Journal of Controlled Release 366 (2024) 221–230

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Recent advances in oral insulin delivery technologies

Ershuai Zhang, Hui Zhu, Boyi Song, Yuanjie Shi, Zhiqiang Cao *

Department of Chemical Engineering and Materials Science, Wayne State University, Detroit, MI, USA

ARTICLE INFO

Keywords:
Oral delivery
Insulin
Diabetes
Bioavailability
Barriers

ABSTRACT

With the rise in diabetes mellitus cases worldwide, oral delivery of insulin is preferred over subcutaneous insulin administration due to its good patient compliance and non-invasiveness, simplicity, and versatility. However, oral insulin delivery is hampered by various gastrointestinal barriers that result in low drug bioavailability and insufficient therapeutic efficiency. Numerous strategies have been developed to overcome these barriers and increase the bioavailability of oral insulin. Yet, no commercial oral insulin product is available to address all clinical hurdles because of various substantial obstacles related to the structural organization and physiological function of the gastrointestinal tract. Herein, we discussed the significant physiological barriers (including chemical, enzymatic, and physical barriers) that hinder the transportation and absorption of orally delivered insulin. Then, we showcased recent significant and innovative advances in oral insulin delivery technologies. Finally, we concluded the review with remarks on future perspectives on oral insulin delivery technologies and potential challenges for forthcoming clinical translation of oral insulin delivery technologies.

1. Introduction

Diabetes is one of the most prevalent chronic metabolic diseases that occurs either when the pancreas does not produce enough insulin (a hormone regulating blood glucose) or when the body cannot effectively use its insulin [1–3]. Since insulin was discovered almost a century ago [4], insulin replacement therapy has proven to be a lifesaver for people with type 1 diabetes mellitus and an essential treatment for many patients with type 2 diabetes mellitus [5,6]. To date, subcutaneous insulin administration (needle-based injections or pump-based infusion) is still the primary clinical treatment for millions of people with diabetes in the world, while extensive efforts have explored the feasibility of alternative insulin delivery strategies (such as oral, transdermal, inhalation, and mucosal delivery) [7–9]. However, the painful and repetitive needle-based injections can cause trauma and side effects to people with diabetics such as weight gain [10], hypoglycemia [11], and lipoatrophy [12,13] since subcutaneous insulin does not precisely mimic the action of physiological insulin secretion [14–16]. Currently, the insulin infusion pump with improved compliance and glycemic control has been developed as a convenient route for subcutaneous insulin delivery [17,18], but subcutaneously inserted catheter and subsequent infused insulin also induce subcutaneous tissue response and skin-related complications at the infusion site [19,20]. Specifically, our group currently developed a zwitterionic cream gel that can resolve early skin irritations, drastically extend the longevity of the subcutaneous insulin infusion catheter, and enable faster pharmaceutical absorption as well [21].

Compared with subcutaneous administration, oral delivery of peptide/protein drugs shows the advantage of good patient compliance and ease of administration [22,23]. More importantly, oral insulin administration closely mimics the physiological path of endogenous insulin secretion because the delivered insulin is directly absorbed to the liver via the portal vein, and the first pass effect leads to greater insulinization of the liver and reduced peripheral hyperinsulinemia, thereby avoiding adverse effects of weight gain and hypoglycemia [24,25]. Therefore, oral insulin is recognized as a life-changing solution for diabetes patients who routinely receive insulin by the subcutaneous route [26]. Unfortunately, despite researchers aspiring to develop oral insulin for several decades, commercial oral insulin product is yet to be available since no formulation can successfully overcome the various gastrointestinal (GI) barriers and properly clear all clinical hurdles [27–29].

There were intense research activities in search of efficient oral insulin technologies, and numerous articles have been published on developments of oral insulin with the potential to improve the bioavailability in different animal models [30–34]. However, the oral delivery technologies for which success has been reported in preclinical studies have often failed to achieve sufficient safety and efficacy in clinical trials, indicating that the transition from animal studies to clinical application remains a major scientific challenge [35–37]. This

* Corresponding author.
E-mail address: zcao@wayne.edu (Z. Cao).

https://doi.org/10.1016/j.jconrel.2023.12.045
Received 1 September 2023; Received in revised form 23 December 2023; Accepted 26 December 2023
Available online 4 January 2024
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review introduces the gastrointestinal tract barriers that must be tackled to achieve efficient oral insulin delivery. Then it summarizes current significant and innovative advances in oral insulin delivery technologies. Lastly, we present future perspectives on oral insulin delivery technologies and potential challenges for future clinical translation.

2. Barriers to oral insulin delivery

For an orally administered protein and peptide drug to work, it must transit along the GI tract, adhere and infiltrate through the mucus layer, traverse the intestinal epithelium, enter the portal vein, and finally reach the peripheral circulation [38]. Nevertheless, as the first line of defense against exogenous toxins and pathogens, the GI tract poses several physiological barriers to orally administered insulin, which can be classified as chemical, enzymatic and physical barriers [39–41]. The chemical (ultra-acidic pH in the stomach) and enzymatic (proteolytic enzymes in the GI tract) barriers can destabilize the formulation and denature or degrade the insulin [42,43]. Moreover, the physical barriers, including the mucus layers and intestinal epithelium, can prevent the penetration and absorption of orally delivered insulin [42,44]. As a result, protein and peptide drugs, including insulin, have a negligible oral bioavailability of <1% in the clinic [35,37,42]. To develop an effective oral insulin system, a deep insight into the characteristics of these barriers is essential. Several comprehensive reviews already exist to extensively discuss these barriers [39–42]; here, we briefly summarize and show them in Fig. 1.

