Chinese Chemical Letters 37 (2026) 111170

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

Emerging trends in permeation-enhancing technologies for oral peptide delivery

Juan Tao [a,b,1], Jinlong Yang [c,1], Mengyu Zhao [a], Quangang Zhu [c], Zhongjian Chen [c,*], Jianping Qi [a,c,*]

[a] School of Pharmacy, Fudan University, Key Laboratory of Smart Drug Delivery, Ministry of Education, Shanghai 201203, China
[b] School of Chinese Medicine, Jiangsu College of Nursing, Huaian 223001, China
[c] Shanghai Skin Disease Hospital, School of Medicine, Tongji University, Shanghai 200443, China

ARTICLE INFO

Article history:
Received 16 December 2024
Revised 27 March 2025
Accepted 1 April 2025
Available online 1 April 2025

Keywords:
Oral peptides
Permeation-enhancing technologies
Targeted delivery
Physiological barriers
Nanocarriers

ABSTRACT

Peptides are increasingly favored as therapeutic agents due to their high efficacy, selectivity, and minimal side effects. However, they often face challenges related to poor stability and limited permeability through the gastrointestinal tract (GIT) and epithelia, necessitating parenteral administration. Despite this, there is a considerable demand for oral administration in clinical practice. To address the urgent clinical need for oral delivery, researchers have developed various technologies to surmount these challenges, including device-related systems, permeation enhancers (PEs), nanocarrier-based systems, and more. This review systematically explores the physiological barriers impacting peptide permeability and discusses the permeation-enhancing technologies designed to overcome them. It also reviews the oral peptide delivery systems currently available or under clinical investigation, offering insights into future developments in this field.

© 2025 Published by Elsevier B.V. on behalf of Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences.

1. Introduction

The biopharmaceutical industry has witnessed substantial growth recently, with peptides emerging as a vital class within this sector [1]. Occupying a unique niche between small organic molecules and larger proteins, peptides are renowned for their high potency, selectivity, and low toxicity, making them ideal candidates for treating a variety of ailments such as diabetes, cancer, and chronic conditions [2]. Although this method has several benefits, the predominant mode of administering peptides is through injections, which is often viewed negatively by both patients and caregivers. Oral administration, considered safer and more compliant, faces formidable challenges due to physiological barriers that severely limit oral bioavailability of peptides [3]. Most peptides, except for smaller peptides like cyclosporine, are ineffective when administered orally. The poor oral bioavailability of larger peptides is mainly attributed to the severe gastrointestinal conditions and the restricted absorptive capability of the intestine [4,5]. Recent advancements in technologies such as encapsulation, physical coatings, anti-acid agents, and enzyme inhibitors have somewhat improved peptide stability in the stomach [6–9]. However, the major obstacle remains the low intestinal permeability. Peptides, particularly those larger than 1 kDa and between 5 nm and 10 nm in diameter, struggle to traverse the mucus layer and epithelium to access the systemic circulation. This underscores the urgent need for innovative technologies to enhance permeability and facilitate oral delivery of peptides.

To tackle the difficulties related to oral drug administration, especially peptides, and propel it forward as a potentially groundbreaking therapy, various permeation-enhancing technologies have been explored. These technologies include device-related systems, permeation enhancers (PEs), nanocarrier-based systems, and more [10–22]. Among them, device-related systems, such as microneedles, address the barriers to drug absorption by penetrating physical mucus obstacles and improving permeability without causing tissue or nerve damage. Meanwhile, PEs enhance the permeability of intestinal epithelial cells (IECs), aiding the transport of large molecules that are typically obstructed due to their size and poor permeability [23–25]. Notably, several oral formulations containing PEs have already been approved. The first, Rybelsus® (Novo Nordisk), received approval from the U.S. Food and Drug Administration (FDA) in 2019, followed by Mycapssa® (Chiasma Pharma) in June 2020 [25]. These formulations primarily utilize PEs such as medium-chain fatty acids (MCFAs) like sodium caprylate [26],

* Corresponding authors.
E-mail addresses: aajian818@163.com (Z. Chen), qijianping@fudan.edu.cn (J. Qi).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cclet.2025.111170
1001-8417/© 2025 Published by Elsevier B.V. on behalf of Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences.

salcaprozate sodium (SNAC) [22], various surfactants, and combinations of acylcarnitines and citric acid [27]. In addition to PEs, nanocarriers offer another promising strategy, as they can penetrate the mucus layer and be absorbed by epithelial cells or M cells in Peyer's patches (PPs). Additionally, nanocarriers can incorporate PEs or be modified with ligands to enhance oral absorption, making them a versatile platform for overcoming physiological barriers.

While these permeation-enhancing technologies have indeed improved the oral bioavailability of peptides, the enhancements remain relatively modest, with bioavailability typically ranging from 0.4 % to 1 % [28]. This limitation hampers the possibility of oral administration of many peptides. To overcome this, it is crucial to optimize the selection of PEs, understand their mechanisms of action, and develop innovative permeation-enhancing technologies. Such efforts are essential to increase the oral absorption of peptides and expand the range of peptides suitable for oral delivery, thereby offering more extensive treatment options for patients.

This review has delved into the physiological barriers to peptide permeation and showcased the latest technologies developed to improve peptide permeability. It also provides a comprehensive overview of oral peptide products currently on the market or undergoing clinical trials, as well as an outlook on future developments in this field.

2. Physiological factors hindering permeation of peptides

The oral bioavailability of peptides faces significant challenges due to various physiological factors within the gastrointestinal tract (GIT). The GIT is pivotal in digesting carbohydrates, proteins, and other nutrients into basic components such as amino acids and monosaccharides, while also acting as a barrier against microbial invasion. After ingestion, peptides encounter multiple structural and functional obstacles throughout the GIT before they can reach systemic circulation and exert their therapeutic effects.

As previously mentioned, the stability of peptides in the stomach has been improved through innovative encapsulation and formulation technologies [6]. The next section will focus on the physiological factors that impede peptide permeation.

2.1. Mucus barrier

Mucus serves multiple physiological roles as a sticky, viscoelastic gel layer that envelops the entire GIT. This layer not only captures foreign substances but also provides effective protection for the epithelium against microorganisms.

2.1.1. Mucus composition

The mucus primarily consists of water and branched-chain glycoproteins, with mucins being especially critical. Mucins, large and complex glycosylated proteins, are distinguished by a unique "mucin structural domain" [29]. This domain encompasses a core of amino acids including proline (Pro), threonine (Thr), and serine (Ser), known collectively as proline-threonine–serine (PTS)-rich sequences. These sequences, often in tandem repeats, undergo extensive *o*-glycosylation, leading to a brush-like structure (Fig. 1) [30]. Pro is crucial for mucin synthesis as it keeps mucins unfolded within the Golgi apparatus, enhancing further *o*-glycosylation [31]. The oligosaccharide side chains of mucins not only shield them from degradation by internal proteases but also enable the molecules to expand their volume and facilitate interactions both within and between mucins. The protein backbone, enriched with cysteine (Cys), helps form disulfide bonds, thus creating a 3D network characterized by unique viscoelastic and space-filling properties [32]. Researchers have identified over 20 mucin subtypes to date. Among these, mucins (MUCs), including MUC2, MUC5AC, and MUC6, are gel-forming mucins produced by goblet cells and released into the GIT [33]. MUC2 is particularly notable as the most clearly defined secreted mucin and a key component of intestinal mucus, forming a dense gel layer that serves as an effective barrier protecting the epithelial lining.

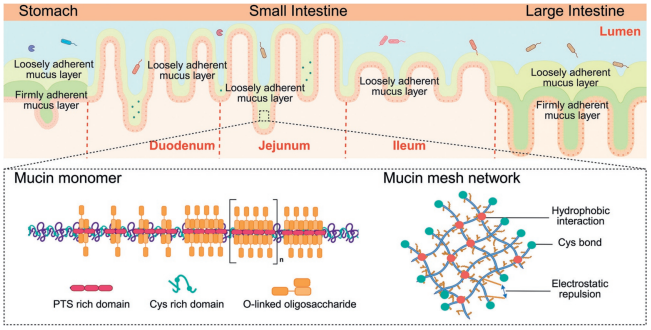


Fig. 1. Schematic illustration of the distribution and structure of the mucus in the stomach, small intestine, and large intestine. Created in BioRender. com.

2.1.2. Structure and function of mucus

It is important to note that the thickness of the mucus varies significantly across different sections of the GIT (Fig. 1) [33,34]. In the stomach, where protection against strong acids like hydrochloric acid and digestive enzymes such as pepsin is essential, the gastric mucus layer is exceptionally thick, measuring 200–500 μm [35]. This layer is primarily composed of mucins MUC5AC and MUC6, establishing a formidable barrier. It is structured into two distinct layers: a looser luminal layer and a denser medial layer, the latter of which adheres closely to the epithelial layer. This configuration not only safeguards the gastric mucosa but also provides effective protection from the corrosive effects of gastric acid and pepsin.

In contrast, the mucus barrier in the small intestine, which serves as the main area for nutrient absorption, is relatively thin and sparse. The mucus layer here varies in thickness from 30 μm to 100 μm and is predominantly composed of MUC2 mucin [36].

Similarly, the mucus layer of the large intestine, also primarily composed of MUC2 mucin, mirrors the thickness found in the stomach, ranging from 200 μm to 500 μm. This layer is organized into an inner layer that is dense and sterile, and a looser outer layer. Together, these layers effectively prevent microorganisms from making direct contact with the epithelial cells [37].

2.1.3. Barrier effect of mucus on peptide delivery

Mucus plays a complex and critical role in blocking peptide delivery to submucosal tissues. Firstly, the highly viscous nature of mucus significantly slows the diffusion of molecules like peptides, directly impacting their residence time in the small intestine and hindering their rapid penetration through the mucus layer to reach target sites. Secondly, the dynamic nature of mucus, characterized by its constant secretion and renewal, poses additional obstacles to peptide delivery. In the intestinal environment, mucus turnover occurs every 50–270 min. This rapid renewal process continuously removes particles or peptides trapped within the mucus, further limiting their adhesion and residence time, thus making effective delivery to epithelial cells challenging [38]. Moreover, the negatively charged nature of mucins also impedes peptide delivery. Due to glycosylation involving Ser and the presence of Thr and Pro structural domains, mucins carry a significant negative charge, which can result in peptides being firmly adsorbed within the mucin layer, impeding further penetration [39]. The brush-like scaffold construction of mucin also acts as a size-exclusion filter, effectively reducing the movement of macromolecular substances such as peptides and making it more difficult for them to

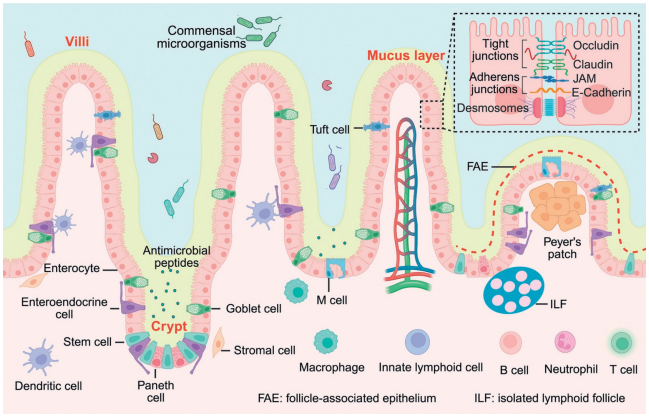


Fig. 2. Schematic illustration of the structure of the intestinal epithelium. Created in BioRender. com.

cross the mucus barrier [40]. Finally, non-covalent interactions between mucin fibers and peptides or particles, including van der Waals forces, electrostatic interactions, hydrogen bonds, and hydrophobic interactions, also pose significant hindrances. These interactions can lead to structural changes in peptide molecules or their sequestration within the mucus layer, further decreasing the bioavailability of oral peptides [41].

