demands because of their direct contact with the complex microenvironment of the digestive tract[8,99–102]. They should be stable to tolerate physical and chemical obstacles and shield vulnerable drugs from inactivation or degradation before reaching target sites. Importantly, biocompatibility and biosafety should be guaranteed by following ISO standards, for example, ISO23419, ISO19617 and ISO19609. Long-term in vivo effects, including degradation, should also be carefully assessed. In addition, the extraction and processing of materials and fabrication procedures of formulations need to be simplified and unified to reduce fabrication costs and batch variability. Drugs can be loaded into oral delivery devices through physical or chemical processes. Physical loading can be achieved by absorption, coating or encapsulation, which requires the biological materials and drugs to either have similar properties (for example, hydrophilicity)[103] or undergo electrostatic interactions or hydrogen bonding[104]. Chemical loading typically requires the formation of covalent bonds between the drugs and the carrier[96]. Moreover, the drug release profile needs to be regulated, including timing, speed and type of release. Various materials can be used to improve drug bioavailability by assisting in permeation through physiological barriers, reducing mucus viscosity, forming chemical or physical linkages to mucus components, or even modulating paracellular or transcellular transport processes. Based on these material considerations, natural polysaccharides, proteins, peptides, lipids and nucleic acids are candidates for oral delivery devices (Supplementary Table 1).

Polysaccharides. Polysaccharides participate in many biological activities, such as cytoskeleton formation, energy metabolism, blood glucose regulation and immunity modulation, are biocompatible and biodegradable, and can be easily extracted, processed and modified. Polysaccharides extracted from plants (for example, alginate[105,106], cellulose[107], starch[108], carrageenan[109], pectin[110], guar gum[109], mannan[111], glucomannan[112] and inulin[113]), animals (for example, chitosan[101,114], hyaluronate[5] and chondroitin sulfate[115]) and microbes (for example, pullulan[116] and β-glucan[117]) are being explored for oral drug delivery. Polysaccharide nanoparticle formulations can orally deliver small molecules, oligonucleotides, peptides and proteins[94]. In addition, polysaccharide microparticles can be fabricated through physically or chemically induced gelation[118]. For example, alginate hydrogel microspheres can be generated through ionic crosslinking of alginate with Ca^{2+} ions using extrusion or emulsion techniques such as microfluidics; therapeutic agents can then be encapsulated during microparticle fabrication[106]. Alginate microspheres can provide resistance to acids and degradation at pH > 7, and thus protect drugs in the stomach and achieve targeted delivery; for example, silver-crosslinked, thiolated hyaluronan[5] or indole-3-propionic acid[106] have been orally delivered to the intestinal tract in a mouse model of colitis.

Proteins and peptides. Proteins, such as gelatin[119], collagen[120] and silk protein[121], as well as protein derivatives[122] can be used for the design of protein-based drug vehicles that can interact with GI membranes; for example, gliadin nanoparticles can provide mucoadhesion[95]. Bacteria-produced peptides, such as enterotoxin peptides and their derivatives, can be incorporated into oral delivery devices to facilitate intestinal permeation[8]. Furthermore, proteins and peptides can form complexes or composites with other materials, such as metals and metal oxides[122], polysaccharides[123], and synthetic polymers[124], through chemical reactions or gelation induced by changes in temperature, pH, or salt concentrations. Moreover, proteins and peptides can be modified to form or functionalize microparticles and nanoparticles; for example, methacrylated gelatin was polymerized by photocrosslinking to fabricate oral delivery particles[112]. Genetically engineered silk sericin nanospheres, which remained negatively charged in the intestine, were used for targeted delivery to positively charged proteins at inflammatory sites of the colon in a mouse model of ulcerative colitis[121].

Lipids. Lipids play an important role in metabolism regulation, energy storage and as part of membrane structures. Lipids are biocompatible, can be easily modified and promote drug absorption[96,103]. Lipid nanoparticles are excellent carriers for poorly water-soluble pharmaceuticals[125]. Lipid–polymer hybrid systems can further provide synergistic effects; for example, lipid nanoparticles can be entrapped in hydrogels for oral administration[126] to improve drug availability and to allow controlled release. Liposomes, which are versatile drug delivery vehicles, can be positively or negatively charged, consist of one or multiple lipid layers, and encapsulate both hydrophilic (inside the aqueous core) and lipophilic (within the lipid layers) drugs[104]. Liposomes can also be applied for oral protein delivery. For example, insulin was loaded in the layer-by-layer coating of anionic liposomes with the aid of cationic chitosan. These coated liposomes had a high insulin-loading capacity and showed rapid intestinal absorption, increasing the plasma insulin levels of rats 30 min after oral administration[104].