2.1. Chemical barriers

It is well known that the luminal pH varies from ultra-acidic (1–3) in the stomach to slightly basic (6.5–8) in the intestine [42,43]. Due to undesirable physicochemical properties such as high molecular weight and hydrophilicity, orally administered peptide/protein drugs are highly susceptible to pH variation in the GI tract. For oral insulin, its disulfide bonds can be readily cleaved by gastric acid, the fluid in the stomach composed of HCl and NaCl, thus leading to degradation and denaturation [44]. This barrier can be effectively addressed with various encapsulation strategies that have been developed to circumvent the acidic environment of the stomach and protect insulin throughout the entire GI transition against the pH variation [45,46].

2.2. Enzymatic barriers

The second challenge for orally administered protein drugs is enzymatic degradation, which starts in the stomach with pepsin and cathepsin that are highly efficient at proteolysis and continues throughout the small intestine by chymotrypsin, elastase, and carboxypeptidases. Most oral protein drugs are vulnerable to enzymatic degradation by the proteases in the GI tract; thus, they pose a major obstacle to achieving desired efficacy for oral delivery [47,48]. Oral insulin is mainly degraded by trypsin, chymotrypsin, and carboxypeptidases in the intestinal lumen and mucus layer [37,39]. To circumvent the enzymatic degradation, many studies have reported the protection of insulin with different enzyme inhibitors (Fig. 2a) such as aprotinin, trypsin inhibitors, bacitracin, and camostat mesilate [22,39,49]. For example, an oral insulin formulation developed by Oramed, known as ORMD-0801, used a soybean trypsin inhibitor as a component of an oral peptide formulation for direct enzyme inhibition [37,50,51]. However, the utility and safety of enzyme inhibition as a general strategy for enhancing oral insulin absorption still need to be made clear [37]. In addition, with the rapid development of nanotechnology, many types of nanocarriers, including liposomes [52,53], nanoparticles [30–32,46], polymersomes [54,55], and metal–organic frameworks [33,44,56], have been designed to encapsulate and protect insulin from enzymatic degradation and allow it to reach the intestine unmolested.

2.3. Physical barriers

The mucus layer is a negatively charged viscous mixture that enables the exchange of nutrients, water, and small molecules while impermeable to bacteria and pathogens. Due to the mucus's continuous resynthesis, secretion, and detachment from the epithelial surface, it can efficiently trap bacteria, pathogens, and foreign particles and rapidly clear them from penetrating the epithelia. This, however, poses significant challenges to oral peptide/protein drugs absorption into the systemic circulation [57,58]. Thus, before approaching the surface of the intestinal epithelium, the orally administered drugs must first pass through the highly dynamic intestinal mucus layer (Fig. 2b). To address this barrier, some mucus-penetrating particle carriers with a neutral charge and hydrophilic surface have been reported to reduce adsorption of mucins and improve the penetration through the mucus layer [59–62]. Despite these improvements, the current oral delivery of protein drugs remains low in absorption and bioavailability [22,37,42,63]. In addition, the safety and efficacy of these mucus-penetrating strategies have not yet been validated in large clinical trials [37,64].

After penetrating through the mucus layer, the intestinal epithelium presents another hurdle for insulin absorption. The intestinal epithelium comprises a tightly bound single layer of columnar epithelial cells [40]. To enter systemic circulation, drug absorption may occur across the epithelium either through the transcellular or paracellular routes (Fig. 2b). Despite most clinical oral drugs being absorbed by transcellular passive diffusion, the absorption by passive diffusion is primarily limited to lipophilic drugs with a molecular weight <700 Da [39,65]. Therefore, hydrophilic insulin, with a molecular weight of 5800 Da, is difficult to traverse through the cell membranes [66]. To facilitate transcellular insulin delivery, strategies involving cell

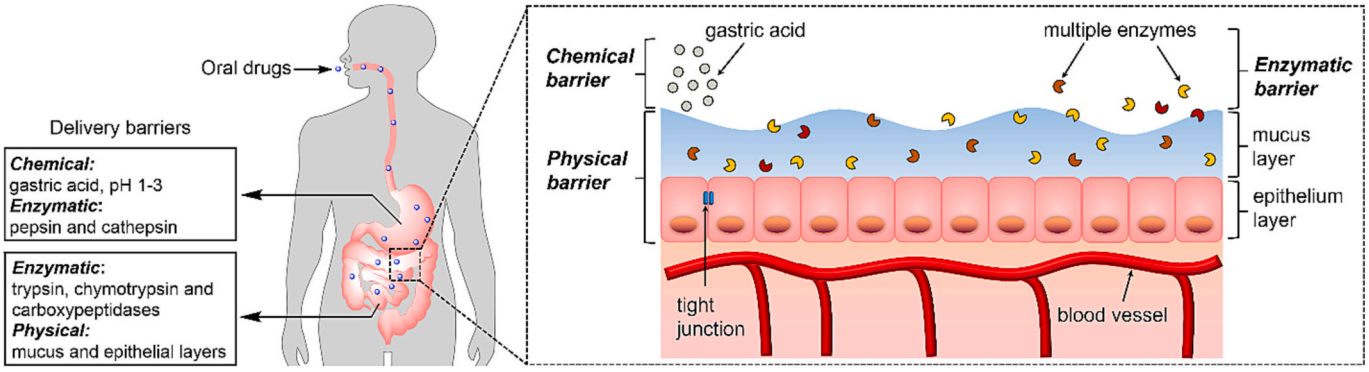

Fig. 1. Schematic representation of physiological barriers in the gastrointestinal tract to oral drug delivery. Oral delivery faces three main barriers, including chemical barriers (highly acidic in the stomach with pH 1–3), enzymatic barriers (multiple enzymes such as pepsin and cathepsin in the stomach and trypsin, chymotrypsin and carboxypeptidase in small intestine), and physical barriers (mucus layer, epithelial layer, and their tight junction).

