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REVIEW

Transepithelial transport of nanoparticles in oral drug delivery: From the perspective of surface and holistic property modulation

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Abstract Despite the promising prospects of nanoparticles in oral drug delivery, the process of oral administration involves a complex transportation pathway that includes cellular uptake, intracellular trafficking, and exocytosis by intestinal epithelial cells, which are necessary steps for nanoparticles to enter the bloodstream and exert therapeutic effects. Current researchers have identified several crucial factors that regulate the interaction between nanoparticles and intestinal epithelial cells, including surface properties such as ligand modification, surface charge, hydrophilicity/hydrophobicity, intestinal protein corona formation, as well as holistic properties like particle size, shape, and rigidity. Understanding these properties is essential for enhancing transepithelial transport efficiency and designing effective oral drug delivery systems. Therefore, this review provides a comprehensive overview of the surface and holistic properties that influence the transepithelial transport of nanoparticles, elucidating the underlying principles governing their impact on transepithelial transport. The review also outlines the chosen of parameters to be considered for the subsequent design of oral drug delivery systems.

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1. Introduction

With the rapid advancement of nanotechnology, nanoparticles have been extensively utilized as carriers for oral drug delivery in the treatment of various diseases[1−4]. These nano-delivery systems can mitigate drug degradation in the gastric acid and enzymatic environment while enhancing their stability within the gastrointestinal tract[5,6]. However, augmenting the oral bioavailability of drugs remains challenging due to limitations imposed by both the intestinal mucous barrier and epithelial cell barrier[7,8]. The mucus is a hydrophilic gel layer secreted by intestinal goblet cells, which intercepts foreign substances through electrostatic and hydrophobic interactions, as well as its dense mesh-like structure[9]. Orally administered nanoparticles are easily entrapped within the mucus, preventing them from effectively reaching the intestinal epithelial cells[10−12]. The intestinal epithelial cell layer mainly consists of epithelial cells, goblet cells, and M cells, providing a pathway for water, nutrients, and other exogenous substances to enter the systemic circulation or lymphatic circulation from the intestinal lumen[13,14]. Meanwhile, the intestinal epithelial cells form a barrier that maintains segregation between luminal microbial communities and the mucosal immune system[15,16]. Orally administered nanoparticles are insufficient to traverse the intestinal epithelial cell layer *via* simple diffusion, necessitating a transepithelial transport process encompassing cellular uptake, intracellular trafficking, and basolateral exocytosis in order to access the bloodstream and elicit their pharmacological effects[17−19] (Fig. 1). Therefore, the promotion and enhancement of transepithelial transport of nanoparticles represent pivotal and formidable challenges in the realm of oral drug delivery.

The surface properties of nanoparticles, including their hydrophilicity/hydrophobicity, charge, and surface ligands, play a crucial role in determining their interactions with tissues, cells, and organelles. These factors ultimately dictate the fate of the payloads[20−22]. For instance, appropriate modification of surface ligands can enhance the affinity of nanoparticles and intestinal epithelial cells, improve cellular uptake efficiency, modulate intracellular trafficking pathways, and ultimately impact the stability and transepithelial transport efficiency of nanoparticles[23−25]. In addition to surface properties, the holistic properties of nanoparticles, such as particle size, shape, and elasticity, are also closely related to their transepithelial transport[26−29]. Therefore, this article provides a comprehensive review of the research progress on the impact of surface and holistic properties of nanoparticles on transepithelial transport and summarizes the strategies and future exploitation for the design of oral drug delivery systems.

2. The transepithelial transport of nanoparticles

2.1. Paracellular transport

Paracellular transport refers to the translocation of drugs into the bloodstream through the space between intestinal epithelial cells, instead of directly transport across the epithelial monolayers[30]. The tight junctions between intestinal epithelial cells serve as a barrier against the invasion of exogenous substances and pathogens[31,32], but also present a challenge for paracellular drug delivery to cargos with a radius greater than 6 nm[33]. However, absorption enhancers such as chitosan can effectively increase the paracellular permeability of drugs by reversibly opening the tight junctions[34]. It is worth noting that even when the tight junctions are fully opened, the intercellular gaps measure only approximately 20 nm, posing a significant challenge for most nanoparticles to traverse[35]. When the intestinal mucosa is intact, the translocation of nanoparticles through this pathway is generally limited to less than 10%, depending on factors such as particle size and the integrity of epithelial junction[14,36]. Consequently, achieving effective paracellular transport remains an ongoing hurdle for nano-drug delivery systems.

2.2. M cell-associated pathway

M cells are primarily located in Peyer's patches and are a type of specialized type of cell with invaginations in their cell membranes or basement membranes[37,38]. The unique structure of M cells facilitates the selective entry of specific substances into the lymphatic tissue beneath the intestinal mucosa through active−transport pathways, offering a potential strategy to enhance drug bioavailability by bypassing first-pass metabolism and reducing toxicity[39,40]. Despite constituting less than 1% of the absorptive intestinal epithelium's total surface area, the absorption capabilities of M cells primarily rely on the specific types of nanoparticles involved. M cells have a preference for internalizing particles with diameters below 10 μm[41]. Nanoparticles ranging from 550 to 1100 nm demonstrate improved retention within Peyer's patches compared to nanoparticles measuring at 280 nm. Particles smaller than 1 μm can be taken up by M cells before being transported into lymphatic vessels and entering systemic circulation[42−44]. However, comparing findings across various studies proves challenging due to differences in animal models used as well as variations in materials employed and measurement techniques[45]. It is estimated that this pathway accounts for approximately 0.2%−70% of nanoparticle delivery efficiency range-wise depending on the factors such as particle size and surface modifications. For example, polystyrene particle (PS, 2 μm) exhibited 0.2% of uptake through the M cell-associated pathway, while PS (60 nm) exhibited 60% uptake in the M cell-associated pathway[46,47]. The improvement of nanoparticle targeting to M cells can also be enhanced by identifying appropriate strategies. He et al.[48] designed aptamer-modified liposomes (Apt-Lip) targeted to M-cells for the oral delivery of exenatide. The Apt-Lip was found to increase the transport efficiency of exenatide by 2-fold in M cells and showed better absorption in Peyer's patches. The *Ulex europaeus* agglutinin 1 (UEA-1, a representative lectin) was modified as ligands targeted to the fucose residues on the apical surface of M cells. The UEA-1 modified nanoparticles enhanced insulin uptake by 4.1-fold in the Peyer's patches and 2.6-fold in intestinal epithelium[49]. Oral delivery of ovalbumin could also be improved using the nanocapsules with

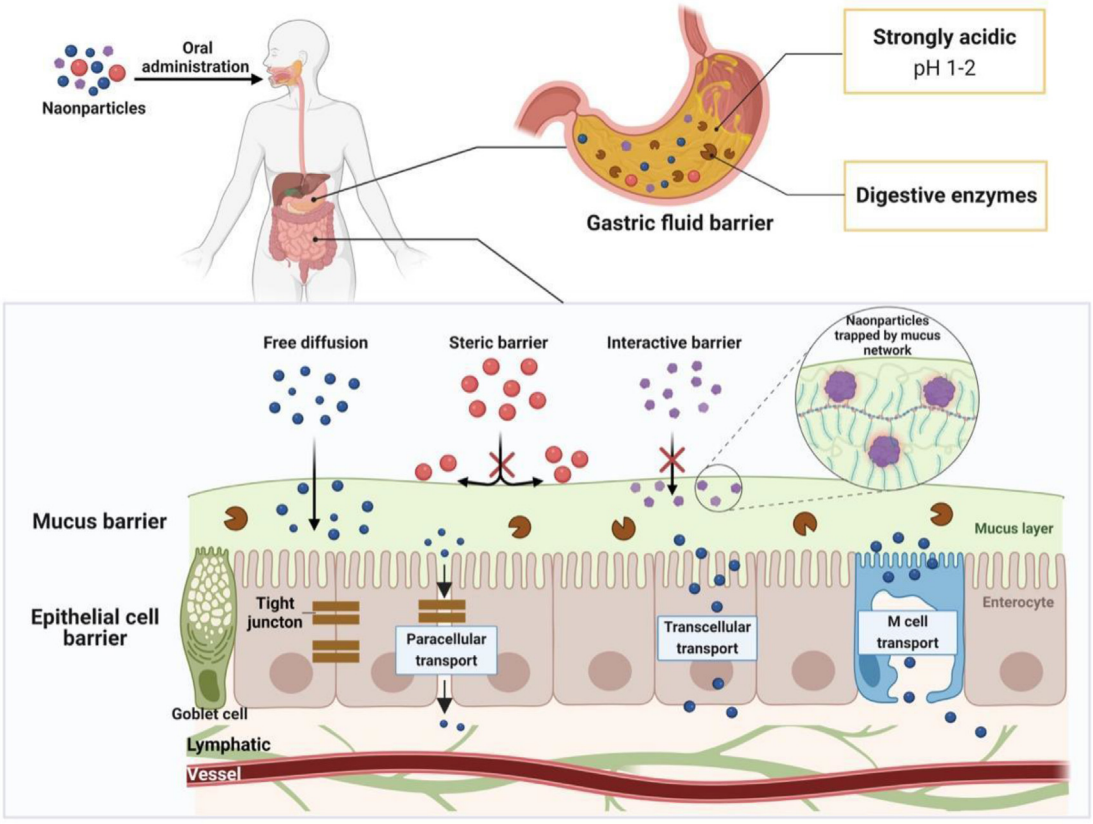

Figure 1 Schematic diagram of the physiological barriers in the gastrointestinal tract of nanoparticles for oral administration. Made using BioRender.

higher binding ability and transport efficiency to M cells[50]. However, the limited receptor expression poses a formidable challenge for the internalization of most nanoparticles by M cells[44,45,51]. Furthermore, nanoparticles within the M cell-associated pathway have the potential to be delivered and intercepted by immune cells such as dendritic cells and macrophages, thereby impeding their eventual absorption into the systemic circulation[1]. Therefore, the M cell-mediated transport is well-suited for oral vaccine delivery as this route promotes mucosal immunity activation[52]. Although some nanoparticles in this pathway may ultimately undergo phagocytosis by immune cells, leading to restricted systemic absorption[45,53].

