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Recent advancement in polymeric nanoparticles for oral chemotherapy: Transforming cancer treatment

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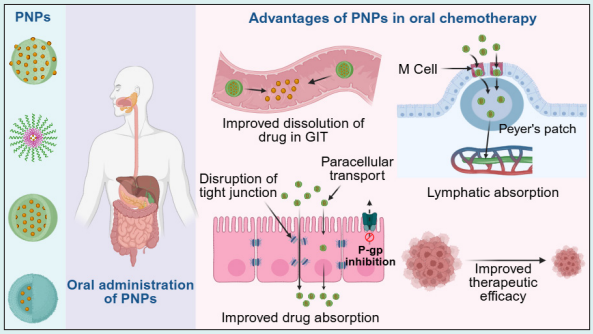
Abstract



Oral chemotherapy offers an attractive alternative to conventional intravenous administration by providing high patient compliance and improved treatment adherence. However, several challenges, like poor drug solubility, enzymatic degradation, and extensive first-pass metabolism, have significantly limited the oral bioavailability of chemotherapeutic agents. Recently, polymeric nanoparticles (PNPs) have become an alternative strategy to overcome these challenges and revolutionize the oral chemotherapeutic approach. PNPs offer unique advantages, including drug protection from harsh gastrointestinal conditions, controlled release profiles, and enhanced mucosal adhesion, which collectively improve drug absorption and therapeutic efficacy. Additionally, surface-modified PNPs can bypass efflux transporters such as P-glycoprotein and promote receptor-mediated endocytosis to achieve targeted delivery and minimize systemic toxicity. While these advancements highlight the transformative potential of PNPs in oral chemotherapy, potential clinical challenges such as scalability, reproducibility, and regulatory hurdles must be addressed to enable successful clinical translation. The present review comprehensively explores the role of PNPs in enhancing the oral delivery of cancer therapeutics, emphasizing strategies to improve drug stability, prolong gastrointestinal retention, and facilitate efficient cellular uptake. The advancements discussed herein underscore the transformative potential of PNPs as a pivotal approach for improving oral chemotherapy outcomes and expanding therapeutic possibilities in cancer management.

Introduction

Cancer remains one of the most significant global health challenges, posing a substantial burden on healthcare systems and patients worldwide.[1] Despite extensive research and advancements in treatment modalities, cancer remains a leading cause of mortality globally.[2] Among the various therapeutic strategies available, chemotherapy has remained the primary method for cancer treatment. Chemotherapy employs cytotoxic drugs to eliminate rapidly dividing cancer cells and inhibits cancer progression.[3] However, traditional chemotherapy administration, predominantly through intravenous routes, presents several limitations that impact patient outcomes and quality of life.[4]

Intravenous (IV) chemotherapy, though effective in delivering drugs directly into the bloodstream, requires frequent hospital visits, invasive procedures, and strict medical supervision. This increases healthcare costs and imposes considerable physical and emotional stress on patients.[5,6] Furthermore, intravenous administration often leads to non-specific drug distribution, which can result in severe side effects such as myelosuppression, gastrointestinal disturbances, alopecia, and organ damage.[7,8] These adverse effects substantially reduce patient adherence to treatment regimens that ultimately affect the therapeutic outcomes.[9]

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Oral chemotherapy has emerged as a promising alternative that offers numerous advantages over traditional intravenous administration. Oral administration enhances patient comfort by eliminating the need for invasive procedures, which reduces hospital visits and treatment-related stress. Additionally, oral chemotherapy facilitates long-term treatment regimens, which are particularly helpful in managing chronic cancers that require prolonged maintenance therapy. Improved patient adherence can come from better convenience and self-administration that further supports the potential of oral chemotherapy to improve clinical outcomes.[10,11] However, it is crucial to emphasize that patient acceptance plays a pivotal role in the success of oral chemotherapy. Even if oral delivery achieves 100% bioavailability, the approach remains systemic in nature, and therapeutic efficacy will only improve if the encapsulated drug successfully enters systemic circulation and reaches the tumor site.[12,13] Without targeted delivery, oral administration may not necessarily reduce off-target effects or enhance treatment outcomes. Despite these advantages, the oral route for chemotherapy delivery faces considerable challenges that limit its widespread application. Many chemotherapeutic agents exhibit poor aqueous solubility, which impairs their dissolution and absorption in the gastrointestinal tract (GIT).[14] Furthermore, some drugs, after oral administration, often encounter significant enzymatic degradation in the GIT, which reduces their stability and bioavailability.[15] The presence of efflux transporters such as P-glycoprotein (P-gp) and metabolic enzymes like cytochrome P450 enzymes reduces the drug absorption from the GIT.[16] Additionally, the oral route is associated with hepatic first-pass metabolism, where drugs undergo extensive metabolic degradation in the liver before reaching the bloodstream, which further reduces their bioavailability and therapeutic efficacy.[17] As a result, innovative strategies are required that can circumvent biopharmaceutical challenges.

Nanoparticles (NPs) have emerged as promising tools in pharmacology and medicine that enable targeted and efficient drug delivery. Their nanoscale size, high surface area, and tunable surface properties allow for improved drug stability, controlled release, and improved tissue distribution.[18,19] Over the last three decades, various types of NPs have been explored for drug delivery applications. Among these, polymeric nanoparticles (PNPs), whether derived from natural or synthetic polymers, offer unique advantages such as biodegradability, biocompatibility, ease of functionalization, and the ability to modulate drug release profiles.

PNPs have shown promise as a viable strategy to circumvent these challenges and revolutionize oral chemotherapy. PNPs are nanoscale carriers composed of biodegradable and biocompatible polymers capable of encapsulating chemotherapeutic agents within their polymeric matrix. The encapsulation of chemotherapeutic drugs in the polymeric matrix protects the entrapped drugs from the harsh gastrointestinal (GI) environment, prevents their premature degradation, and enhances their stability.[20] Furthermore, PNPs can be engineered to improve drug solubility, facilitate controlled drug release, and enhance mucosal adhesion, all of which promote better drug absorption from the GIT. A high surface-to-volume ratio due to the nanometric size of PNPs further improves their potential to traverse the mucosal barrier and enhance drug absorption, thereby improving oral bioavailability.[21,22] Furthermore, the surface of PNPs can be engineered with PEG or targeting ligands that can inhibit efflux transporters like P-gp, and increase intracellular trafficking by receptor-mediated endocytosis that ultimately results in enhanced therapeutic outcomes with reduced systemic cytotoxicity.[23,24]

This article aims to deliver a holistic perspective on the role of PNPs in revolutionizing the oral delivery of cancer therapeutics. It will highlight different types of PNPs for oral chemotherapy, explore their mechanisms for overcoming biological as well as pharmaceutical barriers, and discuss their ability to enhance drug stability, oral bioavailability, and therapeutic outcomes. By delving into these fundamental aspects, this review strives to elucidate the significance of oral PNPs as a transformative approach for improved therapeutic outcomes with reduced systemic toxicity.

