


Enteral Route Nanomedicine for Cancer Therapy

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Abstract: With the in-depth knowledge of the pathological and physiological characteristics of the intestinal barrier–portal vein/intestinal lymphatic vessels–systemic circulation axis, oral targeted drug delivery is frequently being renewed. With many advantages, such as high safety, convenient administration, and good patient compliance, many researchers have begun to explore targeted drug delivery from intravenous injections to oral administration. Over the past few decades, the fields of materials science and nanomedicine have produced various drug delivery platforms that hold great potential in overcoming the multiple barriers associated with oral drug delivery. However, the oral transport of particles into the systemic circulation is extremely difficult due to immune rejection and biochemical invasion in the intestine, which limits absorption and entry into the bloodstream. The feasibility of the oral delivery of targeted drugs to sites outside the gastrointestinal tract (GIT) is unknown. This article reviews the biological barriers to drug absorption, the in vivo fate and transport mechanisms of drug carriers, the theoretical basis for oral administration, and the impact of carrier structural evolution on oral administration to achieve this goal. Finally, this article reviews the characteristics of different nano-delivery systems that can enhance the bioavailability of oral therapeutics and highlights their applications in the efficient creation of oral anticancer nanomedicines.

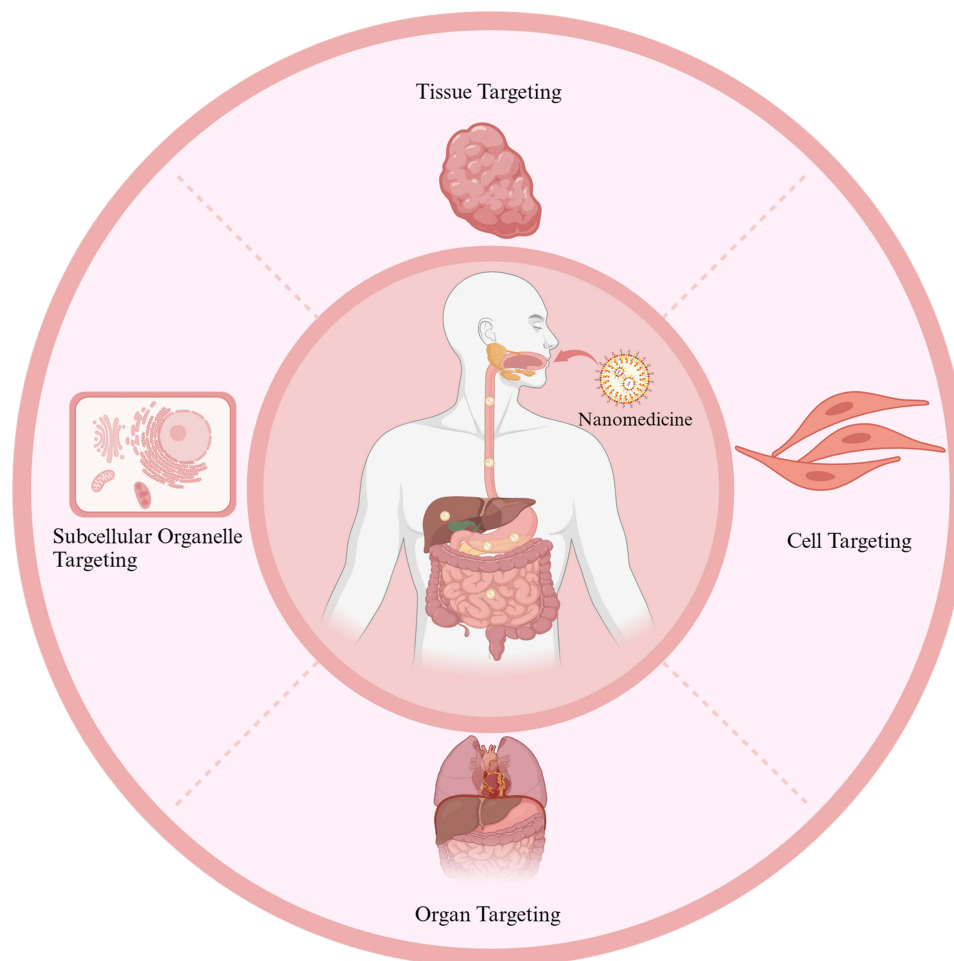
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Introduction

The route of drug administration is the most important factor in determining drug concentration and residence time at the target site.^{1,2} Despite well-known drawbacks such as poor drug bioavailability and rapid degradation rates and metabolism in the intestine and liver, oral therapy is considered the most ideal and convenient route of drug delivery for both systemic and local administration drug delivery.³ It is essential for patients to perceive oral drug delivery positively, particularly when compared to infusions or other parenteral methods, which are common in cancer treatments. Additionally, the economic benefits of reducing hospital stays for patients should also be considered.⁴

The gastrointestinal tract (GIT) encompasses a surface area of approximately 300 square meters and is enveloped with a sticky mucosal layer that aids in the adhesion and absorption of drugs.⁵ Notwithstanding, oral drug delivery poses a daunting task owing to the intricate nature of the GIT and the impediments to drug delivery, such as substandard solubility, stability, and permeability. In addition, an unpleasant taste, gastric irritation, and susceptibility to intestinal and liver barrier metabolism are common drawbacks of oral medications.^{6,7} However, targeted delivery to specific locations in the GIT can be achieved through appropriate drug design or delivery vehicles.⁸ The residence time of digested food in the duodenum is relatively brief, and the pH is lower than that of the remainder of the small intestine. This indicates that the retention of drugs in the duodenum can be successfully avoided by increasing the pKa value of the delivery vehicle. For instance, Lozoya-Agullo et al employed poly(lactic-co-glycolic) acid (PLGA) nanoparticles for colonic delivery, demonstrating that drug release in the duodenum could be significantly avoided due to insufficient ambient pH.⁹

Graphical Abstract



Drug delivery systems (DDSs) are frequently utilized to improve the stability of drugs, regulate drug release, and accumulate drugs at the lesion site, thus improving drug effectiveness.^{10–13} In 1906, Ehrlich first proposed the “magic bullet” hypothesis, which introduced the idea of targeted drugs.^{14,15} Since rituximab, the first targeted treatment was approved by the FDA in 1997, targeted drug delivery systems (TDDSs) have emerged, leading the way for targeted therapy.¹⁴

Some researchers advocate using oral targeted drug delivery systems (OTDDSs) in biomedical applications, citing their promising potential.¹⁶ Oral administration involves the administration of drugs or therapeutic agents that are transported into the systemic circulation and accumulate at target sites beyond the GIT. The proposed OTDDS is considered to have various potential benefits, such as enhanced compliance, improved convenience of medication usage, and lowered expenses for production and healthcare. Historically, oral administration has proven to be more effective for treatments based on small molecules. Due to the diverse and heterogeneous nature of the biological barrier in the GIT, most new biotherapeutics and high-molecular-weight molecules are not ideal for delivery using this route.¹

Recent advancements in materials science are expanding the options for cancer treatments.¹⁷ Specifically, nanomedicines and their bulk carriers demonstrate significant potential in improving the delivery of small molecules and macromolecules.^{18–21} Wang et al demonstrated that tartaric-acid-modified mesoporous silica nanoparticles exhibit excellent mucus penetration, mucosal adhesion, cellular uptake, intestinal transport, and gastrointestinal retention during continuous oral absorption. The nanoparticles are efficiently absorbed into the bloodstream during oral delivery, exhibiting absorption rates that are 1.72–2.05 times higher than

those of other nanocarriers. They also contribute to a more efficient intestinal transit of loaded doxorubicin (DOX), with absorption rates that are 2.32–27.03 times higher than those of other samples. Furthermore, the nanoparticles exhibit satisfactory bioavailability (449.73%) and a stronger anti-tumor effect (up to 95.43%).²² The oral delivery of nanocarriers can both promote regulated drug release and protect the drug payload from adverse biological and chemical conditions in the GIT. In addition, by avoiding first-pass metabolism, oral nanocarriers enhance targeting to specific GIT cell morphologies, penetrate the mucus barrier, and improve drug bioavailability.²² The drug delivery community has shown great interest in the search for novel approaches and materials that facilitate the transition from intravenous to oral drug delivery.^{23,24} The viability of OTDDSs must be taken into account when considering oral targeted therapy. This includes the consideration of transport mechanisms, intestinal and cellular distribution, absorption pathways, and the structural progression of the carriers in the body. The mucosal mucus layer of the intestine has a large surface area (greater than 300 m²), which facilitates the attachment of drugs and subsequent absorption.²⁵ Given the abundance of enterocytes throughout the intestine, particularly in the microfold cells (M cells) lining the lymphatic area of the small intestine. M cells are specialized cells present in the intestinal epithelium and are part of the gut-associated lymphoid tissue. M cells are morphologically different from intestinal epithelial cells. On the surface of the intestine, M cells have short and irregular microvilli, which are different from the highly organized and uniformly and closely arranged microvilli of intestinal epithelial cells. Therefore, M cells have higher permeability than other intestinal epithelial cells and can be used as a channel for nanoparticles to cross the epithelium. After ingestion, the drug carrier will immediately enter the lymphatic system without loss.^{26,27} Other factors that contribute to reduced drug efficiency due to mechanical degradation within the gastrointestinal tract are osmotic pressure along the gastrointestinal tract, the peristalsis of the gastrointestinal muscles, and shear stress generated by gastric fluid flow rates within the gastric lumen.²⁸ Furthermore, the flow of gastric juice may also reduce the contact time between drug molecules and the epithelial layer, thereby hindering drug absorption.²⁹ Enveloped biologics, such as viruses, vaccines, and cells, are frequently the primary components susceptible to mechanical disruption. In a study by Valon et al, the potential effects of mechanical stress on various cell types were investigated. The findings indicated that shear stress and compaction may result in cell apoptosis and death.³⁰ Furthermore, Choi et al demonstrated that high osmotic pressure can compromise the integrity of viruses in acidic environments.²⁸

This review provides a detailed summary of nanotechnologies for oral chemotherapy, highlighting their unique properties and the challenges they face in overcoming intestinal biological barriers. It emphasizes the many advantages of oral administration over injection: avoidance of discomfort, trauma, infection, and complications. A major challenge with oral drug delivery is the relatively low bioavailability of the drug. Nanotechnology can significantly improve the bioactivity and availability of oral drugs. The applications of organic and inorganic nanomaterials in oral nanomedicines are reviewed, demonstrating their respective advantages and application prospects. Specific challenges and potential opportunities for the future development of oral nanomedicines are presented and analyzed. The main physiological barriers facing oral drugs are described, and insights into how nanotechnology can overcome these barriers through a range of mechanisms of action are provided. Research on oral nanomedicines based on nanomaterials and specific application cases in cancer treatment are discussed. Challenges and opportunities encountered in future clinical translation and industrial production are proposed, and coping strategies are emphasized. The review calls for more solutions with innovative designs and applications to promote the clinical transformation and standardized production of oral nanomedicines. The ultimate goal is to benefit patients and improve their quality of life through innovative nanotechnology designs and applications. We also highlight their potential use in the treatment of cancer (Table 1).

Biological Barriers to OTDDSs

Biological barriers to the transport of drugs or carriers hinder the effective accumulation of nanoparticles at sites of disease, impeding the swift targeting of diseased areas. While the transportation of materials within the GIT is highly efficient, biological defense mechanisms have evolved to prevent foreign objects—such as synthetic nanoparticles—from being harmful. In a similar vein, the defense system acts as a built-in impediment to nanoparticle absorption. Orally administered nanoparticles may face challenges in achieving systemic circulation due to resistance and destruction. Multiple barriers must be overcome for nanoparticles to complete their intended tasks. In general, physical and biochemical barriers form an absorption barrier that prevents nanoparticles from traveling from the gastrointestinal lumen to the liver (Figure 1).²⁷

Table I Oral Nanomedicine for Cancer Drug Delivery

Carriers	Nanoparticles (NPs)	Targeted Cancer	Therapeutic Outcomes	References
Polymers	Carnitine coated PLGA NP	–	Increased paclitaxel bioavailability	[31]
	Chitosan coated PLGA NP	Oral mucositis induced by chemotherapy	Increased oral cavity residence time	[32]
	PLGA NP	Oral cavity cancer	Increased local docetaxel delivery	[33]
	Pegylated PLA NP	Breast cancer	Increased raloxifene hydrochloride bioavailability	[34,35]
	Pegylated PLA NP	Lung cancer	Increased paclitaxel bioavailability	[36]
	Hyaluronic acid coated pegylated	Colon cancer	Increased PTC209 delivery and Inhibited cancer stem cell proliferation	[37]
	PCL NP	–	Increased ellagic acid	[38]
	Polymeric micelle	Breast cancer, Hepatocellular carcinoma	Increased paclitaxel bioavailability	[39]
	PEG NP	Breast cancer	Increased SPI41 bioavailability	[40]
	Inorganic materials	Aluminum silicate	–	Increased methotrexate release properties
Selenium NP		Prostate cancer	Reduced side effects and increased tumor growth inhibition	[38]
Metal-organic framework		–	Increased exendin-4 bioavailability	[42]
Mesoporous silica		Breast cancer	Increased doxorubicin bioavailability	[22]
Polysaccharides	Chitosan modified with acrylonitrile and arginine	–	Increased curcumin bioavailability	[43]
	Cyclodextrin micelles	Sarcoma	Increased docetaxel BA and tumor reduction	[44]
	Guar gum NPs	–	Increased mammary gland targeting and tamoxifen bioavailability and decreased liver toxicity	[45]
Protein	Pectin coated casein/zein NP	–	Enhanced curcumin bioavailability	[46]
	Apotransferrin and lactoferrin NP	Hepatocellular carcinoma	Enhanced doxorubicin bioavailability and decreased liver nodule number	[47]
	Milk casein NP	–	Increased resveratrol bioavailability compared with free administered drug	[48]
	Polydopamine NPs	–	Increased gastric targeting and local xanthatin delivery	[49]
	Bioactive mangiferin	Colon cancer	Increased mangiferin bioavailability	[50]
	Succinylated casein	–	Increased paclitaxel bioavailability	[51]
Lipid nanoparticles	Hybrid lipid- poly(ϵ -caprolactone) NP	Subcutaneous model of hepatic cancer	Increased cabazitaxel bioavailability and tumor growth inhibition	[52]
	Hybrid polymer-lipid NP	–	Increased berberine bioavailability	[53]
	Chitosan coated solid lipid NP	–	Increased curcumin bioavailability	[54]
	Amphiphilic and pegylated lipids and cholesterol	–	Increased siRNA delivery to immune cells	[55]
	N-succinic anhydride and D-fructose co-conjugated chitosan	Breast cancer	Increased paclitaxel bioavailability	[56]
	Squalene NP	Colon cancer	Increased paclitaxel delivery and tumor killing properties	[57]
	Chimeric virus-like particles decorated with variant-specific surface proteins	Mesothelioma	Increased immune response against HA-expressing mesothelioma	[58]
	Live attenuated salmonella coated with polymeric particles	Melanoma	Increased immune response against VEGFR2	[59]
Bioinspired systems	Yeast loaded polymeric nanoparticles	Subcutaneous breast cancer	Increased paclitaxel delivery via macrophages	[60]
	Milk exosomes	Subcutaneous lung cancer model	Increased tumor killing properties and safety	[61]

Abbreviation: NP, Nanoparticle.