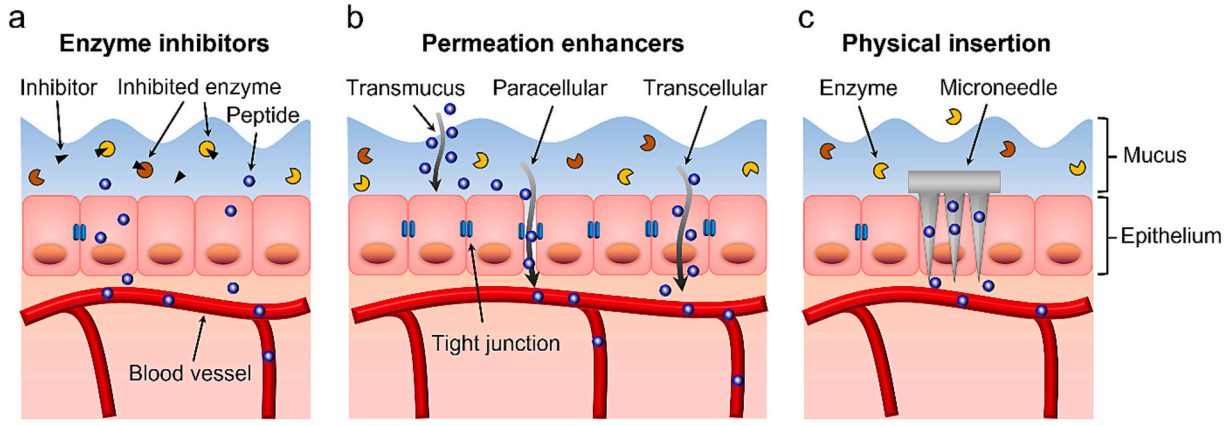

Fig. 2. Strategies that have been used to overcome gastrointestinal barriers for improving oral peptide delivery, including enzyme inhibitors (a), permeation enhancers to enhance paracellular or transcellular transport (b), and physical insertion (such as microneedle injector) (c).

receptors or transporters such as the Fc receptor [67–69] and bile acid transporter [70,71] have been reported, but their potential impact on the tight junctions has rarely been studied. As the major selectively permeable barriers, the tight junctions between the neighboring epithelial cells only permit the passage of molecules with a hydrodynamic radius smaller than 1 nm [31,72]. Thus the systemic bioavailability of hydrophilic proteins and peptides such as insulin is negligible.

To address this barrier, many permeation enhancers [73–75] have been used to facilitate insulin diffusion by temporarily opening tight junctions of the gastrointestinal epithelium (Fig. 2b). It should be noted that tight junction is formed by holding epithelial cells tightly connected to one another to close the gaps among epithelial cells and maintain the integrity of the endothelial barrier function. Transient opening tight junctions with permeation enhancers could generally facilitate oral insulin delivery. Still, safety concerns remain since sustained functional impairment of tight junctions by permeability enhancers potentially enhances absorption of noxious agents (such as bacteria, fungi, viruses, and toxins) and increases the risk of autoimmune disease, bacterial infection, and inflammatory bowel diseases [76–79].

3. Recent innovations in oral insulin delivery

With the emerging global diabetes epidemic, success in oral insulin can significantly improve the quality of life of diabetic patients who must routinely receive injections of this drug. Although the search for an effective and reliable oral insulin delivery system has been a major challenge for several decades, as the holy grail, the efforts in this direction have never stopped and are even accelerating. In the following sections, we highlight significant and representative technologies in this area over the past few years with an emphasis on those with solid promise to move into clinical evaluation and present insights into the counter-strategies for the future development of oral insulin products.

3.1. Ionic liquids for oral insulin delivery

Ionic liquids constitute a group of salts with an organic cation and organic/inorganic anion that are typically liquid below 100 °C [80]. Due to the unique and tunable physicochemical and biological properties such as viscosity, hydrophobicity, solubility, and biodegradability, ionic liquids have been increasingly exploited as solvents, co-solvents and materials for delivery of small- and large-molecule therapeutics in the past few years [81–86].

Recently, Banerjee et al. developed a novel oral insulin formulation using choline and geranate (CAGE) ionic liquid [86]. The insulin-CAGE can be prepared in a single-step process without modifying insulin structure or forming complex nanostructures. In vitro study indicated insulin-CAGE was stable at room temperature for 2 months and at 4 °C for at least 4 months without any loss in bioactivity. Palanisamy et al. subsequently performed molecular dynamics simulations to unravel the molecular-level interactions of CAGE ionic liquid with insulin in an aqueous medium and found that 0.3–0.5 mol fraction of CAGE ionic liquid strongly accumulates on the insulin surface and simultaneously excluded the water molecules from the surface [87]. In vivo, insulin-CAGE demonstrated marked efficacy in enhancing oral uptake of insulin upon intrajejunal administration in nondiabetic rats [85]. After encapsulating insulin-CAGE in enterically-coated capsules and orally administering it to non-diabetic rats, insulin-CAGE produced a similar extent of blood glucose drop compared with s.c. injected insulin, whereas the effectiveness of insulin-CAGE could be sustained till the end of the study at 12 h. The authors attributed the high oral delivery efficacy of CAGE to synergism between its ability to protect the insulin from enzymatic degradation, assist in its transport across the mucus layer, and improve paracellular uptake by opening tight junctions. Histological examination showed no remarkable difference in morphology between CAGE and saline-treated rats after 7 d of once-a-day repeated oral dosing. Subsequently, Samir Mitragotri's team further reported a method of encapsulating CAGE into a gel using poly(vinyl alcohol) (PVA), forming a mucoadhesive ionogel patch (CAGE-patch) to adhere to the intestine for oral insulin delivery [88]. The potential in vivo performance, although it has not been reported, is worth looking forward to.