Pharmacokinetic journey of orally administered drugs

The journey of an orally administered drug begins in the mouth and follows a well-established pathway described by the ADME process: Absorption, Distribution, Metabolism, and Excretion.[25] This pathway determines the drug's pharmacokinetic profile, which in turn influences its therapeutic effectiveness. A general pharmacokinetic journey of the drug after oral administration is diagrammatically illustrated in Fig. 1. After ingestion, the drug must first dissolve in the fluids of the GI tract to be absorbed. This typically occurs in the small intestine, which has a large surface area and a rich blood supply, which makes it the primary site for absorption.[26] The drug crosses the intestinal wall either by passive diffusion (moving from high to low concentration) or active transport (requiring energy and specific transport proteins).[27] Once absorbed, the drug enters the portal circulation and is transported directly to the liver, where it may undergo first-pass metabolism. This process can significantly reduce the amount of active drug reaching the rest of the body.[28] After passing through the liver, the drug enters the systemic circulation and is distributed throughout the body to various tissues and organs.[29] The extent of distribution depends on factors such as blood flow, how easily the drug can pass through tissue

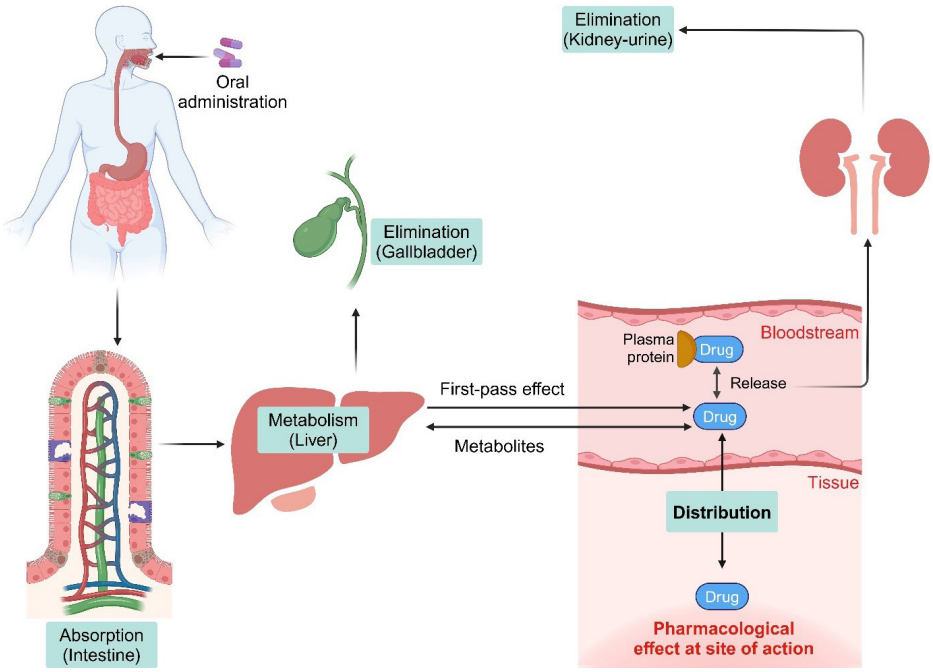

Fig. 1. A diagrammatic illustration of the general pharmacokinetic journey of the drug upon administration via the oral route. Created in BioRender. Rizwanullah M. (2025). https://BioRender.com/r80x564.

barriers (permeability), and how much of the drug binds to proteins in the blood.[30] Next, the drug is metabolized, primarily in the liver, through phase I (modification) and phase II (conjugation) reactions. These chemical changes are carried out by enzymes, most notably those from the cytochrome P450 family, and can convert the drug into either active or inactive forms.[31,32] Finally, the drug and its metabolites are excreted from the body. The kidneys play a major role, filtering the blood and eliminating substances through urine. Other excretion routes include bile (from the liver to the intestines), the lungs (exhalation), and secretions such as sweat or saliva.[33] Together, these processes determine the drug's bioavailability (how much of it reaches the bloodstream), half-life (how long it stays in the body), and overall therapeutic effect.

Advantages and limitations of the oral route

The major advantages of the oral route include improved patient convenience, non-invasiveness, and the potential for self-administration. This approach eliminates the need for healthcare supervision during drug administration and reduces the frequency of hospital visits and medical expenses.[34] Oral drug delivery systems are typically easier to formulate, manufacture, and distribute, making them economically viable and scalable.[35] Furthermore, oral formulations offer diverse dosage forms such as tablets, capsules, syrups, and suspensions, catering to various patient populations, including pediatric and geriatric patients. Additionally, oral drug delivery mimics the natural process of nutrient absorption in the intestine, making it an intuitive and adaptable method for patients.[36]

Despite its numerous benefits, the oral route is associated with several limitations that restrict its universal applicability, especially for certain classes of drugs such as chemotherapeutic agents. One major limitation is the extensive first-pass metabolism that occurs primarily in the liver. Enzymatic degradation in the GIT further limits the bioavailability of susceptible molecules.[37] Another critical challenge with oral drug delivery is the variability in absorption. Factors such as gastric pH, food intake, GI motility, and the presence of bile salts can significantly impact drug dissolution and absorption profiles.[38] Certain classes of drugs, especially BCS class II and IV drugs, face poor solubility and permeability issues that hinder their absorption across the intestinal epithelium.[39] Some drugs, particularly chemotherapeutic agents, possess inherent cytotoxicity that can damage the delicate GI lining, which may lead to undesirable effects, including nausea, vomiting, diarrhea, and mucositis.[40] Furthermore, drug efflux mechanisms such as the P-gp transporter significantly reduce the intracellular accumulation of certain anticancer drugs, which further limits their oral bioavailability.[41] The presence of tight junctions in the intestinal epithelium also restricts the paracellular transport of macromolecules and hydrophilic drugs.[42] Therefore, there is a need to address these challenges by developing novel approaches. PNPs offer a compelling strategy for oral chemotherapy to achieve better therapeutic outcomes.

Importance of the oral route over intravenous administration

Traditionally, IV administration has been the predominant route for delivering chemotherapeutic

agents due to its ability to achieve rapid and complete systemic drug availability. However, in recent years, there has been a significant paradigm shift towards the oral administration of anticancer drugs. This shift is primarily driven by patient-centered considerations, improved drug formulations, and evolving healthcare delivery models. Currently, more than 80 oral chemotherapeutic agents have received regulatory approval in the United States and Europe for clinical use, highlighting the growing acceptance and application of this route in oncology.[43]

One of the most compelling advantages of oral chemotherapy is the convenience it offers to patients. Unlike IV therapy, which typically necessitates hospital visits, infusion facilities, and trained healthcare personnel, oral chemotherapy can often be self-administered at home. This enables outpatient treatment and reduces the burden on healthcare infrastructure, including hospital admissions and infusion-related resource utilization. Consequently, this approach not only enhances patient autonomy but also significantly lowers overall treatment costs by minimizing the need for hospitalization, medical personnel, and infusion equipment.[44] From a clinical perspective, oral chemotherapy provides the potential for prolonged drug exposure, which is critical for drugs exhibiting time-dependent pharmacodynamics.[45] Continuous oral administration may achieve pharmacokinetic profiles comparable to or even better than intermittent IV infusions for drugs with short half-lives, thereby potentially improving therapeutic outcomes.[46] Moreover, several studies have indicated that patients generally prefer oral therapy over IV therapy due to its non-invasive nature, avoidance of venous catheterization, and the psychological comfort associated with home-based treatment.[47]

Patient compliance is a critical determinant of oral chemotherapy efficacy, as non-adherence can lead to suboptimal dose intensity, therapeutic failure, and emergence of resistance. Therefore, oral therapy must be accompanied by appropriate patient education, monitoring strategies, and adherence-support systems to ensure successful outcomes. Furthermore, for oral chemotherapy to be clinically viable, its safety and efficacy must be at least equivalent to conventional IV formulations.[48] When these conditions are met, oral therapy has been shown to offer comparable tumor control with improved patient quality of life and reduced treatment-related fatigue and stress. Overall, the oral route offers a convenient, cost-effective, and patient-preferred alternative to IV chemotherapy.[49]