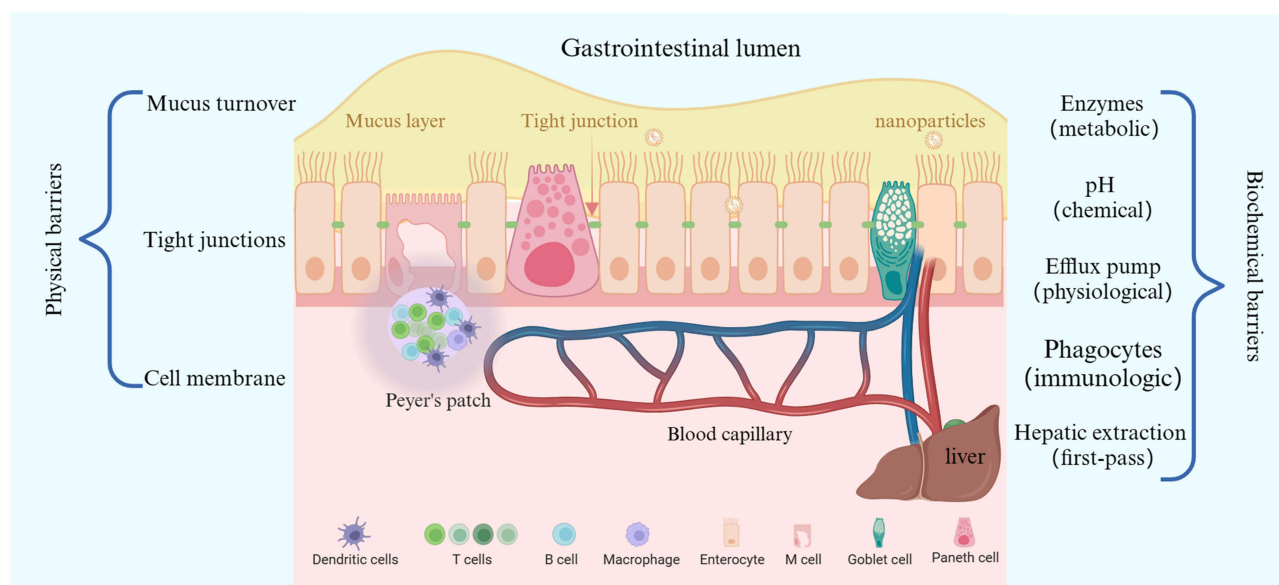


Figure 1 Biological barriers to nanoparticle absorption into the systemic circulation, mainly consisting of physical barriers and biochemical barriers. Physical barriers greatly limit the influx of nanoparticles, and biochemical barriers result in the degradation and clearance of nanoparticles.

Physical barriers restrict the penetration of particles, including mucus, tight junctions (TJs), and cell membranes. The mucus layer is the primary barrier that nanoparticles must overcome to enter into the circulatory system. It has been emphasized that mucus, which safeguards epithelial surfaces, acts as a significant obstruction to nanoparticle penetration.^{62,63} As materials traverse, mucus is continuously released from the mucus layer to wash away pathogens and lubricate the epithelium as substances pass through. The shortening of the nanoparticle residence time in mucus turnover results in their incapability to penetrate the loosely adherent layer.⁶⁴ To overcome these barriers, Wang et al developed a strategy to modify the nanocarrier surface with cationic cell-penetrating peptides, which are hidden by a hydrophilic succinylated casein layer. Succinylated casein is a mucus-inert natural material that degrades specifically in the intestine, thereby protecting nanocarriers from the harsh gastric environment. This degradation also promotes mucus penetration and induces cell-penetrating peptide exposure upon degradation, which, in turn, facilitates efficient transepithelial transport.⁵¹ During the breakdown of the mucus layer, the nanoparticles encounter cellular barriers, such as TJs and cell membranes. These TJs between adjacent epithelial cells permit the passage of only small water-soluble molecules while limiting the movement of lipophilic compounds, macromolecules, and particles.⁶⁵ Li et al prepared nanocarriers with variable physical properties through the self-assembly of hydrolyzed α -lactalbumin peptide fragments. The nanotubes can instantaneously and reversibly open the TJs between cells, thereby facilitating the entry of mangiferin into the blood circulation and enhancing its bioavailability.⁵⁰ The confinement of macromolecules or aggregates at TJs obstructs the potential uptake pathway of nanoparticles, which is referred to as the paracellular route. Similarly, cell membranes either favorably or unfavorably allow foreign particles to pass through them. The direct penetration of cell membranes by nanoparticles is impracticable. Therefore, the primary absorption mechanism is membrane transport.⁶⁶ Biochemical barriers present additional factors that substantially impede nanoparticle uptake and transport. Harsh gastrointestinal conditions, including immune cells, efflux pumps, variable pH, and digestive enzymes, combined with hepatic clearance, result in significant transport barriers.⁶⁶ For oral targeted nanoparticles to enter the circulation, they must successfully avoid chemical destruction and metabolic enzymes, as well as physiological efflux immune phagocytosis, and hepatic first-pass effects. Meeting these requirements necessitates a careful overall design of the nanoparticles.¹⁴ A novel delivery system has been developed, comprising polymeric liposomes modified with N-succinic anhydride and D-fructose-conjugated chitosan. This system has been designed to achieve the delivery of paclitaxel by targeting the dual transporters of monocarboxylic acid transporters and glucose transporters.⁵⁶ The system is therefore capable of efficient targeted delivery.

The oral bioavailability of these drugs can be significantly enhanced by the use of nanocarriers, which can increase drug solubility, prevent drug degradation by gastrointestinal enzymes, and facilitate drug passage through mucus gel layers and absorptive membranes. The aforementioned properties of nanocarriers, including self-emulsifying drug delivery systems, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, polymeric nanoparticles, inorganic nanoparticles, and polymeric micelles, are largely dependent on their surface chemistry. In particular, the following determined by the surface chemistry of the nanocarrier: interactions with food, digestive enzymes, bile salts, and electrolytes; diffusion behavior across the mucus gel layer; and fate on the absorptive membrane. Bioinert surfaces that limit interactions with gastrointestinal fluids and contents and mucus, adhesive surfaces that provide intimate contact with the gastrointestinal mucosa, and absorption-enhancing surfaces can be designed. Furthermore, a charge conversion surface is capable of converting its zeta potential from negative to positive directly at the absorbing membrane, thereby providing a surface for targeted drug release, which is advantageous. In addition to the aforementioned passive surfaces, it is even possible to create active surfaces that cleave mucus glycoproteins during their passage through the mucus gel layer.

Paracellular and Transcellular Transport Pathways and Mechanisms of OTDDSs

DDS carriers are typically fashioned using functional nanoparticles, which are commonly referred to as nanocarriers for delivering therapeutic drugs. These molecular aggregates, known as nanocarriers, are larger and heavier than the molecular threshold that separates the gap between the TJs and the cell membrane pores. The likelihood of nanoparticles penetrating through the cell membrane or intercellular space directly is nearly non-existent. Many nanocarriers are engineered to undergo transepithelial transport in a self-regulated manner, such as briefly opening TJs and inducing membrane deformation. Based on this, Lamson et al reported that a negatively charged silica nanoparticle can indirectly cause TJ disruption by binding to integrins, thereby enhancing the paracellular delivery of protein drugs.⁶⁷ Nevertheless, two primary pathways, the paracellular and transcellular pathways, are responsible for the movement of particulate matter throughout the GIT (Figure 2).

The TJ gap spans from 10 to 30 and 50 angstrom, implying that entities with molecular radii surpassing 151 angstrom (around 3.5 kDa) would be barred from accessing this absorption pathway.⁶⁸ Paracellular transport's passive mode necessitates that particles possess sufficient smallness or deformability to cross the intercellular space. Nanocarriers smaller than 5 nm are delivered to the basolateral blood or lymphatic capillaries beneath the GIT wall via paracellular pathways that follow concentration gradients. For example, 5 nm ionic gold nanoparticles have been found to preferentially penetrate epithelial Caco-2 cell monolayers via the paracellular pathway.⁶⁹ Paracellular transport via endothelial leakage induced by nanoparticles has recently been demonstrated, which is likely to also occur within the intestinal epithelium.⁷⁰ Additionally, the size distribution of artificial nanoparticles frequently exhibits inhomogeneity and polydispersity. A small proportion of ultrafine nanoparticles consistently exists within the system. These minute nanoparticles can be carried into the microcirculation via paracellular pathways. However, compared to overall uptake, the quantity transported is minimal. Moreover, by momentarily opening the TJ pathway, carefully engineered nanoparticles can pass through the intestinal epithelium and reach the underlying microcirculation.^{71–73} By mimicking the natural mechanism of pathogen interaction with intestinal epithelial cells, lectin-modified methacrylic acid-based NPs were used to encapsulate a small bacterial fragment, C-CPE, which was able to interact with the tight junction protein Claudin-4, leading to the opening of tight junctions.⁷⁴ Although it is not nanoparticles' primary means of transportation, they can evade lysis due to their inability to enter cells. Enzymatic digestion is advantageous for the realization of OTDDSs. The transcellular route through endocytosis remains the primary transport pathway for most nanocarriers. The uptake of oral nanoparticles primarily involves membrane mobile transport. When nanoparticles approach cells, the interactions between the particles and the cell membrane arise from various sources, resulting in the deformation of the membrane to enclose the nanoparticles, which are then taken up by the cell.⁷⁵

Endocytic and Transcytotic Transport Pathways and Mechanisms of OTDDSs

Endocytosis is a cellular physiological process whereby cells absorb molecules via the phagocytosis of extracellular molecules through cell membrane movement.⁷⁶ Particle uptake is significantly influenced by endocytosis, especially carrier-mediated endocytosis. Specifically, phagocytes—monocytes, dendritic cells, neutrophils, and macrophages—are

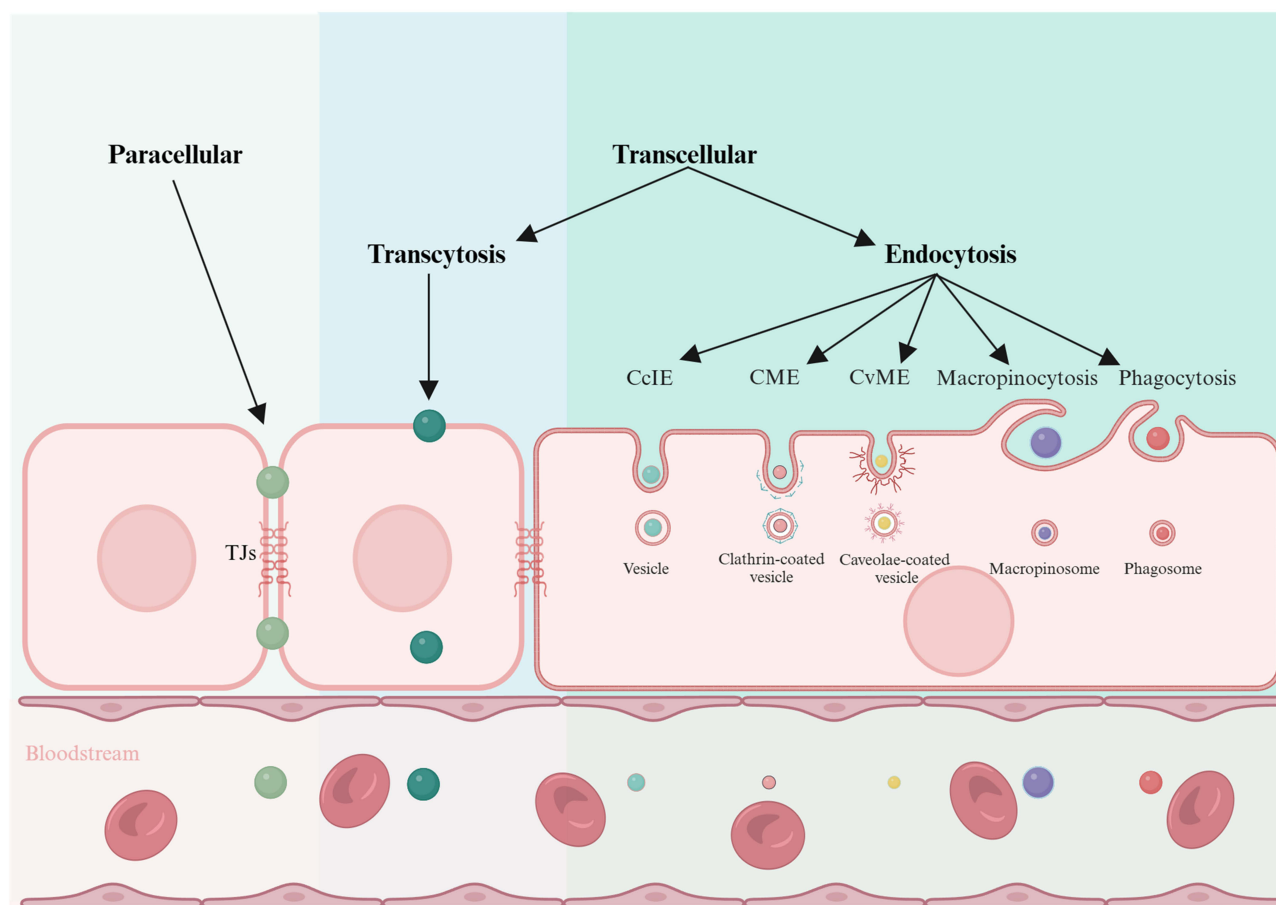


Figure 2 Transport mechanisms of nanoparticles across cells. Nanoparticles are first taken up by apical epithelial cells through endocytosis followed by transcytosis across the intestinal wall consisting of multiple layers of cells into the underlying capillaries.