2.2. Epithelial barrier

The epithelial barrier beneath the mucus represents another significant obstacle in the delivery of oral peptides. This barrier is not just a monolayer of epithelial cells organized into villi and crypts, but it also includes a variety of specialized cell types (Fig. 2). These cells are linked by junctional complexes, forming a highly dynamic barrier that substantially restricts the delivery of oral peptides.

2.2.1. Composition and structure of the epithelial barrier

The epithelial boundary is composed of a single layer of tightly packed epithelial cells, arranged into a specific morphology of protrusions (villi) and depressions (crypts), forming the complex structure of the intestine [42]. IECs, which make up about 90 % of the cells in this barrier, control the release and uptake of ions, water, fats, peptides, immunoglobulins, hormones, and additional substances, maintaining the normal physiological function of the intestine. Additionally, the intestinal epithelium includes various cell types such as goblet cells, enteroendocrine cells, Paneth cells, stem cells, and M cells, each with distinct roles [42,43]. Goblet cells secrete gels to produce mucin, forming the gut's primary defense barrier along with mucus. Enteroendocrine cells respond to external signals by releasing a variety of intermediaries and responsive proteins, including glucagon-like peptide-1 (GLP-1), gastric inhibitory peptides, and somatostatin. Located in the crypts, Paneth cells secrete antimicrobial peptides like alpha-defensin, lysozyme C, and regenerating islet-derived protein 3-alpha (REG3A), crucial for sustaining intestinal microecological homeostasis and safeguarding adjacent stem cells [44]. Intestinal stem cells proliferate in the crypts, and their progeny differentiate during migration along the crypt-villus axis before being exfoliated into the lumen [45]. This continual turnover renders the intestinal epithelium an extremely dynamic construction, renewing itself every 4–7 days.

2.2.2. Specialized cells and functions of the epithelial barrier

PPs are specialized immune organs located mainly in the ileal region of the small intestine, serving as a crucial defense line against intestinal microorganisms [46]. These patches house a substantial number of immune cells such as T-cells, B-cells, and macrophages, all of which collaborate to maintain intestinal immune homeostasis. Within PPs, M cells play a pivotal role. These cells are unique to PPs and are adept at ingesting and translocating various particles from the gut, such as gut antigens and large proteins. Through this activity, M cells transport these foreign substances to the immune cells within PPs, initiating an immune response that safeguards the organism against pathogens [47,48]. Additionally, a discontinuous type of follicle-associated epithelium (FAE) is found in the small intestine. These epithelial cells, located in mucosal lymphoid follicles, contribute to the synthesis of secretory IgA and have antigen-presenting capabilities. FAEs overlie both PPs and isolated lymphoid follicles (ILFs), which are notable for their low mucus secretion. This characteristic enables them to efficiently pick up antigens directly from the intestinal lumen and convey them to immune cells, enhancing the body's immune response [46].

2.2.3. The junctional complexes of the epithelial barrier

Intestinal epithelial boundary cells are interconnected through an intricate array of junctional complexes, which are crucial not only for maintaining barrier integrity but also for finely regulating the paracellular transport of solutes and fluids [49,50]. The principal components of these complexes are tight junctions (TJs), which serve a pivotal function in the intestinal epithelial barrier. Comprising transmembrane proteins like claudins and occludins, along with peripheral membrane proteins (*e.g.*, zonula occludens-1 (ZO-1), ZO-2, ZO-3), and junctional adhesion molecules (*e.g.*, JAM-A), these proteins collaborate to create a dense network that effectively blocks the entry of external substances *via* the paracellular pathway [45]. Notably, the binding of TJs is reversibly regulated, allowing for dynamic responses to environmental changes. For instance, haptoglobin can reversibly alter intestinal permeability by simulating the epidermal growth factor receptor *via* protease-activated receptor 2 (PAR-2) on IECs, leading to the detachment of TJ proteins like ZO-1 [51]. This adaptive mechanism enables the intestinal epithelial barrier to quickly respond to external stimuli, protecting the organism from potential harm. Occludins and claudins are particularly significant in regulating paracellular permeability, maintaining the permeability balance through their interactions with other TJ proteins [52]. Moreover, claudin family proteins are vital for the structural integrity of TJs, enhancing the stability of the intestinal epithelial barrier by tightly interlinking neighboring cells through a transmembrane network.

In addition to TJs, adhesion junctions (*e.g.*, cadherin-1) and desmosomes play a vital role in preserving the mechanical integrity of the intestinal boundary [53]. These structures provide additional junctional support, ensuring the stability of the intestinal epithelial barrier against mechanical stress. Moreover, gap junctions create channels between neighboring cells, allowing for the direct passage of small molecules and ions. This direct intercellular communication is essential for maintaining intestinal homeostasis and regulating cellular functions.

2.2.4. Limitations of intestinal absorption of oral peptide

The intestinal absorption of drugs primarily occurs *via* two pathways: transcellular and paracellular. The transcellular pathway involves direct penetration through IECs, but the permeability of peptides *via* this route is typically very low [3,54]. According to Lipinski's "Rule of 5", certain physicochemical properties of a drug, such as Log*P* value, count of hydrogen bond donors or acceptors, and molecular mass, significantly influence its transcellular permeability. Peptides generally have Log*P* values below 1, much lower than the threshold of 5, and possess numerous hydrogen bond donors or acceptors with molecular weights well above 500 Da [55]. These characteristics hinder efficient absorption *via*

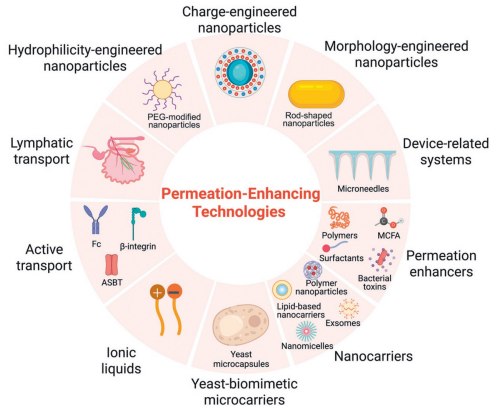


Fig. 3. Flow diagram of the general considerations in permeation-enhancing technologies for oral peptides. Created in BioRender. com.

the transcellular route. In contrast, the paracellular pathway entails drug permeation through TJs between IECs [56]. The aqueous pore sizes of TJs typically range from 3 Å to 10 Å, too narrow for molecules larger than 500 Da to pass. Even though certain permeation PEs, like transient permeation enhancers (TPEs) and SNAC, can modulate TJs to increase pore sizes, these remain under 20 nm in width when fully open, and the overall surface area of the water-saturated pores constitutes merely 0.01 %–0.1 % of the entire intestinal epithelial cell surface [57]. Consequently, the oral bioavailability of peptides continues to be low, even with the use of PEs. M cells, specialized cells in the gut, efficiently translocate antigens, macromolecules, and pathogenic particles to gut-associated lymphoid tissues [58]. This suggests a potential route for oral peptide delivery, although M cells make up less than 1 % of the intestinal epithelium, limiting their utility as a route for peptide absorption [59]. Moreover, certain endogenous peptides carried by M cells could trigger an immunological reaction, posing potential health risks.

The primary challenges to enhancing the oral bioavailability of peptides stem from their limited ability to penetrate the mucosal layer and their inefficient transport across the intestinal epithelium. To overcome these hurdles, various permeation-enhancing technologies (Fig. 3) have been developed, which are further elaborated upon below.

3. Permeation-enhancing technologies overcoming mucus barrier

The mucus on the intestinal membrane plays a vital role as a formidable factor hindering peptide absorption due to its numerous barriers. To bypass the mucus barrier, successive proposals for mucoadhesive and mucus-penetrating technologies have been introduced. Mucus-penetrating technology is of interest for its ability to rapidly traverse the unstirred layer and thereby access the intestinal epithelium for absorption. Here, we primarily discuss four mucus-penetrating technologies: mucolytic agents, surface-engineered nanoparticles (NPs), morphology-engineered NPs, and device-related systems. These technologies are explored for their potential to enhance permeability to overcome mucus barriers.

3.1. Mucolytic agents

Mucolytic agents are initially employed to disrupt the mucus barrier, aiding in the penetration of the mucus layer. These agents find common use in eliminating abnormal mucus in lung diseases like chronic obstructive pulmonary disease, while also transiently reducing the mucus boundary in healthy mucous membranes [60]. *N*-Acetyl-L-cysteine [61], a frequently utilized mucus-dissolving agent, enhances the uptake of 3.2 μm fluorescent polystyrene microparticles in PPs by 6-fold. Despite their ability to clear mucus from the epithelial layer, thus facilitating particle adhesion to the intestinal epithelium and bolstering oral absorption, the disruption of the mucus barrier may result in harm to the intestinal epithelium due to direct exposure to protein-hydrolyzing enzymes and acids [23]. Hence, it is imperative to utilize materials or carriers with unique properties to penetrate mucus for oral peptide delivery.

3.2. Surface-engineered NPs

NPs can improve solubility, promote medication accumulation at target sites, and facilitate the simultaneous delivery of multiple therapeutic agents [62]. However, NPs encounter numerous physiological barriers during their transit within the body, which significantly limit the delivery efficiency of NPs-based systems. For instance, NPs delivered to the mucosal linings are often ensnared and eliminated by mucus, thus reducing their efficacy. Proper control of the physicochemical characteristics of NPs can enhance the delivery and behavior of drugs [63,64]. Research has demonstrated that the hydrophilic surface and the neutral charge are critical for efficient trans-mucosal medication carriers.