Overview of PNPs for oral chemotherapy

Over the previous two decades, PNPs have evolved into a promising strategy for oral chemotherapy owing to their unique physicochemical characteristics. PNPs are nanoscale colloidal systems fabricated from biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, polycaprolactone (PCL), and eudragit.[50] PNPs enable improved drug solubility, stability, sustained drug release, and enhanced bioavailability. The selection of polymers is critical as it directly influences the stability of the PNPs, encapsulation efficiency, and release kinetics.[51] PNPs are engineered to safeguard chemotherapeutic agents from the harsh GI milieu and facilitate drug absorption through the intestinal epithelium. By encapsulating lipophilic chemotherapeutics within the polymer matrix, PNPs can increase the solubility in the GI milieu of these drugs and enhance their dissolution rate and subsequent absorption from the intestine. Furthermore, PNPs offer protection against enzymatic degradation in the GIT, particularly for drugs susceptible to hydrolysis or oxidation. The polymer matrix serves as a protective barrier and ensures the structural integrity of the chemotherapeutic drugs until they reach the site of absorption.[52,53] Another crucial advantage of PNPs is their ability to promote mucoadhesion and enhance permeation across the intestinal epithelium. Polymers such as chitosan, known for their cationic nature, can interact with negatively charged mucosal surfaces and prolong the residence time of PNPs in the GIT.[54] Controlled and sustained drug release is another significant advantage of PNPs in oral chemotherapy. By tuning the polymer composition, molecular weight, and cross-linking density, PNPs can be fabricated to provide prolonged drug release and ensure a sustained therapeutic drug concentration in the bloodstream. This controlled release reduces dosing frequency, thereby enhancing patient adherence and mitigating the risk of adverse effects linked to plasma drug level fluctuations.[55,56] The ability of PNPs to inhibit P-gp transporter on intestinal epithelial cells further enhances oral bioavailability. Many chemotherapeutic agents are P-gp substrates, and the presence of P-gp on intestinal epithelial cells often limits their absorption. PNPs can effectively inhibit these efflux mechanisms by incorporating excipients like D-α-tocopheryl polyethylene glycol succinate (TPGS) or Pluronic block copolymers, which act as P-gp inhibitors.[57] Moreover, surface modification of PNPs by conjugating receptor-specific ligands can further increase intracellular trafficking via receptor-ligand interaction that results in improved drug accumulation in cancerous tissues and reduces off-target toxicity.[58] Different mechanisms by which PNPs enhance bioavailability upon oral ingestion are diagrammatically illustrated in Fig. 2.

Different types of PNPs for oral chemotherapy

Different types of highly efficient PNPs for effective oral chemotherapy are discussed as follows. The different types of PNPs widely used for oral chemotherapy are diagrammatically illustrated in Fig. 3.

Nanospheres

Nanospheres are matrix-type PNPs in which the chemotherapeutic agent is uniformly dispersed throughout the polymer matrix. With a high drug-loading capability, these systems facilitate prolonged drug release by controlling polymer degradation and diffusion mechanisms.[59] The uniform dispersion of drugs within the polymeric matrix facilitates stable drug encapsulation, reducing premature drug degradation in the GIT and ensuring prolonged drug release. Nanospheres are particularly advantageous for poorly water-soluble drugs by improving their dissolution rates and enhancing oral absorption.[60] Furthermore, the surface of nanospheres can be functionalized with targeting ligands for site-specific drug delivery.[61] This targeted approach minimizes systemic toxicity while improving therapeutic outcomes in cancer management.

Nanocapsules

These are vesicular polymeric systems with a core-shell structure in which the hydrophobic drug is confined within a liquid or polymeric core surrounded by a polymeric shell.[62] This core-shell architecture provides enhanced protection for encapsulated drugs against enzymatic degradation, acid hydrolysis, and bile salt-induced degradation in the GIT, ultimately improving oral bioavailability. Nanocapsules are particularly effective for lipophilic anticancer drugs that suffer from poor aqueous solubility and chemical instability.[63,64] The polymeric shell, often composed of PLGA, polyethylene glycol (PEG), or chitosan, acts as a protective barrier and can be further engineered with targeting ligands to promote active targeting of cancer cells.[65] Moreover, the surface functionalization of nanocapsules enhances mucoadhesion and improves drug absorption through different transport mechanisms.[66]

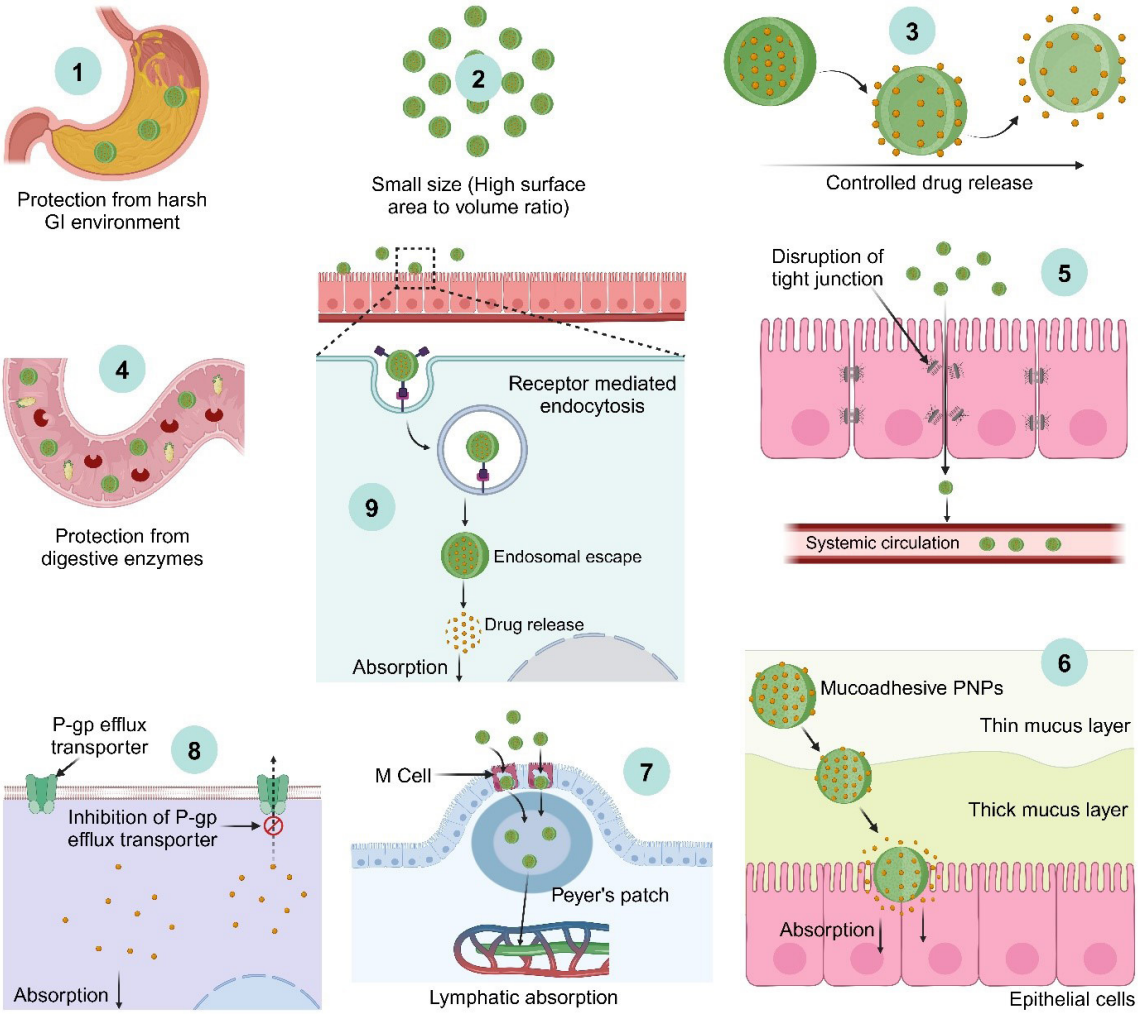

Fig. 2. Diagrammatic representation of the diverse mechanisms by which PNPs enhance the oral bioavailability of chemotherapeutics. (1) PNPs provide protection from the harsh GI environment that ensures drug stability. (2) Their small size offers a high surface area-to-volume ratio, which results in improved dissolution and absorption. (3) Controlled drug release from PNPs ensures sustained therapeutic drug levels. (4) PNPs protect drugs from digestive enzymes and improve drug stability. (5) PNPs disrupt tight junctions and promote paracellular transport. (6) Mucoadhesive PNPs interact with the mucus layer, extend residence time, and enhance absorption. (7) PNPs utilize M cells in Peyer's patches to achieve lymphatic absorption and bypass the first-pass metabolism. (8) PNPs can inhibit P-gp efflux transporters, thereby reducing the drug efflux and improving intracellular drug retention. (9) Receptor-mediated endocytosis improves overall intracellular drug trafficking. Created in BioRender. Rizwanullah M. (2025). https://BioRender.com/n74p262.