3.2. Silica nanoparticles as physiochemical permeation enhancers for oral insulin delivery

Nanoparticle-based drug delivery platforms received considerable attention since the unique physiochemical properties and high surface area to volume ratio of nanoparticles enable the high loading of drugs through encapsulation or the formation of chemical-physical bindings with their functional groups [42,89]. These oral drug nanoparticles mainly include lipid nanoparticles [90,91], polymer nanoparticles [30,32,69,92], mesoporous silica nanoparticles [31,93,94], metal-organic frameworks [33,44,56] and hybrid nanoparticles [95,96]. Previous studies of nanoparticle-based oral insulin delivery platforms primarily utilize nanoparticles as carriers for insulin loading and transportation through transcytotic and/or paracellular pathways.

Inorganic materials-based nanoparticles are considered more stable and biologically inert than organic materials and have also been explored as drug carriers for treating diabetes mellitus [97]. Specifically, mesoporous silica nanoparticles have been widely studied as oral insulin delivery carriers due to their large internal surface area and pore volumes (enabling high encapsulation efficiency) and excellent physicochemical stability. Nevertheless, due to their non-biodegradability, the clearance and immune response of inorganic materials-based

nanoparticles need closer attention. Safety concerns become significant for people with diabetes, who often require long-term insulin administration [42,98].

Recently, Whitehead and co-authors reported a serendipitous discovery that small, negatively charged inorganic silica nanoparticles can act as physiochemical permeation enhancers to facilitate the oral delivery of insulin by inducing tight junction relaxation [31]. They first investigated the effects of commercially available silica nanoparticles with different sizes (20–200 nm) and different surface charges on the intestinal-barrier function via cellular and in vivo experiments. They found that negatively charged nanoparticles in 50 nm diameter can transiently (within a 4 h period) and reversibly induce increased permeability of the intestinal wall. In healthy mice, an intestinal injection of insulin after oral administration of 50-nm silica nanoparticles resulted in an excellent relative bioavailability of 85%. However, in a more realistic model, when the insulin was placed into the enteric capsules and administered to the pre-diabetic and diabetic mice, respectively, through oral gavage at a high dose of 10 U/kg, the relative bioactivities were <30%. By studying the different integrins and kinase inhibitors targeting different signaling enzymes on intestinal epithelial cells, they found the nanoparticles increase intestinal permeability by binding integrins and activating myosin light chain kinase (MLCK) (Fig. 3b). This is consistent with previous study that MLCK-induced phosphorylation of myosin leads to the contraction of the cytoskeleton, the opening of tight junctions and increasing intestinal paracellular permeability for insulin delivery (Fig. 3) [99–101]. The novel use of silica nanoparticles might represent a new direction for nanoparticles in oral insulin delivery. Instead of drug carriers, they act as physiochemical permeation enhancers to facilitate oral insulin delivery by inducing tight junction relaxation. It should be noted that this work did not observe any signs of altered intestinal morphology or inflammation 24 h post-nanoparticle administration [31]. For future translation, the safety and feasibility of potential long-term repeated dosing will require investigation in preclinical and clinical models due to the general nonbiodegradability of inorganic materials-based silica nanoparticles.

3.3. Zwitterionic nano/micro systems for oral insulin delivery

So far, the general strategy to improve the absorption of oral peptide therapeutics is using permeation enhancers to open tight junctions between the neighboring intestinal epithelial cells or by targeting transport routes across the intestinal wall, such as aforementioned ionic liquid and negatively charged silica nanoparticle platforms. However, tight junction openings can potentially elicit a series of side effects, such as bacterial infection, autoimmune disease, and inflammatory bowel diseases [76–79]. Therefore, a strategy that enables enhanced oral absorption of insulin without opening the tight junctions is preferred and possesses significant promise for future clinical translation.

In nature, capsid viruses, which show net-neutral surfaces without any hydrophobic patches (typical zwitterionic characteristics), can diffuse unhindered through mucus and readily infect mucosal epithelia. Inspired by nature, our lab reported a zwitterionic DSPE−PCB (DSPE-PCB: zwitterionic betaine polymer (polycarboxybetaine, PCB) of 5000 Da molecular weight conjugated to 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) lipid) micelle platform featuring a virus-mimetic zwitterionic surface, a betaine side chain and an ultralow critical micelle concentration, enabling insulin penetration through the mucus and efficient transporter-mediated epithelial absorption without the need for tight junction opening (Fig. 4) [102]. Due to the zwitterionic surface characteristics and unique ultra-low critical micelle concentration, the zwitterionic betaine polymer micelle enabled enhanced mucus penetration and efficient proton-assisted amino acid transporter 1 (PAT1)-mediated epithelial absorption. The prototype oral insulin can be easily manufactured by encapsulating a freeze-dried powder of zwitterionic micelle insulin into an enteric-coated capsule. Different from other preclinical oral insulins, this formulation utilized PAT1 as a mechanism for epithelium penetration, achieving a remarkable bioavailability of over 40% in diabetic rats as well as not inducing tight junction opening and leaky gut. In contrast, the bioavailabilities of the Polysorbate 80/insulin capsule and the free insulin capsule were below 10% and nearly 0%, respectively.