3.2.1. Surface hydrophilicity-engineered NPs

To enhance the hydrophilicity of the particle surfaces, polyethylene glycol (PEG) coating is widely employed to augment permeability through the mucus layer [65]. Recently, Nie *et al.* used linear polyethyleneimine as a carrier to form a complex with plasmid DNA encoding GLP-1 [66]. The NPs were modified with a mixture of 1,2-dipalmitoyl-*sn*–glycero-3-phosphocholine and 1,2-dimyristoyl-rac–glycero-3–methoxy PEG, making the surface hydrophilic. These modifications significantly improved the NPs' diffusivity and transport capacity within the gastrointestinal mucus layer, resulting in high transfection efficiency *in vitro* and *in vivo*. Similarly, a PEGylated liposome complex for oral insulin gene delivery was developed [67]. This system showed excellent stability in simulated gastrointestinal fluid, suggesting that the PEG layer minimizes mucin interactions, thereby enhancing permeability and improving *in vivo* insulin gene expression. In another study, Guo *et al.* investigated the mucus penetration behavior of surface-modified silica NPs (SNPs) in microenvironments with varying pH values [68]. Using multiparticle tracking, they observed that PEG-modified SNPs showed pH-stable immobilization in isopycnic environments due to their strong hydrophilicity. In contrast, carboxylate-modified SNPs exhibited increased mobility only in mildly alkaline mucus (Fig. S1A in Supporting information).

Besides PEG, polyvinyl alcohol (PVA) and copolymer of *N*-(2-hydroxypropyl) methacrylamide copolymer (pHPMA) can be utilized to devise mucus-inert particles as well, enhancing the intestinal uptake of peptides. Samuel *et al.* developed self-assembled NPs for oral insulin delivery, aiming to overcome both the mucus diffusion and epithelial absorption barriers. The NP core encapsulated insulin and cell-penetrating peptide (CPP), while the outer layer featured a detachable hydrophilic pHPMA coating. This coating enhanced mucus permeability, whereas the CPP promoted epithelial uptake. Notably, the NPs exhibited 20-fold higher absorption in mucus-secreting epithelial cells compared to free insulin, leading to a significant hypoglycemic response (Fig. S1B in Supporting information) [69].

3.2.2. Surface charge-engineered NPs

The surface charge of NPs also stands as a critical determinant influencing mucus penetration. The negative charges carried by the carboxylic acid and sulfate moieties in mucin fibrils

cause cationic NPs to become trapped, thus hindering the efficiency of drug administration. Motivated by the reality that most viruses' surface charge is neutralized by an equal amount of positive and negative charges, researchers have incorporated electrically neutral surfaces into the engineered NPs [70]. Zhang *et al.* crafted mesoporous silica NPs (MSN–NH_2@COOH/CPP5) with modified groups that could efficiently penetrate the mucous layer by mimicking viral surfaces [71]. These NPs, with an inner pore diameter of 6 nm, were efficiently loaded with insulin and coated with a cationic CPP and anionic glutaric anhydride to obtain the hydrophilic MSN–NH_2@COOH/CPP5. In experiments simulating intestinal mucus, the apparent permeability coefficient was found to be 14.61×10^{-5} cm/s. Importantly, MSN–NH_2@COOH/CPP5 maintained the bioactivity of insulin and exhibited a substantial decrease in blood glucose concentrations by approximately 50%. Moreover, its bioavailability was significantly higher compared to insulin delivered directly into the jejunum (Fig. S2A in Supporting information).

Amphiphilic ionic polymers have gained attention as effective nanocarriers for mucus penetration owing to their excellent antifouling characteristics. Betaine derivatives are amphiphilic ionic polymers containing balanced proportions of cationic and anionic groups, including sulfobetaine (SB), phosphorylcholine [72], and polycarboxybetaine (PCB), have been extensively used for preparing mucus-penetrating NPs. However, different pH microenvironments can affect the surface charge state of these amphiphilic polymers and hence the fate of the NPs in penetrating mucus. Ma *et al.* recently developed polydopamine-coated silica NPs (SiNPs-PDA) possessing an isoelectric point (IEP) of 5.6 [73]. Their studies revealed that these NPs moved three times faster in mucus at pH 5.6 compared to pH 3.0 or 7.0. Optimal diffusion occurred when the IEP of the NPs aligned with the mucus' pH, resulting in enhanced transport performance both *in vitro* and *in vivo*. Biophysical analysis additionally indicated that matching the IEP with the mucus pH reduced the NPs' mucus affinity, facilitating their movement (Fig. S2B in Supporting information). Therefore, when designing pH-sensitive amphiphilic polymers for efficient delivery across mucus, it is crucial to match the charge equilibrium state of NPs with the pH of the mucus microenvironment.

3.3. Morphology-engineered NPs

Besides surface hydrophilicity and neutral charge, particle morphology significantly influences mucus penetration. Many non-spherical bacteria, such as bacilli and helical spirochetes, are present in the mucosal tissue [34]. Studies show that bacterial motility is related to shape, with the spiral shape being crucial for *H. pylori*'s effective penetration of the gastric mucosa. Inspired by this, researchers are exploring shape modulation to overcome the mucus barrier. Nanorods, for instance, exhibit rapid diffusion through the mucus layer *via* rotation [74]. Their robust mucus-penetrating capability allows them to deeply infiltrate the mucus, prolonging their residence time in the GIT [75,76]. Given their excellent penetration properties, both the non-spherical shape of nanorods and their specific aspect ratios are considered in designing carriers for mucosal delivery. Lee *et al.* systematically investigated how NP size and shape influence oral drug delivery [77]. Their findings revealed that rod-shaped NPs achieve higher absorption efficiency than spherical ones. This advantage stems from their elongated structure, which reduces friction along the long axis when their length exceeds the mucus network's pore size. As a result, rod-shaped NPs exhibit improved diffusion within the mucus and enhanced transport in mucus-secreting cells due to their larger aspect ratio. Despite these promising findings, rod-shaped NPs face significant challenges before they can be clinically implemented. To advance the clinical application of rod-shaped NPs in oral drug delivery, extensive research is required. This involves the development of biodegradable NPs and conducting scaled-up studies to resolve bulk manufacturing issues, such as the flowability of elongated particles.

3.4. Device-related systems

Device-related systems for oral delivery of peptides mainly refer to microneedles here. Microneedles typically entail affixing an array of micron-sized needles to a specific substrate. Initially conceived for minimally invasive drug administration procedures in the outermost skin layer, microneedles have evolved to encompass various tissue types, including the GIT [78]. Their application in oral drug delivery is advantageous as they deliver drugs directly into the intestinal wall while minimizing pain. Given the gut's high mucus turnover, any epithelial damage caused by microneedles is easily repaired.

The distinct advantage of microneedles lies in their broad applicability to a wide spectrum of peptides with fewer constraints on molecular size. Traverso *et al.* performed groundbreaking validation experiments, employing a standard endoscopic needle for submucosal injections in the GIT of intubated pigs [79]. They demonstrated that microneedles could penetrate the mucosa and epithelium fully, thus improving the oral bioavailability of bioactive molecules.

In contrast to visible skin surfaces where microneedles can be manually applied, special injection controllers or triggers are necessary to deploy microneedles in the GIT. Recently developed devices, such as the oral self-orienting millimeter applicator (SOMA) [80] and the lockable unitized microneedle injector (LUMI) [21], have been designed for delivering insulin to the stomach and intestine, respectively. The SOMA system (Fig. S3A in Supporting information), draws inspiration from the leopard tortoise's ability to orient and regulate, enabling precise placement of the applicator on the gastric mucosa during injection, which exhibits a glucose-lowering effect comparable to subcutaneous insulin injection. The LUMI device (Fig. S3B in Supporting information) features three flexible arms, each with a 0.5 cm^2 microneedle patch. Upon capsule administration, the bundled arms unfold as they move from stomach to intestine, pressing the patches against the wall to breach the epithelial barrier. It is crucial to highlight, however, that both of the devices described are injectable delivery modes and require assistance from a gastric endoscope for application to the GIT. Their suitability for swallowable oral formulations remains to be verified.

In the realm of pharmaceutical innovation, Rani Therapeutics has pioneered a device featuring microneedles designed to deliver macromolecules in the gut. Dubbed the "robot pill", this device consists of an enteric-coated capsule housing a folded polyethylene balloon attached to a dissolvable hollow needle made of PEG (Fig. S3C in Supporting information) [15]. A needle capable of encapsulating approximately 3.5 mg of sterile solid peptides can be utilized. Upon intestinal release, a reaction between citric acid and potassium bicarbonate causes the balloon to expand, facilitating needle penetration of the intestinal wall. In a porcine model, the bioavailability of insulin from this formulation is comparable to that of intravenous administration [81]. Furthermore, Cai *et al.* engineered micromotor microneedle systems featuring effervescent materials using methacrylated gelatin, resembling a scaled-down version of a rocket (RIEMs) (Fig. S3D in Supporting information) [82]. Enclosed within an enteric capsule, the RIEMs encounter water in the intestine, triggering gas that propels the microneedle to inject into the intestinal wall, thus penetrating the epithelial barrier to release the drug. Despite the promising potential of these microneedle-based devices, several concerns need addressing before they can enter the market. Specifically, the potential risk of frequent microneedle punctures into the GIT must be thoroughly

assessed, the relationship between device size and total drug delivery must be explored, and attention should also be paid to the difficulty and cost of production [83].

4. Permeation-enhancing technologies overcoming intestinal epithelia

In addition to the mucus barrier, another crucial limitation to the oral bioavailability of peptides stems from their exceedingly low permeability across epithelial cell membranes. Enhancing the intestinal epithelial permeability of peptides is vital for developing oral peptides. Currently, various technologies are available to enhance the permeation of peptides, with PEs emerging as one of the most utilized methods in clinical or preclinical studies.

4.1. PEs

The primary obstacle associated with oral peptides lies in their poor permeability across the intestinal epithelium. Since a study in 1961 revealed that sodium ethylene diamine tetraacetic acid (EDTA) improved the oral absorption of heparin, PEs are believed to enhance intestinal permeability by transiently modifying the epithelial construction, making them widely utilized in oral peptide formulations. These enhancers must cause sufficient but temporary disruption of the intestinal epithelial layer to substantially enhance the oral absorption of peptides, while also maintaining a satisfactory safety profile with minimal local or systemic toxicity. PEs can improve both transcellular transport by inducing fluidity in cell membranes and paracellular transport by rearranging TJs [23]. A variety of semi-synthetic and synthetic compounds have been created as PEs, such as chelating agents, biosurfactants, bacterial toxins, polymers, and MCFAs and their derivatives, as outlined in Table S1 (Supporting information).