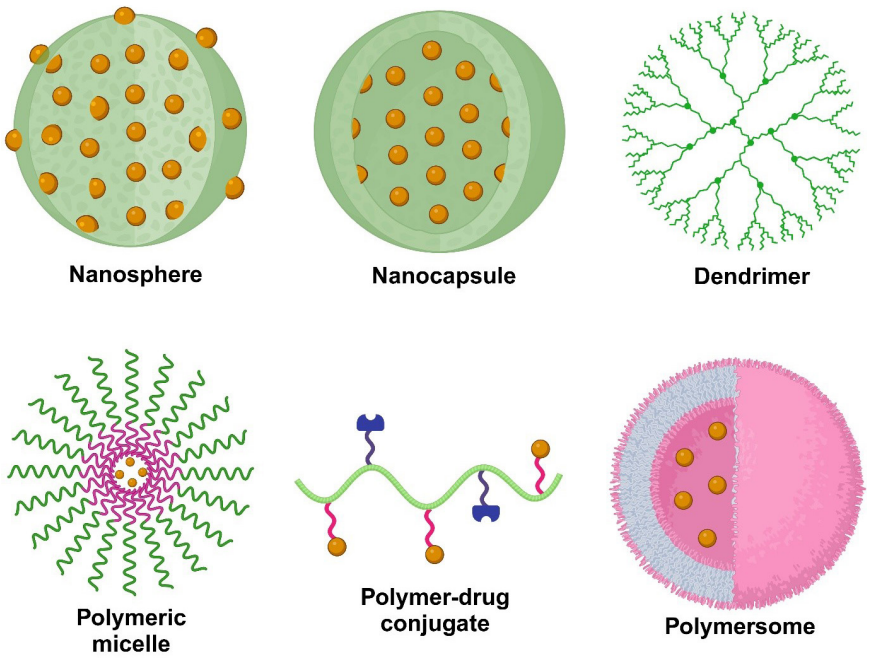

Fig. 3. Schematic illustration of different types of PNPs employed for oral chemotherapy. Created in BioRender. Rizwanullah M. (2025). https://BioRender.com/o29i997.

Dendrimers

These are highly branched, monodisperse PNPs characterized by a well-defined structure with multiple functional groups on their surface. This distinctive architecture enables the ability to control the size, shape, and surface functionality and offer higher loading capacity, stability, and targeted delivery.[67] Dendrimers are extensively explored for oral chemotherapy owing to their potential to traverse the GI epithelium.[68] The surface of dendrimers can be engineered with PEG, targeting ligands, or bioadhesive polymers to enhance mucosal adhesion, prolong intestinal residence time, and promote receptor-mediated endocytosis, thereby improving drug absorption and systemic availability.[69,70] Their nanoscale size and tunable surface chemistry further enable precise drug release control through pH-sensitive or enzymatic degradation mechanisms.[71]

Polymeric micelles

These are self-assembled polymeric nanocarriers composed of amphiphilic block copolymers that possess lipophilic cores and hydrophilic shells. The hydrophobic core serves as a reservoir for lipophilic anticancer agents, while the hydrophilic corona stabilizes the micelle in aqueous environments and enhances systemic circulation.[72,73] Polymeric micelles fabricated using copolymers such as polyethylene glycol-polycaprolactone (PEG-PCL) or polyethylene glycol-polylactic acid (PEG-PLA) have shown remarkable potential in enhancing the oral absorption of chemotherapeutics by promoting lymphatic uptake and bypassing first-pass metabolism.[74,75] Their ability to incorporate P-gp inhibitors like TPGS further enhances oral bioavailability.[76]

Polymer-drug conjugates (PDCs)

PDCs are innovative nanosystems in which the chemotherapeutic agent is covalently linked to a polymer backbone via biodegradable linkers. This conjugation strategy enhances the pharmacokinetic stability of the drug, protects it from premature enzymatic degradation within the GIT, and facilitates controlled release at the target site.[77,78] The tumor specificity of PDCs is primarily achieved through the rational design of stimulus-responsive linkers that undergo cleavage in response to distinct physicochemical or enzymatic conditions prevalent in the tumor microenvironment.[79,80] Acid-sensitive linkers, such as hydrazone or cis-aconityl bonds, remain stable at physiological pH but are hydrolyzed in the mildly acidic conditions of tumor interstitium or intracellular endo/lysosomes.[81] Similarly, enzyme-sensitive linkers composed of peptide sequences are cleaved by overexpressed proteolytic enzymes such as cathepsins and matrix metalloproteinases, while disulfide bonds serve as redox-sensitive linkers that respond to elevated glutathione levels typically found in the intracellular milieu of cancer cells.[82] These intelligent linker designs ensure that the active drug is selectively released at the tumor site, thereby minimizing systemic toxicity and improving therapeutic index. Compared to traditional chemotherapeutic formulations, PDCs offer several distinct advantages, including enhanced biopharmaceutical stability, prolonged systemic circulation, and significantly reduced off-target effects.[83] The site-specific release of the payload results in a high

localized drug concentration at the tumor site, which can substantially enhance antitumor efficacy even at lower doses. Moreover, the polymer backbone can be engineered to enable sustained drug release, reduce dosing frequency, and improve patient adherence.[84]

Polymersomes

These are bilayered vesicular nanoparticles formed by the self-assembly of amphiphilic block copolymers, closely resembling liposomes but with improved stability and tunable properties. The hydrophobic bilayer membrane encapsulates hydrophobic therapeutics, while the aqueous core can encapsulate hydrophilic drugs, which enables simultaneous delivery of multiple therapeutics.[85,86] Polymersomes constructed from copolymers provide enhanced protection for encapsulated drugs against gastrointestinal degradation, improving oral absorption.[87] Additionally, polymersomes can be designed with pH-sensitive or redox-responsive elements to achieve controlled release at the target site. Surface modification with PEG or targeting ligands further enhances systemic circulation, cellular uptake, and tumor-targeted delivery.[88,89] Polymersomes demonstrate significant potential for oral chemotherapy by improving drug stability, enhancing transmembrane permeability, and promoting receptor-mediated endocytosis that ultimately enhances the therapeutic outcomes with reduced off-target toxicity.[90,91]

Further, a comparative analysis of different PNPs for oral chemotherapy is summarized in Table 1.

Different strategies to enhance the oral efficacy of chemotherapeutic drugs with PNPs

To enhance the oral bioavailability and therapeutic outcomes of chemotherapeutic drugs using PNPs, various strategies have been discussed. The subsequent section discusses different strategies to improve therapeutic outcomes on oral chemotherapy.