Abbreviations: CclE, clathrin-/caveolin-independent endocytosis; CME, clathrin-mediated endocytosis; CvME, caveolin-mediated endocytosis; TJs, tight junctions.

the targets of phagocytosis. Intestinal immune cells carry out most phagocytosis that occurs in the intestine.⁷⁷ The primary function of phagocytosis is to eliminate dead cells, pathogens, and cellular debris. However, its involvement in intestinal particle uptake remains unclear. Pinocytosis is present in almost all eukaryotic cells and serves as an essential method for capturing external fluids and soft particles.⁷⁸ Due to its capacity to rapidly engulf large quantities of droplets, pinocytosis is also known as macropinocytosis. Pinocytosis is typically a non-selective method of uptake.⁷⁹ In the case of liquids or soft particles, macropinocytosis serves as the primary endocytic pathway. It is now generally accepted that actin regulates the endocytic process of pinocytosis, which is not directly triggered by cargo or receptor molecules.⁸⁰ Compared to other endocytic vesicles, macropinosomes are larger and lack cytoplasmic membranes. They are produced by the process of macropinocytosis. Their size and shape vary a lot, ranging from 0.5 to 10 μm . Consequently, pinocytosis plays a role in transporting large, delicate nanostructures in the GIT.⁸¹

The main mechanism of particle uptake is thought to be carrier-mediated endocytosis, as opposed to phagocytosis and macropinocytosis. However, its efficiency and speed are not yet fully understood. Certain proteins or receptors on the cell membrane enable the selective process known as carrier-mediated endocytosis.⁸² Utilizing specialized biological macromolecules, this form of transport is responsible for transporting particles into the cytoplasm. The two types of biological macromolecules are receptors and transporters. Different transmembrane proteins, called transporters, allow extracellular materials to be selectively transported across biological membranes.⁸³ Receptors are biological macromolecules that respond to particular ligands. The carrier proteins located within the cell membrane typically assist in receptor-mediated endocytosis. During membrane transport, carrier proteins—typically self-assembling proteins—cover transport vesicles. They have the ability to assemble into polyhedral lattices that aid receptor-mediated endocytosis by

organizing and sorting essential membrane proteins.⁸⁴ A mechanism for the selective uptake of various endogenous and exogenous particles is provided by carrier-mediated endocytosis. After endocytosis, molecular aggregates or particles first bind to specific cell surface receptors, resulting in the formation of carrier protein-coated pits. Technical terms are clarified when they are initially used. These pits subsequently emerge from the membrane, generating small vesicles that possess the carrier and its ligands. The presently recognized carrier proteins contain clathrin, caveolin, RhoA, CDC42, flotillin, and ARF6.⁸⁵ Among the proteins involved in carrier-mediated endocytosis, clathrin and caveolin have been identified as the key proteins responsible, for diverse endocytotic functions. These three main modes of carrier-mediated endocytosis are outlined below.

In mammalian cells, the main endocytic pathway is called clathrin-mediated endocytosis (CME). It regulates the recycling of transporters and transmembrane receptors to change the composition of the plasma membrane in response to external stimuli and to control cell surface signaling.⁸⁶ Particles initially adhere to the cell membrane during clathrin-mediated endocytosis through non-specific electrostatic or hydrophobic interactions, or by recognizing specific receptors. This causes the cell membrane to invaginate and form endocytic pits.⁸⁷ Extracellular particles are encapsulated in clathrin-coated vesicles at the neck of the pore through the fusion of cell membranes. After merging with early endosomes, the contents of these vesicles undergo sorting for either recycling back into the plasma membrane or transportation to lysosomes. Endocytic particles are predominantly degraded within lysosomes. However, there are occasional instances whereby these particles evade degradation and successfully exit the endocytosis/lysosome pathway, thus permitting their subcellular delivery.⁸⁸

Particles are internalized via caveolae-mediated endocytosis (CvME) in the plasma membrane, leading to the creation of small, cup-shaped invaginations known as caveolae. These invaginations possess a unique caveolae protein shell, which measures 50–100 nm in diameter, and they are abundant in the lipid rafts of cholesterol and sphingolipids.⁸⁹ They are involved in many different transport processes, such as endocytosis, and caveolin is regarded as one of the most significant membrane proteins because it helps move different cargoes.^{90,91} Studies have indicated that intestinal epithelial cells demonstrate significant activity in CvME.^{82,92} In contrast to CME, CvME has the potential to allow micro-/nano-particles to directly enter the cytoplasm, avoiding endo-/lyso-somal compartments.⁹³ This could have a beneficial impact on targeted oral drug delivery. As a result of caveolae's small size, the CvME internalization of large particles (>100 nm) is challenging. Research has indicated that the size of the particle alone (excluding ligands) determines its entry route.⁹⁴ The CvME pathway establishes an approximate 60 nm limit that mainly internalizes the particle, with negligible entry via CME.⁹⁵

In cells lacking clathrin and caveolin, endocytosis occurs in a manner that is independent of these proteins.⁹⁶ In the absence of fluids and cytokines that are similar to clathrin and caveolin, cells take up various cargos via this pathway. This pathway requires specific lipid components, predominantly cholesterol. Because only a small number of particles are capable of inducing this type of endocytosis, the endocytic pathway is unique. Occasionally, bacteria and viruses hijack target particles and enter host cells through this pathway. Vesicles or pits of around 90 nm in diameter are formed through clathrin-/caveolin-independent endocytosis, with the internalized particles progressing into early and late endosomes.⁹⁷ Folate-modified nanoparticles serve as a notable instance of internalization pathway employment via this mechanism.⁹⁸

Transcytosis is a form of transcellular transportation utilized for larger molecules or particles. It serves as a mechanism for carrying cargo through the cell interior and into neighboring cells through a series of coordinated endocytosis and exocytosis.⁹⁹ The cargo penetrates the membrane of the cell through endocytosis from one side and is subsequently transported to the opposing side through exocytosis. Epithelial cells, particularly secretory cells, are the most frequent sites of transcytosis. Transcytosis serves as a convenient means for pathogens to invade tissues and, thus, is essential for the transmembrane transportation of nanoparticles before reaching the portal vein. It is the main mechanism for transporting nanoparticles across cells among a variety of transcellular transport mechanisms. Despite the ability of nanoparticles, especially ligand-modified nanoparticles, to be internalized into cells, there exists an “easy entry but difficult transcytosis” phenomenon.¹⁰⁰ For instance, researchers investigated intestinal mucins in a Caco-2/HT29 coculture cell model.¹⁰¹ Their goal was to promote endocytosis while limiting the transcytosis of nanoparticles across enterocytes. Notably, zwitterionic nanoparticles demonstrated significant basolateral exocytosis.¹⁰² However, in contrast to transcytosis, nanoparticles become trapped inside the cell and are unable to leave the cell and enter the bloodstream.

Fate of OTDDS in the GIT

OTDDS carriers are typically composed of micro-/nano-particles that feature functional ligands.¹⁰³ By improving absorption and distribution, they can control the pharmacokinetics of administered drugs, which can lead to attenuation and synergy. Nonetheless, these carriers undergo a sequence of biological processes prior to entering the systemic circulation, which results in substantial uncertainty regarding their effectiveness in targeted oral delivery.¹⁰⁴ To investigate the practicality of OTDDSs, an understanding of the mechanism of OTDDS vectors as they journey through the GIT and into the systemic circulation is crucial.

OTDDS carriers undergo immediate physiological and/or biochemical processing upon exposure to harsh gastrointestinal conditions. This processing may include depolymerization, digestion, degradation, and excretion in feces.¹⁰⁵ During this process, some carriers appear as intact particles, while others undergo deformation prior to absorption. Depolymerization is associated with the disintegration of carriers (molecular aggregates). When nanoparticles, such as small-molecule micelles, self-assemble from amphiphiles with a high critical micelle concentration, this phenomenon is easily observed in physiological settings.¹⁰⁶ The biotransformation of nanomaterials by gastric acid or gastrointestinal enzymes is known as “digestive degradation”. While degradation refers to the breaking down of large molecules that shorten the polymer’s molecular chain, digestion primarily refers to the breaking down of large particles into small particles or conversion into small molecular substances.¹⁰⁷ In the discoid bodies of enterocytes, certain degradation products of lipid carriers can be reconstituted into novel nanostructures or form chylomicrons for subsequent transport.^{108,109} In addition to dissociation, digestion, and degradation, intestinal peristalsis is also responsible for the removal of certain particles from the body.

Previous information relates to the fate transition of foregut cells to absorptive epithelial cells in OTDDS vectors.¹¹⁰ Upon reaching the absorptive epithelium, trans-epithelial transport takes place alongside intestinal epithelial post-transformation, which leads to the further disposal of the OTDDS vector in the intracellular environment. When orally consumed, drug carriers may undergo digestion either in the lumen of the GIT or in the cytoplasm. The post-disposal of OTDDS vectors in intestinal epithelial cells mainly involves two aspects: apical exocytosis and lysosomal degradation through efflux pumps.¹¹¹ The OTDDS carrier collapses as a result of intracellular digestion by lysosomes, blocking the particles’ ability to transcytose into capillaries intertwined with the intestinal endothelium.¹¹² In addition, apical exocytosis increases the likelihood of rectal excretion and decreases vector internalization. The OTDDS carrier is extracted and eliminated by the liver after successfully crossing the intestinal epithelium and entering the portal vein, further reducing the risk of systemic circulation.¹¹³

After being orally administered, most OTDDS carriers undergo the biological processes mentioned above. OTDDS vectors generally follow a predictable path from the gastrointestinal lumen to the liver, although this can vary depending on the specific vector.¹¹⁴ While some OTDDS vectors are excreted or digested before reaching the portal vein, others can cross the oral barrier and enter the bloodstream. The efficacy of OTDDSs is determined by their ability to survive the liver clearance process, internalize into intestinal epithelial cells, penetrate the mucus layer on the intestinal epithelium, and remain intact during gastrointestinal transit.¹¹⁵ It is therefore crucial to investigate the ability of OTDDSs to perform these tasks.

The structural evolution of OTDDS vectors has a significant impact on oral administration. The OTDDS carrier will be exposed to the harsh environment of the GIT. Oral targeted delivery can have unpredictable consequences due to the potential for structural and morphological changes in OTDDS carriers during intestinal lumen and transmembrane transport.¹¹⁶ Premature drug release often occurs, even when nanocarriers remain intact in gastrointestinal fluids.¹¹⁷ Variations in transport routes also lead to variations in the biological disposal of the vehicle. This is particularly important given the high probability of lysosomal degradation during transcellular transport. The carrier may degrade or break down, causing the payload and ligand to detach from the carrier. It can be expected that, for environmentally and enzymatically unstable vectors, off-target effects will occur in vivo. It is imperative that the OTDDS delivery vehicle retains its structural integrity both before and after absorption to facilitate the flow of payload and ligands into the circulatory system.¹¹⁸

The destabilization of oral OTDDSs is facilitated by gastrointestinal pH, enzymes, and digestive aids (including bile salts, lecithin, and bicarbonate), as well as intracellular lysosomal enzymes.^{119,120} Fragile nanostructures may deteriorate or disintegrate during transport across membranes. The inefficacy of oral insulin utilizing different nanocarriers suggests that the stability of the nanostructures determines their systemic absorption. Furthermore, the stability and integrity of the

OTDDS vector have a significant impact on how it enters the systemic circulation and subsequently affects biological processes. Any alteration to the microstructure of the vehicle makes it impossible to address the concept of “aiming”. Therefore, when designing OTDDSs, drug developers should focus on the structural evolution of the carrier both before and after intestinal absorption.