Nucleic acids. Nucleic acids are carriers and transmitters of genetic information; they can also serve as building blocks for constructing 3D networks and complex architectures such as DNA and RNA cages, DNA origami and DNA hydrogels[127]. DNA hydrogels, consisting solely of DNA or in combination with other polymers, can be fabricated by chemical or physical reactions such as enzyme catalysis, covalent bonding, chain entanglement and electrostatic interactions[128]. DNA hydrogels are biocompatible and biodegradable, and their porosity and structural and mechanical properties can be easily tuned. In addition, stimuli-responsiveness features can be implemented in DNA hydrogels, making them interesting candidates for applications in wound repair[129], tissue engineering[130], gene editing[128] and drug delivery[131]. DNA hydrogels have mainly been tested in rodent models thus far, and few large animal experiments and clinical trials have been conducted. To apply DNA hydrogels in oral drug delivery, the oligonucleotide sequences need to be tailored[34] or the hydrogel needs to be modified with biomaterials[131] to improve their stability in the GI environment. For example, an acid-resistant and pH-sensitive DNA hydrogel consisting of adenine (A)-rich and cytosine (C)-rich oligonucleotides has been copolymerized with acrylamide monomers[34]. In the acidic environment of the stomach (pH ~1.2) and duodenum (pH ~5.0), the A-rich strands and C-rich strands form parallel A-motifs and quadruplex i-motifs to maintain the stability of the DNA hydrogel. At pH 1.2–3, the protonated A-rich strands are crosslinked into a parallel A-motif configuration through reverse

Hoogsteen interactions and electrostatic attraction; at pH 4–6, the hemi-protonated C-rich strands assemble into a quadruplex i-motif configuration through Hoogsteen interactions. In the small intestine, where the pH is higher than 6, both the A-motif and i-motif separate, leading to hydrogel dissociation and drug release[34].

Bioinspired structures

Bioinspired adhesion. Owing to the continuous movement of the digestive tract, orally delivered devices are typically rapidly cleared. To avoid clearance, the devices need to adhere to the GI tract[26,98], in particular through wet adhesion because the digestive tract is rich in mucus and digestive fluid. Microscale and nanoscale structures can be applied[132,133] or, alternatively, adhesive chemical components[134] can be added to the delivery device to enhance wet adhesion by generating mechanical interlocking, negative pressure and topological adhesion. For example, spike-like structures can be implemented to prolong retention time, inspired by the structures of parasitic worms that can live in the GI tract for years. A microdevice with sharp, hook-shaped microtips, imitating the teeth of *Ancylostoma duodenale*[132], can be inserted into rat colons through the transrectal route and retain in the colon for over 24 h. Oral administration of this device may be achieved by adjusting its size and by loading it into capsules to reduce discomfort during administration. Similarly, an oral microneedle device can mimic the attachment and penetration abilities of thorny-headed worms. The microneedle device swells after tissue penetration and anchors to the mucosa, achieving a stronger adhesive force to swine stomach tissue (0.25 N) compared to commercial Carbopol 971P NF polymer (0.18 N)[24] (Fig. 4a). Some aquatic animals, such as octopi, evolved suction cups or other wet-adhesive microarchitectures that have inspired the design of oral delivery devices. For example, orally delivered microspheres can be designed into suction cup-like asymmetrically cupped structures[97]. The adhesive capacity of wall-climbing plants and pollens of entomophilous plants has also served as a blueprint for the design of oral delivery devices. For example, microdevices with an ivy-mimetic concave structure[26] (Fig. 4b) or a pollen-like wrinkled surface have been fabricated by microfluidics[135]. More than 60% of these devices can adhere to the rat intestinal tissue after administration, compared with devices with a spherical[26] or smooth surface[135].