4.1.1. Chelating agents

Chelating agents represent a class of small molecule ligands capable of forming two or more covalent bonds with metal ions in solution. These ligands encompass EDTA, diethylene triamine pentaacetic acid (DTPA), and ethylene glycol tetraacetic acid (EGTA). Chelating agents like EDTA are believed to enhance extracellular transport by depleting extracellular Ca^{2+}, which is vital for the formation of TJs and apical junction complexes, thus maintaining epithelial boundary function [54]. As Ca^{2+} is also required for the maintenance of enzyme activity, chelators like EDTA possess some enzyme-inhibitory effects. In practical terms, it is unfeasible to use chelating agents alone acting as enzyme inhibitors. For instance, a 7.5 % (w/v) EDTA solution was ineffectual in suppressing purified trypsin, a calcium-dependent enzyme, probably due to the presence of elevated concentrations of Ca^{2+} in the body [84,85]. Therefore, the challenge of using chelators *in vivo* is to maintain high enough concentrations of these chelators to achieve adequate protease inhibition in local tissues, without producing cytotoxic effects or excessively reducing micronutrient levels [23].

4.1.2. Biosurfactant

Bile is a multifaceted fluid produced and secreted by the liver that is composed of bile acids, cholesterol, and various other constituents necessary for lipid breakdown in the intestine. Bile acids are derived from cholesterol in hepatocytes and are ionic amphiphilic molecules characterized by a sterol backbone. Most bile acids are conjugated with glycine or taurine forming monovalent bile salts that function as amphiphilic steroid biosurfactants. These bile salts are essential for the excretion of cholesterol from the body, emulsifying intestinal lipids, enhancing lipid proteolysis, and promoting lipid absorption. Sodium deoxycholate and sodium taurocholate have been employed as PEs to assist medication absorption through various biological barriers, such as the GIT [86,87]. Bile salts foster paracellular transport by disrupting TJs and bolster drug stability against enzyme activity, while also rendering intestinal epithelial cell membranes more fluid [88]. However, their clinical application is curtailed by their propensity to induce irreversible damage, irritation, and cell membrane hemolysis.

4.1.3. Bacterial toxins

Various PEs derived from toxins have been increasingly utilized to enhance the oral administration of peptides by modifying cellular bypass or transcellular transport permeability [89]. To mitigate safety concerns associated with natural toxins, a common approach involves developing short peptide sequences through structure-activity relationship (SAR) studies. For instance, zonula occludens toxin (ZoT) enhances intestinal permeability through protein kinase C (PKC)-dependent cytoskeletal contraction, primarily mediated by the six amino acids at its front terminus [90]. CPPs, derived from the trans-activator of transcription protein of human immunodeficiency virus type-1 (HIV-1 TAT), enhance peptide membrane permeability by promoting both paracellular and transcellular transport *via* the endocytic pathway [91]. Uhl *et al.* coated polylactic acid NPs with a polyarginine-rich cyclic CPP and loaded them with liraglutide [92]. This innovative formulation exhibited high tolerability with significantly enhanced epithelial cell penetration. The novel NPs demonstrated a significant 4.5-fold enhancement in the oral absorption of liraglutide. Despite CPPs' effectiveness in enhancing membrane permeability, they have yet to undergo thorough validation in clinical studies for the oral delivery of peptides due to their cytotoxicity at high concentrations, stability issues owing to susceptibility to enzymatic degradation *in vivo*, and high production and purification costs.

4.1.4. Polymers

Chitosan (CS) is the most widely used polymer for augmenting oral peptide delivery, owing to its positive charge density and strong bioadhesive properties. It is frequently formulated into NPs to encapsulate peptides, thereby improving their oral absorption. A detailed discussion of this approach is provided in Section 4.2.2.

4.1.5. MCFAs and their derivatives

MCFAs are naturally occurring fatty acids with chain lengths typically ranging from C6 (six-carbon chain) to C12 (twelve-carbon chain). Initially, it was discovered that they could enhance the absorption of β-lactam antibiotic drugs in rectal suppositories [93]. The proposed mechanism suggests that carboxylic acid derivatives enhance drug permeation by disrupting TJs and temporarily chelating calcium ions, which is essential to maintaining the integrity of TJs. Among the tested compounds, sodium decanoate (C10) and sodium caprylate (C8) emerged as the most effective PEs, with C8 exhibiting particularly promising results.

C10, C8, and their derivatives are already utilized in products like oral octreotide and oral semaglutide [25]. C8, typically existing in its ionic form and exhibiting surface-active properties at intestinal pH levels, enhances peptide permeation *via* both transcellular and paracellular pathways. Transcellular transport depends on interactions with the epithelial membrane, while paracellular transport is mediated by junction proteins. At the molecular level, C8 activates phospholipase C, leading to an increase in inositol triphosphate levels, calcium release, and a rise in intracellular calcium concentration. This results in calmodulin-dependent actomyosin contraction, opening TJs and boosting paracellular transport (Fig. 4A). Additionally, SNAC, identified based on observations that microspheres derived from acylated amino acids enhance peptide absorption [94], is generally recognized as safe (GRAS) status and was initially believed to improve both transcellular and paracellular permeability.

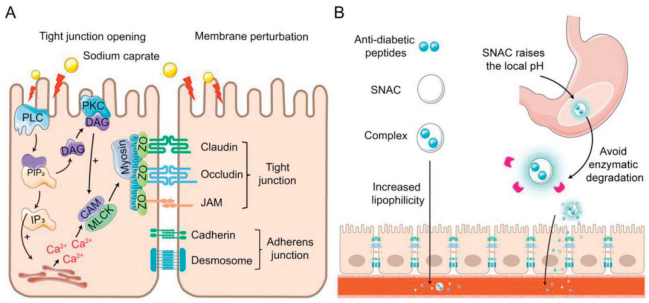


Fig. 4. The permeation enhancement mechanism of MCFAs and their derivatives. (A) Opening TJs and inducing membrane perturbation to facilitate peptide permeation. (B) Permeation enhancement through the formation of complexes between peptides and SNAC, thereby increasing their lipophilicity (left); and elevating the local pH of peptides to reduce enzymatic degradation (right). Copied with permission [95]. Copyright 2024, The Authors.

Research on oral semaglutide offers an alternative perspective on the mechanism of action for SNAC. Novo Nordisk proposes a mechanism whereby SNAC facilitates the absorption of oral semaglutide, supported by various studies [22]. It also enhances the transcellular absorption of semaglutide by inducing monomerization of semaglutide, increasing its lipophilicity and augmenting transmembrane permeation. Therefore, in the development of oral semaglutide, SNAC's mechanism is defined as a carrier system relying on noncovalent bonds and a mechanism is only effective against semaglutide (Fig. 4B) [95]. Subsequent research on SNAC's mechanism has largely concurred that SNAC functions as a transcellular transporter of PEs [96].

PEs have shown promise in enhancing the oral absorption of peptides, with certain ones, like SNAC and C8, even being utilized in commercial products. However, safety and effectiveness remain the primary concerns in their application to oral peptide delivery [23]. Unlike general oral excipients, PEs are specifically included in oral formulations to improve bioavailability. Since the active ingredients are typically low-permeability drugs, biowaivers do not apply to generic versions. Regulatory authorities in the United States, Europe, and Japan evaluate PE formulations individually, as there are no standardized guidelines for excipient selection. As a result, PE selection is carried out with caution. While many successful PEs have been used as food additives or excipients, simply choosing a PE from the FDA's inactive ingredient list does not guarantee safety. Dedicated toxicology studies may be needed. Historically, some PEs were removed from Phase III clinical trials due to safety concerns [97]. However, with the accumulation of more clinical safety data, confidence is growing that more potent PEs will be incorporated into oral dosage forms in the future.

4.2. Nanocarriers/microcarriers

The low oral bioavailability of peptides stems primarily from their low epithelial permeability. Efforts have focused on exploring the construction of oral nanocarriers capable of encapsulating peptides. These nanocarriers are engineered to address the challenges posed by the GIT and improve the oral bioavailability of peptides [98]. Such oral peptide nanocarriers primarily comprise lipid-based nanocarriers, polymeric NPs, and nanomicelles [99].

4.2.1. Lipid-based nanocarriers

Lipid-based nanocarriers serve as drug delivery systems based on lipids, efficiently encapsulating both hydrophilic and hydrophobic medications [100–102]. Liposomes are characterized by a spherical shape, consisting of an outer hydrophobic lipid bilayer and an inner aqueous space. Hydrophilic peptides can be shielded from harsh enzymatic degradation environments by encapsulating them in the internal aqueous compartment of the liposomes [40,103]. Moreover, liposomes exhibit enhanced cellular uptake due to their biomimetic bilayer structure. Liposomes are divided into three categories: positive, negative, and neutral. Although neutral liposomes facilitate mucus penetration, they have weak cell interactions, so their surface-targeting ligands are often modified to enhance intestinal epithelial penetration. Yu *et al.* introduced a glucose-sensitive oral insulin delivery system designed to regulate postprandial blood glucose [104]. The core of the system is based on FcRn-targeted liposomes enveloped in a hyaluronic acid (HA) shell with glucose-sensitive functions (Fig. S4A in Supporting information). Upon oral administration, the HA shell is rapidly shed in response to elevated intestinal glucose concentrations. Glucose competitively binds to the HA-conjugated phenylboronic acid moiety. The exposed Fc fragment on the liposome surface then facilitates intestinal drug absorption through the FcRn-mediated transepithelial transport pathway. An *in vivo* study in type 1 diabetic mellitus (T1DM) mice demonstrated the effectiveness of this glucose-sensitive oral insulin delivery system in reducing postprandial blood glucose concentrations.

While liposomes can enhance the oral bioavailability of peptides, it is evident from existing studies that liposomes are less efficient in encapsulating peptides. Low encapsulation efficiency increases therapeutic costs. Furthermore, the low stability of lipid-based nanocarriers during storage in physiological solutions poses a challenge for researchers and hinders their clinical application.

4.2.2. Polymer NPs

NPs derived from various polymers have been investigated for oral delivery of peptides due to their favorable biocompatibility, degradability, and diverse chemical properties [105–108]. These polymers are classified into natural and synthetic categories based on their origin [109]. Natural polymers utilized for oral delivery of peptides primarily contain CS, alginate, dextran, and gelatin. CS, a polysaccharide derived from natural chitin, is nontoxic and biocompatible with soft tissues [110]. By adjusting its molecular weight and deacetylation degree, CS can achieve various biodegradability and charge density under physiological pH conditions [111]. CS possesses a distinctive ability to transiently disrupt intercellular TJs within intestinal epithelia, thereby promoting peptide penetration through the paracellular pathway [112]. As an intestinal PE, CS helps peptides cross the intestinal epithelium more effectively. The cationic amino groups in the CS backbone bind with anionic macromolecules on the cell membrane, such as integrin $\alpha\gamma\beta3$. This interaction triggers the translocation of claudin-4 from the cell membrane to the cytoplasm, where it undergoes degradation in the lysosome, increasing paracellular permeability [113–115]. Kim *et al.* optimized the ionotropic gelation process using Cs and phytic acid (PA), resulting in an exceptional encapsulation efficiency of 97.1 % and a high bioavailability of 10.6 % for insulin [116].