2.3. *Transcytosis pathway*

Transcytosis serves as the principal pathway for nanoparticles to access the systemic circulation[14]. Most nanoparticles undergo a series of processes, including apical endocytosis, intracellular trafficking, and basolateral exocytosis, within the transcytosis pathway to traverse the intestinal epithelial cell layer[54]. Initially, nanoparticles can enter epithelial cells through macropinocytosis, caveolae-mediated endocytosis, or clathrin-mediated endocytosis from the apical surface of these cells[55−57]. Subsequently, they undergo intricate intracellular trafficking within transport vesicles or endosomes[7,58,59]. The intracellular trafficking of nanoparticles typically involves the degradation pathway, secretion pathway, and recycling pathway[60,61]. The degradation pathway refers to the transportation of nanoparticles through the endosome−lysosome route after endocytosis. Nanoparticles enter lysosomes *via* clathrin-mediated endocytosis through the endosome−lysosome pathway[58,62]. The acidic environment (pH 4.5−5.5) and enzymes in lysosomes can degrade lipid and protein components of nanoparticles as well as encapsulated drugs, significantly reducing transcytosis efficiency[63]. In contrast, transport through the secretion and recycling pathways can bypass lysosomal degradation, thereby maintaining structural integrity and facilitating nanoparticle transcytosis[64,65]. Functionalized nanoparticles are transported through early endosomes to the endoplasmic reticulum or Golgi apparatus, and subsequently delivered to the extracellular space *via* secretory pathways such as the endoplasmic reticulum-Golgi pathway and Golgi-to-cell membrane pathway[66]. Moreover, recycling pathways like caveolae and recycling endosomes enable the direct transportation of nanoparticles to the cell membrane for release into the extracellular space[64]. It is important to note that intestinal epithelial cells exhibit polarity, with differential expression of receptors/transporters on their apical and basolateral membranes[38,67]. The nanoparticles are internalized into cells and subsequently excreted from the apical membrane into the intestinal lumen, resulting in a reduction in oral absorption[64,68,69]. While some nanoparticles could be transported from the basolateral membrane to enter into blood circulation to exert therapeutic effects[62,70,71]. Therefore, developing suitable strategies to bypass lysosomes, and achieve unidirectional transport from the apical to the basolateral side is a prospective strategy for effective

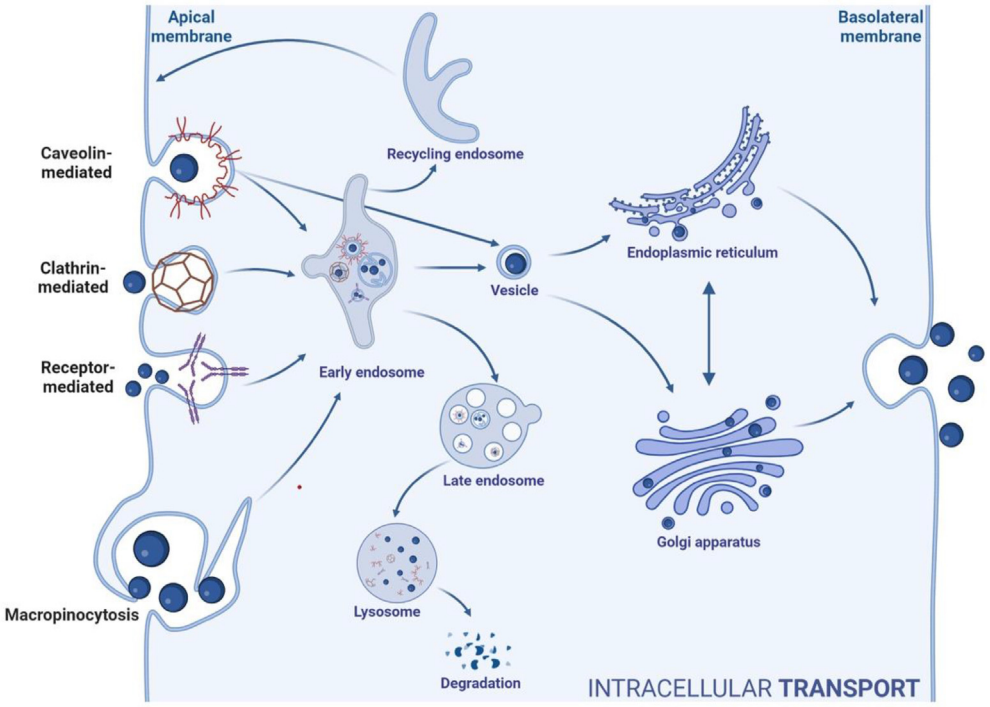

Figure 2 Schematic diagram of the potential endocytic pathway for nanoparticle transportation across intestinal epithelial cells. Made using BioRender.

transcytosis (Fig. 2). The absorption efficiency of diverse nanoparticles exhibits significant variations when undergoing transcytosis to traverse the intestinal epithelial cell layer. Hodges et al.[47] found that 73.7% of PS (2 um) particles were transported through the transcytosis pathway. However, The transcytosis pathway exhibited a limited transport efficiency of 5%−10% for PLGA nanoparticles[64,72]. It was estimated that approximately 5%−70% of nanoparticles were transported across the intestinal epithelium in the transcytosis pathway.

2.4. *The pathway to reach the systemic circulation*

After transport across the intestinal mucosa, nanoparticles may take different routes until they reach the systemic circulation. For transepithelial transport and paracellular pathway, most nanoparticles are usually absorbed into blood capillaries. Subsequently, they are transported to the liver *via* hepatic portal veins where they undergo hepatic first-pass metabolism[1]. The metabolic enzymes in the liver can lead to drug wastage and reduce the amount of intact drugs entering the systemic circulation for therapeutic effect.

Alternatively, some nanoparticles can be absorbed into lacteals after crossing epithelial monolayers[16,73]. Nanoparticles in the M cell-associated pathway were generally transported into the lymphatic tissue beneath the intestinal mucosa. In addition to reaching lymphatic vessels through the M cell-related pathway, nanoparticles can also be absorbed by lymphocytes through transcytosis across epithelial cells. These nanoparticles then travel with lymph fluids to lymphatic capillaries that converge into collecting vessels before finally entering systemic circulation at thoracic ducts *via* mesenteric lymph nodes[1,74]. A representative pathway of intestinal lymphatic transport is the uptake and transport using chylomicrons. The efficiency of nanoparticle routes, however, depends on various factors[16]. One crucial factor influencing the transport of nanoparticles is the lipid type employed, including its chain length and degree of saturation. The lipophilicity of fatty acids (FAs) correlates with their chain length, which also determines their binding capacity to nanoparticles[75,76]. Supporting this observation is the discovery that a self-nano emulsifying drug delivery system composed of long chain FAs exhibited higher recovery in the lymph compared to those containing medium-chain FAs[77]. Moreover, the internalization of nanoparticles *via* specific transporter-mediated pathways and chylomicron transport pathways can facilitate their transportation into the lymphatic vessel. Bae's group[78] found that approximately 47% of bile acid-conjugated particles are transported to the systemic circulation through the gut lymphatic system. Intestinal lymphatic transport may be an obvious route to overcome the first-pass metabolism. The lymphatic capillaries serve as an optimal conduit for the targeted delivery of nanoparticles to the lymph node, while concurrently mitigating the potential diminishment in pharmaceutical bioavailability resulting from first-pass metabolism following nanoparticle absorption within the body.

3. Impact of surface properties on oral drug delivery systems

The surface properties of oral delivery nanoparticles play a pivotal role in governing the interactions of nanoparticles within the intricate physiological environment of the gastrointestinal tract[79]. These surface properties primarily encompass ligand modification, hydrophilicity/hydrophobicity, and charge, etc., all of which significantly determine the *in vivo* fate of nanoparticles. Furthermore, it is essential to consider the impact of protein corona formation on nanoparticle surfaces[80]. This section provides an overview of the surface properties that influence the transepithelial transport of nanoparticles while elucidating the key parameters to be considered for oral drug delivery systems.

3.1. Ligand modification

Receptors located on the membrane surface of intestinal epithelial cells could interact with signaling molecules and nutrients, facilitating signal transmission and substance transport[81]. Previous studies have demonstrated that ligand modification can activate the specific transport pathways *via* facilitating the specific interaction between nanoparticles and cell surface receptors, thereby mediating the endocytosis and transepithelial transport of nanoparticles across intestinal epithelial cells[70,82,83]. The type of ligands and density of ligand modification are both the key factors influencing the transepithelial transport[84,85]. Therefore, rational ligand modification is essential for achieving the high-efficient transepithelial transport and intestinal absorption of nanoparticles. The orally administered nanoparticles modified by different types of ligands were summarized in Table 1[18,61,64,72,78,86−99].

3.1.1. Peptide and protein ligands

The incorporation of ligands on the drug delivery platforms enables targeted drug delivery to specific cells and tissues, thereby reducing the required dosage and minimizing potential side effects. Some peptides and proteins can specifically bind to receptor proteins highly expressed on the surface of intestinal epithelial cells, thereby serving as ligands for nanoparticles to achieve targeted effects.

3.1.1.1. Goblet cells-targeting. The peptide CSKSSDYQC (CSK) was previously identified from a random phage-peptide library using an *in vivo* phage display technique. It was found to exhibit affinity for goblet cells while evading mucus blockage. The specific targeting ability of CSK towards goblet cells facilitated the transport of M13 bacteriophage across the intestinal epithelium, suggesting that the CSK holds potential as a ligand for targeted delivery of nanocarriers *via* oral administration[100]. Jin et al.[86] found that nanoparticles functionalized with a CSKSSDYQC (CSK) targeting peptide exhibited a specific affinity towards goblet cells and facilitated insulin uptake in the villi. The results of the uptake inhibition assay demonstrated that the internalization of CSK-NPs was facilitated by clathrin-dependent and caveolin-dependent endocytosis pathways. Despite potential mucus interference with ligand-receptor recognition, CSK-modified nanoparticles further increase the cellular internalization and cross-cell penetration, and finally exhibit a higher relative oral bioavailability of drugs compared to unmodified one[10,86,101].

3.1.1.2. Transferrin receptor-targeting. Transferrin, a protein molecule exhibiting high specificity and affinity, plays a crucial biological role in the transportation, release, and protection of iron elements within living organisms[102−104]. Zhu et al.[87] discovered that transferrin-coated polyacrylamide nanoparticles (Tf-coated NPs) can be effectively absorbed through transferrin receptor-mediated transepithelial transport. In comparison to bovine serum albumin-coated nanoparticles (BSA-coated NPs), Tf-coated NPs exhibited a remarkable 6.14-fold increase in oral pharmacological bioavailability of insulin. Further investigation conducted by Yang et al.[61] revealed that Tf-modified NPs were found to be involved in intracellular transport through the endoplasmic reticulum, Golgi apparatus, and lysosomal pathways. The utilization of transferrin receptor-mediated transport and multiple intracellular pathways significantly augmented the transcytosis efficiency of Tf-modified NPs.

3.1.1.3. N-Acetyl-D-glucosamine and sialic acid-targeting. Wheat germ agglutinin (WGA) is a widely studied lectin for oral delivery, specially targeting *N*-acetyl-D-glucosamine and sialic acid on the surface of intestinal epithelial cells. WGA has been used for modification of oral nanoparticles, significantly increasing the oral absorption of drugs through specific interaction with intestinal cells, thereby improving the oral bioavailability of drugs by 17.5-fold[88]. Gao et al.[89] demonstrated that WGA-NPs could be absorbed *via* clathrin and caveolae-dependent endocytosis pathways. Meanwhile, Golgi apparatus and lysosome were involved in their intracellular transport during the transcytosis. Despite the mucus adhesion property of WGA, the modification of hydrophilic materials such as polyethylene glycol (PEG) can potentially enhance the ability of WGA-NPs to traverse the mucus layer and facilitate their internalization.

3.1.1.4. Fc receptor (FcRn)-targeting. Proper modification with peptide and protein ligands can allow nanoparticles to bypass lysosomes and transport from the apical to the basolateral side of cells, overcoming the challenge of "hard in, harder out". Immunoglobulin G (IgG) has been found to bind to the neonatal Fc receptor (FcRn) on intestinal epithelial cells under lower pH conditions in the intestinal lumen (pH 6.0−6.5), thereby avoiding the lysosomal degradation through FcRn-mediated transport. However, the pH-sensitive binding between FcRn and IgG occurs at pH < 6.5 rather than at physiological pH 7.4. After reaching the basolateral side of cells, IgG is released into the bloodstream under higher pH conditions (pH 7.4)[18,38,105,106]. Exploiting this phenomenon, nanoparticles were modified with fragments of IgG (IgG Fc) to obtain active-targeted nanoparticles (NP-Fc), which exhibited an approximately 11.4-fold increase in transepithelial transport efficiency compared to unmodified nanoparticles. Approximately 13.7% of NP-Fc successfully crossed the intestinal epithelial cell layer[18]. Albumin-decorated nanoparticles were also engineered for improved pH-dependent binding to the FcRn, and the functional nanoparticles showed improved transepithelial transport. The albumin-modified nanoparticles loaded with insulin exerted a hypoglycemic effect of around 40% reduction after oral administration for 1 h (Fig. 3A)[38].