In addition to physical structures, many organisms rely on chemical components to achieve adhesion; for example, mussels produce substances that contain catechol groups[136,137]. Mussel adhesive protein derivatives have been used to modify the surface of doxorubicin-loaded microspheres[2] (Fig. 4c), enabling them to stably adhere to tissue in vitro in flow conditions (7.57 cm/s, simulation of the velocity of bolus in oesophagus) and to deliver drugs to the oropharyngeal conduits of BALB/c nude mice[2]. Similarly, PDA can provide firm adhesion owing to its catechol groups. For example, an oral solution of dopamine supplemented with hydrogen peroxide led to the formation of a PDA layer on the porcine small intestine through catalase-catalyzed reactions[138]. Catalase exists more abundantly in the small intestine than in other parts of the digestive tract, thus allowing this formulation to achieve targeted drug delivery. The PDA layer remained stable after food intake, showing a distinct signal in the pig small intestine 2 h after administration, which decreased by 28% 6 h after administration[138].

However, challenges remain for the clinical translation of bioinspired adhesive oral delivery devices. For example, the size, surface morphology and mechanical strength of microscale and nanoscale structures need to be optimized. In particular, surface topography impacts adhesion strength; here, a smooth surface decreases adhesion strength, and rough or rigid surfaces may cause tissue damage. Thus, both adhesion and safety should be considered in the design of surface topographies. In addition, devices need to be removed after drug release, which may be addressed by using fully degradable materials. Moreover, the adhesion ability of oral delivery devices with adhesive chemical components might be affected by environmental changes such as drinking or eating. The combination of physical and chemical adhesion designs may address some of these challenges.

Bioinspired permeation. Oral drug delivery systems face three physiological barriers, that is, biochemical, mucous and cellular barriers[8] (Fig. 1c). Numerous digestive enzymes and varying pH constitute the major biochemical barrier, which can be overcome by selecting appropriate material constituents such as alginate and cellulose[5,106]. The mucous barrier, which consists of viscoelastic mucus that coats the digestive tract, not only restricts drug diffusion but can also trap or deactivate drug molecules. The epithelial cell barrier is located under the mucous barrier and reduces drug absorption from the gut lumen into the bloodstream through the paracellular or transcellular route. To overcome these barriers, the permeation of oral delivery devices needs to be improved, which can be achieved by learning from the mechanisms that bacteria and viruses apply to invade their host[139–142].

For example, bacteria can inject virulence factors into host cells using arginine–glycine–aspartic acid (RGD) peptides located on their type IV secretion pili. By modifying drug-loaded nanoscale systems with RGD peptides, oral delivery devices can be designed with high affinity to microfold (M) cells. M cells, which are located in the small intestine and GI tract, enable the transport of microbes and particles across the epithelial cell layer from the gut lumen to the lamina propria. Therefore, targeting M cells through RGD peptides allows the transcellular transport of drugs[143] (Fig. 4d). Such devices have shown high permeability coefficients in vitro, indicating passage through M cells.

Viruses can also infect mucosal tissues, overcoming the mucous and cellular barriers, owing to their muco-inert, neutral surface (with densely packed opposite charges). In addition, viruses have specific surface proteins that enable membrane fusion or membrane perforation to facilitate entry into host cells. Virus-mimetic oral delivery devices can be designed by decorating devices with inert material shields (for example, polyethylene glycol)[141,144] and cell-penetrating peptides (for example, cationic octa-arginine peptides (R8), polyarginines)[27,145]. Such devices can be further modified with functional molecules to enable intracellular trafficking; for example, nanoparticles modified with R8 and L-cysteine (a Golgi position-related amino acid) showed a 4.75-fold increase in cellular internalization in Caco-2 cells compared with unmodified nanoparticles. Furthermore, the R8 peptide and L-cysteine promoted nanoparticle exocytosis and drug absorption in BALB/c mice and diabetic Sprague–Dawley rats[10] (Fig. 4e). However, long-term membrane interference, membrane damage and latent antigenicity of bacterial and viral components remain concerns.

Bioinspired adaptation. Bionic oral delivery devices can be equipped with auxiliary functions to adapt to the various environments of the digestive tract. For example, a microneedle device with self-orienting capability is designed by constructing a leopard tortoise-inspired structure with a changing centre of mass, high-curvature upper shell and low-curvature bottom shell[3] (Fig. 4f). This device maintains an upright position and steadily attaches to the stomach of pigs[3]. As gastric fluids gradually flow inside the device, a concealed drug-carrying microneedle is released to penetrate the mucosal layer and deliver