However, CS's permeation-enhancing effect is highly influenced by pH, and its absorption-promoting activity is relatively low when used alone, which imposes certain limitations on its application. Furthermore, CS's adhesion properties may hinder its interaction with the epithelial surface [10,117]. To address these limitations, synthetic polymers were incorporated. Zhou *et al.* developed PC6/CS NPs, which were achieved by encapsulating CS NPs with the synthetic polymer poly(acrylic acid-cysteine-6-mercaptonicotinic acid) (PC6) (Fig. S4B in Supporting information) [118]. The thiol groups on PC6 can form covalent bonds with Cys-rich receptors, such as epidermal growth factor receptor and insulin-like growth factor receptor, inducing TJ opening. As a result, the oral absorption of PC6/CS NPs was significantly enhanced to 16.22 % compared to CS NPs.

The encapsulation rate of peptides in polymer NPs is significant, and the varied chemical properties of the polymers render them multifunctional. However, the polymer NPs degrade rapidly when diluted in biological fluids, resulting in abrupt or premature release of the peptides in the GIT, thereby reducing oral bioavailability.

4.2.3. Nanomicelles

Nanomicelles are nanosized structures formed through the self-assembly of amphiphilic polymers when their concentration exceeds the critical micellar concentration (CMC). They offer higher scale-up feasibility and relatively high stability [119]. These nanomicelles have shown promise in improving drug targeting to the colon through enhanced epithelial permeability and retention [120]. Recently, Xiong *et al*. demonstrated that galactosylated carboxymethyl CS nanomicelles can effectively target and release cyclosporine A in the colon, offering a promising approach to enhance therapeutic efficacy and reduce systemic side effects for ulcerative colitis (UC) treatment [121]. Nanomicelles bound to specific ligands not only enhance drug delivery but also enable oral immunotherapy. Wang *et al*. designed an innovative micellar delivery system by grafting the nine-amino-acid peptide CKSTHPLSC (CKS9) onto starch stearate [122]. The system self-assembles into nanomicelles through hydrophobic interactions and hydrogen bonds, which can stably target M cells and maintain structural stability under a variety of biological conditions, such as concentration, pH, and ionic strength changes. The CKS9 peptide sequence directly promotes the aggregation of antigens around M cells (Fig. S4C in Supporting information). Nanomicelles are susceptible to hydrolysis upon dilution, making it crucial to select polymer materials with a lower CMC as carriers. Additionally, it is essential to assess the potential for micelles to be absorbed into the bloodstream and their behavior during blood circulation [123].

4.2.4. Exosome-biomimetic nanocarriers

Exosomes are naturally occurring nanovesicles secreted by living cells and are an important class of biomaterials. They encapsulate various endogenous active macromolecules including DNA, miRNAs, mRNAs, and proteins, efficiently ferrying them to receptor cells for intercellular communication [124,125]. Due to their excellent biocompatibility, prolonged circulation time, and ability to encapsulate biomolecules, exosome-biomimetic nanocarriers have garnered increasing attention as novel carriers for biologic agents [126–128]. Wu *et al*. formulated insulin-loaded lactogenic exosomes (EXO@INS) and evaluated their hypoglycemic effects *in vivo* in TIDM rats [129]. The findings indicated that EXO@INS elicited superior and longer-lasting hypoglycemic effects compared to subcutaneously administrated insulin (Fig. S5A in Supporting information). Nevertheless, the low drug loading and encapsulation rates of lactogenic exosomes, coupled with the absence of stringent and consistent purification standards, present significant constraints on their application [130]. Recently, Xiao *et al*. engineered hybrid vesicles (mExos@DSPE-Hyd-PMPC) featuring adaptive surface characteristics by fusing natural mExos with functionalized liposomes [131]. Compared to natural mExos, these hybrid vesicles achieved a 2.4-fold increase in the encapsulation efficiency of semaglutide. The adaptive surface characteristics of the hybrid vesicles resulted in an oral bioavailability of 8.7%, significantly enhancing their pharmacological therapeutic effects (Fig. S5B in Supporting information). Milk exosomes have excellent therapeutic potential, but it should be noted that the conditions for isolating exosomes from milk and further purifying exosomes from co-released impurities have not yet been standardized. At the same time, future research should focus on analyzing all possible combinations of loading and surface modification of milk exosomes to enhance the therapeutic targeting of milk exosomes [132].

4.2.5. Yeast-biomimetic microcarriers

Yeast-biomimetic microcarriers hold promise for medication and vaccine delivery because of their specific targeting of phagocyte and immunogenicity, enabling diverse routes of administration. With several yeast strains endorsed by the FDA as a safety-grade microorganism, utilizing yeast as a carrier offers advantages in biosafety and biotolerance. Saba *et al*. devised alginate-coated yeast microcapsules (YMC), with insulin affixed through electrostatic interaction [133]. These YMCs can enter the systemic circulation through intestinal M cell-mediated endocytosis in the intestine, facilitated by lymphatic circulation. Following oral delivery of alginate-coated insulin-loaded YMCs, it was observed a significant hypoglycemic effect in T1DM rats. Various processes successfully convert yeast cells into microencapsulated forms for peptide delivery. However, the advancement of detailed quantitative analyses and predictive models faces challenges due to the lack of standardized procedures for variables such as yeast type, culture specifics, microencapsulation process fluid dynamics, and post-encapsulation handling and storage conditions [134].

4.3. Ionic liquids (ILs)

ILs are substances consisting of macromolecular organic cations, like alkyl pyridinium salts, alkyl imidazolium salts, alkyl quaternary ammonium salts, and heterocyclic aromatic compound derivatives, paired with organic or inorganic anions [135]. Widely utilized in chemical engineering as solvents, catalysts, and reagents, ILs exhibit remarkable solubilizing capabilities for insoluble drugs and potent permeation-enhancing properties for biomolecules [136,137]. However, many ILs in the realm of chemistry lack biocompatibility for drug delivery and other biological applications [138]. Recently, a subgroup of ILs derived from natural components like choline and organic acids has emerged, demonstrating improved drug delivery potential owing to their favorable biocompatibility and permeation properties [139]. Initially employed to enhance transdermal delivery of peptides like insulin, choline, and ergate ILs (CAGE-ILs) have been shown to significantly promote peptide diffusion through the mucus layer, and improve absorption by disrupting TJs, thereby surmounting the GIT barrier. Banerjee *et al*. designed a capsule resistant to acid, which contains caged polyimide for encapsulating insulin [140]. The ILs' component in this system has a dual role: its anions engage with the mucus layer to decrease its viscosity; and its cations interact with intestinal cells, causing TJs to open, thereby improving the absorption efficiency of insulin through the paracellular pathway. Whether administered intrajejunally or orally through enteric-coated capsules, CAGE-ILs loaded with 3–10 IU/kg of insulin can produce a significant hypoglycemic effect. In addition, CAGE-ILs can enhance the stability of insulin. It spontaneously forms self-assembled nanostructures in gastrointestinal fluids, optimizing oral absorption and drug distribution *in vivo* [141].

However, it is worth noting that the impact of ILs can differ based on the constituent ions and their relative ratios. The configuration of the inert ion largely dictates its eventual absorption effect on absorption, underscoring its significance in formulation design. Additionally, given water's pervasive presence in living organisms, paramount importance must be placed on understanding the interaction between ILs and water, particularly regarding whether water mitigates the permeation-enhancing effect of ILs.

4.4. Active transport by targeting transporter or receptor

Specific ligand-modified colloidal carriers have emerged as a promising strategy to enhance the absorption of oral peptides by targeting receptors, transporters, and specific cells within the intestinal epithelium, thereby improving active transport [142].

The intestinal epithelium houses folic acid receptors, and sugar receptors including mannose, galactose, and HA receptors [143], which facilitate active transit. For instance, NPs modified with galactose demonstrate enhanced cellular uptake and *ex vivo* permeability across the intestinal epithelial relative to unmodified NPs [144]. The Fc receptor (FcRn) stands out as a promising ligand for transporting biomolecules actively from the small intestine into circulation owing to its significant efficacy in transporting immunoglobulin G (IgG) antibodies across the epithelial barrier. Avezedo *et al*. designed a new biodegradable PLA-PEG NPs [145]. These NPs were surface-conjugated with human albumin at specific sites to enhance interaction with the neonatal FcRn binding. The designed albumin-conjugated NPs, containing 10 % insulin, exhibited strong pH-dependent binding to human FcRn and demonstrated improved transport across polarized cell layers. After orally delivered to diabetic mice expressing FcRn, these NPs led to a remarkable 40 % reduction in blood glucose levels within just one hour.

Transporters situated on the surface of epithelial cells selectively facilitate the movement of specific molecules into the cytoplasm. For example, NPs functionalized with an anionic bile salt, sodium glycodeoxycholate (SGDC), overcome multiple barriers, facilitating insulin uptake by targeting the apical sodium-dependent bile acid transporter (ASBT) [146,147]. Bashyal *et al*. developed this novel nanocarrier platform by combining insulin with SGDC to form a hydrophobic ion pair [148]. This HIP nanocomplex (C1 and C2) significantly enhances insulin absorption through the bile acid pathway. Compared to insulin solution, both C1 and C2 demonstrate a significant enhancement in permeability through the Caco-2 cell monolayer, with apparent permeability increased by 6.36-fold and 4.05-fold, respectively.

Targeting specific cells within the intestinal epithelium to enhance oral peptide delivery has garnered considerable attention, including M cells in PPs, goblet cells, and certain immune cells. M cells, renowned for their specialized physiological functions, are commonly the focus of efforts to deliver antigens or peptides orally [149,150]. These cells express various targeted receptors on their surface, like intercellular adhesion molecule-1 (ICAM-1), L-fucose, β1 integrin, and glycoprotein 2 (GP2). Particles conjugated with lectins and loaded with insulin demonstrate a significant reduction in blood glucose levels and an extended retention time on the intestinal membrane [151].

While active targeting may enhance absorption among intestinal cell populations, achieving substantial improvement in oral bioavailability presents challenges. These challenges stem from the limited absorption area, which constrains peptide absorption to a considerable extent. Exploring alternative targets with more extensive distribution across IECs is warranted to enhance oral delivery.

4.5. Lymphatic transport

The lymphatic system is crucial for oral drug uptake, with the transport route influenced by the drug's properties. Hydrophilic small molecules or larger molecules under 10 nm (such as proteins around 16–20 kDa) typically pass through the intestinal epithelium and enter the capillaries [152,153]. In contrast, highly lipophilic drugs can form complexes with lipoproteins, creating chyme particles that are transported *via* the lymphatic system. Researchers have utilized various lipid formulations to enhance absorption *via* the lipid pathway, mimicking the absorption process of dietary fat to improve the oral lymphatic delivery of peptides. For instance, insulin-loaded solid lipid NPs (SLNs) exhibit substantial drug accumulation in the intestinal lymphatic system [154]. It is found that the incorporation of bile salts into this system promoted endolymphatic transport and increased oral bioavailability, thereby greatly improving enterocyte permeability and enhancing delivery to the mesenteric lymph nodes. Lin *et al*. presented an orally administered phase-changeable nanoemulsions (PC/NEMs) facilitating exenatide (EXT) transport through the intestinal lymphatics, significantly improving bioavailability [155].