Oral Targeted Drug Delivery Strategies

For patients, oral administration is still the preferred route, with over two-thirds of clinically used drugs being delivered orally. The unique advantages of oral drug delivery, such as high compliance, low manufacturing costs, and low sterility requirements, make it ideal for chronic disease management and long-term medication.¹²¹ Therefore, researchers are increasingly focusing on developing OTDDSs. The hallmark of OTDDSs is their ability to target distant sites beyond the GIT. This allows therapeutic drugs to penetrate the biological barrier of the GIT and enter the systemic circulation, enabling them to concentrate on the desired target area.¹²² Nevertheless, administering nanomedicines orally and reducing off-target effects are complex tasks. The varying and distinct physiology of the entire GIT, including variable pH, digestive enzymes, mucin turnover, and efflux pumps, generates a formidable obstacle to nanocarriers entering the systemic circulation, confronting them with several limitations to overcome.^{25,123} It has been reported that over four-fifths of nanoparticles administered orally are not absorbed by the GIT.¹²⁴ It is evident that OTDDSs still encounter numerous obstacles. For instance, the lipids and surfactants present in oral lipid drug carriers may act as substrates for gastrointestinal lipases. The levels of these enzymes, in conjunction with pH and bile secretion, are crucial parameters that determine the fate of lipid formulations and the dispersion, dissolution, and absorption of lipophilic drugs in the gastrointestinal tract. It is therefore essential to have a basic understanding of lipase, pH, and bile acid levels *in vivo* in order to develop relevant *in vitro* models.¹²⁵ Furthermore, these parameters and their changes in healthy subjects are now well documented. However, *in vivo* data for specific populations (age groups, patients with various diseases, patients receiving treatments affecting gastrointestinal parameters, etc.) are rare, and obtaining these data from clinical studies is sometimes difficult due to ethical restrictions. Therefore, it is highly desirable to gain a better understanding of the biological fate, absorption, and transport properties of nanoparticles to expedite the rational design of OTDDSs.

Generally, OTDDSs refer to delivery systems that focus on gastrointestinal tissues located locally or remote tissues outside of the GIT. Colon-specific drug delivery systems are primarily included in the former category, as they are more concerned with particles' local activities than their systemic absorption. For the purpose of this discussion, we concentrate on the systemic targeting outcomes of oral administration and do not elaborate further on the nanocarriers used. Several requirements must be met to achieve targeted oral drug delivery. Several biological barriers prevent nanotherapeutics from effectively entering the bloodstream and accumulating at diseased sites.⁷ The idea is to preserve the full composition of the drug delivery systems that can be designed after passing through the hepatic and gastrointestinal absorptive epithelium. Two necessary conditions are required to achieve oral targeted medication administration. Firstly, once the drug escapes hepatic extraction through the portal vein and the absorptive epithelium, OTDDS must maintain structural integrity during delivery to withstand both extracellular and intracellular biodegradation, ensuring the drug and ligand smoothly reach the tumor site.

In the latter scenario, the delivery system can undergo destruction within the gastrointestinal lumen. However, the resultant components can be reassembled into fresh and targeted nanostructures once the GIT has evolved. Qin et al reported a method to achieve specific release and activation of the prodrug 5-fluorocytosine (5-FC) in the tumor microenvironment by utilizing the tumor tropism of yeast and the extracellular hyaluronidase level. The enzyme cytosine deamination on the surface of yeast can catalyze the conversion of 5-FC into cytotoxic 5-fluorouracil (5-FU), thereby effectively inhibiting tumor growth and prolonging the survival of tumor-bearing mice.¹²⁶ To maintain a stable low-energy state, molecules naturally organize themselves into stable structures, usually micro-/nano-particles, through the action of van der Waals forces, hydrogen bonding, hydrophobic effects, and electrostatic interactions.¹²⁷ Even after digestion in the gastrointestinal tract, targeted drug carriers can still combine with ligand materials to form new nanostructures, regardless of whether endogenous chemicals such as bile salts are present.^{128,129} It has been demonstrated that self-assembled peptides with β -sheet motifs are capable of forming nanofiber structures. These structures are stabilized by hydrophobic packing in the core of the fiber and a network of hydrogen bonds along the long axis. By modulating electrostatic interactions between the peptide and the pH and salt composition of the

solvent, the length of the nanofibers can be significantly extended, leading to fiber entanglement and the formation of hydrogels. Furthermore, the nanofibers can be customized with extensive modifications to enable the delivery of small molecules, proteins, and cells.¹³⁰ These nanostructures include mixed micelles and vesicles, and they can emerge due to physicochemical interactions after remodeling during the evolution of the GIT. Once OTDDSs have surpassed gastrointestinal and hepatic barriers and entered the systemic circulation, they can act as intravascular vehicles for the targeted delivery of payloads to disease sites. To overcome the strong mucus and villus barrier, a polymeric micelle has been synthesized that can rapidly penetrate mucus and be absorbed by villi, effectively delivering paclitaxel to tumors. The therapeutic effect of this polymeric micelle on hepatocellular carcinoma and triple-negative breast cancer is even more pronounced than that of an intravenous polyethylene glycol-based micelle. The alcohol-free counterpart of PTX, or free PTX, is more effective.³⁹

The development of effective oral cancer nanomedicines necessitates overcoming a series of physiological and anatomical obstacles, including those encountered along the gastrointestinal tract and mesenteric capillaries, as well as those within the tumor itself.^{8,131} The first barrier to nanomedicines reaching intestinal villus cells is the intestinal mucus on epithelial cells.¹³² Polyethylene glycol (PEG)-modified self-emulsifying drug delivery systems can improve the hydrophobicity of the carrier surface. When highly lipid-soluble drugs are administered orally, they can enhance the carrier's mucus layer penetration and cellular internalization, effectively increasing intracellular drug concentrations, which provides a promising method for improving the bioavailability of oral drugs.¹³³ It is now evident that a non-fouling surface, ie, not bound to any biomacromolecules in the intestinal mucus, is of paramount importance for nanomedicine penetration into the viscous mucus.¹³⁴ For instance, nanoparticles coated with dense hydrophilic polymers, such as polyethylene glycol, are capable of rapidly penetrating physiological mucus secretions and are therefore designated as mucus-penetrating particles.¹³⁵ However, such nanoparticles are invisible to cells, which renders them difficult to internalize, even in villous cells.^{40,136} A zwitterionic betaine polymer has recently been identified as a specific interactor with proton-assisted amino acid transporter 1 (PAT1), which is overexpressed in epithelial cells. This binding enables the deep penetration of intestinal mucus and efficient transepithelial absorption for insulin delivery.⁷³

OTDDSs are different from vascular targeted drug delivery systems (VTDDSs), which are involved in the selective concentration and localization of drugs to specific sites, such as organs, tissues, cells, subcellular organelles, and structures. This is achieved through vascular delivery pathways utilizing carriers, ligands, or antibodies. In contrast, VTDDSs use functional vectors containing payloads that are delivered to target sites through systemic circulation via affinity and contact with specific cells.²⁷ In the previous several decades, VTDDSs have made significant progress in the field of anti-tumor treatment via intravascular administration.^{137,138} However, intravenous drug administration is an invasive method that causes considerable inconvenience.

Similar to VTDDSs, OTDDSs require various nanocarriers, such as metal-organic hybrid nanocarriers, organic nanocarriers, and inorganic nanocarriers. Combined diagnostics and treatment frequently use inorganic carriers. Nanotubes, quantum dots, silicon/carbon/selenium nanoparticles, and gold nanoparticles are commonly used to provide targeted delivery. Due to their excellent biocompatibility and biodegradability, the nanocarriers commonly employed in drug delivery are primarily made of organic biological materials, such as cell-originated exosomes, which are used as carriers; liposomes; nanoemulsions; micelles; nanovesicles; nanogels; lipid nanoparticles; and polymer nanoparticles. It is imperative to use carriers that maintain the physiological environment of the body while delivering drugs to targeted tissues, which these organic nanocarriers provide. Metal-organic frameworks have also been adequately examined as hybrid nanoparticles for specific drug delivery.¹³⁹ Zhou et al designed a pH-triggered self-unfolding capsule that encapsulates zwitterionic hydrogel-coated metal-organic framework (MOF) nanoparticles. MOF nanoparticles exhibit a high loading capacity for exendin-4, while the zwitterionic hydrogel layer confers unique transmucosal penetration capabilities and the effective internalization of nanocarriers by epithelial cells.⁴² The ligands utilized to modify nanocarriers may include vitamins, sugars, antibodies, aptamers, oligopeptides, biomimetic cell membranes, lectins, transferrin, and lactoferrin.^{140,141} OTDDSs with ligand-specific biomarkers can be abundantly expressed in lesions but less so in normal tissues.¹⁴² The influence of endogenous and exogenous factors, including pH, enzymes, light, temperature, and magnetism, enables OTDDSs to achieve the specific delivery and controlled release of their cargo.^{143,144} In order to achieve the systemic administration of OTDDSs, it is necessary to consider a number of obstacles, including digestion, absorption, and transportation. As long as the target particles remain in circulation for an extended period, they can be concentrated at the target site.

OTDDSs for Cancer Treatment

In contrast to the wide range of research applications for VTDDSs, there have been few advances in OTDDSs. Recent research suggests that the primary determinants of oral carrier absorption and transport are particle size, carrier type (material), and the mode of transport.¹⁴⁵ OTDDSs are delivered by a variety of carriers, including liposomes, micro-/nano-emulsions, micelles, polymer/composite nanoparticles, quantum dots, and yeast microcapsules.¹⁴⁶ These carriers can be classified into two groups: gastrointestinal digestible carriers and non-digestible carriers (although they biodegrade in the body). Bioimaging has strongly supported the explanation of the transmembrane transport of various vectors.^{147,148} It is clear that both digestive and dyspeptic vectors can be transported across intestinal epithelial cells as a group.^{149,150} However, the transport of intact nanoparticles depends on their size.¹⁵¹ Particles larger than 200 nm, such as those measuring 500, 550, 600, 1000, and 2000 nm, are unable to effectively cross the intestinal membrane and primarily attach to the villous surface.^{152,153} In addition, bioimaging has shown that most of the digestion of the digestive vehicle takes place in the GIT, especially for lipid-containing formulations.^{154–156} Only a small proportion of nanoparticles are able to withstand lipolysis in the GIT, traverse the intestinal epithelium, and migrate to the liver or systemic circulation. Transepithelial absorption is severely restricted for carriers that are poorly digested, such as silicon- and polymer-based nanoparticles, even those with particle sizes smaller than 200 nm.^{157,158} Fluorescence is a sign that smaller polymer carriers, such as micelles smaller than 50 nm, can be fully absorbed in the liver and blood.¹⁵⁹ Nevertheless, the overall absorption of nanoparticles is relatively limited in comparison to oral dosages, especially when administered through the enterocyte pathway. Several oral nanomedicines currently in clinical trials are listed in Table 2.

Polymers

Poly(lactic acid) (PLA) and poly(lactic acid-co-glycolic acid) (PLGA) offer excellent biocompatibility and resistance to the gastrointestinal environment.¹⁶⁰ They have recently been shown to increase the stability of liposomal formulations and are widely used to stabilize oral pharmaceutical formulations, such as tablets and capsules.¹⁶¹ As such, they could improve the oral delivery properties of other materials. However, due to the high cost of processing, synthesis, and subsequent large-scale production, PLGA nanoparticles pose significant challenges for real-world applications.⁸ The commonly used polymer PLGA has been shown to effectively target the Na⁺-coupled organic cation/carnitine transporter 2 (OCTN2) expressed in the lumen of the small intestine, enhancing paclitaxel delivery (Figure 3A).³¹ Studies have demonstrated that the lymphatic system can absorb most PLA through pathway caveolin-mediated transport, indicating a high level of biocompatibility, safety, and sustained drug release capabilities.¹⁶² However, low gastrointestinal absorption and rapid elimination are evident when administered orally. Raloxifene hydrochloride that has been PEGylated and encapsulated in PLA nanoparticles can have enhanced bioavailability, and it has been demonstrated to be useful in treating breast cancer.^{34,163} Since the gastrointestinal epithelium is rich in folate receptors, the pharmacokinetic properties of hydrophobic chemotherapeutic drugs such as paclitaxel can be improved via the modification of PLA particles with folate (Figure 3B).¹⁶⁴ Folic acid stimulates the internalization of particles by gastrointestinal epithelial cells and improves their diffusion within the mucus layer. In a previous study, D-alpha-tocopheryl polyethylene glycol (PEG) succinate was added to the delivery system, resulting in a decrease in the release rate of paclitaxel and an increase in the loading rate of the drug.³⁶ The system's safety and efficacy were successfully

Table 2 Recent Clinical Trials on Nanoparticle Formulations for OTDDSs

Formulation	Formulation	Cancer	Phase	NCT Number
Pegylated liposomes	Doxorubicin	Breast cancer	I	NCT03719326
Ethylcellulose-based polymeric NPs	Cetuximab	Colorectal cancer	I	NCT03774680
Lipid-based	Paclitaxel	Stage IV gastric cancer	I and 2	NCT02890511
Nonviral lipid NPs	Osimertinib	Non-small-cell lung carcinoma	2	NCT04486833
Nanostructured lipid curcumin	Avastin/FOLFIRI	Colorectal cancer	2	NCT02439385
Nanoparticle suspensions	AZD4635	Carcinoma	I	NCT02740985
Albumin-stabilized NPs	Lapatinib	Various cancers	I	NCT00313599

Abbreviation: NPs, nanoparticles.