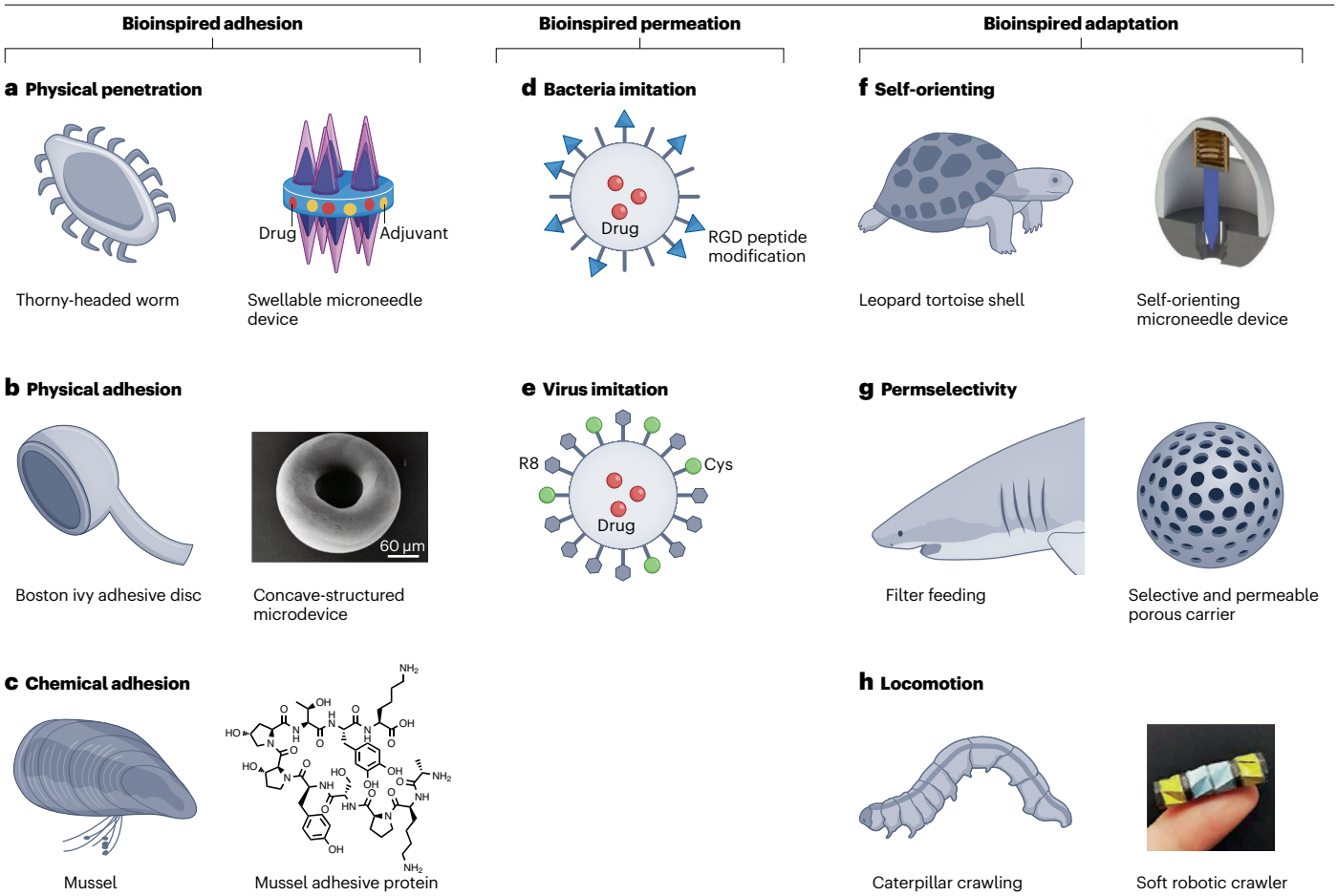

Fig. 4 | Bioinspired structures. a, Oral microneedle devices can be inspired by the physical penetration and self-expansion abilities of thorny-headed worms. These devices can adhere to the stomach. **b**, Ivy-inspired microdevices can be designed by mimicking the concave structure of the ivy, enabling physical adhesion to the intestine. **c**, Mussel adhesive proteins can be used to decorate oral delivery devices to improve adhesion. **d**, Bacteria-inspired, nanoscale vehicles can be engineered through modification with arginine–glycine–aspartic acid (RGD) peptides. These bioinspired vehicles improve the permeation and transcellular transport of drugs. **e**, Virus-inspired oral delivery nanoparticles can be engineered by modifying nanoparticles with the cell-penetrating peptide octa-arginine (R8) and Golgi position-related amino acid L-cysteine (Cys). These bioinspired nanoparticles promote drug permeation and absorption. **f**, Oral microneedle devices can be inspired by the leopard tortoise. With a changing centre of gravity, a high-curvature upper shell and a low-curvature bottom shell, this device can keep upright, enabling self-orientation and self-stabilization for gastric drug delivery. **g**, Bioinspired porous drug carriers allow the selective passage of molecules based on their molecular weight. **h**, A worm locomotion-inspired soft robotic crawler can move in a confined space and may carry drugs. Part **a** is adapted from ref.[24], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **b** is reprinted from ref.[26], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **f** is reprinted with permission from ref.[3], American Association for the Advancement of Science. Part **h** is reprinted with permission from ref.[147], American Association for the Advancement of Science.