3.1.1.5. Heparan sulfate proteoglycans (HSPGs)-targeting. Membrane heparan sulfate proteoglycans (HSPG) are found at the cell surface and act as endocytic receptors[107]. Zheng et al.[64] developed a nano-drug delivery system with targeting characteristics towards HSPGs known as EGP NPs (Fig. 3B). The researchers demonstrated that EGP NPs undergo transepithelial transport *via* the caveolae-mediated pathway, wherein Caveolin-1, the primary protein component in caveolae, specifically inhibits the activity of protein phosphatase 2A (PP2A), which regulates endosome−lysosome fusion[108−111]. Nanoparticles in caveolae could dominantly bypass lysosomes without disruption of endosomal integrity, thereby preserving the bioactivity of biotherapeutics. Compared to unmodified nanoparticles (C NPs), EGP NPs exhibited significantly enhanced retention of loaded insulin's bioactivity while C NP-delivered insulin experienced

Table 1 Intracellular transport pathways and advantages of nanoparticles targeting different targets.

Target	Ligand	Intracellular transport pathway	Advantage	Ref.
Goblet cell	CSK peptide	The cellular transport of CSK-NPs occurred through clathrin and caveolae dependent endocytosis	Increased the relative bioavailability of insulin to 7.05%	86
Transferrin receptors	Transferrin	Transferrin NPs were transported in endoplasmic reticulum, Golgi apparatus and lysosome during their intracellular transport	Increased insulin bioavailability by 6.14 times compared to BSA-coated NPs	61,87
N-Acetyl-D-glucosamine and sialic acid	Wheat germ agglutinin (WGA)	WGA-NPs were absorbed *via* clathrin and caveolae dependent endocytosis pathways, and Golgi apparatus and lysosome were involved in intracellular transport	Improved the oral bioavailability of drugs by 17.5-fold	88,89
Neonatal Fc receptor (FcRn)	Fc fragment of IgG	FcRn can then guide bound NP-Fc through a transcytosis pathway, avoiding lysosomal degradation	Enhanced the transport efficiency of NPs through intestinal epithelium	18,90
	Albumin		Increased the amount of insulin penetrating the epithelium by about 5-fold compared to free insulin	91
Heparan sulfate proteoglycans (HSPGs)	EGP peptide	EGP NPs were transported *via* caveolae-mediated mechanisms, enabling evasion of lysosomal entrapment, and facilitating direct apical-to-basolateral transcytosis	Increased the cellular uptake by 4.5-fold and transcytosis by 4.2-fold	64
Monocarboxylate transporter-1 (MCT-1)	Butyric acid (Bu)	Bu-NPs were absorbed *via* clathrin, caveolae-dependent endocytosis and macropinocytosis. endoplasmic reticulum, Golgi apparatus, microtubule and lysosome were involved in intracellular transport	Increased the oral bioavailability of insulin-loaded Bu-PEG NPs by 2.87-fold compared to bare PEG NPs	92
Transporters NPC1L1 and ABCA1	2,5-Hydroxycholesterol (25HC)	The 25HC NPs achieved unidirectional transport across the intestinal epithelium with NPC1L1-mediated uptake on the apical side and ABCA1-mediated basolateral exocytosis	Long-term administration of oral liraglutide loaded 25HC NPs could elevate glucose metabolism and relieve the diabetic symptom of *db/db* mice, with a similar degree achieved by s.c. free liraglutide	93
Glucose transporter type 2	Fructose (Fru)	Fru-PEG NPs underwent internalization and basolateral exocytosis *via* GLUT2-dependent process, an important fructose assimilation pathway	Increased epithelial transport efficiency by 8.8-fold and bioavailability by 3.2-fold compared with PEG NPs	72
Folic acid receptor	Folic acid	/	Increased the bioavailability of DTX by approximately 6.8-fold	94
VB_{12} receptor	VB_{12}	/	Enhanced oral relative bioavailability of curcumin	95
Sodium-dependent bile acid transporter	Bile acids and their derivatives	The NPs entered cells *via* the ASBT pathway and were transported within the endoplasmic reticulum-Golgi apparatus network	Enhanced the transport efficiency of NPs through intestinal epithelium by ASBT-mediated cell uptake and chylomicron transport pathways	78,93,96–99

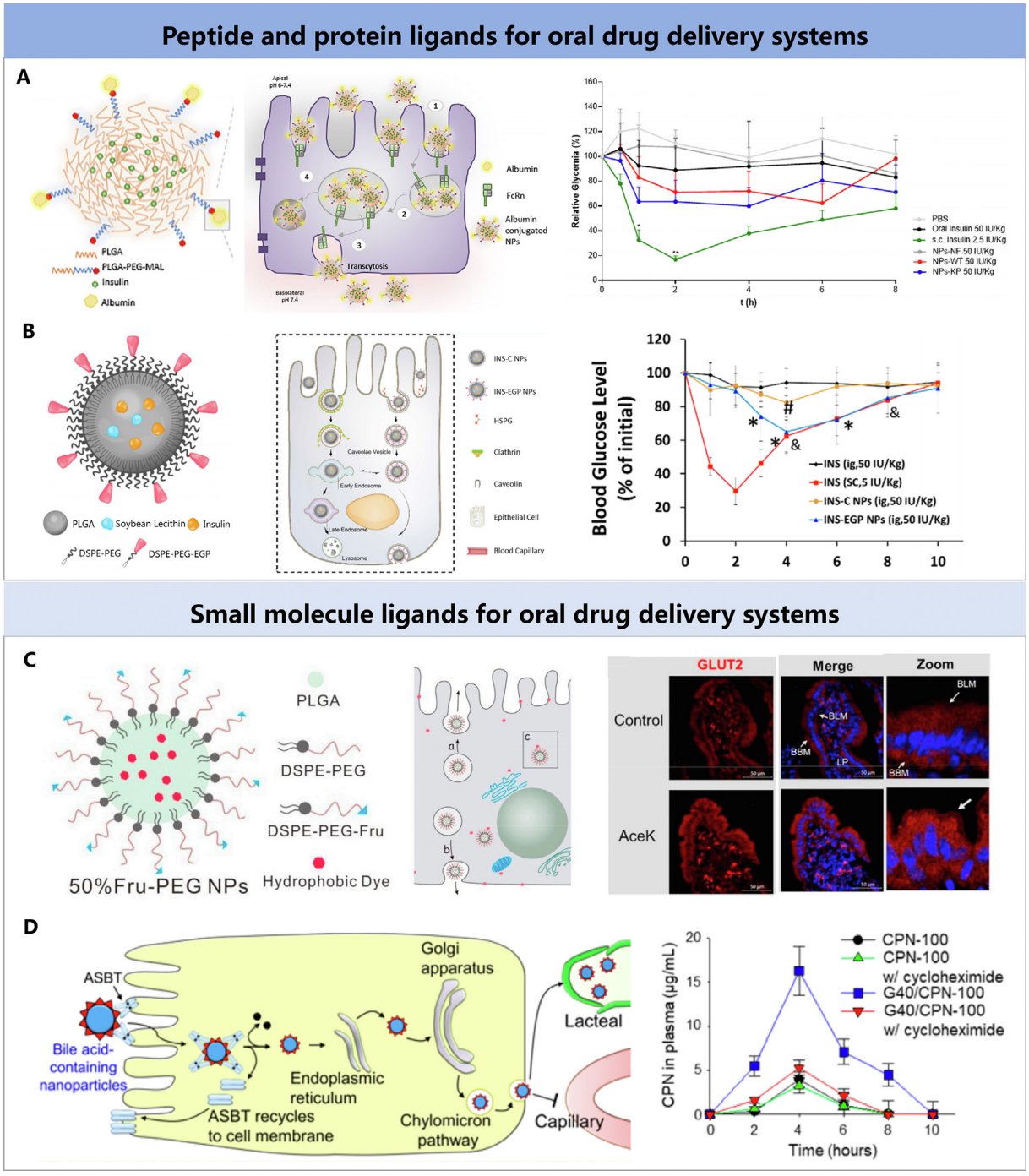

Figure 3 (A) Albumin modified nanoparticles target to the neonatal Fc receptor (FcRn) for oral insulin delivery. Reprinted with permission from Ref. 41. Copyright © Elsevier. (B) EGP peptide modified nanoparticles target to heparan sulfate proteoglycans (HSPGs) for caveolae-mediated transepithelial transport. Reprinted with permission from Ref. 64. Copyright © 2018 American Chemical Society. (C) Fructose-modified nanoparticles transport *via* glucose transporter type 2 (GLUT2), and administrated with acesulfame potassium (AceK). Reprinted with permission from Ref. 97. Copyright © Elsevier. (D) Glycocholic acid-modified nanoparticles transport *via* the sodium-dependent bile acid transporter (ASBT) and chylomicron pathway. Reprinted with permission from Ref. 81. Copyright © 2018 American Chemical Society.

substantial degradation. Further mechanistic investigations revealed that unlike C NPs delivered through the endo/lysosomal pathway, EGP NPs were transported *via* caveolae-mediated mechanisms, enabling efficient evasion of lysosomal entrapment and facilitating direct apical-to-basolateral transcytosis. Therefore, rational ligand modification could effectively prevent lysosomal degradation, improve drug stability, and increase cellular uptake by 4.5-fold and transcytosis by 4.2-fold while partially overcoming the challenge of "hard in, harder out" [64].

3.1.2. *Small molecule ligands*

Virtually nutrients from the diet are absorbed into the bloodstream through the highly polarized epithelial cell layer[112,113]. Certain small molecules, such as short-chain fatty acids, carbohydrates,

cholesterol, bile acids, and their derivatives can specifically interact with receptors or transporters expressed on the surface of intestinal epithelial cells[114–118]. Inspired by this phenomenon, the physiological absorption pathways have been explored for nanoparticles to promote oral absorption[3].

3.1.2.1. Monocarboxylate transporter-1 (MCT-1)-targeting. The monocarboxylate transporter 1 (MCT1) is a proton-dependent transporter which is located on the apical membrane of intestinal epithelial cells. MCT1 can transport substrates like short-chain, unbranched, aliphatic carboxylates, like C2- or C3-substituted monocarboxylates. Huang et al.[92,119] developed butyric acid-modified PEG NPs (Bu-PEG NPs). Compared with PEG NPs, Bu-PEG NPs specifically targeted the MCT-1 expressed on epithelial cells, resulting in a remarkable 3-fold increase in oral bioavailability of the nanoparticles. Mechanism studies confirmed that Bu-PEG NPs and PEG NPs were both internalized *via* clathrin-dependent, caveolae-dependent endocytosis and macropinocytosis and then transported in endoplasmic reticulum, Golgi apparatus, microtubule and lysosome related pathway. Thereby, the modification of some ligands may enhance the transcytosis of nanoparticles without affecting their intracellular trafficking.

3.1.2.2. Niemann-Pick C1 like 1 (NPC1L1)-targeting. Cholesterol plays a pivotal role in the nutritional metabolism. Within the intestinal tract, there exists an inherent pathway for cholesterol absorption: initially, ingested cholesterol binds to Niemann-Pick C1 Like 1 (NPC1L1) located on the apical membrane of intestinal epithelial cells, facilitating its cellular entry. Subsequently, it is transported towards the basolateral membrane of cells *via* ATP binding cassette transporter A1 (ABCA1), thereby establishing an efficient and unidirectional "top-down" route for cholesterol absorption. By utilizing this cholesterol absorption pathway, Wu et al.[93] designed nanoparticles modified with 2,5-hydroxycholesterol (25HC), which could cross the intestinal epithelial cell barrier in a unidirectional manner by interacting with transporters NPC1L1 and ABCA1. Moreover, long-term administration of oral liraglutide-loaded 25HC NPs could elevate glucose metabolism and relieve the diabetic symptoms of *db/db* mice, with a similar degree achieved by subcutaneous injection of free liraglutide.

3.1.2.3. Glucose transporter type 2 (GLUT2)-targeting. Glucose transporters, serving as a crucial transporter for glucose and its analogues transportation, exhibit extensive expression on the surface of intestinal epithelial cells. Wu et al.[72] designed fructose-modified nanoparticles to specially target glucose transporter type 2 (GLUT2). To further promote the absorption of fructose-modified nanoparticles, the absorption promoters were used in combination. A self-amplifying nanoplatform composed of fructose-modified polyethylene glycol-coated nanoparticles (Fru-PEG NPs) and acesulfame potassium (AceK) was utilized to facilitate the absorption (Fig. 3C). Fru-PEG NPs were internalized and exocytosed basolaterally *via* a glucose transporter type 2 (GLUT2)-dependent process, while co-administration of AceK primed epithelial cells for increased apical distribution of GLUT2, thereby amplifying the unidirectional transcytosis of nanoparticles.