However, the lymph flow rate within the intestinal lymphatic system is roughly 500 times slower than the blood flow rate in the intestinal capillaries and portal veins, resulting in an insufficient amount of therapeutics being absorbed into the systemic circulation [156]. Consequently, the potential for increasing the oral bioavailability of peptides by lymphatic system targeting is severely restricted. As of now, no clinical or commercial peptide products have been developed using lymphatic targeting technologies.

It is worth noting that the gastrointestinal mucus and epithelial barriers play crucial roles in oral drug delivery, yet their functions are often contradictory. Overcoming both barriers simultaneously is a significant challenge. Traditional nanocarriers struggle to address these two obstacles because they require conflicting surface properties: hydrophilic and neutral surfaces are beneficial for mucus penetration, while surfaces that favor epithelial absorption typically need to be hydrophobic or cationic. To tackle this, Gao *et al*. modified mesoporous silica NPs (MSNs) with deoxycholic acid (DC) and coated them with sulfobetaine 12 (SB12), creating the zwitterionic nanocarrier MSN-DC@SB12 [157]. This design effectively overcame both the gastrointestinal mucus and intestinal epithelial barriers, improving oral drug delivery efficiency. The SB12 coating aids mucus penetration, while the DC coating enhances epithelial cell uptake after passing through the mucus layer. Similarly, Yang *et al*. developed M@Tf-NPs by pre-coating transferrin (Tf)-functionalized NPs with mucin [158]. This approach reduces the protein corona's negative effects and enhances protein adsorption related to endoplasmic reticulum-Golgi functions, improving internalization and transcellular transport of the NPs. These strategies show promise in enhancing the bioavailability of oral drugs by overcoming both mucus and epithelial barriers.

5. Oral delivery systems for peptides: Commercially available and under clinical investigation

5.1. Current oral peptides on the market

Oral peptides are available for both systemic administration and local retention within the GIT. For systemic treatment, certain oral peptides are formulated into soft capsules or oral solutions utilizing technologies like the self-nanoemulsifying drug delivery system (SNEDDS). Additionally, some oral enzyme products are specifically designed for the local treatment of gastrointestinal disorders. Please refer to Table S2 (Supporting information) for a comprehensive list of commercially available oral peptides.

5.1.1. Systemic-acting oral peptides

Oral peptides designed for systemic absorption undergo specific formulations to enhance their bioavailability and therapeutic efficacy. Cyclosporin A, a cyclic lipophilic undecapeptide, is one of the most successful examples, achieving an oral bioavailability of 19 %–40 % when formulated with SNEDDS technology [159]. The SNEDDS formulation (Neoral®) effectively controls droplet size, increases intestinal permeability, inhibits P-glycoprotein efflux, and reduces P450 metabolism, thus minimizing pharmacokinetic variability across patients. Desmopressin acetate (Ddvap®), an arginine vasopressin analog chemically modified for stability, was formulated into an oral tablet by Ferring Pharmaceuticals in 1995, and later approved by the FDA for generic versions [160]. However, without permeation-enhancing technology, the oral bioavailability of Ddvap® remained low, approximately 0.1 %. Octreotide, a synthetic analog of somatostatin offering enhanced stability in

gastric fluids, received FDA approval for oral enteric capsules containing sodium caprylate in June 2020, but its oral bioavailability is only 0.5 % [161,162]. Novo Nordisk developed an oral version of semaglutide, a GLP-1 agonist for type 2 diabetes mellitus (T2DM) and weight management, using SNAC to improve lipophilicity and absorption through localized pH buffering; this formulation received FDA approval in September 2019 [163,164]. Voclosporin (Lupkynis®), a structural analog of cyclosporin A, was modified to enhance potency by 3–4 times and improve its safety profile, particularly in relation to cholesterol, triglycerides, and diabetes risk; it received FDA approval in February 2021 for use in a combined immunosuppressive treatment for lupus nephritis. Additionally, trafinetide (Daybue®), a synthetic analog of insulin-like growth factor I (IGF-1), was approved by the FDA in March 2023 for treating Rett syndrome by reducing neuroinflammation and supporting synaptic function.

5.1.2. Locally-acting oral peptides

Certain peptides are specifically designed for localized treatment within the GIT rather than systemic circulation. For instance, liraglutide, utilized for treating irritable bowel syndrome (IBS) and other gastrointestinal disorders, acts locally in the small intestine as a guanylate cyclase C agonist. It is formulated into an oral capsule specifically for chronic idiopathic constipation and IBS with constipation [165]. Importantly, oral liraglutide has minimal absorption into the systemic circulation. Another example is vancomycin, a glycosylated tricyclic heptapeptide antibiotic, which due to its high hydrophilicity and complex ring structure, has limited absorption [166]. Consequently, oral vancomycin capsules are FDA-approved for treating pseudomembranous colitis, ensuring that the drug remains within the gut to exert its local effects.

5.2. Overview of the current clinical studies

Non-invasive drug delivery, particularly through oral peptide formulations, has gained substantial attention in recent years, with numerous formulations under clinical evaluation for both systemic and localized treatments (Table S3 in Supporting information). A significant focus among these technologies is the development of oral insulin [167]. Presently, two oral insulin products are in phase I clinical trials. Novo Nordisk (Denmark), in collaboration with Merrion Pharmaceuticals (Ireland), employs gastrointestinal permeation enhancement technology (GIPET) to create micelle-based tablets using sodium caprate as a PE. NOD Pharmaceuticals Inc. [168] has designed a formulation that encapsulates insulin in bioadhesive calcium phosphate NPs (Nodlin™), which demonstrated glucose-lowering effects comparable to injected insulin in phase I clinical trials [169]. Oramed Pharmaceuticals (Israel) developed an oral insulin capsule (ORMD-0801) containing a protease inhibitor and PE, showing significant glucose-lowering effects in T1DM patients during phase II clinical trials [170]. Although the phase III clinical trials in the U.S. did not meet primary endpoints, the drug received approval in China in April 2023 due to positive results in specific patient subgroups. Oshadi Drug Administration Ltd. (Israel) is utilizing silica NPs for oral insulin delivery, and Biocon Ltd. (India) has developed Tregopil, an orally modified insulin, which yielded positive outcomes in phase II clinical trials. Moreover, other oral peptides like parathyroid hormone (PTH) for osteoporosis and reserpine for endometriosis are also advancing through phase II clinical trials. Diasome Pharmaceuticals (USA) is at the forefront with its development of hepatocyte-targeting oral insulin using liposome technology that emulates natural insulin delivery, currently advancing into phase III clinical trials [171]. Emisphere Technologies Inc. (USA) has advanced an oral sCT formulation (SMC021), which is in phase III clinical trials and uses 5-cyano-*N*-acetylcysteine (5-CNAC) to enhance oral uptake similar to oral semaglutide [172].

Several innovations are also propelling the advancement of topical peptide delivery. Protagonist Therapeutics has engineered the Vectrix™ platform to create stabilized peptides, with two products currently undergoing clinical tests for UC (JNJ-2113) and polycythemia vera (rusfertide). Furthermore, Avaxia Biologics has designed a milk-derived antibody (AVX-470) for treating UC, currently undergoing phase I clinical trials. Additionally, emerging technologies for treating localized digestive tract diseases with orally administered peptides include Vorabodies™ from ActoBio Therapeutics [173].

6. Conclusion and future prospect

Over the past decade, the focus of pharmaceutical research has shifted significantly towards oral peptide delivery, driven by the growing market share of peptides. This review comprehensively explores a variety of exemplary strategies aimed at improving oral delivery, including engineered NPs, microneedles, PEs, nanocarriers, ionic liquids, and more. These technologies are meticulously developed to overcome the challenges of permeation and absorption, thus improving the oral absorption of peptides. However, despite these efforts, the conversion efficiency of oral peptides remains disappointingly low. For example, traditional PEs often fail to maintain the necessary dose threshold and spatial localization in the dynamic intestinal environment, leading to low bioavailability [174]. Additionally, animal models such as dogs and pigs, which are commonly used in preclinical studies, exhibit significant differences in gastrointestinal dynamics compared to humans, complicating the accurate prediction of PE performance in human trials. While smart delivery systems, including microneedles and nanocarriers, offer the potential for improved local drug absorption, they face critical challenges, including insufficient targeting and difficulties in large-scale production. Addressing these challenges is essential for the successful clinical application of these technologies.

In conclusion, the current bioavailability of oral peptides significantly lags behind that of injectables and is characterized by instability and inefficiency. This highlights the urgent need for further optimization. New approaches in peptide formulation are required, such as incorporating recent biopharmaceutical advancements, discovering novel targets for more effective PEs, or integrating multiple permeation-enhancing technologies to achieve synergistic effects. To validate the effectiveness of these new technologies, robust preclinical data are crucial. This requires comprehensive assessments of bioavailability in large animal models, as well as the development of more reliable and physiologically relevant *in vitro* models. The integration of 3D intestinal chips with primary cell models is essential to improve *in vitro* evaluation. Such an approach will facilitate the development of oral delivery systems for a broader range of peptides.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Juan Tao: Writing – review & editing, Writing – original draft, Visualization, Funding acquisition. **Jinlong Yang:** Writing – review & editing, Funding acquisition. **Mengyu Zhao:** Writing – review & editing. **Quangang Zhu:** Writing – review & editing. **Zhongjian Chen:** Writing – review & editing, Resources. **Jianping Qi:** Writing

– review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 82073801), the Postdoctoral Fellowship Program of China Postdoctoral Science Foundation (No. GZC20241240), and the Natural Science Research of Huaian Science and Technology Project (No. HAB2024073).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111170.