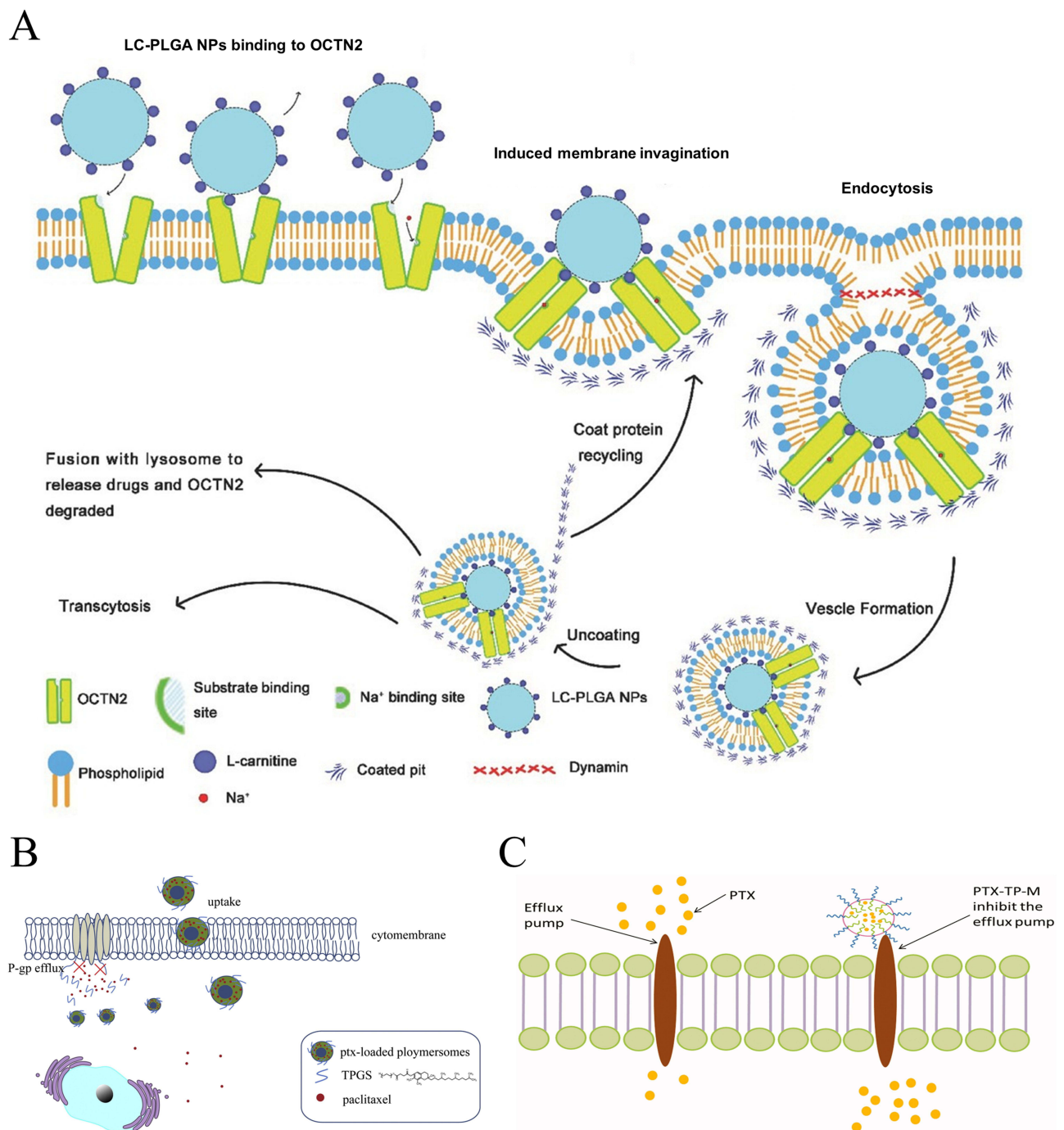


Figure 3 Therapeutic role of PLA and PLGA-loaded drugs in tumors. **(A)** LC-PLGA NPs and Na⁺ bind to the specific sites of OCTN2, and OCTN2 changes its confirmation from outward-facing to an occluded state, inducing the following membrane invagination and endocytosis. In this process, multipoint binding could increase the interaction and accelerate NP absorption. Additionally, Na⁺ is also essential in this process. Adapted with permission from Kou L, Yao Q, Sun M, et al. Cotransporting ion is a trigger for cellular endocytosis of transporter-targeting nanoparticles: a case study of high-efficiency SLC22A5 (OCTN2)-mediated carnitine-conjugated nanoparticles for oral delivery of therapeutic drugs. *Adv Healthc Mater.* 2017;6(17). Copyright © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.³¹ **(B)** Schematic diagram of the possible inhibiting mechanism of the P-gp efflux transport of paclitaxel-loaded TPGS mixed polymersome. Reprinted from *International Journal of Biological Macromolecules*, 139, Xiao Qian Pan, Yan Chun Gong, ZiLing Li, Yu Ping Li, Xiang Yuan Xiong. Folate-conjugated pluronic/poly lactic acid polymersomes for oral delivery of paclitaxel, 377-386, Copyright 2019, with permission from Elsevier.¹⁶⁴ **(C)** Schematic illustration of PTX-TP-M inhibiting the efflux system and contributing to absorption. Adapted with permission from Hou J, Sun E, Zhang ZH, et al. Improved oral absorption and anti-lung cancer activity of paclitaxel-loaded mixed micelles. *Drug Deliv.* 2017;24(1):261–269. Copyright © 2017 Taylor & Francis.³⁶

tested in a rat lung cancer model (Figure 3C).³⁶ Polycaprolactone (PCL) is a polymer commonly utilized to create biocompatible nanoparticles for delivering various chemotherapeutic drugs. These drugs include docetaxel,¹⁶⁵ cisplatin,¹⁶⁶ methotrexate,¹⁶⁶ and paclitaxel.¹⁶⁷ Ellagic acid, an anticancer drug, has been shown to have improved

oral bioavailability when delivered via PCL nanoparticles. Furthermore, the PCL nanoencapsulation of ellagic acid has been found to increase its hydrophilicity and uptake by M cells in the lymphatic system, resulting in more than a threefold increase in bioavailability.³⁸

In recent years, Eudragit[®] polymers, synthesized from esters of acrylic and methacrylic acids, have demonstrated significant potential in developing pH-sensitive and innovative drug delivery systems capable of binding various therapeutic agents, including proteins, vitamins, hormones, vaccines, and genes. Utilizing Eudragit[®] EPO (EEP) as a carrier for curcumin can substantially enhance its serum concentration.¹⁶⁸ Additionally, coating nanoparticles with Eudragit[®] S100 allows for pH-dependent drug solubility, increased gastrointestinal stability, and enhanced cellular uptake of protein drugs.^{169,170} Amorphous solid dispersions of Eudragit E neutralized with hydrochloric acid (Eudragit E/HCl) have been shown to optimize the solubility of trans-resveratrol, achieving an oral bioavailability of 40% in rat studies.¹⁷¹ Different grades of Eudragit[®] are tailored to target therapeutic agents to specific sites via oral delivery, such as stomach-specific and colon-specific delivery.¹⁷² Existing research underscores the unique ability of Eudragit[®] polymers to precisely target incorporated drugs to specific sites. Eudragit S100 (ES)-coated doxorubicin hydrochloride (DOX) nanoparticles are increasingly recognized for their precision in colon cancer treatment and reduced systemic distribution.^{173,174} Various nanoformulation technologies leveraging Eudragit[®] polymers enhance drug solubility, stability, and bioavailability. The application of Eudragit[®] polymers in drug formulation holds significant research value and broad potential, particularly in improving the oral absorption of poorly soluble drugs, developing colon-targeted drug delivery systems, and achieving controlled and targeted drug release.

Inorganic Materials

Currently, oral drugs loaded with inorganic nanoparticles are more stable under the acidic conditions of the intestine, although select materials do completely dissolve at low pH values. Silica nanoparticles, which possess favorable biocompatibility, have undergone significant investigation as a means of improving the oral delivery of therapeutic drugs.¹⁷⁵ These nanoparticles may be produced in a porous form to accommodate diverse payloads.¹⁷⁶ Silica has been approved as a safe food and drug additive by the US FDA and European FSA.¹ Its oral ingestion is deemed safe, although amorphous silica dissolves slowly at a low pH and quicker at a higher pH. Thus, exploiting GIT pH gradients with amorphous silica is a lucrative tool. Additionally, silica nanoparticles, porous and adjustable, can hold various payloads (Figure 4),¹⁷⁵ including biologics, and they can protect them from digestive enzymes after encapsulation. Engineered mesoporous silica particles encapsulate biologics, safeguarding them from the digestive enzymes pancreatic alpha-amylase and lipase.¹⁷⁷ Recently, there has been talk of using silica nanostructures to create floating drug delivery systems that allow for prolonged gastric retention in the presence of plant polymers and sodium bicarbonate.¹⁷⁸ Utilizing similar technology based on aluminum silicate aims to enhance the delivery of the antineoplastic drug methotrexate, which has a particularly short half-life.¹⁷⁹ Moreover, organometallic silicate nanocomposites decorated with gold nanoparticles (AC-Au), whose surface coating is pH-sensitive, can significantly enhance the oral delivery of methotrexate for colorectal cancer treatment.¹⁸⁰ Additionally, selenium is another element that can be employed in oral nanomedicines due to its high anticancer potential.⁴³ However, the clinical utilization of selenium is associated with notable adverse effects that restrict its application.^{44,181} Therefore, certain scholars have generated synthetic biological selenium nanoparticles via *Bacillus licheniformis* bacteria, which exhibit low toxicity.⁴⁴

Chitosan

Polysaccharides are amphiphilic molecules with the innate capability to enclose anti-tumor therapeutics and exhibit favorable wetting properties to overcome the mucus barrier. These molecules are obtained from various biological sources, such as chitosan from animals, alginates from algae, pectins from plants, and glucans from bacteria.¹⁸² They exhibit remarkable biocompatibility and are easy to formulate into nanoparticles, finding wide usage in multiple fields. Polysaccharide nanoparticles, such as other nanoformulations, have been found to inhibit efflux pump activity and can be selectively taken up by M cells in certain cases (Figure 5A).^{45,183} Chitosan is considered a benchmark biomaterial due to its ability to promote the relaxation of TJs and enhance paracellular uptake.^{180,184,185} This occurrence is most notable at lower pH levels, where chitosan becomes protonated, resulting in the destabilization of the linkage.¹⁸⁶ However, chemical adjustments such as methylation can expand these traits and enhance chitosan's potential to operate over a broader pH spectrum, increasing its solubility within.¹⁸⁷ Because chitosan is partially soluble in water, hydrogel formulations can contain a variety of payloads, including biologics such as proteins and siRNA.⁴⁷ The

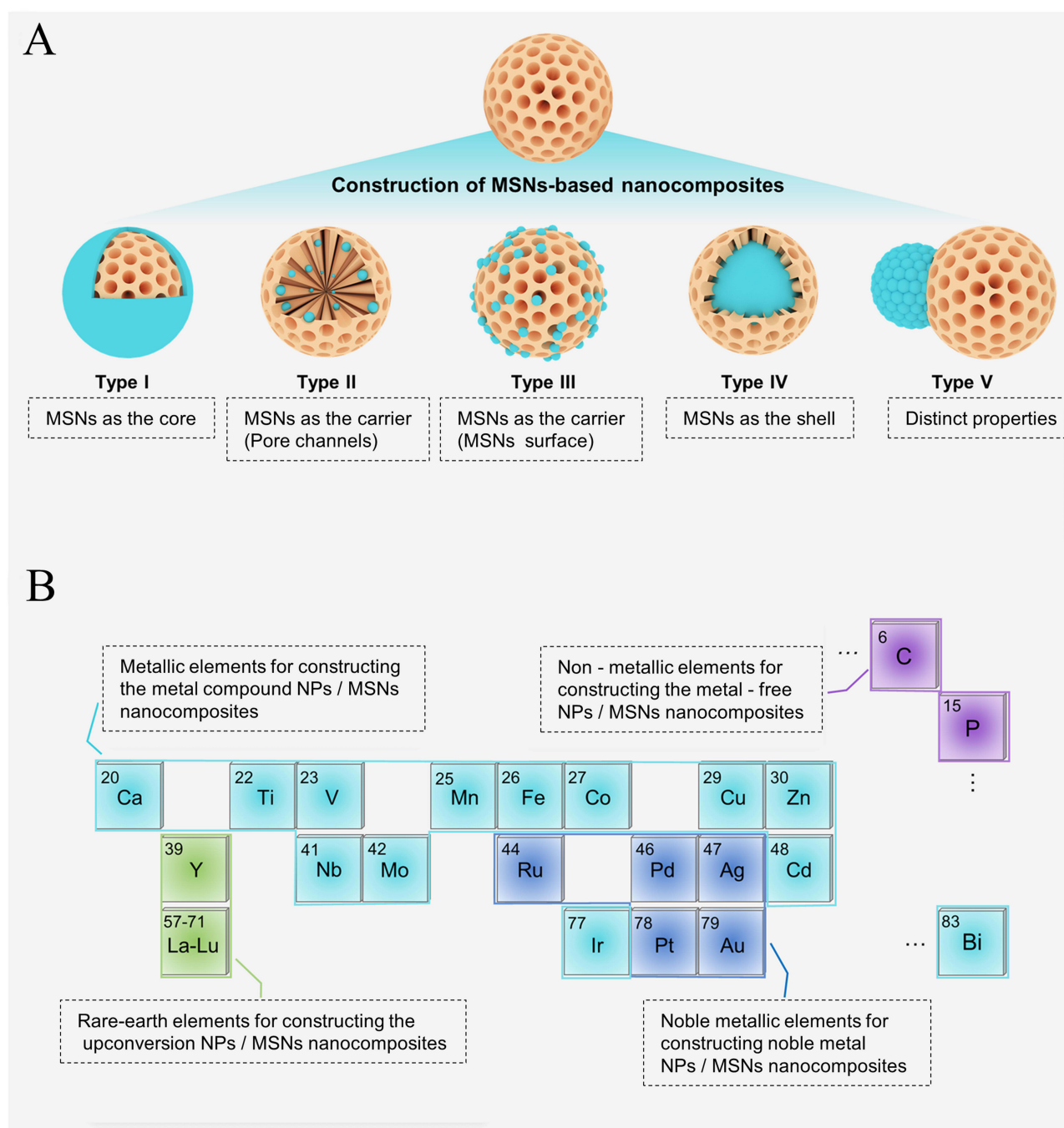
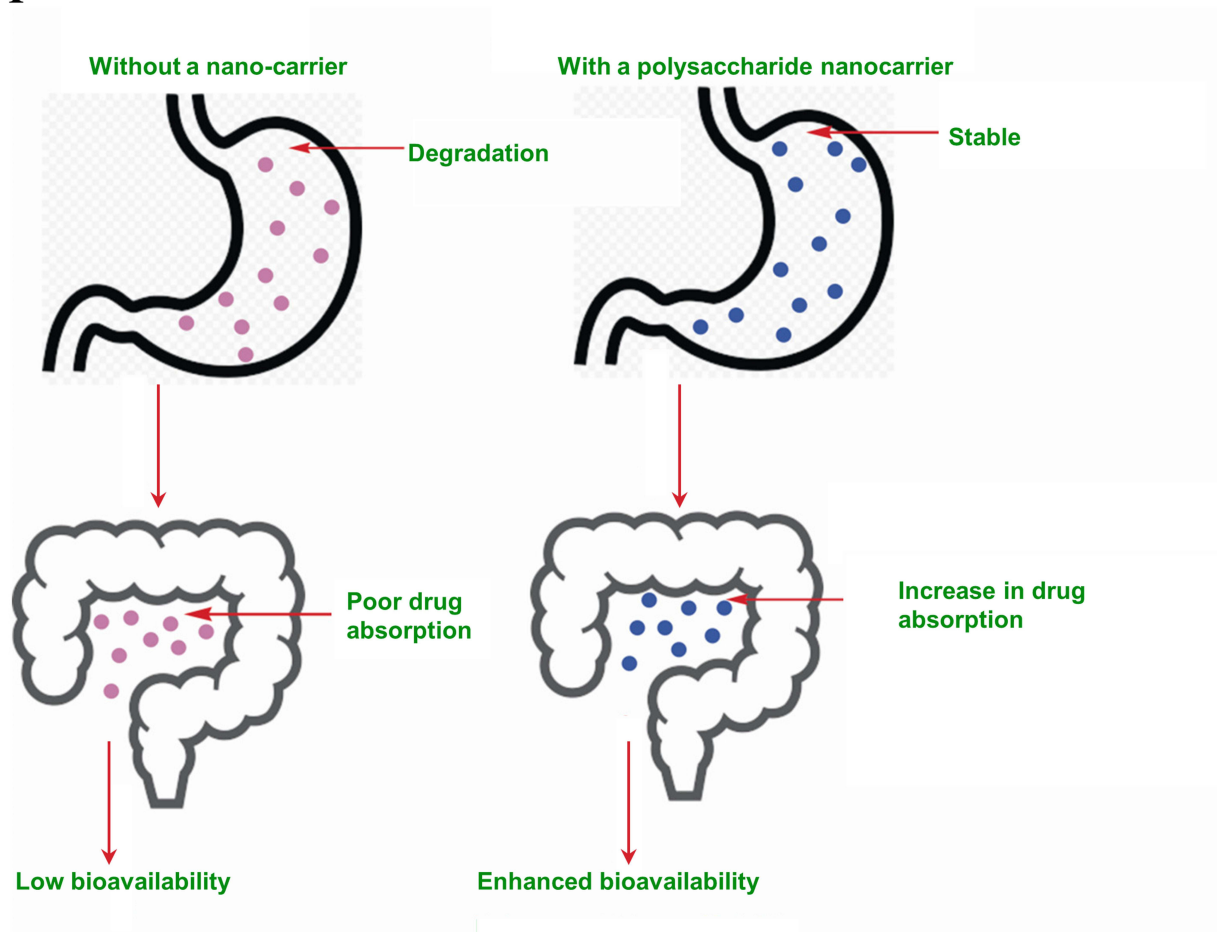