More important, even after the long-term repeated dose challenge

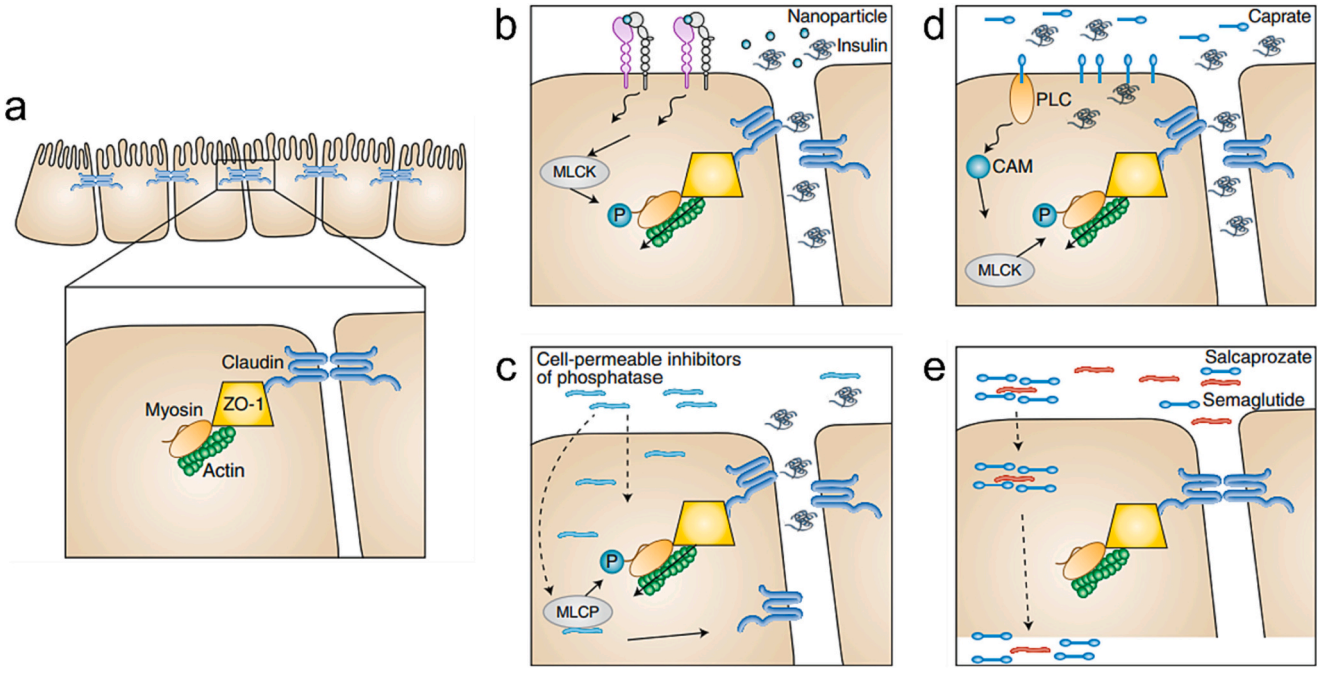

Fig. 3. Mechanisms of tight junction opening for enhancing intestinal wall permeability. (a) Claudins (a family of proteins) make up the external barrier of the tight junctions and are expressed in tissue-specific combinations. (b-e) Potential mechanisms of action of different types of absorption enhancers: silica nanoparticles (b), Cell-permeable inhibitors of phosphatase (c), classical permeation enhancer caprate (d), and salcaprozate sodium (e). Reprinted with permission from ref. [101], Copyright 2020, Springer Nature.

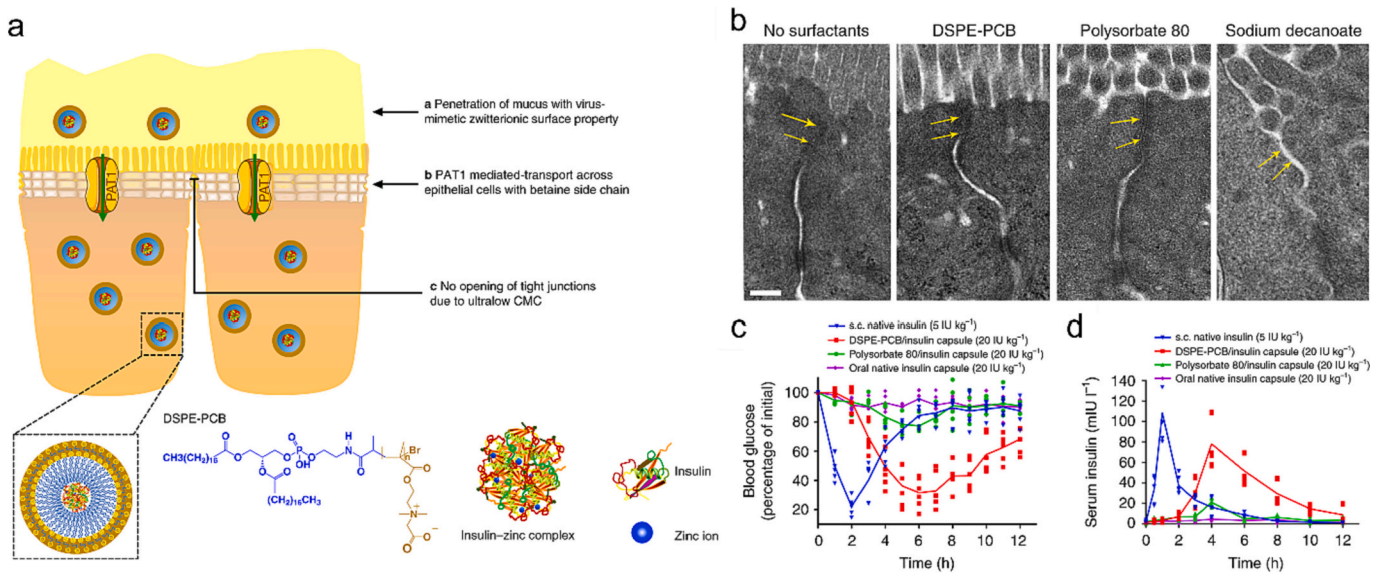

Fig. 4. Zwitterionic micelles efficiently deliver oral insulin without opening tight junctions. (a) The schematic representation of DSPE-PCB micelles addresses both the mucus and the epithelial cell layer barriers without opening tight junctions for oral insulin delivery. (b) Representative TEM images of epithelial tissues at 1 h post ileum injection of different types of surfactants, indicating zwitterionic micelle/insulin treatment did not open intestinal tight junctions (indicated by arrows). (c,d) Pharmacological activity (blood glucose-lowering in c) and bioavailability (serum insulin concentration in d) of the DSPE-PCB/insulin capsule in diabetic rats through oral gavage, compared with the Polysorbate 80/insulin capsule and native insulin capsule. Adapted with permission from ref. [102]. Copyright 2020, Springer Nature.