3.1.2.4. Sodium-dependent bile acid transporter-targeting. Bile acids are regulatory molecules which are derived from cholesterol in the hepatocytes and transported to the intestine for the ingestion of food[120]. Sodium-dependent bile acid transporter (ASBT), located on the surface of intestinal epithelial cells, acts as a transporter for bile acids and their derivatives, facilitating the active transportation of bile acid-modified nanoparticles across the epithelial barrier[96,97]. Gan et al.[59] found that deoxycholic acid-modified nanoparticles (DNP) could specifically target to ASBT, thus avoiding lysosomal degradation. Subsequently, these nanoparticles undergo apical-to-basolateral exocytosis through intracellular bile acid binding protein (IBABP), ultimately leading to a significant improvement in oral bioavailability compared to unmodified nanoparticles.

The study by Bae et al.[78] demonstrated that surface-conjugated solid nanoparticles of glycocholic acid (GCA) could significantly enhance oral bioavailability by utilizing both the ASBT-mediated cellular uptake and chylomicron transport pathways (Fig. 3D). These nanoparticles were able to enter cells through the ASBT pathway, bypassing the endosome−lysosome pathway, and trafficking within the endoplasmic reticulum-Golgi apparatus network. Once inside the cytosol, these nanoparticles appeared to share the chylomicron transport pathways in the enterocytes, following a route involving mesenteric lymph nodes, and finally entering systemic circulation *via* the left subclavian vein. The same research group also discovered that the conjugation of bile acids onto solid nanoparticles significantly enhanced ASBT-mediated endocytosis and the chylomicron pathway. Detailed mechanistic studies revealed that GCA conjugation altered the mechanisms of endocytosis and downregulated cellular responses to transport at the gene level, establishing a negative feedback loop that induced higher cellular retention of nanoparticles[98]. The metabolic and immunomodulatory functions of bile acid-derived nanoparticles were observed, presenting potential translational opportunities for the prevention and treatment of type 1 diabetes. Polymerized ursodeoxycholic acid, derived from bile acid polymers, was formulated into nanoparticles for oral insulin delivery. These nanoparticles served as protective carriers for insulin while also acting as high-avidity agonists for bile acid receptors. This dual functionality enhanced intestinal absorption of insulin, induced polarization of intestinal macrophages towards the M2 phenotype, and exhibited preferential accumulation in the pancreas of mice. Furthermore, these nanoparticles demonstrated a strong binding affinity to the islet-cell membrane receptor TGR5 and effectively activated the secretion of glucagon-like peptide and endogenous insulin[99].

3.1.3. Ligand modification density

The density of ligand modification is a crucial factor that influences the efficiency of nanoparticle transport[121,122]. Previous studies have demonstrated a close relationship between ligand density and cellular uptake as well as transepithelial transport of nanoparticles. Song et al.[84] investigated the impact of modification density for three different ligands targeting neonatal Fc receptor (FcBP), transferrin receptor (7pep), and αvβ3 integrin receptor (c(RGDfK)) on the cellular uptake and transepithelial transport of nanoparticles. They observed that ligand density could influence the distribution of nanoparticles in the degradation pathway, recycling pathway, and secretion pathway, thereby affecting transepithelial transport efficiency. Furthermore, the effect of ligand density on transepithelial transport was found to be closely associated with the type of ligand used. Cellular uptake and transepithelial transport were positively correlated with ligand density for nanoparticles modified with 7pep and c(RGDfK).

Conversely, nanoparticles modified with moderate density of FcBP exhibited the highest levels of cellular uptake and transepithelial transport. Therefore, the optimization of ligand density is advantageous for enhancing the transport of nanoparticles across intestinal epithelial cell barriers.

3.2. *Surface charge*

The surface charge of nanoparticles is mainly determined by the surface materials with cationic or anionic groups. The surface charge is an important parameter to effect the absorption of nanoparticles[123]. Due to the negative charge of intestinal mucus and intestinal epithelial cell membranes, usually, a contradictory requirement exists for the surface charge of nanoparticles. On one hand, nanoparticles with strong positive or negative charge are prone to be trapped in mucus or are totally repelled by the mucus, while electrically neutral nanoparticles are more likely to overcome the mucus barrier[124,125]. On the other hand, positively charged nanoparticles can improve their affinity with cell membranes through electrostatic interaction, thus enhancing the epithelial cell uptake[12,126]. Wu et al.[127] designed nanoparticles with equal amounts of a positive and negative charge, as well as intestinal alkaline phosphatase (IAP) responsive charge-reversal ability (P−R8-Pho NPs). Following traversal through the mucus layer, the outermost surface of nanoparticles undergoes deshielding of its negatively charged group facilitated by IAP activity on the membrane. This timely exposure of the positively charged group enhances cellular uptake and transepithelial transport of nanoparticles. Compared with electrically neutral nanoparticles that cannot undergo charge reversal (P NPs), the oral bioavailability was improved by 2.3 times.

In some studies, compared with negatively charged nanoparticles, positively charged nanoparticles exhibit higher cellular uptake but show reduced transepithelial transport efficiency. For example, the proportion of negatively charged (carboxyl-modified) nanoparticles transported across intestinal epithelial cells is three times that of positively charged (amino-modified) nanoparticles. Mechanism studies revealed that the positively charged nanoparticles are mainly transported through the clathrin-mediated endocytosis pathway, while negatively charged nanoparticles are mainly the caveolin-mediated pathway[128]. In addition, Lin et al.[128] found that the cellular uptake of nearly neutral or negatively charged gold nanoparticles is only 50% of positively charged nanoparticles, but the transepithelial transport efficiency is 10−20 times that of positively charged nanoparticles. Some studies revealed that positively charged NPs cause more pronounced disruption of plasma-membrane integrity, and stronger mitochondrial and lysosomal damage than anionic NPs, indicating that the positively charged NPs would be more prone to bypass the endo-lysosomal pathway[129,130]. The influence of the surface charge on the transepithelial transport of nanoparticles may be a comprehensive reflection of its effect on endocytosis, intracellular transport, and exocytosis. Therefore, in the design of orally administered nanoparticles, it is necessary to choose the appropriate surface charge based on the specific transport requirement.

3.3. *Hydrophilicity/hydrophobicity*

The surface hydrophilicity/hydrophobicity is an important parameter that affects the absorption and final fate of nanoparticles. Since the cell membrane is composed of a lipid bilayer and owns a certain degree of lipophilicity, nanoparticles with stronger hydrophobicity are more easily internalized by cells[131,132]. Qiao et al.[133] demonstrated the penetration of hydrophobic fullerene nanoparticles through the lipid bilayer membrane upon their embedding in the inner phase. A distinct response mechanism was elucidated for the hydrophilic derivatives, which exclusively underwent adsorption onto the bilayer. This phenomenon was corroborated by Li et al.[134], who computationally simulated and demonstrated that hydrophilic nanoparticles exhibit a preference for surface adsorption rather than incorporation into the bilayer.

Huang et al.[119] prepared a series of butyrate-modified nanoparticles with different hydrophobicity by controlling the ratio of hydrophilic polyethylene glycol (PEG) and hydrophobic poly(-lactic-*co*-glycolic acid) (PLGA). The studies demonstrated that while hydrophobicity did not influence the transport pathway of butyrate-modified nanoparticles within intestinal epithelial cells, it did impact the efficiency of exocytosis from either the apical or basolateral side. Specifically, PLGA nanoparticles with higher hydrophobicity exhibited a greater tendency for exocytosis from the basolateral side. Rieux et al.[135,136] found that nanoparticles with stronger hydrophobicity were more easily taken up by M cells and could achieve more efficient oral absorption through transepithelial transport by M cells. Additionally, hydrophobic polymers such as polystyrene, polymethyl methacrylate, polyhydroxybutyrate, and glycolic acid polymer nanoparticles demonstrate enhanced absorption in the intestinal Peyer's patches compared to the less hydrophobic lactic acid. The absorption capacity of hydrophobic particles is approximately 100 times greater than that of the hydrophilic cellulose polymer[137].

However, though higher hydrophobicity is beneficial to transport across the epithelial cell layer, it goes against the penetration of the mucus layer because surface hydrophilicity is necessary for mucus permeation[126]. For this dilemma, Cui et al.[132] developed nanoparticles with surface "hydrophilicity/hydrophobicity balance" by modulating the ratio of hydrophilic *N*-(2-hydroxypropyl) methacrylamide (HPMA) and hydrophobic methacrylamido fatty acid ester (FA) analogues. They found that nanoparticles coated with 20% amount of HPMA−cetyl methacrylate copolymer (NPs-C16 (20%)) showed the best hypoglycemic effect *in vivo*. Therefore, finding an appropriate balance is important for the hydrophilicity/hydrophobicity modulation.

3.4. *Intestinal protein corona*

When nanoparticles are exposed to the physiological fluids, several thousand proteins would interact with these colloidal nanoparticles and then form the protein adsorption layer on the surface, also known as the "protein corona"[138]. The protein corona on nanoparticles can modify the diverse physicochemical properties of nanoparticles such as size, surface charge, and surface composition, thereby imparting a novel biological identity to the nanoparticles. The protein corona has been reported to effect the biological destiny of nanoparticles, such as cellular uptake, blood circulation time, biodistribution, and even toxicity[139,140].

Upon oral administration, nanoparticles interact with substances in the gastrointestinal tract, forming a protein corona on the surface, which is called the intestinal protein corona[80,141]. Zhang et al.[142] discovered that incubating gold nanoparticles with mucin resulted in the formation of a mucin-protein corona on their surface (Fig. 4A). Although this mucin-protein corona significantly enhanced epithelial cell uptake of gold nanoparticles, it did not effectively improve their transepithelial transport. Further