References

[1] J. Fetse, S. Kandel, U.F. Mamani, K. Cheng, Trends Pharmacol. Sci. 44 (2023) 425–441.
[2] L.B. Knudsen, J. Lau, Front. Endocrinol. 10 (2019) 155.
[3] P. Tyagi, S. Pechenov, J.A. Subramony, J. Control. Release 287 (2018) 167–176.
[4] J. Yuan, M. Guo, S. Zhao, et al., Chin. Chem. Lett. 34 (2023) 107943.
[5] E. Moroz, S. Matoori, J.-C. Leroux, Adv. Drug Deliv. Rev. 101 (2016) 108–121.
[6] H. Peng, J. Wang, J. Chen, et al., Expert Opin. Drug Deliv. 20 (2023) 1349–1369.
[7] P. Singh Chauhan, I. Abutbul Ionita, H. Moshe Halamish, A. Sosnik, D. Danino, J. Colloid Interface Sci. 592 (2021) 156–166.
[8] G.H. Kim, Gut Liver 15 (2021) 646–652.
[9] R. He, J. Wang, Z.H. Yu, et al., J. Med. Chem. 65 (2022) 13892–13909.
[10] M. Lopes, N. Shrestha, A. Correia, et al., J. Control. Release 232 (2016) 29–41.
[11] X. Han, Y. Lu, J. Xie, et al., Nat. Nanotechnol. 15 (2020) 605–614.
[12] J.S. Lee, P. Han, R. Chaudhury, et al., Nat. Biomed. Eng. 5 (2021) 983–997.
[13] S. Bonengel, M. Jelkmann, M. Abdulkarim, et al., J. Control. Release 273 (2018) 21–29.
[14] F. Hubálek, H.H.F. Refsgaard, S. Gram-Nielsen, et al., Nat. Commun. 11 (2020) 3746.
[15] A.K. Dhalla, Z. Al-Shamsie, S. Beraki, et al., Drug Deliv. Transl. Res. 12 (2022) 294–305.
[16] A. Taverner, J. MacKay, F. Laurent, et al., Tissue Barriers 8 (2020) 1710429.
[17] C. Menzel, T. Holzeisen, F. Laffleur, et al., J. Control. Release 277 (2018) 165–172.
[18] S. Fattah, M. Ismaiel, B. Murphy, et al., Eur. J. Pharm. Sci. 154 (2020) 105509.
[19] A. Abramson, M.R. Frederiksen, A. Vegge, et al., Nat. Biotechnol. 40 (2022) 103–109.
[20] W. Chen, J. Wainer, S.W. Ryoo, et al., Sci. Adv. 8 (2022) eabk1792.
[21] A. Abramson, E. Caffarel-Salvador, V. Soares, et al., Nat. Med. 25 (2019) 1512–1518.
[22] S.T. Buckley, Sci. Transl. Med. 10 (2018) 7047.
[23] S. Maher, R.J. Mrsny, D.J. Brayden, Adv. Drug Deliv. Rev. 106 (2016) 277–319.
[24] S. Verma, U.K. Goand, A. Husain, et al., Drug Dev. Res. 82 (2021) 927–944.
[25] T.D. Brown, K.A. Whitehead, S. Mitragotri, Nat. Rev. Mater. 5 (2020) 127–148.
[26] S. Maher, T.W. Leonard, J. Jacobsen, D.J. Brayden, Adv. Drug Deliv. Rev. 61 (2009) 1427–1449.
[27] N. Binkley, M. Bolognese, A. Sidorowicz-Bialynicka, et al., J. Bone Miner. Res. 27 (2012) 1821–1829.
[28] H.X. Weng, L.F. Hu, L. Hu, et al., Chin. Chem. Lett. 33 (2022) 1889–1894.
[29] M.E. Johansson, G.C. Hansson, Nat. Rev. Immunol. 16 (2016) 639–649.
[30] T. Pelaseyed, G.C. Hansson, J. Cell Sci. 133 (2020) jcs240929.
[31] L. Etienne-Mesmin, B. Chassaing, M. Desvaux, et al., FEMS Microbiol. Rev. 43 (2019) 457–489.
[32] M. Bohley, J.C. Leroux, Adv. Sci. 11 (2024) e2400843.
[33] R. Bansil, B.S. Turner, Adv. Drug Deliv. Rev. 124 (2018) 3–15.
[34] C. Liu, X. Jiang, Y. Gan, M. Yu, Med. Drug Discov. 12 (2021) 100110.
[35] F.J. Varum, F. Veiga, J.S. Sousa, A.W. Basit, J. Pharm. Pharmacol. 64 (2012) 218–227.
[36] A. Ermund, A. Schuette, M. Johansson, et al., Am. J. Physiol. Gastrointest. Liver Physiol. 305 (2013) G341–G347.
[37] P. Paone, P.D. Cani, Gut 69 (2020) 2232–2243.
[38] B. Homayun, X. Lin, H.J. Choi, Pharmaceutics 11 (2019) 129.
[39] X. Zhang, H. Cheng, W. Dong, et al., J. Control. Release 272 (2018) 29–38.
[40] S. Haddadzadegan, F. Dorkoosh, A. Bernkop-Schnürch, Adv. Drug Deliv. Rev. 182 (2022) 114097.
[41] D. Dahlgren, T. Olander, M. Sjöblom, M. Hedeland, H. Lennernäs, Acta Pharm. Sin. B 11 (2021) 1667–1675.
[42] M. Shan, M. Gentile, J.R. Yeiser, et al., Science 342 (2013) 447–453.
[43] S. Kong, Y.H. Zhang, W. Zhang, Biomed. Res. Int. 2018 (2018) 2819154.
[44] C.L. Bevins, N.H. Salzman, Nat. Rev. Microbiol. 9 (2011) 356–368.
[45] M.A. Odenwald, J.R. Turner, Nat. Rev. Gastroenterol. Hepatol. 14 (2017) 9–21.
[46] J. Qi, J. Zhuang, Y. Lv, Y. Lu, W. Wu, J. Control. Release 275 (2018) 92–106.
[47] C. Jung, J.P. Hugot, F. Barreau, Int. J. Inflam. 2010 (2010) 823710.
[48] N.A. Mabbott, D.S. Donaldson, H. Ohno, I.R. Williams, A. Mahajan, Mucosal Immunol. 6 (2013) 666–677.
[49] C.T. Capaldo, D.N. Powell, D. Kalman, J. Mol. Med. 95 (2017) 927–934.
[50] M. Vancamelbeke, S. Vermeire, Expert Rev. Gastroenterol. Hepatol. 11 (2017) 821–834.
[51] C. Sturgeon, A. Fasano, Tissue Barriers 4 (2016) e1251384.
[52] Z. Lu, L. Ding, Q. Lu, Y.H. Chen, Tissue Barriers 1 (2013) e24978.
[53] S. Lechuga, A.I. Ivanov, Biochim. Biophys. Acta Mol. Cell Res. 1864 (2017) 1183–1194.
[54] Q. Zhu, Z. Chen, P.K. Paul, et al., Acta Pharm. Sin. B 11 (2021) 2416–2448.
[55] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Adv. Drug Deliv. Rev. 64 (2012) 4–17.
[56] C. Liu, Y. Kou, X. Zhang, et al., Expert Opin. Drug Deliv. 15 (2018) 223–233.
[57] Z. Antosova, M. Mackova, V. Kral, T. Macek, Trends Biotechnol. 27 (2009) 628–635.
[58] A. Mortensen, F. Aguilar, R. Crebelli, et al., Efsa J. 15 (2017) e04785.
[59] B. Singh, S. Maharjan, T. Jiang, et al., Mol. Pharma. 12 (2015) 3816–3828.
[60] T. Yu, J. Chisholm, W.J. Choi, et al., Adv. Healthc. Mater. 5 (2016) 2745–2750.
[61] M. Kidron, S. Dinh, Y. Menachem, et al., Diabet. Med. 21 (2004) 354–357.
[62] J.K. Patra, G. Das, L.F. Fraceto, et al., J. Nanobiotechnology 16 (2018) 71.
[63] Q. Liu, J. Guan, L. Qin, X. Zhang, S. Mao, Drug Discov. Today 25 (2020) 150–159.
[64] Q. Liu, J. Guan, R. Song, X. Zhang, S. Mao, Acta Biomater. 140 (2022) 76–87.
[65] J.T. Huckaby, S.K. Lai, Adv. Drug Deliv. Rev. 124 (2018) 125–139.
[66] T. Nie, Z. He, Y. Zhou, et al., ACS Appl. Mater. Interfaces 11 (2019) 29593–29603.
[67] T. Nie, Z. He, J. Zhu, L. Liu, Y. Chen, Adv. Ther. 3 (2020) 2000016.
[68] Y. Guo, Y. Ma, X. Chen, et al., ACS Nano 17 (2023) 2813–2828.
[69] W. Shan, X. Zhu, M. Liu, et al., ACS Nano 9 (2015) 2345–2356.
[70] J. Wu, Y. Zheng, M. Liu, et al., ACS Appl. Mater. Interfaces 10 (2018) 9916–9928.
[71] Y. Zhang, M. Xiong, X. Ni, et al., ACS Appl. Mater. Interfaces 13 (2021) 18077–18088.
[72] N. Sahatsapan, B. Pamornpathomkul, T. Rojanarata, et al., J. Drug Deliv. Sci. Technol. 69 (2022) 103173.
[73] Y. Ma, Y. Guo, S. Liu, et al., Nano Lett. 23 (2023) 7552–7560.
[74] M. Guo, M. Wei, W. Li, et al., J. Control. Release 307 (2019) 64–75.
[75] D. Li, J. Zhuang, H. He, et al., ACS Appl. Mater. Interfaces 9 (2017) 42492–42502.
[76] M. Yu, J. Wang, Y. Yang, et al., Nano Lett. 16 (2016) 7176–7182.
[77] B.J. Lee, Y. Cheema, S. Bader, G.A. Duncan, JCIS Open 4 (2021) 100025.
[78] A.S. Rzhevskiy, T.R.R. Singh, R.F. Donnelly, Y.G. Anissimov, J. Control. Release 270 (2018) 184–202.
[79] G. Traverso, C.M. Schoellhammer, A. Schroeder, et al., J. Pharm. Sci. 104 (2015) 362–367.
[80] A. Abramson, E. Caffarel-Salvador, M. Khang, et al., Science 363 (2019) 611–615.
[81] M. Hashim, R. Korupolu, B. Syed, et al., Pharmacol. Res. Perspect. 7 (2019) e00522.
[82] L. Cai, G. Chen, L. Sun, et al., Adv. Mater. 35 (2023) 10679.
[83] Z. Luo, N. Paunovic, J.C. Leroux, Adv. Drug Deliv. Rev. 175 (2021) 113814.
[84] N.G. Ilbäck, T. Stålhandske, U. Lindh, Biol. Trace Elem. Res. 76 (2000) 133–148.
[85] R.S. Lanigan, T.A. Yamarik, Int. J. Toxicol. 21 (2002) 95–142.
[86] S. Ahmed, M.M. Amin, S. Sayed, Drug Deliv. 30 (2023) 2179129.
[87] V. Suvarna, R. Mallya, K. Deshmukh, et al., Curr. Drug Deliv. 21 (2024) 961–977.
[88] D.J. Brayden, V. Stuettgen, Eur. J. Pharm. Sci. 159 (2021) 105737.
[89] A. Fasano, J.P. Nataro, Adv. Drug Deliv. Rev. 56 (2004) 795–807.
[90] M.J. Cano-Cebrián, T. Zornoza, L. Granero, A. Polache, Curr. Drug Deliv. 2 (2005) 9–22.
[91] E. Böhmová, D. Machová, M. Pechar, et al., Physiol. Res. 67 (2018) S267–S279.
[92] P. Uhl, C. Grundmann, M. Sauter, et al., Nanomedicine 24 (2020) 102132.
[93] C. Twarog, S. Fattah, J. Heade, et al., Pharmaceutics 11 (2019) 78.
[94] N. Kommineni, V.G.S. Sainaga Jyothi, A. Butreddy, et al., Pharm. Res. 40 (2023) 633–650.
[95] B. Ding, Z. Zhu, C. Guo, et al., Acta Pharm. Sin. B 14 (2024) 2006–2025.
[96] S. Hossain, P. Joyce, A. Parrow, et al., Mol. Pharm. 17 (2020) 4226–4240.
[97] S. Maher, C. Geoghegan, D.J. Brayden, Expert Opin. Drug Deliv. 18 (2021) 273–300.
[98] D.J. Brayden, T.A. Hill, D.P. Fairlie, S. Maher, R.J. Mrsny, Adv. Drug Deliv. Rev. 157 (2020) 2–36.
[99] X. Qin, C. Yu, J. Wei, et al., Adv. Mater. 31 (2019) e1902791.
[100] S. Das, A. Chaudhury, AAPS PharmSciTech 12 (2011) 62–76.
[101] T.R. Wang, Y.C. Luo, Nano Res. 14 (2021) 4487–4501.
[102] Z. Niu, I. Conejos-Sánchez, B.T. Griffin, C.M. O'Driscoll, M.J. Alonso, Adv. Drug Deliv. Rev. 106 (2016) 337–354.
[103] L. Zou, M. Cheng, K. Hu, J. Feng, L. Tu, Chin. Chem. Lett. 35 (2024) 109129.
[104] J.C. Yu, Y.Q. Zhang, J.Q. Wang, et al., Nano Res 12 (2019) 1539–1545.
[105] C. He, L. Yin, C. Tang, C. Yin, Biomaterials 33 (2012) 8569–8578.
[106] J. Palacio, N.A. Agudelo, B.L. Lopez, Curr. Opin. Chem. Eng. 11 (2016) 14–19.
[107] P. Ojer, A.L. de Cerain, P. Areses, I. Peñuelas, J.M. Irache, Pharm. Res. 29 (2012) 2615–2627.
[108] L.R. Volpatti, M.A. Matranga, A.B. Cortinas, et al., ACS Nano 14 (2020) 488–497.
[109] S. Mansoor, P.P.D. Kondiah, Y.E. Choonara, V. Pillay, Polymers (Basel) 11 (2019) 1380.