Increasing chemotherapeutic drug stability

Ensuring the GI stability of drugs and drug-loaded formulations is crucial to achieve better therapeutic outcomes in oral chemotherapy. PNPs can protect the encapsulated drug from harsh gastric conditions, enzymatic degradation, and hydrolysis, thereby preserving their therapeutic efficacy.[104] Polymers such as PLGA, chitosan, and Eudragit are commonly employed due to their pH-responsive properties and ability to form protective matrices around the drug.[105] Moreover, surface modification with PEG can improve stability by preventing nanoparticle aggregation and reducing premature drug release.[106] For instance, Sorasitthiyanukarn et al developed fucoxanthin (FX)-loaded alginate/chitosan nanoparticles (FX-ALG/CS-NPs) that demonstrated improved stability in simulated GI conditions with a controlled release profile.[107] FX bioaccessibility increased 2.7-fold, and FX-ALG/CS-NPs retained 3 times more FX content under UV exposure than free FX. FX-ALG/CS-NPs reduced MDA-MB-231 cell viability by 19.5%, showing 2.3-fold greater efficacy than free FX. Sajomsang et al designed pH-responsive N-benzyl-N, O-succinyl chitosan micelles for curcumin (CUR) delivery.[108] These micelles maintained particle size below 200 nm for four months and showed minimal CUR release in SGF but significant release at pH 5.5-7.4. Cellular uptake studies demonstrated a 6-fold increase in intracellular CUR levels, while CUR-loaded micelles exhibited 4.7-, 3.6-, and 12.2-fold reduced IC_{50} in HeLa, SiHa, and C33a cells, respectively. Apoptosis studies showed CUR-loaded micelles increased early apoptosis by 30-55% compared to free CUR. Ünal et al developed PNPs for oral camptothecin (CPT) delivery in colorectal cancer models.[109] These CPT-PNPs improved intestinal permeability 2.7-fold. In vitro studies showed enhanced antiproliferative effects against CT-26 cells. In vivo results confirmed significant tumor reduction and reduced liver metastases in CT-26 tumor-bearing Balb/c mice. Biodistribution studies indicated targeted accumulation in tumor foci, supporting localized CRC treatment. Wang et al fabricated polydopamine nanoparticles (PDA-NPs) for oral delivery of gambogenic acid (GA).[110] These nanoparticles demonstrated enhanced stability and biphasic release profiles. FA-GA-PNPs demonstrated higher intracellular trafficking in 4T1 cells than unmodified PNPs. The IC_{50} value for FA-GA-PNPs was 2.58 μM, significantly lower than free GA (7.57 μM). Cellular uptake studies using C6 dye showed stronger fluorescence intensity with FA-GA-PNPs. In vivo pharmacokinetics in Sprague Dawley (SD) rats showed 2.97-fold improved oral bioavailability (Fig. 4A). In 4T1 tumor-bearing Balb/c mice, FA-GA-PNPs showed significantly greater tumor suppression than the pure drug (Fig. 4B). Additionally, FA-GA-PNPs enhanced GA distribution in key organs such as the liver, lung, and kidney without noticeable toxicity. In another study, Alshehri et al fabricated chitosan-coated PLGA-NPs for the oral delivery of thymoquinone (TQ-PNPs) to enhance its efficacy against breast cancer.[111] The CS coating significantly improved GI stability and prolonged TQ release. The CS coating enhanced mucoadhesion and intestinal permeation, with TQ-PNPs demonstrating 1.92- and 3.15-fold higher permeation than uncoated TQ-PNPs and TQ suspension, respectively. Further, TQ-PNPs demonstrated 1.89- and 1.72-fold lower IC_{50} values than pure TQ in MDA-MB-231 and MCF-7 cells, respectively. These findings underscore the potential of PNPs in enhancing the stability and therapeutic efficacy of oral chemotherapeutics.

Prolonging residence time in the GIT

Prolonging the retention time in the is crucial for

Table 1. Comparative analysis of different PNPs for oral chemotherapy

PNPs type	Structural features	Key advantages	Limitations	Reference
Nanospheres	Solid matrix system with drug uniformly dispersed	High drug-loading capacity, simple design, sustained release, high transepithelial transport	Limited control over release kinetics, potential for burst release	92,93
Nanocapsules	Core-shell structure with drug in the core and polymeric shell	Enhanced drug protection from GI degradation, controlled release, comparatively high bioavailability	Complex formulation, stability of the shell may affect the release profile	94,95
Dendrimers	Highly branched, monodisperse macromolecules with functional end groups	Precise control over size and surface, high drug payload, surface modifiability, excellent intracellular uptake, and receptor-mediated targeting	High production cost, potential toxicity if the surface is not modified	96,97
Polymeric Micelles	Amphiphilic block copolymers self-assemble into a core-shell structure	Good solubilization of hydrophobic drugs, improved lymphatic uptake, potential for high oral absorption	Instability in dilute environments, possible premature disassembly	98,99
PDCs	Drug covalently linked to polymer backbone via a cleavable linker	High stability, site-specific release, minimized systemic toxicity	Synthesis complexity; slower release may delay the onset of action	100,101
Polymersomes	Bilayer vesicular structures formed by amphiphilic block copolymers	Dual drug loading (hydrophilic and lipophilic), excellent membrane stability, Efficient tumor targeting, and reduced off-target toxicity	Slow degradation, potential scale-up challenges	102,103

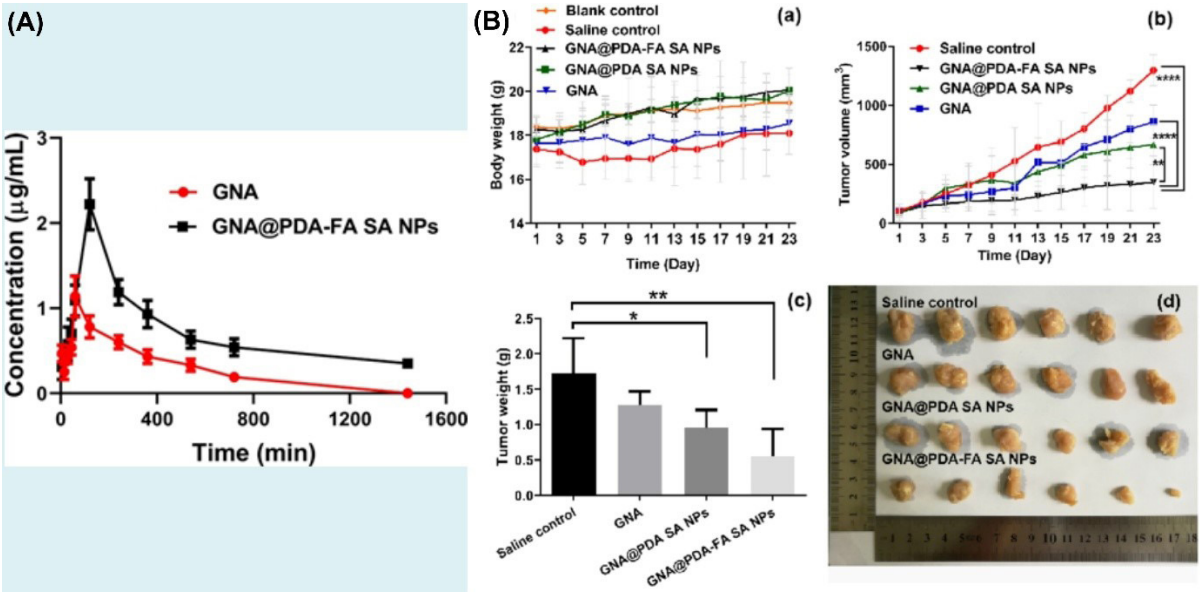

Fig. 4. Image showing (A) pharmacokinetic profiles of FA-GA-PNPs and pure GA and (B) in vivo therapeutic effect of developed formulation on (a) body weight, (b) tumor volume, (c) tumor weight, and (d) tumor morphology. Reprinted with permission from Wnag et al.[110] Copyright (2025) American Chemical Society.

enhancing oral drug delivery using PNPs. The extended residence in the GIT ensures that the drug-loaded PNPs have ample opportunity to interact with the intestinal epithelium and facilitates their transport into the lymphatic system or bloodstream.[112] PNPs can be engineered with mucoadhesive materials, which allow them to adhere to the intestinal mucosa for extended periods. Polymers such as chitosan and carbopol are commonly employed for this purpose due to their bioadhesive nature. These polymers interact with mucins in the intestinal lining and form strong adhesive bonds that resist peristaltic movement and gastric emptying. This prolonged residence time enhances the drug absorption window and improves bioavailability.[113,114] In this context, Antonio et al fabricated chitosan-modified PLGA-NPs to improve the oral bioavailability of ursolic acid (UA).[115] The CS coating improved stability in simulated GI fluids and enhanced mucoadhesion, sustaining drug release. The UA-CS-PNPs showed superior intracellular trafficking and cytotoxicity against B16-F10 and HEp-2 cells. In vivo pharmacokinetic studies revealed UA-CS-PNPs achieved a 4.14-fold higher half-life, 3.84-fold higher oral bioavailability, and 3.3-fold slower clearance than free UA. Lima et al fabricated CS-coated PLGA-NPs (FA-CS-PNPs) for better oral delivery of ferulic acid.[116] In vitro release studies displayed a biphasic profile with