Figure 4 MSNs-based nanocomposites developed in the biomedical field. **(A)** Various nanostructured MSNs-based nanocomposites. Depending on the assembly process, the functional nanostructures can be introduced as the shell (Type I) or core (Type IV), can be loaded in the pore channels (Type II) or surface (Type III), and can form Janus-type hierarchical structure (Type V). **(B)** Typical elements used for constructing various types of MSNs-based nanocomposites. There are four main categories of nanocomposites based on the elemental type, including noble metal NPs/MSNs, metal compound NPs/MSNs, upconversion NPs/MSNs, and metal-free NPs/MSNs nanocomposites. MSNs: Mesoporous silica nanoparticles. Adapted with permission from Xu B, Li S, Shi R, Liu H. Multifunctional mesoporous silica nanoparticles for biomedical applications. *Signal Transduct Target Ther.* 2023;8(1):435. Copyright © 2023, The Author(s).¹⁷⁵

most promising material for oral nanomedicine may be chitosan because of its chemical modification and hybridization with other materials. Adding arginine and acrylonitrile groups to chitosan nanoparticles has been shown to increase the bioavailability of curcumin (Figure 5B).¹⁸⁸ Acrylonitrile induces the self-assembly of nanoparticles and provides the hydrophobic structure needed to host hydrophobic therapeutics. By increasing solubility, promoting cell surface interactions, and prolonging the GIT residence time, arginine regulates drug release.¹⁸⁸ Cyclodextrin, another polysaccharide widely utilized to develop oral

A



B

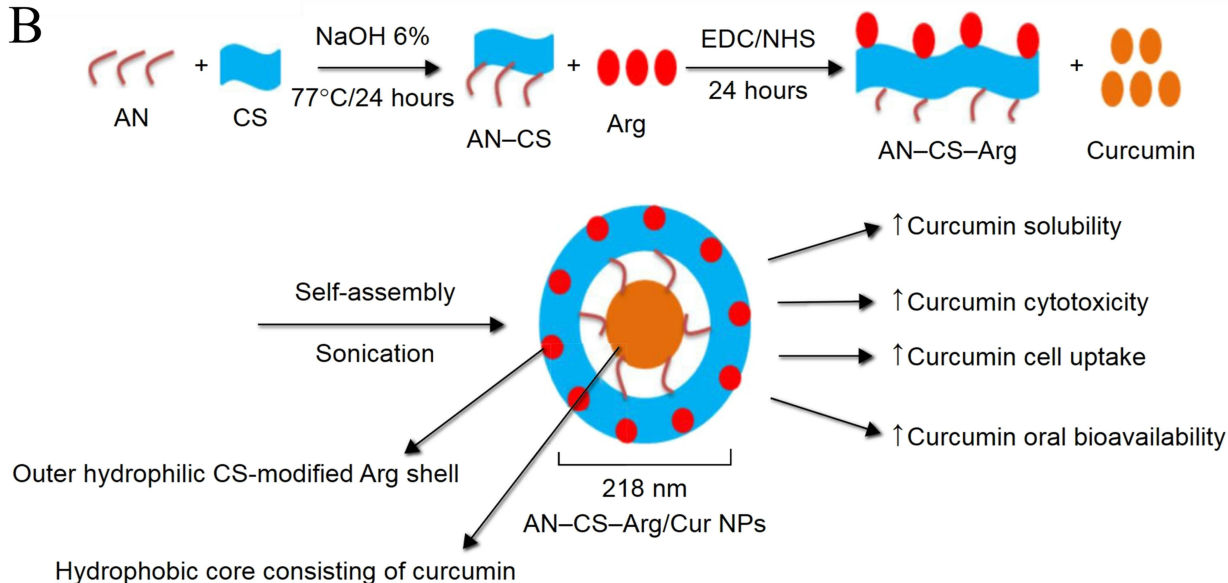


Figure 5 (A) Enhancement of drug absorption through polysaccharide nanocarriers. Reprinted from International Journal of Biological Macromolecules, 130, Madhumita Dey, Madhurima Das, Anindita Chowhan, TapanKumar Giri, Breaking the barricade of oral chemotherapy through polysaccharide nanocarrier, 34-49, Copyright 2019, with permission from Elsevier.¹⁸³ **(B)** Schematic drawing of self-assembled cur-encapsulated AN-CS-Arg NPs. Adapted with permission from Raja MA, Zeenat S, Arif M, Liu C. Self-assembled nanoparticles based on amphiphilic chitosan derivative and arginine for oral curcumin delivery. Int J Nanomed. 2016;11:4397-4412. Copyright © 2016 Dove Medical Press.¹⁸⁸

nanomedicines, effectively encapsulates the hydrophobic drug docetaxel and can impede efflux pump activity.¹⁸⁹ In a previous study, when given orally, cyclodextrin nanoparticles considerably enhanced the bioavailability of paclitaxel. The drug was observed in the bloodstream 24 hours after administration, demonstrating encouraging outcomes in the treatment of mouse sarcoma models.^{190,191} The therapeutic efficacy of celecoxib in the treatment of colorectal cancer has been demonstrated in clinical trials. Segale et al prepared a chitosan-coated NP microsphere of celecoxib, which can avoid the rapid release of celecoxib when encountering an acidic environment and enhance its release in the intestinal lumen.¹⁹² Furthermore, Sinha et al developed a novel biopolymer composite multi-system comprising chitosan, succinate, and alginate, which is employed to wrap capecitabine for the treatment of colorectal cancer. The study also examined the efficacy of the biopolymer composite multi-joint system in the treatment of rectal cancer. The results demonstrated that the multi-system exhibited the greatest degree of swelling in an intestinal environment with a pH of 7.4, with minimal swelling observed in an acidic environment. This results in the protection of the drug and the effective targeting of the colon.¹⁹³ A layer-by-layer self-assembly approach was also employed to develop chitosan nanoparticles for oral delivery, with the objective of treating colorectal cancer.¹⁹⁴ The layer-by-layer self-assembly method employed polycaprolactone (PCL, 95% w/w) as the substrate, which markedly enhanced the high loading efficiency of 5-fluorouracil (5-FU). Moreover, the outermost layer was functionalized with folic acid, thereby conferring selective tumor lesion binding and targeting capabilities. The findings demonstrated that 5-FU exhibited remarkable stability and a pronounced cytotoxic effect on colon cancer cell lines.

In order to enhance the pH-dependent properties of chitosan NPs, Zhang et al developed an automated oral insulin delivery system comprising ion attraction between polyglycolic acid (PGLA), chitosan, and alginate. This approach has been shown to enhance the *in vitro* efficacy of chitosan NPs against gastric acid erosion.¹⁹⁵ Furthermore, studies have been conducted to enhance the stability of chitosan NPs in acidic environments via the addition of gelatin.¹⁹⁶ Consequently, the exploration of more effective and non-toxic pH-stable materials represents a crucial avenue for the advancement of chitosan NPs as cancer-specific treatments. The resulting GIT presents a series of physical, chemical, and enzymatic obstacles that hinder oral drug delivery and stability. These obstacles are considered to be some of the major issues to overcome. At present, the application of chitosan NPs is still in the verification stage of *in vitro* and animal experiments. There is still a considerable distance to travel before chitosan NPs can be considered a viable option for oral therapy and intestinal disease treatment.

Protein

In addition, protein carriers made from proteins exhibit hydrophilic and lipophilic properties, rendering them suitable for accommodating drugs with various chemical and physical characteristics. Moreover, protein nanoparticles can traverse the M cells found in the GIT.⁴⁸ Previous research has demonstrated that the disintegration of protein nanoparticles in the GIT can be prevented through the use of protease inhibitors.¹⁹⁷ The methodology for producing protein nanoparticles influences their susceptibility to enzymatic degradation. Protein carriers generated by desolvation have a greater sensitivity to degradation by pepsin than particles synthesized via emulsification, potentially due to dissimilarities in the cleaved peptide bonds of pepsin.¹⁹⁸ Furthermore, protein stability in the GIT may be improved by integrating proteins with other materials.¹⁹⁹ For instance, the incorporation of the carbohydrate pectin can guard the particles while increasing curcumin loading efficiency when applied to casein/zein nanoformulations.⁵² The surface of the protein carrier allows for chemical modification at multiple sites, which promotes particle accumulation at the intestinal epithelial level.²⁰⁰ The protein carrier's cellular specificity is also a notable feature. Interestingly, the accumulation of doxorubicin in liver cancer is effectively increased after the oral administration of nanoparticles composed of apotransferrin and lactoferrin. However, further examination is required to determine its absorption mechanism.⁵³ Bovine casein nanoparticles can be efficiently loaded with resveratrol through hydrogen and hydrophobic bonds.^{201,202} Research has illustrated that resveratrol is exceptionally proficient at encasing casein nanoparticles, and these particles can be released in a regulated fashion in both gastrointestinal fluids.²⁰³ Moreover, this casein nanoparticle showcases superb interactions, which consequently lead to the enhanced bioavailability of resveratrol within the body.