[110] M. Sun, H. Hu, L. Sun, Z. Fan, Chin. Chem. Lett. 31 (2020) 1729–1736.
[111] P.Y. Lin, Y.L. Chiu, J.H. Huang, et al., Adv. Sci. 5 (2018) 1701079.
[112] P. Joyce, A. Wignall, K. Peressin, et al., Int. J. Pharm. 612 (2022) 121382.
[113] L.W. Hsu, P.L. Lee, C.T. Chen, et al., Biomaterials 33 (2012) 6254–6263.
[114] L.W. Hsu, Y.C. Ho, E.Y. Chuang, et al., Biomaterials 34 (2013) 784–793.
[115] T.H. Yeh, L.W. Hsu, M.T. Tseng, et al., Biomaterials 32 (2011) 6164–6173.
[116] J.U. Kim, H.M. Shahbaz, H. Lee, et al., Int. J. Pharm. 588 (2020) 119736.
[117] S. Seyam, N.A. Nordin, M. Alfatama, Pharmaceuticals (Basel) 13 (2020) 307.
[118] S. Zhou, H. Deng, Y. Zhang, et al., Mol. Pharm. 17 (2020) 239–250.
[119] V. Junnuthula, P. Kolimi, D. Nyavanandi, et al., Pharmaceutics 14 (2022) 1860.
[120] H. Ibaraki, N. Hatakeyama, N. Arima, et al., Eur. J. Pharm. Biopharm. 170 (2022) 170–178.
[121] M. Xiong, Y. Li, H. He, et al., Eur. J. Pharm. Biopharm. 189 (2023) 152–164.
[122] T. Wang, K. Liu, L. Zhang, et al., Ind. Crop. Prod. 184 (2022) 115074.
[123] W. Chen, A. Yan, T. Sun, et al., Colloids Surf. B: Biointerfaces 241 (2024) 114057.
[124] F. Liu, F. Meng, Z. Yang, et al., Chin. Chem. Lett. 35 (2024) 109335.
[125] B. Yang, Y. Chen, J. Shi, Adv. Mater. 31 (2019) e1802896.
[126] F. Aqil, R. Munagala, J. Jeyabalan, et al., Cancer Lett. 449 (2019) 186–195.
[127] D. Li, S. Yao, Z. Zhou, et al., Carbohydr. Res. 493 (2020) 108032.
[128] D. Rufino-Ramos, P.R. Albuquerque, V. Carmona, et al., J. Control. Release 262 (2017) 247–258.
[129] L. Wu, L. Wang, X. Liu, et al., Acta Pharm. Sin. B 12 (2022) 2029–2042.
[130] M.Y. Tian, D.X. Hao, Y. Liu, et al., Food Funct. 14 (2023) 1320–1337.
[131] P. Xiao, H. Wang, H. Liu, et al., ACS Nano 18 (2024) 21091–21111.
[132] A.M. Timofeeva, A.P. Paramonik, S.S. Sedykh, G.A. Nevinsky, Int. J. Mol. Sci. 24 (2023) 10194.
[133] C. Sabu, D. Raghav, U.S. Jijith, et al., Mater. Sci. Eng. C Mater. Biol. Appl. 103 (2019) 109753.
[134] G. Coradello, N. Tirelli, Molecules 26 (2021) 3123.
[135] Z. Lei, B. Chen, Y.M. Koo, D.R. MacFarlane, Chem. Rev. 117 (2017) 6633–6635.
[136] X. Wu, Z. Chen, Y. Li, et al., Int. J. Pharm. 558 (2019) 380–387.
[137] X. Wu, H. Zhang, S. He, et al., Int. J. Biol. Macromol. 150 (2020) 528–535.
[138] K.S. Egorova, E.G. Gordeev, V.P. Ananikov, Chem. Rev. 117 (2017) 7132–7189.
[139] M. Zakrewsky, K.S. Lovejoy, T.L. Kern, et al., Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 13313–13318.
[140] A. Banerjee, K. Ibsen, T. Brown, et al., Proc. Natl. Acad. Sci. U. S. A. 115 (2018) 7296–7301.
[141] Y. Shi, Z. Zhao, Y. Gao, et al., J. Control. Release 322 (2020) 602–609.
[142] A. Verma, S. Sharma, P.K. Gupta, et al., Acta Biomater 31 (2016) 288–300.
[143] N. Di Tommaso, A. Gasbarrini, F.R. Ponziani, Int. J. Environ. Res. Public Health 18 (2021) 12836.
[144] Y. Li, B. Yang, X. Zhang, Int. J. Pharm. 568 (2019) 118508.
[145] C. Azevedo, J. Nilsen, A. Grevys, et al., J. Control. Release 327 (2020) 161–173.
[146] S. Bashyal, J.E. Seo, Y.W. Choi, S. Lee, J. Control. Release 338 (2021) 644–661.
[147] J. Wang, Y. Sun, L. Meng, et al., Chin. Chem. Lett. 36 (2025) 110529.
[148] G. Bhardwaj, J. O'Connor, S. Rettie, et al., Cell 185 (2022) 3520–3532.
[149] J. Kunisawa, Y. Kurashima, H. Kiyono, Adv. Drug Deliv. Rev. 64 (2012) 523–530.
[150] X. Fang, R. Miao, J. Wei, H. Wu, J. Tian, Comput. Struct. Biotechnol. J. 20 (2022) 5935–5951.
[151] B.Y. Kim, J.H. Jeong, K. Park, J.D. Kim, J. Control. Release 102 (2005) 525–538.
[152] G.M. Ryan, L.M. Kaminskas, C.J. Porter, J. Control. Release 193 (2014) 241–256.
[153] A. Supersaxo, W.R. Hein, H. Steffen, Pharm. Res. 7 (1990) 167–169.
[154] M. Trotta, M.E. Carlotti, M. Gallarate, et al., J. Dispers. Sci. Technol. 32 (2011) 1041–1045.
[155] P.Y. Lin, K.H. Chen, Y.B. Miao, et al., Adv. Funct. Mater. 29 (2019) 1809015.
[156] M.J. Hackett, J.L. Zaro, W.C. Shen, P.C. Guley, M.J. Cho, Adv. Drug Deliv. Rev. 65 (2013) 1331–1339.
[157] Y. Gao, Y. He, H. Zhang, et al., J. Colloid Interface Sci. 582 (2021) 364–375.
[158] D. Yang, Y. Feng, Y. Yuan, et al., ACS Nano 18 (2024) 7455–7472.
[159] D.J. Hauss, Adv. Drug Deliv. Rev. 59 (2007) 667–676.
[160] M. Zaoral, Biopolymers 90 (2008) 213.
[161] M. Cui, W. Wu, L. Hovgaard, et al., Int. J. Pharm. 489 (2015) 277–284.
[162] S. Tuvia, J. Atsmon, S.L. Teichman, et al., J. Clin. Endocrinol. Metab. 97 (2012) 2362–2369.
[163] H.S. Kim, C.H. Jung, Int. J. Mol. Sci. 22 (2021) 9936.
[164] A. Andersen, F.K. Knop, T. Vilsbøll, Drugs 81 (2021) 1003–1030.
[165] D.S. Weinberg, J.E. Lin, N.R. Foster, et al., Cancer Prev. Res. 10 (2017) 345–354.
[166] S. Rao, Y. Kupfer, M. Pagala, E. Chapnick, S. Tessler, Scand. J. Infect. Dis. 43 (2011) 386–388.
[167] T.A. Aguirre, D. Teijeiro-Osorio, M. Rosa, et al., Adv. Drug Deliv. Rev. 106 (2016) 223–241.
[168] M.A. Momoh, K.C. Franklin, C.P. Agbo, et al., Heliyon 6 (2020) e03650.
[169] J. Li, Y. Wang, L. Han, et al., Clin. Ther. 34 (2012) 2333–2338.
[170] R. Eldor, E. Arbit, A. Corcos, M. Kidron, PLoS One 8 (2013) e59524.
[171] W.B. Geho, H.C. Geho, J.R. Lau, T.J. Gana, J. Diabetes Sci. Technol. 3 (2009) 1451–1459.
[172] M.A. Karsdal, I. Byrjalsen, K. Henriksen, et al., Osteoarthritis Cartil. 18 (2010) 150–159.
[173] M. Durán-Lobato, Z. Niu, M.J. Alonso, Adv. Mater. 32 (2020) e1901935.
[174] M.A. Nauck, J. Wefers, J.J. Meier, Lancet Diabetes Endocrinol. 9 (2021) 525–544.