15% FA released in SGF and minimal release in SIF. Further, the formulation revealed 27.7% FA release in phosphate buffer solution. FA-CS-PNPs achieved 20% permeation in a Caco-2/HT29-MTX/Raji B co-culture model, significantly higher than uncoated NPs. FA-CS-PNPs preserved FA's antioxidant activity and showed comparable cytotoxicity to free FA against B16-F10 and HeLa cells, with improved mucoadhesion and drug retention. Mehandole et al developed dasatinib-loaded mucoadhesive chitosan-based hybrid NPs (DAS-CS-HNPs) for enhanced oral delivery against triple-negative breast cancer.[117] DAS-CS-HNPs demonstrated sustained release over 48 hours, 10.27-fold greater mucus adhesion, and a 10-fold enhancement in permeability coefficient versus free DAS. In vitro studies in MDA-MB-231 cells showed DAS-CS-HNPs reduced IC_{50} by 4.14-fold, increased ROS generation by 3.82-fold, and enhanced apoptosis by 2.10-fold. In vivo pharmacokinetics in Balb/c mice revealed a 5.08-fold increase in oral bioavailability. Toxicity studies confirmed improved safety profiles with no significant organ damage. In another study, Huang et al formulated SN38-loaded deoxycholic acid-grafted N'-nonyl-trimethyl chitosan-based micelles (SN38-PMCs) for improved oral delivery and anticancer efficacy.[118] In vitro studies showed sustained release with enhanced mucoadhesion and intestinal retention. SN38-PMCs exhibited 2.36-fold higher intestinal permeability than free SN38. In vivo pharmacokinetics in SD rats revealed a 2.99-fold improved oral bioavailability. In H22 tumor-bearing mice, SN38-PMCs represented much higher tumor inhibition potential, while histological evaluation confirmed biocompatibility with no major toxicity in vital organs. Collectively, these studies highlight the significance of prolonging the GIT residence time of PNPs in enhancing oral bioavailability and therapeutic outcomes.

Enhancing transmembrane permeability

Poor transmembrane permeability is one of the major limiting factors behind poor therapeutic outcomes with oral chemotherapy. Enhancing transmembrane permeability is crucial in improving oral bioavailability, especially for chemotherapeutic drugs that exhibit limited permeability due to their (i) physicochemical properties and (ii) active efflux by the P-gp efflux pump.[119,120]

Inhibition of P-gp efflux pump

Inhibiting the P-gp efflux pump can significantly improve drug absorption. PNPs can incorporate P-gp inhibitors such as TPGS, Pluronic copolymers, or verapamil to block P-gp activity and reduce drug efflux.[121] TPGS, in particular, has demonstrated substantial efficiency in enhancing the intracellular trafficking of chemotherapeutic agents by inhibiting P-gp, which promotes transcellular transport.[122] In a study, Jiang et al fabricated thiolated TPGS-based chitosan-modified PNPs for oral lung cancer chemotherapy using paclitaxel (PTX).[123] The TPGS incorporation and thiolated chitosan modification improved mucoadhesion, intestinal permeation, and drug absorption. Cellular uptake studies in Caco-2 and A549 cells revealed 1.67-fold and 1.93-fold enhanced internalization for PTX-TPGS-CS-PNPs than unmodified PNPs, respectively (Fig. 5A). Cytotoxicity studies demonstrated superior efficacy with reduced IC_{50} values compared to Taxol® (Fig. 5B). Ex vivo intestinal permeation studies confirmed enhanced PTX absorption due to improved mucoadhesion and P-gp inhibition (Fig. 5C). Chen et al fabricated multifunctional chitosan polymeric micelles (PTX-PMCs) for oral PTX delivery.[124] The GA-CS-TPGS copolymer, synthesized by combining chitosan (CS), gallic acid (GA), and TPGS, improved mucoadhesion, inhibited P-gp efflux, and reduced CYP3A-mediated metabolism. In vitro studies showed enhanced mucoadhesion (692.5 µg mucin adsorption/mg micelles) and increased PTX permeability compared to PTX alone. CYP3A inhibition by PTX-PMCs reached 89.94% at the highest concentration. Pharmacokinetic studies in SD rats showed PTX-PMCs improved bioavailability by 3.8-fold over Taxol®, with a higher C_{max} and extended T_{max}. In vivo, PTX-PMCs significantly reduced tumor volume and weight compared to Taxol®. Overall, incorporating P-gp inhibitors in PNPs is a promising strategy to improve drug absorption and therapeutic efficacy of chemotherapeutics.

Targeting intestinal epithelial receptors/transporters

Targeting intestinal epithelial receptors and transporters with PNPs can enhance drug uptake through active transport mechanisms.[125] PNPs can be engineered with receptor-specific ligands such as biotin, transferrin, or RGD peptides, which bind to corresponding receptors or transporters on the intestinal epithelium. Engineered PNPs facilitate receptor-mediated endocytosis and can enhance cellular uptake of PNPs and the subsequent release of chemotherapeutic drugs into the systemic circulation.[126,127] In this context, Lin et al developed PTX-loaded biotin-PEG-biotin (BPB) conjugated TPGS-modified carboxymethyl chitosan-rhein-based mixed micelles aimed to achieve improved oral bioavailability and breast cancer treatment.[128] Mucoadhesion and permeation studies showed over 3-fold improved PTX absorption via biotin receptor-mediated endocytosis. Targeted PTX-PMCs exhibited significantly higher uptake in Caco-2 and 4T1 cells than non-targeted PTX-PMCs or pure PTX. Cytotoxicity studies revealed targeted PTX-PMCs were 4.65- and 1.98-fold more potent than non-targeted PTX-PMCs in Caco-2 and 4T1 cells, respectively. Pharmacokinetic studies in SD rats showed 8.92-fold higher PTX bioavailability versus Taxol®. In 4T1 tumor-bearing Balb/c mice, targeted PTX-PMCs achieved superior tumor accumulation and enhanced antitumor efficacy compared to non-targeted PTX-PMCs and Taxol®.