macromolecules such as insulin[3]. The device (about 7.5 mm × 9 mm in size) could be further improved by reducing its size to address swallowing discomfort and the risk of blockage in the digestive tract. Inspired by intestinal scavengers, a selectively permeable porous drug carrier is developed to prevent digestive enzymes from entering the carrier to protect protein drugs from degradation[146] (Fig. 4g) and to allow entry of small molecules, for example, to remove intestinal lipopolysaccharides and treat metabolic syndrome in mice[146]. Mimicking the locomotion of worms, a controllable soft robotic crawler can carry drugs, move in confined spaces and release drugs on demand, as shown in a simulation[147] (Fig. 4h); whether the robot can perform in the complex environment of the GI tract remains to be shown.

Formulations

Bioinspired oral delivery devices can be fabricated into various types of formulations and dosage forms, including capsules[148], tablets[149], nanoparticles[145], microspheres[5], bubbles[133], films[1], coatings[138] and sprays[39], depending on their composition, structure and application. Tablets are typically formed by compressing or moulding[8,149], and capsules are prepared by filling drug substances into a hard gelatin shell followed by sealing and polishing[8,149] (Box 1). Tablets and capsules are easy to manufacture on a large scale. Their size should be less than 8 mm in diameter to minimize swallowing difficulties (Guidance for industry: size, shape, and other physical attributes of generic tablets and capsules). The size restriction limits drug-loading capacity, in particular,

for hygroscopic drugs and drugs in aqueous solution or emulsion. Nanoparticles can be fabricated by self-assembly, sol–gel transition and hydrothermal methods, depending on material properties, stabilities, and the desired nanoparticle size and yield[11,96,114,150]. Alternatively, microfluidics can be applied to fabricate nanoparticles, lipid vesicles, microspheres and microbubbles with high uniformity, specific material composition and bioinspired morphological characteristics[35,151]. 3D printing can be used to construct devices that deliver multidrug combinations, for individualized dosing and for bioinspired locomotion; however, such 3D-printed devices have not yet been tested in the clinic[36,73]. Films have been designed as drug-loaded polymer matrices that can either be swallowed to dissolve in the mouth or can adhere to the oral mucosa to release drugs[152]. Such films can also be made with natural polymers and can be formed by casting, extrusion or electrospinning. Coatings and sprays, which are dispersions of functional particles, can be designed to rapidly form gels in the oral cavity[39] or to stick to the GI tract[137]. However, such coatings and sprays need to be optimized to increase adhesion and to allow sustained drug release over hours or even days. Additionally, the size of devices needs to be reduced to improve patient compliance. To enable the clinical translation of these formulations, drug stabilization during administration, patient compliance and large-scale production need to be achieved (Box 2).

Target tissues

Bioinspired oral delivery devices can be designed to deliver therapeutics or bioactive agents to different parts of the digestive tract, including the oral cavity[1], oesophagus[2], stomach[148] and intestine[99] (Fig. 1b).

Buccal delivery

The oral cavity allows local and systemic drug delivery[153]. To achieve systemic delivery, drugs administered to the buccal cavity have to be absorbed and cross the mucus and oral mucosa to enter the bloodstream and vascular networks. Mucus is mainly made of mucins, which are glycoproteins of 0.5–20 MDa molecular weight[154]. At physiological pH, mucins have negative charges, which enable them to attach to oral epithelial cells and form a gelling layer with complex composition through electrostatic interactions, hydrogen bonding and disulfide bonding. Buccal delivery has the advantages of rapid drug absorption, avoidance of drug elimination by the first pass effect, milder physiological environments than in the GI tract, and easy device administration and removal[155,156]. However, the flow of saliva in the oral cavity constantly dilutes drugs and reduces drug retention time. In addition, vocalizing, swallowing and tongue movement impair drug stability, and prolonged application of drug formulations to the oral cavity may cause discomfort. In addition, the presence of enzymes, although at low concentrations, remains a biochemical barrier, which, in addition to the mucous and cellular barriers, limits macromolecular or hydrophilic drug delivery.