Lipid nanoparticles improve the solubility of hydrophobic drugs when encapsulated.²⁰⁴ They are often mixed with hybrid formulations for oral delivery to improve their stability in the gastrointestinal tract. However, some research suggests that liposomes may interact with bile salts to form vesicles and micelles that are transcytosally absorbed in the upper gastrointestinal

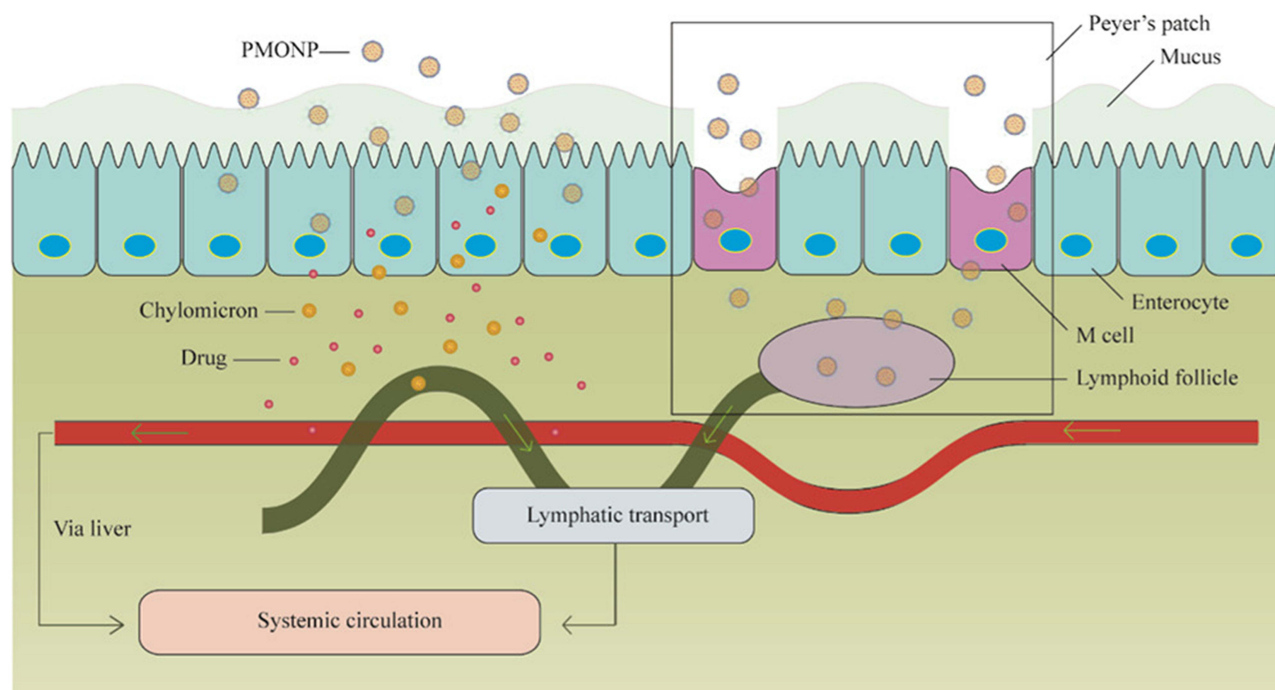


Figure 6 Polymer–lipid hybrid nanoparticles are able to efficiently orally deliver the anticancer drug cabazitaxel into the systemic circulation and can achieve the desired oral anticancer effect. Reprinted from *Journal of Controlled Release*, 269, Tianyang Ren, Qian Wang, Ying Xu, Lin Cong, Jingxin Gou, Xiaoguang Tao, Yu Zhang, Haibing He, Tian Yin, Haotian Zhang, Yan Zhang, Xing Tang, Enhanced oral absorption and anticancer efficacy of cabazitaxel by overcoming intestinal mucus and epithelium barriers using surface polyethylene oxide (PEO) decorated positively charged polymer-lipid hybrid nanoparticles, 423-438, Copyright 2018, with permission from Elsevier.⁵⁵

tract.^{205,206} Mixed lipid–polymer nanoparticles have been formulated to enhance the oral bioavailability of cabazitaxel, which is affected by the common low solubility and high metabolism problems of taxanes (Figure 6).⁵⁵ The ϵ -caprolactone polymeric structure can safeguard it from an acidic environment, and triglyceride can improve the drug-loading capacity. Finally, surface modification with positively charged octadecyl amine and neutrally charged poly (ethylene oxide) improves mucosal penetration and cellular uptake. Due to the known lymphatic transport of cabazitaxel, M cells may be more likely to take up these particles. This technique has the potential to significantly increase the oral bioavailability and efficacy of the chemotherapy drug.⁵⁵

Lipid

Furthermore, a study conducted by a team of researchers revealed that berberine, which has anti-tumor properties, can have improved oral bioavailability when administered using PEGylated PLGA-stabilized lipid nanoparticles.²⁰⁷ Although oral medications are advantageous for clinical purposes, the GIT can degrade the particles, leading to their failure.²⁰⁸ In a previous study, a hybrid lipid–PLGA system with PEGylation was developed to improve particulate drug encapsulation, stability, and interaction with the gastrointestinal epithelium.²⁰⁹ PEG surface modification is necessary to cross the mucus barrier, as demonstrated by the authors' finding of increased *in vivo* intestinal absorption.²⁰⁷ Other research teams have also applied a coating of N-carboxymethyl chitosan onto solid lipid nanoparticles, which are known to enhance the solubility of hydrophobic drugs and steadily release payloads at intestinal pH levels.^{58,210} This process also assists in absorption through the lymphatic system, thereby circumventing first-pass metabolism by the liver.²¹¹ The payload is safeguarded in the stomach's acidic environment and absorbed into the mesenteric lymph nodes thanks to the N-carboxymethyl chitosan coating.²¹² Short interfering RNA and long interfering RNA are biological agents that are well suited for oral administration but are sensitive to the aggressive gastric surroundings and are unable to cross the GIT epithelium.²¹³ The lipid blend that makes up the particles includes amphiphilic lipids that can form complexes with RNA, cholesterol, DSPC, and PEGylated lipids, thereby increasing particle stability and the permeability of short interfering RNA through mucus.⁶⁰ In a previous study, the authors discovered that the optimal concentration of PEG is crucial for short interfering RNA to effectively traverse the mucus barrier, confirming the significance of optimizing surface

modification density.⁶⁰ Although the *in vitro* delivery efficiency is high, pepsin and bile salts impact the stability of these particles, which leads to their aggregation and degradation, respectively. It is crucial to consider all factors that contribute to the gastrointestinal environment because pepsin, the protease, can still have an impact on the therapeutic effectiveness of lipid nanoparticles.^{60,214} The results emphasize the need for a comprehensive analysis of gastrointestinal conditions to ensure the success of lipid nanoparticle-based therapies. The concentration of pepsin in the stomach varies greatly *in vivo* before and after meals and decreases during fasting.⁶⁰ It also readily accumulates in significant amounts in intestinal crypts, where the particles can transfer short interfering RNA to immune cells. This finding highlights the importance of the timing of the dose and diet in the management of gastrointestinal disorders.

Biologics and Others

In recent years, various biologics have been explored and applied for the treatment of cancer, including the delivery of small molecule drugs, nucleic acids, peptides, and proteins.^{215,216} Utilizing different nanoparticles, microparticles, hydrogels, or their combinations significantly enhances bioavailability and targeting specificity within the intestine. Biologic nanoparticles possess features such as robust absorption, immune cell stimulation, pH responsiveness, and attributes of biocompatibility, biodegradability, non-toxicity, selectivity, and specificity, marking them as exceptional carriers or ingredients for oral drug delivery.^{141,217,218} The self-assembly of nanoparticles based on lipid bilayers plays a pivotal role in biological systems.²¹⁹ For instance, hydrogel materials that can mimic bacterial flagellar movement can be used to develop semi-intelligent microrobots akin to drug carriers.²²⁰ Additionally, hydrogel-based pH-responsive biologics can astutely release drugs in accordance with the pH conditions of living cells. The properties of hydrogels can be tailored to match the specific pH environment of the target site.²²¹

There are multiple types of bacterial biologics employed in oral drug delivery systems, including bacterial ghosts, nanoparticle-enhanced bacteria, and recombinant bacteria.^{222–224} Bacterial ghosts are non-viable pseudobacterial constructs devoid of genetic material. Extracted from bacteriophages, they possess an innate capability to target immune cells and boost immunity for disease treatment. Examples include the use of *Salmonella enteritidis* and *Vibrio cholera* in the preparation of biologic vaccines.^{225,226} Similarly, live attenuated *Salmonella* bacteria have been coated with DNA-condensed cationic polymer nanoparticles to produce oral cancer vaccines (Figure 7A).³² The goal of the system is to deliver the immunogenic drug to the cytoplasm while avoiding phagosome entrapment and remaining stable at a low pH. *E. coli* or *Vibrio cholera* ghosts have been utilized to facilitate the delivery of therapeutic agents such as plasmid DNA, hepatitis B virus core protein, and doxorubicin drugs. In a notable development, Tang et al engineered a nanoparticle-coated, attenuated *Salmonella* vector for oral DNA vaccine delivery as a cancer treatment strategy.³² Similarly, Fan et al innovatively merged nanoparticle-based photothermal conversion with thermosensitive plasmids to create oral nanocarriers designed for anti-tumor drug delivery.²²⁷ These nanoparticle-enhanced bacterial systems are frequently referred to as microrobots. Surface-functionalized with nanoparticles and loaded with therapeutic drugs, microrobots are adept at targeted cellular delivery.²¹⁸ Generally, this advanced delivery system facilitates the transport of proteins or genes to specific target sites and proves useful in deploying therapeutic drugs within hypoxic tumor regions. Additionally, bioinspired helical microrobots present potential for drug localization and diagnostic purposes, while biological hybrid vectors embedded with magnesium can adjust stomach pH levels. Nevertheless, the issues of bioavailability and toxicity related to these materials persist as significant concerns.

Viral mimic systems resemble viruses in structure, yet they differ in function or genetic attributes. The primary vectors employed in gene delivery include adenoviruses, retroviruses, and lentiviruses.²²⁸ These vectors possess capabilities such as replication, drug binding, cellular penetration, and system stability. According to Takamura et al, plasmid DNA can be effectively encapsulated within the hepatitis E virus *in vitro*, forming a biological agent that successfully targets the intestinal mucosa.²²⁹ Furthermore, virosomes, circular carriers, and monolayer/bilayer phospholipid membranes have been utilized for the oral delivery of therapeutic agents. The core cavity of the virosome encapsulates DNA, RNA, proteins, or pharmaceuticals. The viral exterior safeguards its contents from proteolytic degradation and the acidic environment of the stomach, effectively delivering therapeutic compounds into the cytoplasm while bypassing endosomal degradation. Nonetheless, the potential for immunogenicity restricts the application of

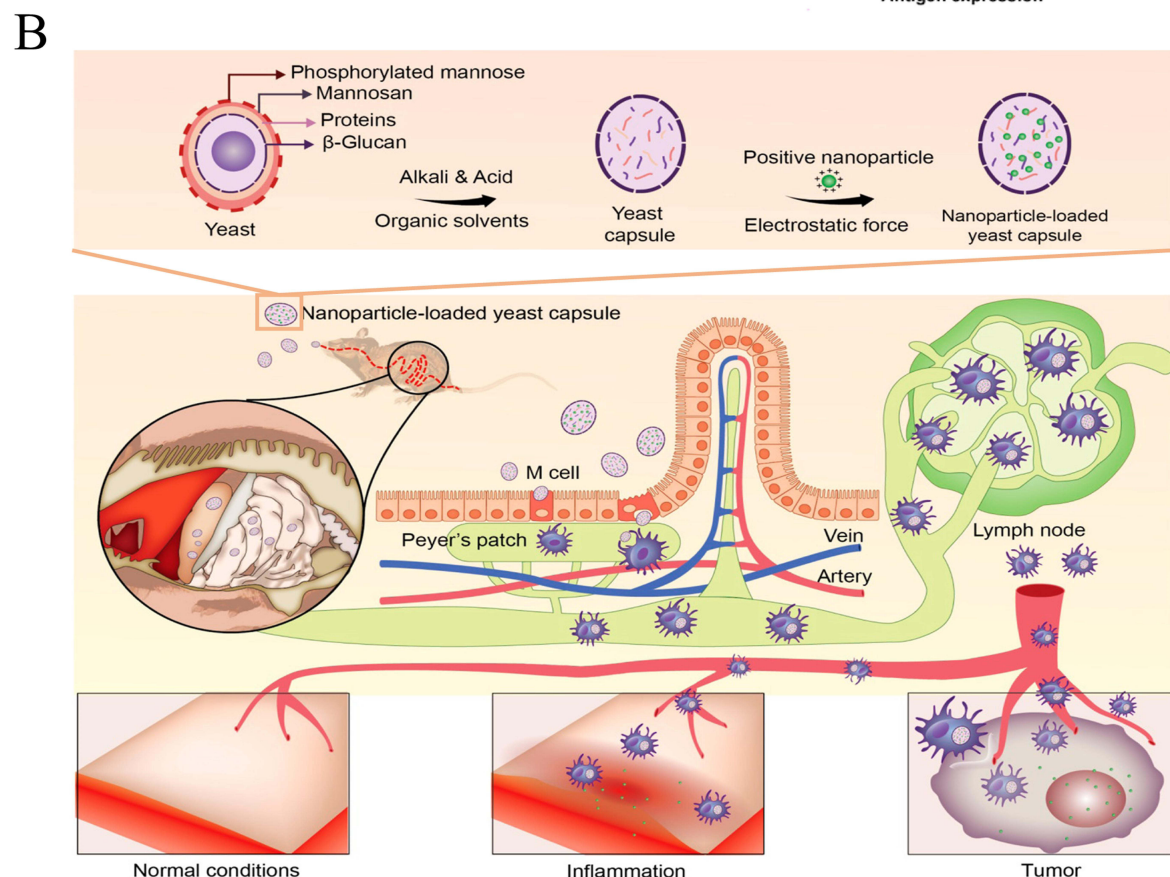
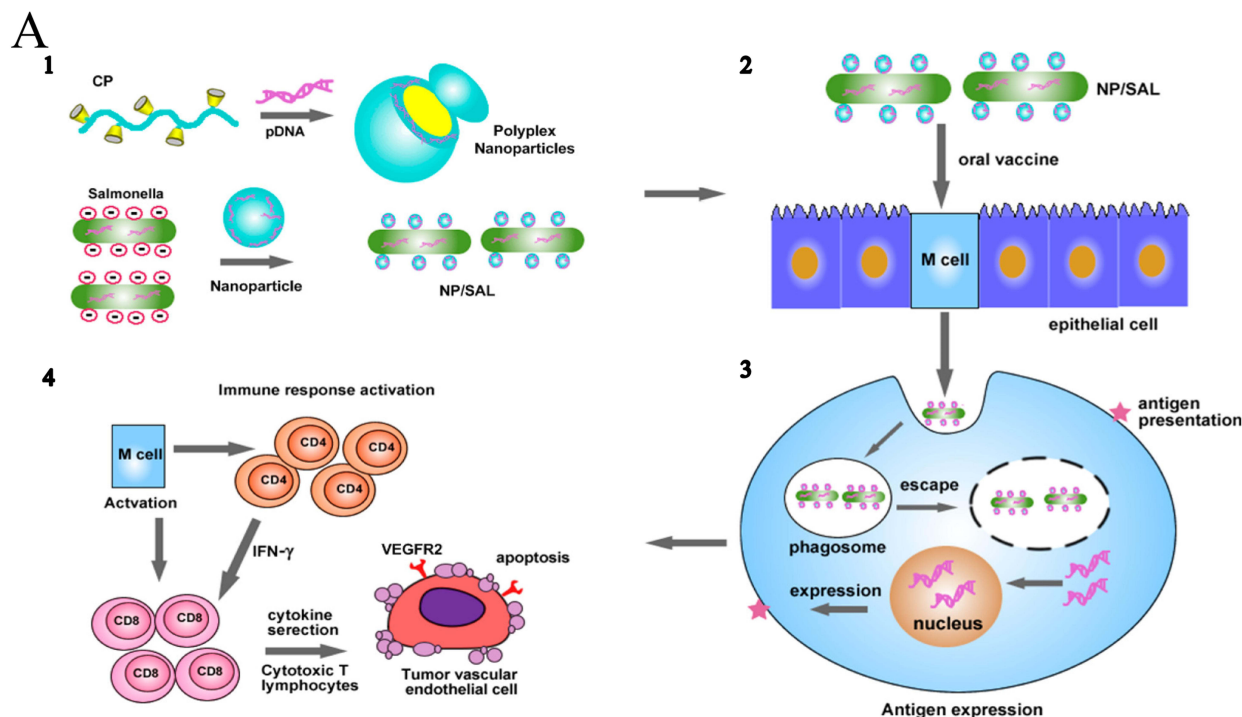