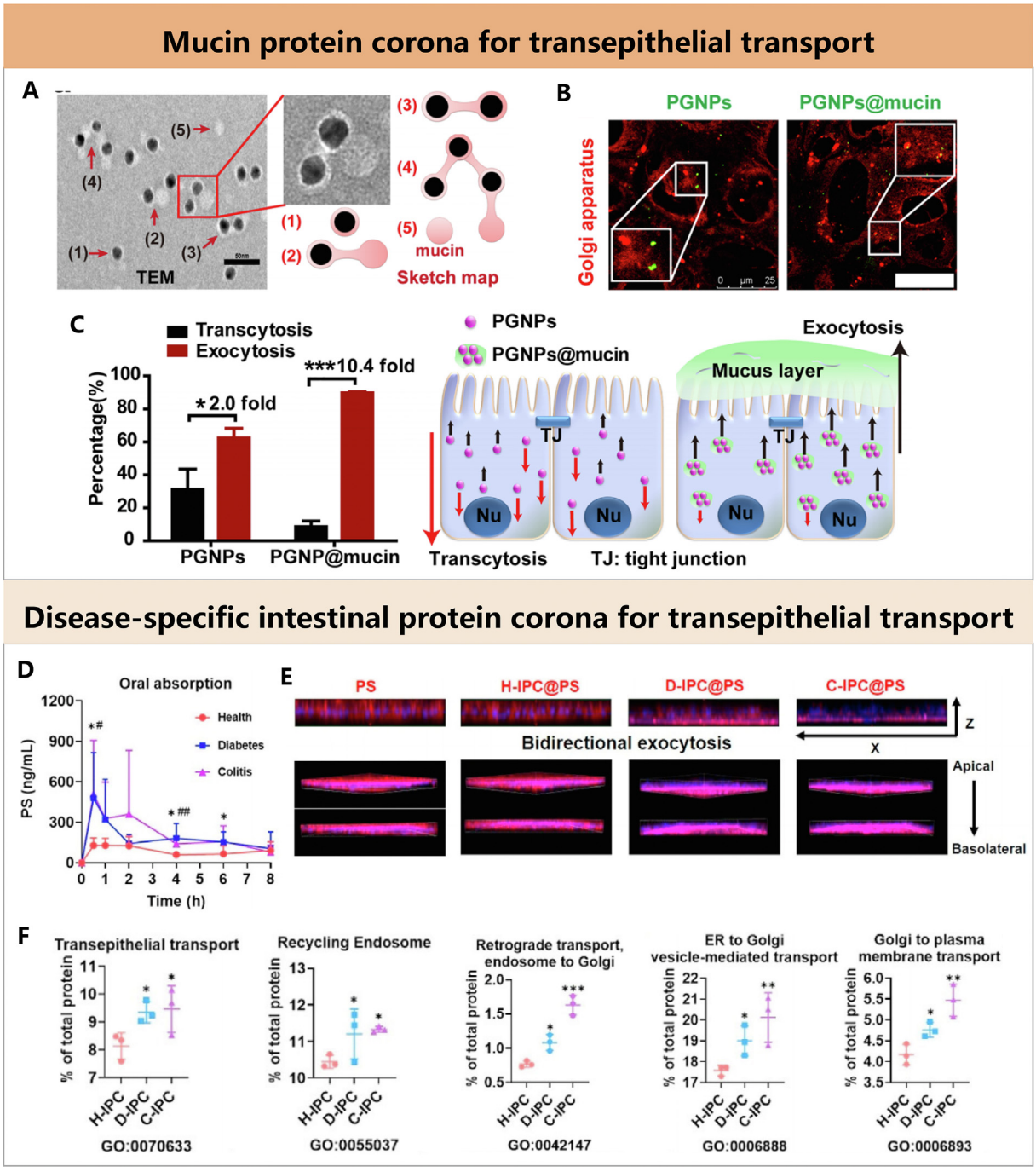

Figure 4 Mucin protein corona for transepithelial transport of nanoparticles. (A) Mucin protein corona adsorbed on PEG-modified gold nanoparticles (PGNPs@mucin). (B) Intracellular distribution of nanoparticles with Golgi apparatus. (C) Transcytosis and exocytosis of nanoparticles, and the schematic diagram for the influence of mucin on the transepithelial transport of nanoparticles. Reprinted with permission from Ref. 147. Copyright © 2018 American Chemical Society. Disease-specific intestinal protein corona (IPC) for transepithelial transport of nanoparticles. (D) The oral absorption of nanoparticles on healthy, diabetic and colitis rats. (E) The bidirectional exocytosis of nanoparticles adsorbed diabetic-IPC (D-IPC@PS) and colitis-IPC (C-IPC@PS). (F) Proteomic analysis for biological functions of D-IPC and C-IPC on the transepithelial transport and intracellular transport of nanoparticles. Reprinted with permission from Ref. 154. Copyright © Elsevier.

investigations revealed that under the influence of the mucin-protein corona, gold nanoparticles were more readily transported to exocytosis-related organelles like the Golgi apparatus and subsequently exocytosed from the apical side of cells back into the intestinal lumen (Fig. 4B and C). This hindered their exocytosis from the basolateral side and entry into the bloodstream. Therefore, the mucin-protein corona may hinder the transepithelial transport of nanoparticles[143]. Additionally, proteins in the gastrointestinal tract can adsorb onto the surface of nanoparticles to form an intestinal protein corona. Wu et al.[144] discovered significant alterations in the protein corona under different physiological conditions within the body. Distinctions

were observed in the intestinal protein corona (IPC) formed in healthy rats compared to those with diabetes or colitis. In cases of diabetes or colitis, disease-specific IPCs can enhance oral nanoparticle absorption (Fig. 4D) by modulating intracellular transport through early endosome, recycling endosome, and endoplasmic reticulum-Golgi apparatus pathways while significantly increasing basolateral exocytosis, ultimately facilitating transepithelial transport (Fig. 4E and F). Thus, disease-specific IPCs have a "positive effect" on intestinal absorption and may benefit systemic drug delivery for diabetes treatment. Conversely, for colitis requiring local treatment in the colon, reducing the formation of disease-specific IPCs can weaken this "positive effect" on intestinal absorption and allow more nanoparticles to reach their intended site. Timely modulation of disease-specific intestinal protein corona formation on nanoparticle surfaces is imperative for effective oral treatment across various diseases.

The presence of adsorbed protein corona can impact the surface properties of nanoparticles, particularly those have been modified with targeted ligands. Previous studies on nanoparticles *via* parenteral administration have demonstrated that the coated protein corona in the blood circulation can mask the target ligand on the surface of nanoparticles, thereby diminishing the targeting efficiency *in vivo*[145−148]. As for oral administration, how intestinal protein corona formed in the gastrointestinal tract influences the transepithelial transport of ligand-modified nanoparticles remains to be elucidated. A recent study found that for transferrin-modified nanoparticles (Tf-NPs) adsorbed protein corona from the mucus layers, which masked, displaced, and dampened the active targeting effects of Tf-NPs, thus reducing the transepithelial transport. However, precoated Tf-NPs with mucin as "active protein corona" could weaken the negative effect of "passive protein corona" from the mucus layers, for improving the transepithelial transport. Based on this, the active target ligands coated with protein corona may also lose or weaken their target ability for orally delivered nanoparticles, which was unfavorable for the transepithelial transport[143].

An alternative possibility that warrants consideration has recently been proposed. Besides the mucin, proteins in the gastrointestinal tract can also be absorbed to form the intestinal protein corona, potentially exerting diverse impacts on the target ligands. According to recent research by Huang's group, the occurrence of diseases could also influence the composition of the intestinal protein corona (such as diabetic-intestinal protein corona), which demonstrated an enhanced effect on the transepithelial transport and oral absorption of nanoparticles[144]. These disease-specific protein coronas can be considered as "special ligand" on nanoparticles, thereby potentially displacing the original target ligand and facilitating the transepithelial transport of nanoparticles even when the modified target ligand is masked. Although intestinal protein coronas may not necessarily compromise the targeting efficiency of ligand-modified nanoparticles, empirical investigations are still required to ascertain whether the protein corona masks or inhibits the role of targeted ligands to what extent. Moreover, it is essential to explore how orally formed protein coronas influence the transepithelial transport of nanoparticles modified with other ligands besides transferrin.

3.5. *Perspective of surface properties*

While numerous studies primarily focus on the impact of an individual property on traversing a specific barrier, it is important to acknowledge that the prerequisites for nanoparticles to cross multiple barriers may exhibit variations and even contradictions. In general, hydrophilic and electrically neutral nanoparticles are more likely to penetrate the intestinal mucus barrier, while hydrophobic and positively charged nanoparticles are more likely to overcome the intestinal epithelial cell absorption barrier. In addition to the studies discussed above, some researchers have developed some nanoparticles with adjustable surface properties. For example, Le et al.[149] developed a charge-transfer surface based on a phosphate portion that is cleaved by membrane-bound phosphatase, thereby converting its charge from anion to neutral or cation. Shan et al.[11] encapsulated insulin-transmembrane peptide complexes in hydrophilic *N*-(2-hydroxypropyl) methacrylamide copolymer (pHPMA), which can be stripped off during mucosal penetration, exposing the transmembrane peptide for easier cellular entry. Wang et al.[150] formed a protein corona by adsorbing BSA onto the surface of cationic liposomes, which can be enzymatically hydrolyzed during mucosal penetration, exposing the positive charge on the liposome surface to enhance intestinal epithelial cell absorption. Ongoing research is currently underway to develop streamlined strategies for the successful traversal of nanoparticles across both the mucus layer and epithelial cells.

4. Impact of holistic properties on oral drug delivery systems

In addition to surface properties, the holistic properties of nanoparticles, such as particle size, shape, and elasticity, are also closely related to their transepithelial transport[151]. For example, nanoparticles with different shapes have different surface areas and flow characteristics, which affect their absorption and transport in intestinal epithelial cells[152,153]. The size of nanoparticles will have a greater impact on their movement in the mucus layer and adhesion in the gastrointestinal tract, and their absorption pathway and absorption efficiency are also affected by their particle size[26]. Rigidity is also one of the key physicochemical properties of nanoparticles. Nanoparticles with moderate rigidity are more likely to change shape as needed during *in vivo* movement, which plays a positive role in transepithelial transport[29]. Moreover, as a crucial part of the nano-drug delivery system, carrier materials play an important role in drug encapsulation, shielding environmental factors, increasing stability, and achieving targeted and controlled release, which is a significant property affecting transepithelial transport[154]. This section provides an overview of the holistic properties including size, shape, rigidity, and material et al. that influence the transepithelial transport of nanoparticles, elucidating the underlying principles governing their impact on transepithelial transport.

4.1. *Particle size*

The particle size of nanoparticles is one of the holistic properties that affect their transepithelial transport, as it plays a regulatory role in the transport processes such as cellular uptake, intracellular transport, and exocytosis[26,151,155−159]. The transport efficiency of vitamin B12-loaded soy protein (SPI) nanoparticles across the Caco-2 cell monolayers was dependent on particle size, with increasing order observed in the transport of 30 nm $>$ 100 nm $>$ 180 nm. Among the varied nanoparticles, those with a size of 100 nm showed the highest cellular uptake[160]. Furthermore, nanoparticle size can modulate intracellular

distribution. Schubbe et al.[161] demonstrated that 32 nm SiO_2 nanoparticles were rapidly internalized by intestinal epithelial cells and prominently localized within the nucleus, whereas 83 nm SiO_2 nanoparticles did not penetrate the nucleus. It is worth noting that the impact of particle size on cellular uptake can vary and even exhibit contradictory outcomes. Desai et al.[162] synthesized a range of PLGA nanoparticles with varying sizes (100 nm, 500 nm, 1 μm, and 10 μm) and observed that the smallest particles (100 nm) demonstrated the highest level of intestinal absorption. Conversely, research conducted by Mitragotri's group[26] revealed that smaller nanoparticles (50 and 200 nm) exhibited significantly greater efficiency in transepithelial transport compared to larger nanoparticles (500 and 1000 nm), with an inverse relationship between particle size reduction and enhanced transepithelial transport. However, no significant difference was observed in transepithelial transport efficiency between nanoparticles sized at 50 and 100 nm. Therefore, selecting nanoparticles within the smaller size range (50−200 nm) may be more advantageous for enhancing their cellular uptake and transepithelial transport.

4.2. *Shape*

The shape of nanoparticles also exerts a significant influence on the cellular uptake and transepithelial transport behavior of epithelial cells[163]. Yu et al.[164] conducted a comparative study between spherical and rod-shaped nanoparticles in terms of their interaction with the intestinal mucosa, revealing that rod-shaped nanoparticles possess superior mucus penetration ability by employing a "rotation-jump" mechanism. Additionally, these rod-shaped nanoparticles exhibit prolonged mucosal retention time and enhanced absorption within the intestinal mucosa. Banerjee et al.[26] conducted a comparison of the cellular uptake, intracellular transport, and transepithelial transport of rod-shaped, disc-shaped, and spherical nanoparticles. Their findings indicate that the efficiency of cellular uptake for nanoparticles is in the order of rod-shaped > disc-shaped > spherical. Upon surface modification with biotin ligands, all groups of nanoparticles showed significant improvement in both cellular uptake and transepithelial transport efficiency; however, the highest enhancement was observed in rod-shaped nanoparticles. Furthermore, nanoparticle shape can significantly influence their intracellular distribution. Compared to spherical and disc-shaped counterparts, rod-shaped nanoparticles are more easily taken up by cells through preferential transportation *via* the endoplasmic reticulum-Golgi apparatus pathway; thus they are more likely to be transported across intestinal epithelial cell layers[165]. The cellular uptake of rod-shaped nanoparticles is higher, and they exhibit ideal intracellular transport pathways and enhanced transepithelial transport efficiency, which can be attributed to their contact area and mode with the cell membrane. However, currently, inorganic materials are predominantly employed for the synthesis of non-spherical nanoparticles to investigate the impact of shape on oral nanoparticle absorption. Challenges still exist in utilizing biodegradable organic materials for the preparation of non-spherical nanoparticles. Therefore, it is worth considering the utilization of 3D printing, microfluidics, and other technologies for designing and fabricating degradable non-spherical oral drug delivery systems[166].