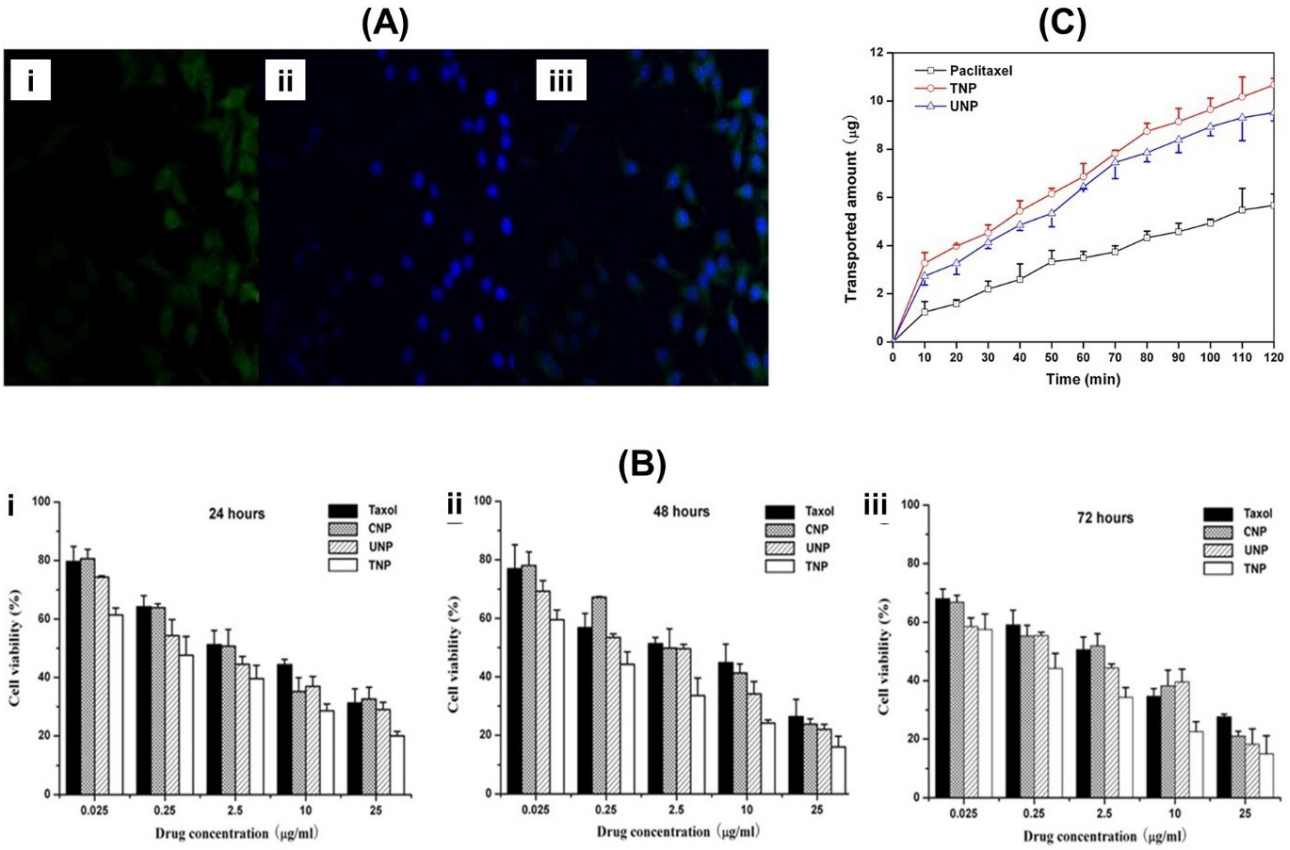

Fig. 5. Image illustrating (A) CLSM images of Caco-2 cells after treatment with coumarin-6-loaded TPGS-CS-PNPs, (B) effect of PTX-TPGS-CS-PNPs against A549 cells at different time intervals, and (C) intestinal permeation of the developed PTX-TPGS-CS-PNPs. Adapted from Jiang et al[123] under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0).

Co-delivery of multiple drugs using PNPs for oral chemotherapy

The co-delivery of multiple drugs via PNPs offers a promising strategy to improve the efficacy of oral chemotherapy. PNPs serve as highly adaptable carriers that can encapsulate both hydrophilic and lipophilic drugs and enable synergistic activity with improved therapeutic outcomes and overcome multidrug resistance (MDR).[129,130] The PNPs ensure controlled drug release, enhanced stability, and better mucoadhesive properties. Upon oral administration, PNPs navigate the harsh GI milieu and protect the drugs from premature degradation. Upon reaching the small intestine, pH-responsive polymers trigger drug release in the alkaline environment and improve absorption. Additionally, the bioadhesive nature of PNPs prolongs their interaction with epithelial cells and facilitates both paracellular and transcellular drug transport for improved bioavailability and therapeutic efficiency.[131] In a study, Jamil et al developed gemcitabine (GM) and simvastatin (SV) co-loaded PLGA-based NPs (GM/SV-PNPs) for pancreatic cancer.[132] Cytotoxicity studies in MIA PaCa-2 cells revealed superior efficacy for GM/SV-PNPs (IC_{50}: 2.9 μM) compared to GM (4.6 μM) and SV (21.4 μM) alone. Flow cytometry confirmed higher cellular uptake, while pharmacokinetic studies in Wistar rats showed 1.4- and 1.3-fold improved bioavailability for GM and SV, respectively. Katiyar et al developed rapamycin (RPM) and piperine (PIP) co-loaded PNPs (RPM/PIP-PNPs) for breast cancer.[133] Ex vivo study showed a 5-fold increase in RPM uptake with PIP-PNPs. Cytotoxicity studies in MDA-MB-231 cells revealed enhanced efficacy (IC_{50}: 11.39 μM vs. 20.35 μM for RPM solution). Pharmacokinetics in SD rats revealed 4.8- and 3-fold improvements in bioavailability and plasma half-life, respectively. Similarly, Dian et al fabricated docetaxel (DTX) and curcumin (CUR) co-loaded PMCs (DTX/CUR-PMCs) using TPGS and Soluplus for drug-resistant breast cancer.[134] DTX/CUR-PMCs revealed higher intracellular trafficking and cytotoxicity in MCF-7/Adr cells, achieving a ~55-fold increase in Rhodamine 123 uptake and the highest apoptosis rate (60.97 ± 3.14%) with elevated ROS levels. Pharmacokinetics in SD rats revealed a 5.95-fold increase in half-life, 5.29-fold higher mean retention time, and 5.74-fold enhanced bioavailability (Fig. 6A). In vivo, DTX/CUR-PMCs achieved tumor inhibition comparable to intravenous Taxotere® with improved safety profiles (Fig. 6B & 6C). Overall, co-delivery of multiple drugs via PNPs offers a versatile and effective strategy to improve oral chemotherapy outcomes.

Table 2 summarizes the key outcomes related to oral chemotherapy.

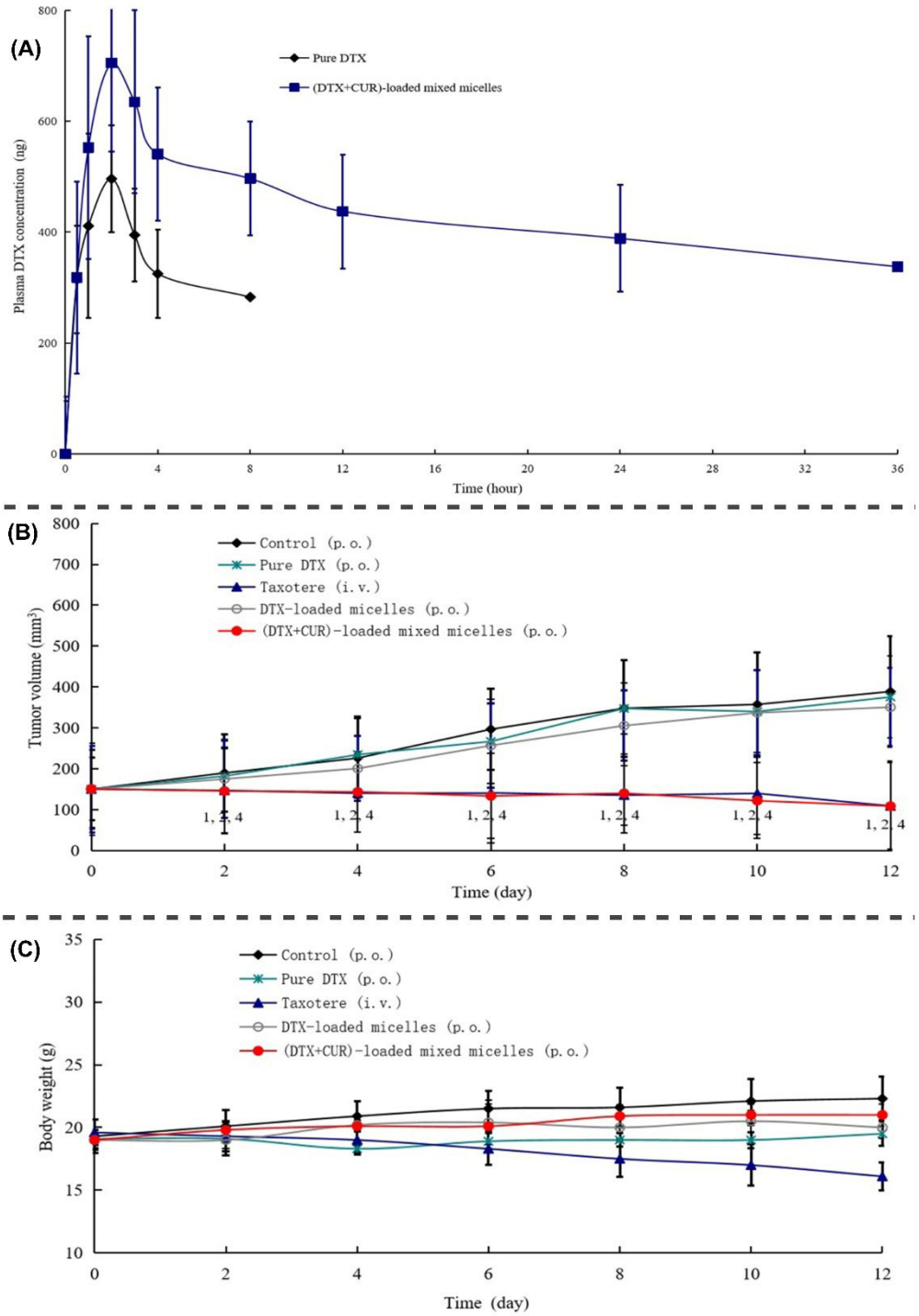

Fig. 6. Image showing (A) pharmacokinetic profiles of DTX/CUR-PMCs and other formulations after oral administration, (B) in vivo therapeutic effects of DTX/CUR-PMCs and other formulations in tumor-bearing mice, and (C) change in body weight of mice of different treatment groups via different routes. Adapted from Dian et al[134] under the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/).