Figure 7 (A) Schematic illustration of cationic nanoparticle-coated attenuated *salmonellae* for improved antigen expression and tumor-targeting immune response activation. (1) Engineering of polyplex nanoparticle-coated *Salmonellae*. (2) Oral DNA vaccine delivery mediated by nanoparticle-coated *Salmonellae*. (3) Intracellular trafficking of nanoparticle-coated *Salmonellae* and antigen expression. (4) Activation of antitumor immune response. Adapted with permission from Hu Q, Wu M, Fang C, et al. Engineering nanoparticle-coated bacteria as oral DNA vaccines for cancer immunotherapy. *Nano Lett.* 2015;15(4):2732–2739. Copyright © 2015 American Chemical Society.³² **(B)** Schematic diagram of yeast capsule-mediated oral delivery of nanoparticles to inflammation-associated disease sites distant from the gastrointestinal tract. Adapted with permission from Zhou X, Zhang X, Han S, et al. Yeast microcapsule-mediated targeted delivery of diverse nanoparticles for imaging and therapy via the oral route. *Nano Lett.* 2017;17(2):1056–1064. Copyright © 2017 American Chemical Society.⁶¹

virosomes in drug delivery systems. Strategic modification and employment of carriers offer promising prospects for future biomedical applications.²³⁰

Various derivatives extracted from yeast cells exhibit promising drug delivery attributes due to their size, morphology, drug loading efficiency, and targeting capabilities. These derivatives are apt for oral administration and M cell targeting; M cells, notably, lack microvilli and mucus layers, facilitating the entry of microparticles into the immune system. Zhou et al demonstrated a cisplatin-derived nanotransmitter administered orally via yeast microcapsules for tumor therapy.²³¹ Post-oral administration, yeast microparticles traverse to the intestine and are channeled to the tumor site through M cells. The yeast's outer layer and cytoplasm are chemically removed and substituted with therapeutic nanoparticles via electrostatic forces. M cells facilitate the movement of yeast-carrying nanoparticles to the lymphatic system, where macrophages identify and transport these particles to tumors, maintaining their potent anti-tumor effects (Figure 7B).⁶¹

Milk-derived exosomes have the potential to produce safe oral nanomedicines,^{33,49} as they form a part of the everyday diet, are easily obtainable, and remain stable at a low pH.^{57,232} In a previous study, it was found that, in vitro, milk exosomes demonstrated high efficacy and permitted the regulated delivery of the paclitaxel drug in gastric juice.³⁷ In vivo, the encapsulated exosomes displayed substantial tumor eradication effects in a subcutaneous lung cancer model without any adverse reactions associated with the drug or carrier.²³³ A slight inhibition of tumor growth was observed upon exosome administration. This effect is possibly attributable to the presence of potentially anti-tumorous molecules, such as complex α -lactalbumin and oleic acid, derived from human milk, contained within the exosomes.²³⁴ The absorption mechanism remains unclear, although a prior report has demonstrated that the oral administration of exosomes can target several organs, notably the liver, spleen, kidneys, and pancreas.²³⁵ Research in this area is currently highly active, and a range of foods such as grapes may serve as feasible sources of exosomes, thereby broadening the selection of oral nanomedicine platforms.²³⁶

Cancer represents a significant global public health concern. The intricate immune microenvironment of malignant tumors renders single treatment methods, such as surgery, radiotherapy, and chemotherapy, inadequate for preventing tumor proliferation and recurrence. Nevertheless, nanotechnology can combine two or more therapeutic methods to achieve synergistic effects in cancer treatment. These include, but are not limited to, improving the solubility and local drug concentration of hydrophobic drugs, overcoming various biological barriers, prolonging the circulation of drug systems, and preventing rapid systemic clearance.²³⁷ Consequently, nanotechnology continues to be developed and used in cancer treatment. For instance, it can be employed to enhance the solubility and stability of drugs, as well as to improve the bioavailability and targeting of drugs. Nevertheless, oral nanomedicines also encounter certain limitations and challenges in the treatment of malignant tumors.

Firstly, one of the primary challenges faced by OTDDSs is the issue of biocompatibility. Given that OTDDSs must enter the body via the gastrointestinal tract, it is of paramount importance that they exhibit stability and biocompatibility in the gastric acid and gastrointestinal tract environment. Some nanomaterials may cause gastrointestinal irritation or toxic reactions, and they may even have adverse effects on intestinal flora, thereby affecting the absorption and efficacy of drugs. Furthermore, nanomedicines may induce adverse reactions or allergic reactions, thereby limiting their clinical applicability. Secondly, another challenge faced by OTDDSs is that of supervision. Due to the distinctive physicochemical properties of nanomedicines, their safety and effectiveness assessment methodologies must differ from those employed for traditional drugs. It is therefore incumbent upon regulatory agencies to formulate corresponding evaluation standards and regulatory policies to ensure the safety and effectiveness of OTDDSs. Finally, the clinical translation of OTDDSs represents another significant challenge. Currently, clinical research on OTDDSs is still in its infancy, and there is a paucity of large-scale clinical trial data to support its development. Furthermore, the preparation technology and production process of OTDDSs also require further improvement to ensure their stability and consistency in clinical applications. In conclusion, although OTDDSs have a wide range of potential applications, they still face significant challenges, including issues related to biocompatibility, regulatory, and clinical obstacles. It is recommended that future research and regulatory work be intensified to facilitate the development and application transformation of oral nanomedicines.

Future Perspectives

Oral drug delivery technology has advanced considerably, from basic tablets to advanced nanoparticle systems. This progress has been facilitated by an improved understanding of the intestinal barrier and potential access points to the systemic circulation through the portal vein and intestinal lymphatic vessels. The extensive literature pertaining to the delivery of small and large molecules across the intestinal barrier has only instilled confidence in unorthodox delivery methods. It is vital to acknowledge that, while delivery technology holds as much significance as the active pharmaceutical ingredient itself, a single technology is not applicable to all cases. To ensure a seamless transfer, it is crucial to strike a balance between innovation and concomitant risks. The main objective is to optimize the minimum effective therapeutic concentration through the use of delivery technology. It should be relatively easy to repurpose existing medication through unconventional oral delivery strategies, as we already possess the knowledge of pharmacology and safety profiles, which can significantly diminish the likelihood of attrition during clinical stage drug development. He et al reported the development of an oral polyphenol-armored nanomedicine coated with chitosan and tannic acid on the surface of the nanomedicine. This coating renders the nanomedicine resistant to the harsh environment of the gastrointestinal tract and enables targeted adherence to specific parts of the colon.²³⁸ Researchers believe that understanding the *in vivo* metabolism of nanomaterials is critical to understanding the safety and effectiveness (endpoints) of nanomedicines. By clarifying these processes, we can connect the carrier's (structural design) features with the endpoints (efficacy and/or safety) of nanomedicines. Nanomedicine presents a burgeoning frontier for advancing oral drug delivery, and it currently offers a promising option for enhancing the delivery of biological agents and chemotherapy. The scientific community has identified chitosan, PLGA, and casein as the best starting materials for success in this field due to their numerous and affordable synthesis options. Current research highlights the benefits of nanomedicine in improving the bioavailability of drugs, but it ignores the possibility of carriers increasing the concentration of drugs at tumor sites. More research is needed to develop methods that overcome the limitations of gastrointestinal epithelial cells, facilitate drug release at their interface, and improve tumor targeting. Ma et al constructed a high-performance Pluronic F127 (P127)-modified gold shell (AuS)-polymer core nano-oral therapeutic drug loaded with curcumin (CUR) (P127-AuS@CUR). P127-AuS@CUR generates brief, mild photothermal effects under near-infrared irradiation, which facilitates nano-penetration of colonic mucus and facilitates cellular internalization, lysosomal escape, and controlled CUR release.²³⁹

OTDD treatment is a non-invasive treatment method that is more popular with patients and has lower time and economic costs. However, poor gastrointestinal barriers (gastric acid barrier and intestinal mucosal barrier) have a significant impact on the bioavailability of oral drugs. With the continuous advancement of nanotechnology, numerous researchers have discovered that, in the process of applying nanotechnology to treat and/or diagnose various diseases, engineered oral nanomedicines are capable of overcoming the gastric acid barrier and effectively crossing the intestinal mucus and epithelial barriers. This process improves the solubility, safety, targeting, and half-life of oral drugs and successfully reaches the delivery area. Consequently, the bioavailability of OTDDS is enhanced, the controlled release of OTDDSs is attained, and the residence time of OTDDSs in the lesion area is prolonged.

Despite the encouraging results that have been achieved thus far, there are still some unresolved issues in the practical applications of OTDDSs that require further attention. Firstly, the current primary method for enhancing the therapeutic efficacy of OTDDSs is to optimize their bioavailability through nanotechnology. However, there are a few notable instances where this approach has been employed to improve the overall performance of OTDDSs. Secondly, the majority of the current research on OTDDSs focuses on organs or tissues, with research on cells or organelles still in its infancy. Thirdly, there is a paucity of nanomaterial design and development strategies based on biomimetic engineering, including OTDDSs based on inorganic and organic nanoparticles. Fourthly, OTDDSs will undoubtedly bring great hope and convenience to the treatment of patients with various diseases in the future. However, they still face many inevitable challenges before clinical transformation and industrialization. For instance, current studies engineer bio-interface interactions (from crossing biological barriers to systemic clearance) between OTDDSs and human tissues by modulating some key physicochemical parameters, such as morphology, surface chemistry, and elasticity. However, biological barriers possess intrinsic dynamic systems that may lead to inaccurate analysis and characterization, thereby affecting the delivery fate of OTDDSs at the target site.^{240,241} Moreover,

a significant number of experiments remain at the proof-of-concept stage in terms of the ambiguous biotoxicity and pharmacokinetics of OTDDSs in animals and humans.²⁴²

In recent years, nanocellulose has emerged as a versatile and sustainable nanomaterial. Analogous to dietary fibers, nanocellulose resists digestion in the human gastrointestinal tract, demonstrating substantial potential in the delivery of biological agents. Additionally, the significance of gut microbiota species cannot be overstated; integrating microbial informatics methods into drug development and clinical practice is anticipated to enhance drug delivery efficiency while mitigating adverse effects on the host and microbial communities. Similarly, a comprehensive understanding of the survival strategies employed by human-associated microbial communities in response to various carrier compounds is essential for the rational design of carrier-targeted microecological regulations of small-molecule drugs. Future research should elucidate the mechanistic basis of carrier-microbe-host interactions, investigate innovative carriers, and translate scientific discoveries into clinical applications. Moreover, pH-sensitive Eudragit polymers combined with other nanozymes offer notable advantages in protein drug delivery. Recently, 3D printing technology has also gained significant attention. 3D-printed carrier nanomedicines can integrate diagnosis, detection, and treatment, enabling multifunctional clinical applications. Some of the latest advancements suggest that smart nanorobots can serve as advanced therapeutic platforms, offering strong targeting capabilities in these intelligent carrier systems.

Finally, the repeatability and controllability of OTDDSs are unstable, and issues such as the manufacturing cost of nanomaterials, regulatory approvals from relevant departments, and the standardization of industrial production must be considered by researchers, experts, and technicians.²⁴² The following suggestions are put forth for the advancement of OTDDSs: (1) Oral administration is a dosage form that is readily accepted by patients and does not unduly encumber their daily lives. Consequently, it is possible to identify a multitude of pharmaceutical resources from animals, plants, microorganisms, and other sources present in our daily diet. These can be utilized through nanotechnology to respond to common diseases through the diet, thereby reducing the economic cost of drugs and the time cost of treatment. It is recommended that treatments be administered simultaneously. Furthermore, OTDDSs are of significant importance for the early detection and screening of diseases. For instance, the use of artificial intelligence, such as nanorobots, or the design of new sophisticated nanomaterials with multiple functions, such as nuclear magnetic resonance and fluorescence imaging, can facilitate the elimination of human diseases in their initial stages through oral administration. (2) In order to achieve effective and real-time control of these diseases, the maximum dose and frequency of oral administration should not be too high. Consequently, in the context of animal models and preclinical trials, it is necessary to adapt the parameters of the nanomedicine system in order to optimize the effective dose and frequency of OTDDSs, thereby facilitating better compliance with treatment and greater comfort for patients. In conclusion, although there are still some issues and challenges to be overcome in the future development of OTDDS, there are also significant potential benefits and opportunities. Once these issues have been resolved, the potential applications of OTDDSs will be numerous and promising.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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