4.3. *Rigidity*

In recent years, rigidity has garnered increasing attention as one of the crucial physicochemical parameters of nanoparticles[2,29,167,168]. Rigidity is commonly characterized by Young's modulus and is closely associated with the material composition[169,170]. In nature, viruses, cells, and certain entities can adapt their rigidity to different stages of physiological activity[171,172]. Previous studies have revealed that rigidity significantly impacts the diffusion of nanoparticles across the mucus layer. Yu et al.[29] designed PLGA core-lipid shell NPs with Young's modulus values ranging from 7 Mpa to approximately 106 Mpa (Fig. 5A). It found that the semi-elastic NPs (50 Mpa) achieved superior mucus-penetrating ability among all, due to the deformation into ellipsoids and displayed rotational motion in mucus (Fig. 5A and B). In contrast, the soft NPs (7 Mpa) deformed excessively and irregularly, while the hard NPs (106 Mpa) almost completely retained their spherical shape (Fig. 5A−B). In another study by Yu et al.[173], a similar phenomenon was observed for liposomes with different rigidity (Fig. 5C). Liposomes with moderate rigidity (Lip4) deformed into the ellipsoidal shape for superior diffusivity compared with soft (Lip1) and hard (Lip6) liposomes (Fig. 5C and D). Therefore, keeping moderate rigidity was ideal for lipid-polymer nanoparticles as well as liposomes to diffuse across the mucus layers and also exhibit superior oral absorption. To further investigate the impact of nanoparticle rigidity on transepithelial transport. Zheng et al.[174] constructed a series of amphiphilic gel nanoparticles with different degrees of crosslinking and explored the cellular uptake, intracellular transport, and transepithelial transport of the nanoparticles. It was interesting to find that nanoparticles with higher elasticity had better cellular uptake and transepithelial transport capabilities. Mechanistic studies revealed that nanoparticles with higher rigidity tended to be transported through exocytosis-related pathways such as the endoplasmic reticulum, Golgi apparatus, microtubules, and caveolae, thus showing higher exocytosis efficiency. On the other hand, nanoparticles with lower rigidity were more likely to be trapped in lysosomes, leading to lower exocytosis efficiency. Furthermore, Yu et al.[25] investigated the strategy of modulating rigidity in ligand-modified nanoparticles and observed that this modulation had a similar impact on the transepithelial transport of both neonatal Fc receptor domain-binding peptide (FcBP) modified nanoparticles and pristine nanoparticles. They found that increasing rigidity was advantageous for enhancing transepithelial transport. It is important to note that the rigidity of nanoparticles primarily relies on the types and proportions of different materials composing them, leading to compositional variations among different nanoparticles. Therefore, further research is needed to explore the relationship and pattern between nanoparticle rigidity and transepithelial transport to broaden its applicability.

4.4. *Materials*

The carrier material of the nano delivery system plays a crucial role in achieving multiple functions, including encapsulating drugs, shielding them from environmental factors and systemic metabolism, prolonging their residence time in the intestines, providing targeted receptors, and controlling drug release[175−178]. These effects significantly enhance the gastrointestinal stability and oral absorption of nanoparticles. The materials can be classified as either inorganic or organic based on their chemical composition[154]. Organic nanoparticles consist of biological macromolecules (*e.g.*, phospholipids, albumin, chitosan, etc.) and polymeric materials (*e.g.*, PLGA and PEG, etc.)[179−182]. Inorganic nanoparticles encompass metallic nanoparticles such as iron, gold, and silver, as well as non-metallic nanoparticles like titanium dioxide, mesoporous silicon, and mesoporous carbon[183−186].

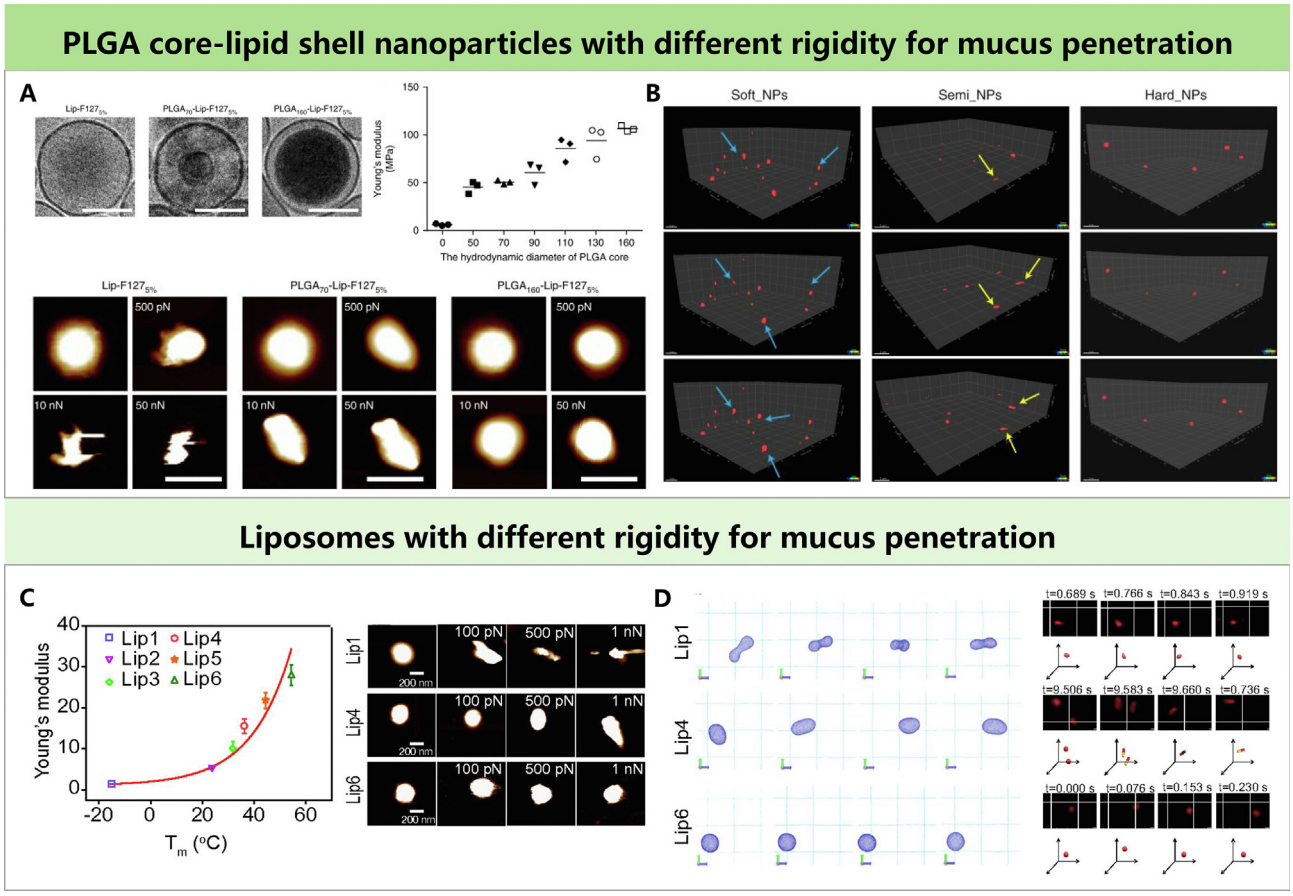

Figure 5 PLGA core-lipid shell NPs with different rigidity. (A) Cryo-TEM images, Young's modulus and atomic force microscopy (AFM) images of NPs. (B) 3D mobility and morphology of NPs in rat intestinal mucus imaged by Airyscan microscopy. Reprinted with permission from Ref. 29. Copyright © 2018, Miaorong Yu et al. Liposomes with different rigidity. (C) Young's modulus and AFM images of Liposomes. (D) Representative snapshots of liposomal structures from the simulation, and trajectory analysis of liposomal formulations in mucus. Reprinted with permission from Ref. 181., this material published after 2008, a copyright note is not needed.

4.4.1. Lipid-based nanoparticles

Lipid molecules can self-assemble in aqueous environments to form liposomes that resemble cell membranes. These miniature vesicles possess both hydrophobic and hydrophilic regions, allowing for the encapsulation of various drugs[187]. Due to their excellent biocompatibility and biodegradability, liposomes are considered ideal materials for nano-delivery systems[188]. Conventional liposomes are susceptible to degradation by gastric acid, lipase, and bile salts in the gastrointestinal tract, resulting in drug leakage and limitations in oral delivery[189]. However, scientists have devised several strategies to address this issue. Hu et al.[190] pre-injected bile salts into liposomes to prevent the destruction of physiological bile salts. Hosny et al.[191] coated the surface of liposomes with an enteric polymer layer to prevent disintegration in the stomach and increase intestinal absorption. The protective coatings formed by polysaccharides, proteins, and silica have also been shown to enhance the gastrointestinal stability of liposomes[192–195]. Additionally, liposomes modified with chitosan, mucin, and other substances have demonstrated stronger mucosal adhesion, prolonged their gastrointestinal retention time, and thus enhanced absorption[150,196,197]. Ezzat et al.[198] found that chitosan-modified liposomes exhibited 1.37 times higher oral bioavailability compared to traditional liposomes and 2.12 times higher than free catechins. Furthermore, liposomes can facilitate oral drug absorption through the M cell-lymphatic pathway[74,199]. By incorporating specific ligands, liposomes can also improve uptake by intestinal epithelial cells through receptor-mediated endocytosis[200,201]. The presence of long-chain fatty acids like oleic acid and surfactants such as Tween-80 in liposomes inhibits P-glycoprotein (P-gp) efflux, thereby increasing cross-cell transport efficiency[202–204]. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) consisting of a phospholipid layer and a solid lipid core demonstrate enhanced gastrointestinal stability and can effectively improve the oral bioavailability of drugs with limited solubility and permeability such as amphotericin B and saquinavir[205–207].

Exosomes are special lipid-based nanoparticles that naturally secrete from cells, featuring a lipid bilayer structure and carrying bioactive substances such as proteins, nucleic acids, miRNA, etc., for intercellular communication[208,209]. In comparison to regular liposomes, exosomes have higher circulatory stability and biocompatibility, lower immunogenicity, and toxicity, as well as the ability to cross the gastrointestinal barrier, making them naturally advantageous vehicles for oral drug delivery[210,211]. Umezu et al.[212] discovered that Acerola-derived exosomes can protect miRNA from degradation by RNase, strong acid, and base *in vitro*, demonstrating their feasibility for oral nucleic acid drug deliver. Zhong et al.[213] reported that intact milk exosomes can be

transported from the intestine into the bloodstream *via* FcRn receptor-mediated endocytosis. Wu et al.[214] employed milk-derived exosomes as vehicles for biomacromolecule drug insulin delivery. Their research demonstrated that milk exosomes exhibited high resistance against the harsh environment of the gastrointestinal tract and can be effectively transported from the apical side of the intestinal epithelium to the basal side, significantly improving the bioavailability of insulin. Munagala et al.[215] used milk exosomes for oral delivery of anthocyanins to treat pulmonary tumors in mice and found that it significantly improved the oral bioavailability of anthocyanins and reduced the toxicity of anthocyanins.