Bioinspired devices can address some of the limitations in buccal drug delivery. By adding natural muco-adhesive components, bioinspired buccal delivery devices can adhere to the oral cavity for hours, thus prolonging drug release[157,158]. Lipid, polysaccharide and other bio-derived nanoparticles have been explored as buccal delivery systems. The size and physicochemical properties of these delivery systems can be optimized to improve patient comfort during oral administration[159]. For example, a mussel-inspired film was fabricated using mussel adhesive protein-modified poly(vinyl alcohol) polymers. PDA-modified drug-loaded poly(lactic-co-glycolic acid) nanoparticles were further incorporated into the film. Owing to the presence of adhesive proteins, the film adhered to wet buccal tissues of Sprague–Dawley rats, and the PDA modification of the nanoparticles increased mucus penetration, facilitating cellular uptake. This mussel-inspired buccal delivery film was applied to administer dexamethasone for the treatment of oral mucositis in rats[1].

Oesophageal delivery

The oesophagus is elastic and has a tubular structure composed of four layers: the mucosa, submucosa, muscularis propria and adventitia[160,161]. In addition, mucus covers the oesophageal mucosa as a protective layer[162]. Drugs can be topically delivered through the oesophageal route to treat oesophagus disorders such as oesophagitis, oesophageal ulcers and oesophageal carcinoma[163]. However, the tubular shape, periodic peristalsis and rapid emptying make it difficult for drugs to remain in the oesophagus. Additionally, mucous and cellular barriers exist as obstacles to drug absorption. Bioinspired oesophageal delivery devices can adapt to the architecture of the oesophagus. Bionic adhesive structures and components, such as adhesive proteins, can also be introduced to improve drug retention and accumulation[2]. Bioinspired barbed injection systems allow crossing of the mucous and cellular barriers, and shape-memory reconfigurable oesophageal delivery devices, inspired by a blooming flower[164,165], have been shown to remain folded during oral administration but unfold in the pig oesophagus to enable mucosal penetration and drug delivery[165]. Following drug release, the device refolds and exits the oesophagus upon administration of warm water.

Gastric delivery

Gastric delivery represents a route for systematic and local drug delivery[166]. Drug absorption in the stomach is mediated by either passive diffusion or active transport[167]. Passive diffusion is affected by the concentration, molecular weight, size and solubility of the drug, whereas active transport mainly relies on membrane proteins. For example, gastric pit cells express SID1 transmembrane family member 1 (SIDT1) protein, which is responsible for the active absorption of microRNA[168]. The intragastric environment is harsh, with pH values of around 2 in fasting states, and contains enzymes, such as pepsin and lipase, that can inactivate drugs. To prevent inactivation, drugs can be encapsulated in acid-resisting biomaterials and biological materials such as alginate and chitosan[169]. In addition, the stomach wall is thicker compared to intestinal tissues and the gastric content is a mixture of viscous chyme and gastric juice in a fed state, affecting drug dissolution and permeation. Bioinspired injection and self-orientation devices can address these challenges; for example, a bioinspired gastric delivery device can be designed with a leopard tortoise-mimicking orienting shell with a hidden spring-powered microneedle for gastric injection[3]. This device and several follow-up designs have enabled gastric delivery of small molecules, mRNA, monoclonal antibodies and peptides to pigs[148,170]. Similarly, clarithromycin-loaded nanoparticles can be coated with gastric epithelial cell membranes to provide surface antigens of gastric epithelial cells for the treatment of *Helicobacter pylori* infection in mice[171]. Owing to natural pathogen–host interactions, these nanoparticles target *H. pylori* and preferentially accumulate on the bacterial surface, where they release the antibiotic.

However, gastric delivery is limited by the rapid gastric clearance of administered vehicles. Naturally derived adhesive materials, such as keratin, can be applied[172] to increase gastric retention time. Moreover, gastric delivery devices can be camouflaged with cell membranes and extracellular vesicles to enable passage through barriers generated

by the gastric mucus, mucosa and epithelial cells[171]. Bioinspired drug-loaded micromotors have also been explored for gastric administration[173–175] to achieve high drug loading, tissue penetration, prolonged gastric residence time and high therapeutic efficacy. For example, the movement of *H. pylori* in the stomach is initiated by a local increase in pH owing to a urease-catalyzed reaction. Similarly, bioinspired urease-conjugated micropropellers have been shown to penetrate mucin gel in vitro[173] and the gastric mucus of BALB/c mice[174]. Mg-based, H^+-consuming gastric micromotors have a retention time of over 2 h in the stomach of mice[175], allowing the sustained release of clarithromycin for the treatment of *H. pylori* infection in mice[175].