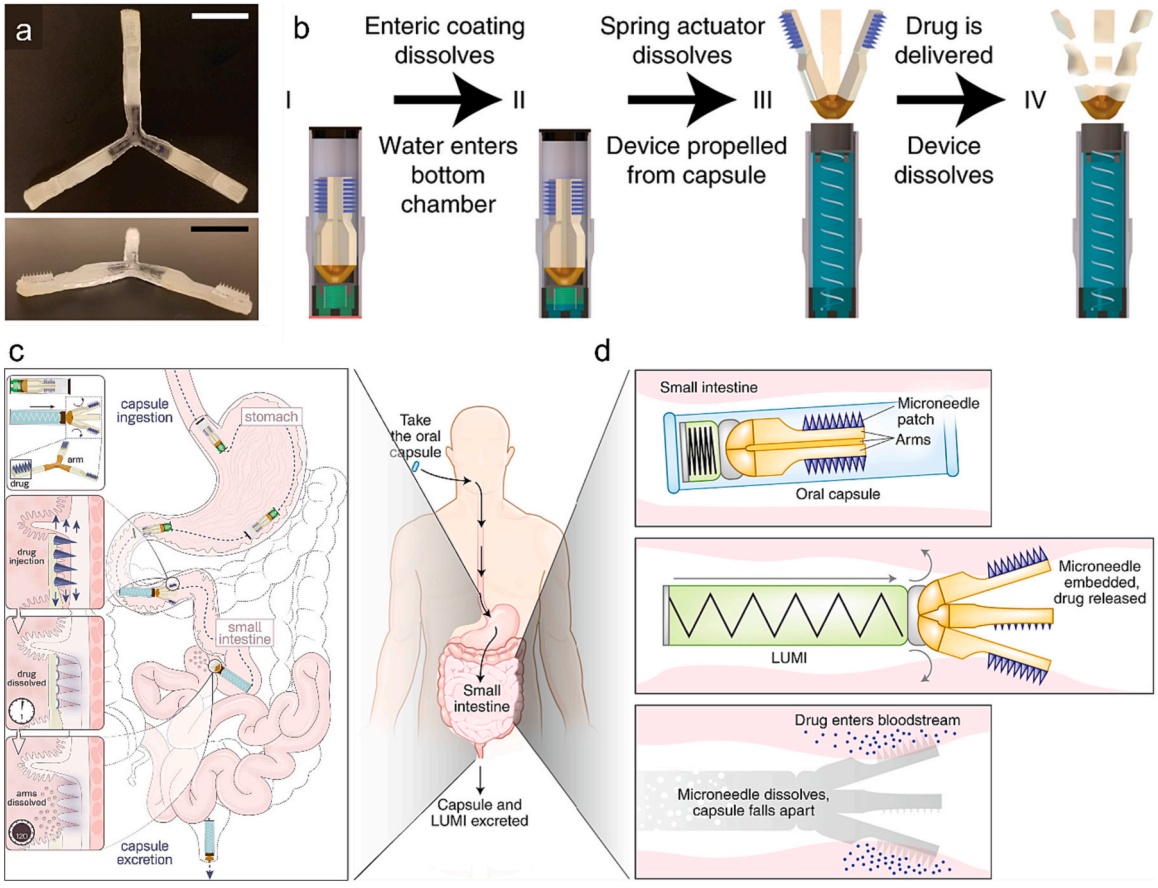

Fig. 5. The luminal unfolding microneedle injector (LUMI) for oral delivery of macromolecules. (a) Overhead (top) and side-view (bottom) images of an unfolded LUMI. (b) LUMI actuation scheme. (c, d) Schematic timeline of LUMI devices for oral delivery of biologics in the gastrointestinal tract after administered in enteric capsules. a-c, adapted with permission from ref. [109]. Copyright 2020, Springer Nature. d, adapted with permission from ref. [110]. Copyright 2020, Springer Nature.

(mice received oral gavage of the DSPE-PCB micelle twice daily for 14 consecutive days), no tight junction opening or leaky gut was observed. With the advancement in bioavailability and gut safety profile, this platform technology can potentially be a practical solution for oral delivery of other protein/peptide payloads [103,104].

Following this pioneering study, Fang et al. developed an oral protein delivery strategy using in situ polymerization of zwitterions to encapsulate proteins [105]. With the polyzwitterion modification, the polyzwitterion/protein nanocomplexes were able to pass through the mucus and cellular barriers by the PAT1 pathway. After oral administration of enteric-coated polyzwitterion/insulin capsules, the blood glucose level could be lowered effectively in different diabetic animal models (mice, rats, and pigs). Ma and coworkers developed crosslinked zwitterionic microcapsules (CB–MCs@INS) based on a carboxyl betaine (CB)-modified poly(acryloyl carbonate-*co*-caprolactone) copolymer via the combination of microfluidics and UV-crosslinking to improve oral insulin delivery [106]. By introducing zwitterionic CB-moieties, CB–MCs@INS possessed a superior affinity for epithelial cells and enhanced insulin transport by the CB-mediated cell surface transporter via the PAT1 pathway.

3.4. Devices for oral insulin delivery

Compared with the technologies mentioned above that aim to overcome GI barriers and enhance uptake, device-based delivery technologies (Fig. 2c) have received considerable attention due to their inherent attractiveness and generalized suitability for delivering a broad range of peptides and proteins [107,108]. Abramson and colleagues recently reported two innovative devices for systemically delivering insulin with high bioavailability via injections to the stomach and small intestine. The first ingestible capsule, termed a luminal unfolding microneedle injector (LUMI), contains multiple drug-loaded microneedles encapsulated within a poly(methacrylic acid-*co*-ethyl acrylate) and polyethylene glycol (PEG) coating and is designed to dissolve at pH levels encountered in the small intestine($\geq$5.5) to propel the LUMI out of the capsule (Fig. 5a,b) [109]. The authors tested microneedle penetration via ex vivo human and in vivo swine studies and observed the device consistently delivered the microneedles to the tissue without animal discomfort, residual devices, and tissue perforation. After swallowing and reaching the intestine in the swine model, the capsule holding the spring dissolves due to the rise in pH, causing actuation that pushes the LUMI out of the capsule. Then, three LUMI arms unfold outward with a microneedle array to penetrate the epithelial barrier, dissolve, and release encapsulated insulin or other macromolecule drugs (Fig. 5c,d) [109,110]. In vivo study showed that the device can serve as a platform to orally deliver insulin, presenting a faster pharmacokinetic uptake profile (insulin levels increased and glucose levels decreased within 15–30 min) and a systemic uptake >10% of that of a subcutaneous injection over a 4-h sampling period.