4.4.2. *Polymer-based nanoparticles*

Polymer nanoparticles prepared from various polymer materials have shown potential as carriers for drug and gene delivery, leading to enhanced drug delivery efficiency[82,216]. Polymer-based nanoparticles have been extensively studied for oral delivery and possess several advantages over other types of materials. First, there is a wide range of polymer materials available with diverse applications, including synthetic polymers such as PLGA, PEG, and polylactic acid, as well as natural polymers such as chitosan, sodium alginate, and proteins[217,218]. Although non-biodegradable types are unsuitable for therapeutic purposes, they can be utilized as model particles to investigate the effects of nanoparticle surface and holistic properties on their ability to cross the physiological barrier of the gastrointestinal tract[26,219]. Biodegradable polymers exhibit excellent biocompatibility, high safety, and great encapsulation efficiency, which are well-suited for drug delivery, but their gastrointestinal stability is relatively limited[220]. Conversely, enteric-soluble polymers have the natural advantage of not being disrupted by gastric acid for oral administration. Singh G et al.[221] prepared polymer nanoparticles loaded with atazanavir using enteric-soluble Eudragit RL 100, which enhanced the absorption and permeability of the drug for transfer through intestinal Peyer's patches collection lymph nodes and significantly improved the bioavailability. Reboredo et al.[222] employed zein nanoparticles to protect insulin from degradation by gastric juice. Moreover, enteric-coated polymers can also serve as surface coatings for other nanoparticles to assist them in conquering the gastric acid barrier[223,224]. Second, polymer nanoparticles exhibit significant design flexibility and controllability. By manipulating the structure, composition, and surface modification of materials, polymer nanoparticles can be designed with different particle sizes and surface charges to perform functions such as controlled release, gastrointestinal stabilization, mucosal penetration, or specific targeting, making them more suitable for oral drug delivery[225−228]. Xie et al.[229] developed PLGA NPs that significantly improved the oral bioavailability of curcumin—a hydrophobic drug—by 5.6 times by enhancing its solubility and permeability while also increasing its retention time within the intestine and inhibiting P-gp-mediated efflux. Inchaurraga et al.[230] used PEG to modify the surface of the poly(anhydride) nanoparticle, which reduces the interactions between the NPs and mucus and allows them to rapidly pass through the intestinal mucus barrier.

Hydrophilic polymers are unique polymer materials that can be physically or chemically crosslinked to form hydrogels with a porous three-dimensional network structure[231]. These hydrogels can rapidly absorb and expand in water and biological fluids without dissolution[232,233]. In terms of oral administration, hydrogels protect against degradation in harsh gastrointestinal environments and enhance drug stability[234]. Additionally, their adhesive properties enable prolonged retention in the intestine, thereby improving oral drug absorption and facilitating controlled release[235,236]. Due to the adjustable physical properties of hydrogels, researchers have invented a variety of intelligent response hydrogels to adapt to various environmental factors in the body, such as pH, temperature, and enzymes[237−239]. Among these responsive hydrogels, pH-sensitive ones exhibit shrinkage in acidic conditions (gastric fluid) for drug protection while swelling occurs in weakly alkaline environments (small intestine) to promote drug release and absorption[240]. Chen et al.[241] successfully fabricated pH-sensitive nanohydrogels with particle sizes ranging from 200 to 300 nm through electrostatic interactions and applied them to oral insulin delivery. The resulting cross-linked structure is dense in gastric fluid and loose in the intestine, which can effectively inhibit the rapid release and degradation of insulin in gastric fluid and control its release in the intestine, thus benefiting the absorption and sustained release of insulin after oral administration.

4.4.3. *Inorganic materials-based nanoparticles*

Based on inorganic materials, inorganic nanoparticles with various morphologies and particle sizes ranging from 1 to 1000 nm could be synthesized through physical or chemical methods[242,243]. Compared with the above-mentioned nanoparticles based on organic materials, they possess the advantages of facile preparation and storage, controllable size and shape, easy surface modification, and excellent physical and chemical stability[244−247]. However, the range of suitable inorganic materials for oral delivery is limited, and their biocompatibility and safety are far inferior to those of certain biological organic materials. Some inorganic nanoparticles such as iron oxide or gold nanoparticles are difficult to degrade and excrete after entering the body which may lead to toxicity and adverse reactions that limit their practical medical applications[248,249]. Nevertheless, inorganic nanoparticles can achieve rapid degradation under specific physiological conditions by changing the particle size and morphology of the nanoparticles and adjusting the surface properties and doping strategies[250−252]. Some inorganic nanoparticles prepared from highly biocompatible inorganic materials such as calcium phosphate and silica are also biodegradable[253,254].

Inorganic nanoparticles can be divided into two major categories: metal and non-metal. Among them, metal nanoparticles are often utilized for molecular imaging and targeted photothermal therapy due to their magnetic and photothermal properties[255,256]. Gold nanoparticles (GNP) exhibit good physiological stability and can resist hydrolysis by gastric acid and enzymes, therefore, they can be employed for oral administration[257]. Wang et al.[258] discovered that Au25 nanoparticles with a diameter of 25 nm could easily reach the intestine intact after oral administration, effectively clearing ROS from inflammatory sites and exerting antioxidant effects. Another study revealed that GNP synthesized *in vivo* after oral administration could be completely absorbed into the blood circulation by the gastrointestinal tract of mice and reach distal sites such as bacterial peritonitis[259]. Kumari et al.[260] developed an apple polysaccharide (MAP) modified AuNPs for oral delivery of insulin, which played a dual role in protecting insulin from being destroyed. Compared with direct oral administration, insulin loaded by AuNPs could significantly reduce blood glucose in the short term and demonstrated an effect of improving blood biochemical indicators in long-term studies. However, due to unclear metabolic mechanisms and potential

toxicity *in vivo*, the application of metal nanoparticles in oral drug delivery is currently limited[261,262].

Based on non-metallic materials such as silica, porous silicon nanoparticles possess abundant pores, providing a spacious capacity for drug loading and high specific surface area, facilitating sufficient contact between the drug and the dissolving media to promote their efficient dissolution and release. At the same time, the nanoparticles can adhere to the intestinal mucosa, prolonging drug residence time and enhancing oral absorption efficiency[263]. Additionally, the hydroxyl-abundant surface of porous silicon nanoparticles is easily modifiable to adapt to various physiological environments[264]. Araújo et al.[265] designed diverse nanosystems for oral delivery of inorganic glucagon-like peptide-1 (GLP-1) to treat diabetes. In comparison, porous silicon nanoparticles exhibited higher association efficiency and drug loading capacity than PLGA NPs and solid lipid nanoparticles and showed the best intestinal permeability of GLP-1 after chitosan surface modification. Another inorganic non-metallic material suitable for oral delivery is mesoporous carbon. Compared with mesoporous silicon, mesoporous carbon exhibits superior safety and structural robustness, and excellent physical and chemical stability[266–269]. Wang et al.[270] investigated the adhesion and absorption between intestinal epithelial cells and mesoporous carbon nanoparticles (UMCS) and found that UMCS could significantly increase cell permeability and uptake, inhibit drug efflux rate, and exhibit remarkable oral bioavailability compared to commercially available capsules.

4.4.4. *In vivo stability of nanoparticles*

Drug-loaded nanoparticles may encounter various harsh physiological environments during oral delivery, resulting in aggregation, precipitation, or degradation. These factors can significantly impact their *in vivo* stability and hinder the successful delivery of drugs to the target site. Firstly, nanoparticles encounter amylase and lipase in the oral cavity and then enter the stomach filled with strong acidic liquid, pepsin, and cathepsin. They reach the intestine where various digestive enzymes pose a threat to their stability. Each component of the gastrointestinal tract possesses distinct anatomical and physiological properties that influence the stability of nanoparticles to varying degrees[7,271]. It is evident that maintaining a certain *in vivo* stability after oral administration is crucial for effective transepithelial transport of nanoparticles. The key factor determining the *in vivo* stability of nanoparticles is the nature of their carrier materials. Stable materials help maintain the integrity and functionality of the drug delivery system over an extended period. For example, enteric-soluble polymer materials have a natural advantage in gastric stability[224,272]. Most inorganic materials are inert and exhibit good physiological stability which can resist the hydrolysis of gastric acid and enzymes[244,257]. Although biodegradable materials derived from natural polymers like proteins and chitosan offer excellent biocompatibility and safety, they are susceptible to hydrolysis by digestive enzymes which limits their gastrointestinal stability[220]. In the above paragraph on carrier materials, we have introduced in detail the *in vivo* stability of nanoparticles formed by various types of carrier materials and the research made by scientists in recent years to improve the oral stability of nanoparticles. Additionally, there is an abundance of proteins present within the gastrointestinal tract that can interact with nanoparticles and form protein corona on their surfaces, thereby modulating the in *vivo* stability of nanoparticles[80,138,273]. Some studies have proposed that protein corona can increase the colloidal stability of nanoparticles[274,275]. When an ample number of proteins form this crown, they can fully encapsulate an individual nanoparticle, thus providing spatial stability between adjacent nanoparticles and reducing their aggregation[275]. However, the interaction between proteins and nanoparticles is highly complex, and there is no unified conclusion on the effect of protein corona on the stability of nanoparticles. This is determined by the combination of protein binding types and proportions, human-specific physiological environment, and the properties of nanoparticle carrier materials[80,144,276,277]. The oral nanoparticles prepared using different types of carrier materials, along with their advantages were shown in Table 2[124,187,188,199,205–209,229,234–236,240,255,256,259,263,265,266,268,278–283].

4.5. *The perspective of holistic properties*

The holistic properties of nanoparticles significantly impact oral transepithelial transport efficiency. However, researchers should prioritize factors based on actual situations and specific needs. Nanoparticle size could be regulated for optimal effect by adjusting parameters like the preparation process or carrier material[26], while the customization of nanoparticle shapes still presents challenges. Although the rod-shaped nanoparticles offer advantages in oral transepithelial transport, the creation of non-spherical organic-based particles is generally limited by the lack of universal technical conditions and methods[26,166]. In addition to the above essential factors, various nanoparticle carrier materials with different performances and advantages must be considered when designing drug delivery systems. These materials may include polymer nanoparticles, liposomes, metal nanoparticles, etc. They have different biocompatibility, stability and drug release characteristics, and the most suitable carrier material needs to be selected according to the specific application. Some researchers have developed aspheric organic nanoparticles using PLGA or liposomes, but their post-administration shape requires further study due to potential expansion or deformation[29,284,285]. The safety of non-spherical nanoparticles in drug delivery systems still requires further observation and investigation, despite the gradual application of 3D printing technology. Moreover, nanoparticles should possess the ability to facilitate efficient drug release. This can be accomplished by employing materials with appropriate holistic properties, including particle size and shape, which enable the controlled release of the drug at the desired rate and location. The development of nanoparticles with distinct characteristics and advantages should be based on the clinical requirements.

5. Summaries and perspectives

Intestinal epithelial cells, as the primary constituent of the intestinal mucosa, possess a substantial theoretical absorption surface area. However, achieving effective transportation of particles across these cells remains challenging, resulting in limited absorption of conventional oral nanoparticles. Various strategies have been explored to enhance transepithelial transport of nanoparticles in intestinal epithelial cells while considering safety concerns. For instance, the material of nanoparticles is generally selected based on their biocompatibility and biodegradability to mitigate potential toxicity risks. Additionally, ligand modification and property modulation can be utilized to enhance transepithelial transport through specific pathways without interfering with the

Table 2 Nanoparticles prepared using different types of carrier materials and their advantages.