Intestinal delivery

Monosaccharides, amino acids and other nutrients are absorbed in the intestine through active transport by membrane transporters. Dietary changes can further regulate the peroxisome proliferator-activated receptor-α (PPARα) pathway, responsible for catabolism and fatty acid oxidation, which in turn regulates villi length and function of intestinal surfaces[176]. Intestinal delivery mainly includes the small intestine[99] and the colon route[177], requiring devices to resist acids from the stomach and to overcome enzymatic, mucous and cellular barriers[8,9]. Devices also need to adapt to the peristaltic movement and the curved, tubular structures of the intestine. Biological materials (for example, pH-responsive DNA hydrogels[34], silk sericin[121], alginate[103] and lipids[104]), modification techniques (for example, surface coating[74] and microfluidics-based encapsulation[76]), bioinspired strategies of adhesion (for example, ivy-mimicking shape)[26], penetration (for example, parasite-mimicking structures)[24] and permeation (for example, cell-penetrating peptide modification)[145,178] can be applied to design vehicles for intestinal delivery.

With a high specific surface area and long food clearance time (typically >10 h) compared to the stomach, the small intestine is the major place for digestion, absorption and therapeutics delivery. Drugs absorbed in the small intestine enter the blood or lymphatic circulation and eventually reach their destination[8,150]. There are special considerations for small intestinal delivery owing to the presence of intestinal villi and the digestion and absorption function of the small intestine, especially in the jejunum, which has abundant villi and is the optimal absorption site[179]. Remotely controllable microdevices, for example, magnetically controlled oral delivery devices, show controlled movement in a magnetic field, stability and easy operation as intestinal delivery devices[180]. Needle-shaped, magneto-responsive devices, inspired by magnetotactic bacteria, can also orally deliver drugs to the small intestine[99]. These magneto-responsive devices have been shown to penetrate the intestine and deliver insulin in a pig model of diabetes[99].

The colon is the primary habitat for microorganisms that form the gut microbiota, including bacteria, fungi and viruses[181]. Drugs have to get from the mouth to the small intestine before reaching the colon. Therefore, the design of colon-targeted delivery devices needs to consider the interaction with gut microbiota and has to contain a colon-targeting function. Various bioinspired oral delivery devices have been explored to interact with the intestinal flora and to target the colon[182,183]. For example, colon-targeting nanoparticles loaded with gefitinib and 5-fluorouracil can be sequentially decorated with chitosan and polyacrylic acid[101]. The pH-sensitive polyacrylic acid layer degrades in the colon (pH ~7.4) and the chitosan layer degrades owing to the expression of β-glycosidase by colonic microbiota. This platform has been used to provide dual control of local drug release in mice with orthotopic colon cancer[101].

Outlook

Biotic components, living organisms and biological materials can be applied to reproduce bionic structures and functions for the design of bioinspired oral delivery devices. Compared with purely synthetic delivery systems, oral devices made from biological components, in particular those extracted or synthesized from edible or medicinal organisms, have the advantage of being naturally sourced. Importantly, various bottlenecks in oral delivery could be addressed through bioinspired designs, including the limited number of orally deliverable drugs, overcoming of physiological barriers, increasing drug efficacy and improving control of the drug release profile. In addition, multiple functions can be incorporated in bioinspired designs such as stimuli responsiveness and adaption or regulation of the GI environment and even immunological effects. Ultimately, these efforts aim at improving the therapeutic efficacy of drugs. However, bioinspired designs still face several limitations (Box 2). For example, bioinspired oral delivery devices cannot yet autonomously interact with the GI environment. In addition, proof-of-concept studies have mainly explored a few model drugs, such as insulin and chemotherapeutic drugs, and have not yet addressed a range of therapeutics, for example, nucleic acid-based drugs. Moreover, imperfect fabrication methods, the lack of specific regulation and inadequate clinical trials have restricted the translation of bioinspired oral delivery devices.