Inspired by a leopard tortoise-like structure with a changing center of mass, high-curvature upper shell, and low-curvature bottom shell, the group of authors also designed an orally ingested self-orienting millimeter-scale applicator (SOMA) that autonomously can insert drug-loaded milliposts into the stomach lining without puncturing the outer layer of the stomach (Fig. 6a) [111]. Unlike most orally delivered drugs absorbed through the small intestine, this device delivers the drugs directly through the gastric mucosa. Thus, the dose delivery time is likely to be more predictable than intestinal absorption, given the recognized variability in gastric emptying. In vivo studies in non-diabetic swine demonstrated that the compressed mixture containing insulin and polyethylene oxide could be delivered from the SOMA device with detectable levels of serum insulin associated with progressive reduction of blood glucose, indicating this device is an effective and reliable system for oral delivery of insulin.

Note that these devices, although represent innovative platforms with the potential for oral insulin delivery, still suffered from

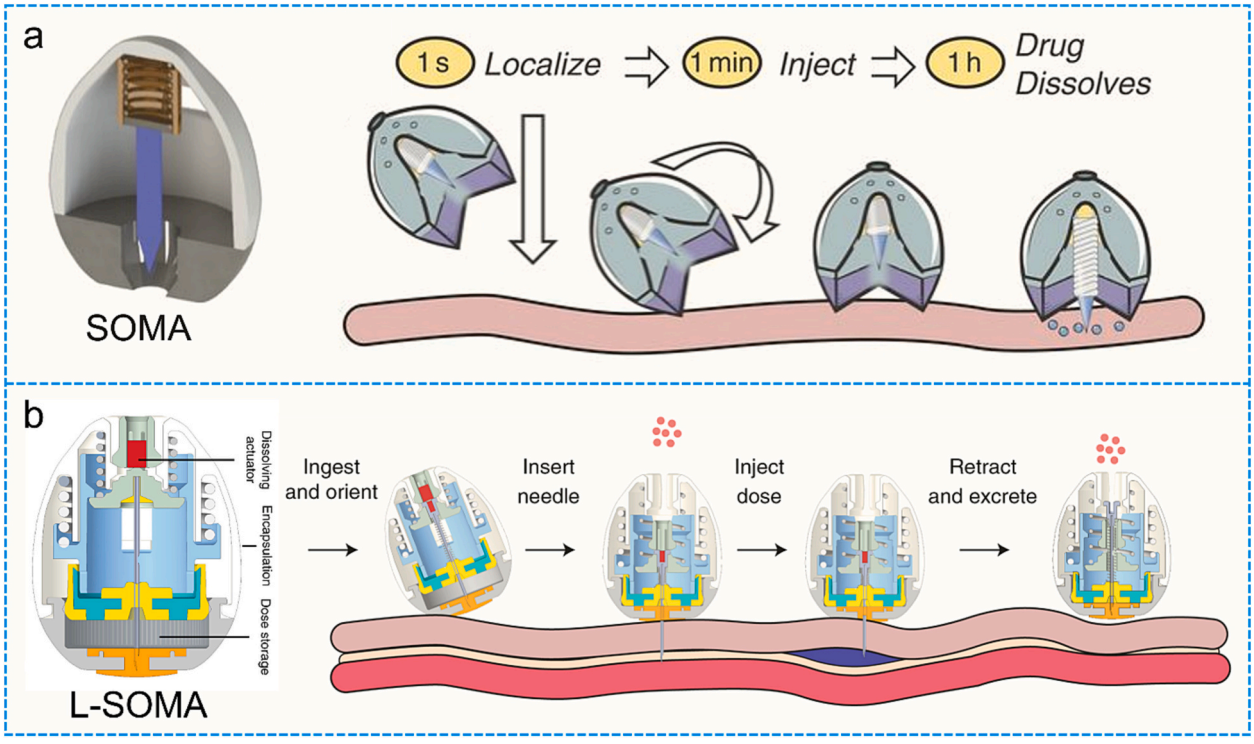

Fig. 6. Schematic illustration of two smart ingestible devices for oral drug delivery. (a) The self-orienting millimeter-scale applicator (SOMA) localizes to the stomach lining, orients its injection mechanism toward the tissue wall, and injects a drug payload through the gastric mucosa. Adapted with permission from ref. [111]. Copyright 2019, The American Association for the Advancement of Science. (b) The liquid-injecting SOMA (L-SOMA) for oral delivery of liquid formulations of pharmaceuticals into the gastric submucosa. Adapted with permission from ref. [112]. Copyright 2021, Springer Nature.

limitations, including low dose capacity (300–700 μg per pill), delayed or zero order kinetic drug delivery rates that limited their absolute bioavailability to 10% or less, and the requirement for enduring the degradative-enzyme-filled GI fluid to interact with the drug formulation before tissue wall injection [113]. These limitations prevented the devices from delivering drugs with large dosage requirements and drugs that require fast action (such as mealtime insulin). To overcome these challenges, Abramson and co-workers further optimized and reported a new version of the SOMA device by redesigning actuation and delivery systems (Fig. 6b) [112]. The liquid-injecting self-orienting millimeter-scale applicator (L-SOMA) consisted of a liquid drug, an injection needle, and a plunger that could squeeze and deliver larger dosing volumes of liquid formulations of pharmaceuticals via an injection into the gastric submucosa. Once the liquid drug was fully released, the plunger pulled the needle back into the pill, which was eventually expelled through the digestive tract. Compared to a solid-dose pellet, the increased surface area of interaction between the liquid formulation and the tissue accelerated drug pharmacokinetics and pharmacodynamics. The in vivo swine model showed that this L-SOMA is capable of delivering a high dose (up to 4 mg) of a bioavailable drug with rapid pharmacokinetic uptake after administration, reaching an absolute bioavailability of up to 80% and a maximum plasma drug concentration within 30 min after dosing.