Material type	Nanoparticle type	Advantage	Ref.
Lipid	Liposome	Wide drug loading range Good biocompatibility and biodegradability Lymphatic absorption	187,188,199
	Solid lipid nanoparticles (SLN) Nanostructured lipid carriers (NLC)	High drug loading capacity Enhanced gastrointestinal tract stability and permeability of intestinal mucus barriers Ease of large-scale manufacture	205−207
	Exosome	Good biocompatibility and permeability Minimal immunogenicity Enhanced gastrointestinal tract stability Intestinal cell-targeted	208,209
Polymer	PLGA NPs	Increased drug solubility Enhanced gastrointestinal tract stability and permeability of intestinal mucus barriers Facile surface modification	124,229,278
	Nanohydrogels	Excellent gastrointestinal stability and intestinal adhesion Intelligent response to physiological environment Controlled drug release	234−236,240
	Polymeric micelles	Increased drug solubility Enhanced gastrointestinal tract stability and permeability of intestinal mucus barriers	279,280
Metallic	Gold nanoparticles CeO_2 nanoparticles	Facile preparation and storage Controlled size, shape, and surface functionalization Resistant against acids and enzymes Available for molecular imaging and GI disease diagnosis	255,256,259,281
Metalloid	Mesoporous silicon nanoparticles Mesoporous carbon nanoparticles	Large drug-loading space and high surface modifiability Increased drug solubility and release Excellent gastrointestinal stability and intestinal adhesion	263,265,266,268
Hybrid	Metal-organic framework	Controlled size, structure and surface functionalization Enhanced gastrointestinal tract stability and permeability of intestinal mucus barriers	282,283

normal function of epithelial cells. Compared to the paracellular pathway that facilitates opening tight junctions but lacks selectivity in promoting substance absorption, we believe that the *trans*-epithelial pathway holds greater significance as a transport route for enhancing oral delivery of nanoparticles. Thereby, finding appropriate strategies to enhance the transepithelial transport efficiency of drug delivery systems holds potential for clinical translation of oral nanoparticles in the future.

Research has demonstrated that manipulating the surface properties of nanoparticles, such as ligand modification, surface charge, hydrophilicity/hydrophobicity, and regulating holistic properties including size, shape, and rigidity can facilitate the transepithelial transport of nanoparticles (Table 3[12,26,29,41,42,125,126,128−130,134−136,142,144,162,164,165,174]). Based on studies on oral nanoparticles and their properties (Fig. 6), we have summarized some common conclusions. For example, small molecule ligands seem to be better suitable for oral drug delivery systems than peptide and protein ligands, due to the potential disruptions caused by the harsh pH environment and digestive enzymes in the gastrointestinal tract. Moreover, small molecular ligands such as fatty acids, glucose, and bile acids are more cost-effective and easily obtainable while aligning with the natural absorption pathway of nutrient molecules for mediating transepithelial transport, thus having better *in vivo* safety. The particle size of nanoparticles has been previously confirmed to have an inverse relationship with mucus entrapment, as smaller particles exhibit enhanced cellular uptake and transepithelial transport efficiency. While the choice of nanocarrier materials may vary, maintaining a particle size within the range of 50−200 nm is advantageous for oral delivery. Moreover, the impact of nanoparticle shape on oral delivery is also summarized. In comparison to conventional spherical nanoparticles, non-spherical rod-shaped nanoparticles demonstrate simultaneous enhancements in mucus penetration, cellular uptake, and transepithelial transport. However, the preparation of non-spherical nanoparticles often entails greater complexity than their spherical counterparts.

When selecting materials for oral nanoparticles, it is crucial to consider the specific drugs being delivered. Lipid-based materials are biocompatible and possess the ability to enhance oral absorption, rendering them suitable for delivering a wide range of drugs orally. In cases where controlled drug release is required, polymer-based materials such as PLGA and chitosan can be considered to modulate the release behavior of drug-loaded nanoparticles by adjusting the composition or proportion of polymers accordingly. Furthermore, if there is a need for enhanced drug loading capacity within the delivery systems, biodegradable

Table 3 Properties that influence the transepithelial transport of nanoparticles.

Property	Classification	Effect	Ref.
Ligands	The information can be found in Table 1		
Surface charge	Positive charge	The positively charged nanoparticles are mainly transported through the clathrin-mediated endocytosis pathway and are more prone to bypass the endo-lysosomal pathway	12,128−130
	Negative charge	The negatively charged nanoparticles are mainly the caveolin-mediated pathway and show enhanced transepithelial transport efficiency	128
	Electric neutrality	The electrically neutral nanoparticles are more proper to overcome the mucus barrier	125
Hydrophilicity /hydrophobicity	Hydrophilicity	The hydrophilic nanoparticles were more easily penetrated the mucus layer	126
	Hydrophobicity	The hydrophobic nanoparticles were more efficiently exocytosis from the basolateral side and were more likely to transport by the M cell-associated pathway	134−136
Protein corona	Mucin-protein corona	The mucin-protein corona facilitated the exocytosis of nanoparticles from the apical side of cells into the intestinal lumen, while impeding their exocytosis from the basolateral side and subsequent entry into the bloodstream	142
	Intestinal protein corona	The disease-specific IPCs can modulate intracellular transport of NPs through early endosome, recycling endosome, and endoplasmic reticulum-Golgi apparatus pathways while increasing basolateral exocytosis and facilitating transepithelial transport	144
Size	<50 nm 50−200 nm 200−1100 nm	The nanoparticles within the size range of 50−200 nm may be more advantageous for enhancing their cellular uptake and transepithelial transport Nanoparticles ranging from 55 to 1100 nm showed improved retention within Peyer's patches compared to nanoparticles with smaller size	26,41,42,162
Shape	Rod-shaped Disc-shaped Spherical	The efficiency of cellular uptake for nanoparticles is in the order of rod-shaped > disc-shaped > spherical The rod-shaped nanoparticles are more easily taken up by cells through preferential transportation *via* the endoplasmic reticulum-Golgi apparatus pathway, thus they are more likely to be transported across intestinal epithelial cell layers	26,164,165
Rigidity	Soft	The soft NPs with lower rigidity were more likely to be trapped in lysosomes, leading to lower exocytosis efficiency	174
	Moderate	The nanoparticles with moderate rigidity exhibit enhanced deformability and possess superior mucosal penetration capability	29
	Hard	The hard NPs with higher rigidity tended to be transported through exocytosis-related pathways such as the endoplasmic reticulum, Golgi apparatus, microtubules, and caveolae, thus showing higher exocytosis efficiency	174
Materials	The information can be found in Table 2		

inorganic materials like mesoporous silicon and mesoporous carbon can be employed due to their porous structure.

Although numerous studies have explored strategies to improve the transepithelial transport of nano-drug delivery systems from the perspective of surface and holistic properties, they are almost limited to achieving certain improvements in animal models (mostly rodent models)[16]. However, the translation of oral nano-formulation from basic research to clinical practice remains challenging. Recently registered clinical trials involving orally administrated nanoparticles showed that the lipid-based nanoparticles account for a large proportion, such as liposomes (NCT03530436, NCT02278822, NCT03719326), nanolipospheres (NCT03877991, NCT01893424), lipid crystal nanoparticles (NCT02971007, NCT02629419), and phospholipid nanoemulsions (NCT05742022). Other types of nanoparticles include polymer-based nanoparticles for ethylcellulose-based polymeric nanoparticles (NCT03774680), protein-based nanoparticles for albumin-stabilized nanoparticles (NCT00313599), and inorganic nanoparticles for silica nanoparticles (NCT01772251), silver nanoparticles (NCT04978025) as well as gold nanoparticles (NCT05347602)[1]. When selecting nanocarriers for drug delivery systems, organic materials with good biocompatibility are preferred. Among them, lipid-based materials are particularly favored due to their advantages of easy availability, large-scale production capability, and good safety profile. Additionally, the clinical translation of nanoparticles will be greatly limited by the requirement for excessive additional materials or more complex manufacturing processes to achieve the ideal surface and holistic properties (such as charge, hydrophilicity, particle size, and rigidity). Therefore, it is crucial to take into account the design of

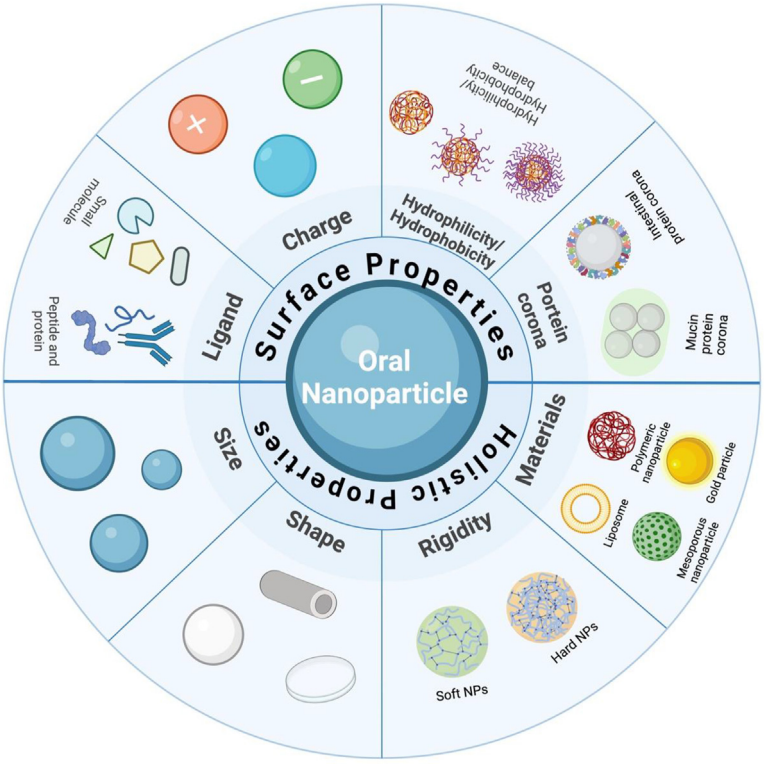

Figure 6 Overview of the surface and holistic properties that influence the transepithelial transport of nanoparticles. Made using BioRender.

oral drug delivery systems from an economic and production perspective right from the beginning.

Furthermore, it is evident that the ligand-modified nanoparticles for oral delivery have hardly progressed to the clinical trial stage. We speculate that this may be attributed to species variations between animals and humans including differences in the small intestinal absorption area, the length and proportion of small intestinal segments (duodenum, jejunum and ileum), and the expressions of intestinal receptors and transporters[286,287]. Among these factors, discrepancies in receptor and transporter expressions of intestinal mucosa may play a more crucial role in the clinical translation of ligand-modified nanoparticles. For instance, for intestine peptide transporters and glucose transporters, human HPET1 and SGLT1 expression is higher than that of mice, but PEPT1, GLUT1 and GLUT5 expression is lower than that of rat[287]. The activity of human apical sodium-dependent bile acid transporter (ASBT) is higher than that of rat[159]. Consequently, for targeting receptors or transporters with lower expression in humans, ligand modification may not achieve the desired effect in humans. Therefore, in the development of ligands for oral delivery, it is crucial to consider specific subtypes of intestinal receptors or transporters and prioritize targets with higher expression levels in humans. At the same time, employing more animal models that are closer to human beings, rather than just rodent models, can more accurately evaluate the effectiveness of the nanoparticles and their potential for clinical translation.

Due to variations in preparation processes, material compositions, and therapeutic drugs employed, these approaches for property modulation may not be universally applicable. Therefore, it is imperative to select suitable strategies based on nanoparticle characteristics and the intended destination for drug delivery. Additionally, several unresolved issues persist: (1) Does a synergistic promotion or mutual inhibition effect exist between surface properties and holistic properties on nanoparticle transepithelial transport? (2) Which specific nanoparticle properties are considered significant contributors? (3) Are there any other influential factors governing nanoparticle transepithelial transport? Furthermore, in addition to commonly used *in vitro* models like epithelial cell monolayers, it is crucial to employ multiple appropriate *in vivo* models collectively to investigate the process, effectiveness, and mechanisms underlying oral drug delivery.

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Jiang Xie: Validation, Visualization, Writing − original draft, Writing − review & editing. Jiawei Wu: Conceptualization, Data curation, Project administration, Validation, Visualization, Writing − original draft, Writing − review & editing. Yuan Huang: Conceptualization, Funding acquisition, Investigation, Project administration, Validation, Writing − original draft, Writing − review & editing.

Conflicts of interest

The authors declare no conflict of interest.

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