Bioinspired oral delivery devices will benefit from the incorporation of biomaterials made of biocompatible and functional peptides, molecules from traditional Chinese medicine and hydrogels[184]. The incorporation of such biomaterials can add more functions to oral delivery devices; for example, antimicrobial peptides isolated from the royal jelly of the honeybee can assemble into hydrogels and act as an anti-infective oral delivery device[184]. Furthermore, synthetic biology tools allow the engineering of microorganisms for oral applications; such microorganisms could produce bioactive molecules, including small molecules and proteins[72]. Designs could also be based on the individual and collective behaviours of living organisms; for example, inspired by the swarm behaviour of animals, microscale or nanoscale devices can be developed with the ability of patterning, stimuli responsiveness and actuation[185,186]; such devices could address the challenge of insufficient drug loading because multiple units, each loaded with a small amount of drug, could act as a swarm for targeted delivery, thereby allowing the delivery of high drug concentrations. Moreover, by simulating cellular communication between bacteria and intestinal cells, smart devices could be engineered that can interact with GI cells[141,142]. For example, inspired by the abilities of *Yersinia pseudotuberculosis* and *Staphylococcus aureus* to adhere to and invade epithelial cells, delivery devices could be decorated with membrane proteins of these bacteria[142]. Bioinspired oral delivery devices could also be designed with self-sensing and self-reporting abilities, allowing theranostic applications. These bioinspired oral delivery devices may carry signalling molecules that can produce colourimetric, fluorescent or luminescent signals in contact with target molecules in the GI tract, which can then be detected in urine or faeces specimens[93].

Bioinspired oral delivery devices could also reduce off-target effects that are caused by drug accumulation in non-target tissues or organs and compromising the safety and therapeutic efficacy of drugs. By anchoring ligand molecules to the devices, their affinity to specific sites can be enhanced, facilitating accumulation at target sites. In addition, the physicochemical properties of oral delivery devices, such as lipophilicity, surface charge and protonation degree, can be modulated to adjust their in vivo distribution and interactions with tissues and

organs to alleviate off-site effects. Programmable delivery systems could allow control over release kinetics and dynamic responsiveness to changing environments[187], which may further reduce off-site risks. Such delivery systems could accommodate more types of drugs and meet their unique delivery demands and thus increase the range of treatable diseases. For example, biomolecular logic gates and Boolean operations can be integrated by gene editing or by constructing and assembling responsive polymer monomers[188–190]. Such programmable delivery devices could interact with the GI tract environment and provide temporal feedback and dynamic responses to body signals to apply the correct drug dose at a given time and location.

To simplify the processing steps and to expand the structural and functional features of bioinspired oral delivery devices, advanced fabrication and characterization techniques could be applied; for example, 4D printing, which refers to the printing of 3D objects that can be transfigured in response to predetermined stimuli[36], could be applied to engineer tailorable, irregular and reconfigurable morphologies of delivery devices. However, optimizing the crosslinking and mechanical strength of bioinks, balancing the printing resolution and bioactivity of living components, and high-throughput printing of multiple biomaterials remain challenging. Alternatively, microfluidics can be applied to manipulate a small volume of fluids and generate uniform microscale and nanoscale objects with various architectures[35], such as core–shell, Janus and eccentric structures, which would allow the design of unusual architectures for oral delivery devices and may increase drug encapsulation concentration and efficiency. 3D cell culture techniques could further enable the thorough characterization of oral delivery devices; for example, intestinal organoids with physiologically relevant shapes, sizes and functions[191] could be used to study the interactions and distribution of oral delivery vehicles in the intestine. Similarly, gut-on-chips[192] could be used to evaluate drug efficacy in specific disease models. Furthermore, vascular flow-linked multi-organ chips[193] could allow the investigation of systematic effects of drugs and delivery devices. We envision that bioinspired oral delivery devices with their inherent biocompatibility and multiple functions could transform oral drug delivery and open oral delivery routes to a variety of drugs currently not susceptible to oral delivery.

Citation diversity statement

We acknowledge that papers authored by scholars from historically excluded groups are systematically under-cited. Here, we have made every attempt to reference relevant papers in a manner that is equitable in terms of racial, ethnic, gender and geographical representation.

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Author contributions
X.Z. gathered information, wrote the manuscript, and prepared the figures and tables. G.C. discussed the manuscript and drafted the figures. H.Z. edited the manuscript. L.S. discussed and edited the manuscript. Y.Z. conceived the concept and reviewed the outline.

Competing interests
The authors declare no competing interests.

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