4. Conclusions and perspectives

Compared with subcutaneously administered insulin, oral insulin delivery is painless and convenient, offering superior patient compliance and potentially improving the quality of life of diabetic patients who routinely receive needle-based injections. Yet formidable challenges remain; oral insulin delivery is still an active and up-and-coming area since the discovery of insulin in 1921. To date, scientists have explored various strategies to administer insulin orally based on the rapid advances in the science of protein chemistry, formulation, and drug delivery. However, the progress of oral insulin technologies toward meaningful efficacy in the clinics has been slow and limited, with most of the vast oral insulin literature reporting on non-clinical data.

There is significant pre-clinical work evaluating oral insulin formulations, including several examples reviewed above, where reagents or penetration enhancers were used to open tight junctions and improve paracellular transport. Despite the beneficial impacts of boosting the oral bioavailability of insulin, the potential risk of opening tight junctions shall be thoroughly examined, particularly the long-term safety under a periodic dosing regimen [77]. In addition, the time window of tight junction opening may not necessarily match the timing for the drug payload to reach the “opened” GI epithelium. This may require separately administered tight junction openers and payloads to optimize the absorption efficacy. It was further reported that some individuals with obesity and/or diabetes have impaired intestinal expression of tight junction proteins, defective intestinal barrier function, and a ‘leaky gut’ [114,115]. This suggests that inter-individual differences in gastrointestinal permeability may influence the expected outcome of the majority of oral insulin formulations, even more so for those relying on tight junction openers. Regarding pre-clinical animal models, the majority of studies employed mice and rats for efficacy evaluation, with a few exceptions where large animal models, such as pigs, were involved to closely mimic human GI absorptions [105,109,111,112].

It is worth noting that some oral insulin formulations have demonstrated efficacy in clinical trials. For example, I338, a long-acting basal insulin analogue formulated in a tablet with sodium caprate developed by Novo Nordisk, showed comparable clinical results in fasting glucose reductions and rates of adverse events with once-daily subcutaneous injections of insulin glargine for 8 weeks in a phase II trial involving 49 individuals with type 2 diabetes mellitus [35]. It should be noted that the needed doses of I338 to achieve the desired therapeutic effect were relatively high (approximately 58 times the dosage of insulin glargine), and the calculated bioavailability was low (<2%); this suggested a high cost in production and resulted to the discontinuation of the commercialization of I338.

ORMD-0801, another notable oral insulin, was developed by Oramed Pharmaceuticals. It is the world's first oral insulin capsule entering Phase 3 clinical trials study. The formulation of ORMD-0801 comprises insulin, packaged in an enteric-coated capsule, together with EDTA and bile salts as penetration enhancers. The capsule facilitates passage through the stomach and into the small intestine, and the enhancers promote drug permeability by opening the tight junctions [116]. ORMD-0801 has been tested in 16 Phase 1 and 10 Phase 2 clinical trials, involving 884 subjects, including healthy volunteers and individuals with type 1 and type 2 diabetes [24,117]. Optimal doses showing reasonable efficacy and safety have been identified and adopted in two larger and longer Phase 3 studies. Unfortunately, as Oramed announced early this year, ORMD-0801 comprehensively failed in the 26-week, Phase 3 randomized, double-blind, placebo-controlled ORA-D-013-1 clinical trial, with the candidate failing to beat the placebo at improving glycemic control [118]. As the most promising oral insulin formulation, ORMD-0801's flunks in Phase 3 trials indicate considerable obstacles to developing and commercializing oral insulin products for treating diabetes.

Despite several recent technologies that have achieved some positive results with high oral bioavailability in preclinical studies in rodents or pigs, including several promising technologies (nano-systems and injector devices) discussed in this perspective, more research is needed to validate these technologies to make meaningful progress toward the clinics and enable an oral insulin product with commercial and clinical viability. Current T1D was treated with multiple injections or pump infusions of insulins with the dosage and pharmacokinetics adjusted in a sophisticated way to address the patients' basal and prandial insulin needs. Compared to oral basal insulin, such as I338, developed by Novo Nordisk, oral meal-time insulin can be technically more challenging due to the additional demand for dosage titration and fast action. For example, oral insulin taken before a meal should be able to deliver the right amount of insulin in accordance with the varied carbohydrate intake and function in time to suppress blood glucose rising. This is beyond the focus of the bioavailability in current oral insulin development, has been less studied, and might limit clinical translation. If oral insulins cannot cover both basal and prandial insulin needs, the T1D patients will still have to receive additional insulin injections or infusions. The value of improved compliance and non-invasiveness will be significantly compromised. Last but not least, since multiple repeated oral administrations are required on a daily basis throughout the patient's life, several concerns for oral insulin, including long-term efficacy, safety, and the effect of food intake, need to be adequately studied and addressed in the future.

CRediT authorship contribution statement

Ershuai Zhang: Writing – review & editing, Writing – original draft, Conceptualization. **Hui Zhu:** Writing – review & editing, Conceptualization. **Boyi Song:** Conceptualization. **Yuanjie Shi:** Conceptualization. **Zhiqiang Cao:** Writing – review & editing, Funding acquisition, Conceptualization.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (R01DK123293).

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