Associated challenges and outlook

PNPs have emerged as a promising solution to circumvent the limitations of conventional chemotherapy and show potential to revolutionize oral drug delivery in oncology. However, despite significant progress, multiple challenges hinder their clinical translation. One critical challenge lies in the complex and hostile GI environment. Harsh acidic gastric conditions, digestive enzymes, and variations in gastric emptying time can compromise the stability and integrity of orally administered PNPs.[135,136] Effective strategies to stabilize PNPs under these conditions are essential to preserve drug efficacy. Surface modifications with PEG or pH-responsive polymers have demonstrated promise in enhancing stability across diverse patient physiologies.[137]

Another major barrier is the low oral bioavailability

Table 2. Different PNPs for improved oral efficacy against various cancers

Drug encapsulated	Main ingredients	Pharmaceutical attributes	Cancer type	Major outcomes	Ref.
Fucoxanthin	Chitosan, alginate, tripolyphosphate	PS: 227 ± 23 nm PDI: 0.31 ± 0.02 ZP: 35.3 ± 1.7 mV EE: 81.2 ± 2.8%	Breast	• Better stability in GI fluids and 3 times improved photostability. • 2.7-fold enhanced bioaccessibility and controlled release profile. • 2.3-fold enhanced cytotoxicity against MDA-MB-231 cells.	107
Curcumin	N-benzyl-N,O-succinyl chitosan	PS: ~94 nm PDI: ~0.085 ZP: −28.3 mV EE: 38.3%	Non-specific	• Better stability in GI fluids and biphasic release profile. • 6-fold increase in intracellular trafficking in HeLa, SiHa, and C33a cells. • 4.7-, 3.6-, and 12.2-fold reduction in IC_{50} against HeLa, SiHa, and C33a cells.	108
Camptothecin	Polycationic cyclodextrin	PS: 135 ± 19 nm PDI: 0.27 ZP: + 40 ± 1 mV EE: 35%	Colorectal	• Better stability and 2.7-folds improved intestinal permeation. • Much better in vitro (CT-26 cells) and in vivo (orthotopic CT-26 colorectal cancer bearing Balb/c mice) anticancer activity. • Much higher accumulation in the colon.	109
Gambogenic acid	Polydopamine, folic acid	PS: 185.3 ± 5.1 nm PDI: 0.203 ± 0.06 ZP: −32.7 ± 1.2 mV EE: 86.88%	Breast	• Better stability in GI fluids and controlled release profiles. • Much higher intracellular trafficking and cytotoxicity against 4T1 cells. • 2.97-fold enhanced oral bioavailability on oral administration in SD rats.	110
Thymoquinone	Chitosan, PLGA	PS: 152.3 ± 5.7 nm PDI: 0.133 ± 0.014 ZP: + 12.2 ± 2.3 mV EE: 77.56 ± 5.48%	Breast	• Better stability in GI fluids and higher mucoadhesion. • 3.15-fold higher intestinal permeation than the free drug. • 1.89- and 1.72-fold reduction in IC_{50} against MDA-MB-231 and MCF-7 cells.	111
Ursolic acid	Chitosan, PLGA	PS: 329.3 ± 37.2 nm PDI: 0.20 ± 0.05 ZP: + 27.8 ± 9.4 mV EE: 97.47 ± 1.3%	Non-specific	• Much better stability in GI fluids, sustained release profile, and mucoadhesion. • High intracellular trafficking and cytotoxicity against B16-F10 HEp-2 cells. • 4.14 and 3.84-fold improved plasma half-life and oral bioavailability.	115
Ferulic acid	Chitosan, PLGA	PS: 242 ± 19 nm PDI: 0.2 ± 0.03 ZP: + 32 ± 5 mV EE: ~50%	Non-specific	• Higher mucoadhesion with biphasic release profiles. • Much higher permeation against Caco-2/HT29-MTX/Raji B co-culture model. • Comparable cytotoxicity against B16-F10 and HeLa cells.	116
Dasatinib	Chitosan, egg lecithin	PS: 179.7 ± 5.42 nm PDI: 0.23 ± 0.01 ZP: + 36.4 ± 0.4 mV EE: 64.65 ± 0.06%	Breast	• 10.27-fold greater mucoadhesion and a 10-fold increase in intestinal permeability. • 4.14-fold reduction in IC50, 3.82-fold increased ROS generation, 2.10-fold enhanced apoptosis against MDA-MB-231 cells. • 5.08-fold improved oral bioavailability and better safety in Balb/c mice.	117
SN38	N'-nonyl-trimethyl chitosan	PS: 203.5 ± 1.75 nm PDI: 0.192 ± 0.07 ZP: 26.25 ± 0.98 mV EE: 73.46 ± 2.56%	Hepatocellular carcinoma	• Stronger mucoadhesion and sustained release profile. • 2.36-fold higher permeation in Caco-2 cells. • 2.99-fold improved oral bioavailability in SD rats. • Significantly greater tumor inhibition in the H22 tumor-bearing mouse model.	118
Paclitaxel	Thiolated chitosan, TPGS	PS: 206.1 ± 3.66 nm PDI: 0.286 ZP: + 24.66 mV EE: 97.56%	Lung	• Improved mucoadhesion, intestinal permeation, and drug absorption by inhibiting the P-gp efflux transporter. • Much better cytotoxicity against A549 cells.	123
Paclitaxel	Chitosan, TPGS, gallic acid	PS: 134.9 ± 10.2 nm PDI: 0.172 ± 0.13 ZP: 34.8 ± 1.3 mV EE: 80 ± 3%	Lung	• Much higher mucoadhesion, permeability, and P-gp efflux inhibition. • 3.80-fold improved oral bioavailability in SD rats. • Significant reduction in tumor volume in A549 lung tumor-bearing mice.	124
Paclitaxel	Chitosan, biotin, TPGS, PEG	PS: 195.9 ± 7.63 nm PDI: 0.08 ZP: −25.4 ± 1.47 mV EE: 55.27 ± 6.62%	Breast	• Better mucoadhesion and 3-fold improved permeation in Caco-2 cells. • Higher intracellular trafficking and cytotoxicity in 4T1 cells. • 8.92-fold improved oral bioavailability in SD rats. • Much higher tumor accumulation and tumor volume reduction in 4T1 tumor-bearing Balb/c.	128

of chemotherapeutic drugs, primarily due to biological barriers such as efflux transporters (e.g., P-gp) and metabolic enzymes like cytochrome P450. Although excipients such as TPGS and Pluronic block copolymers have shown potential in overcoming efflux, further optimization and validation across varied patient groups are necessary to ensure robust and consistent absorption. Variability in intestinal physiology, including pH differences, mucus thickness, and enzyme activity, further complicates drug absorption and residence time. Mucoadhesive polymers such as chitosan have been utilized to enhance GI residence time. However, prolonged retention must be optimized to prevent local irritation or disruption of the epithelial barrier.[138]

Importantly, while reduced systemic toxicity is often emphasized, the potential toxicological effects of PNPs remain a major concern. Long-term exposure risks, organ accumulation, and immunogenicity due to the nature of polymeric materials or surface coatings require careful assessment. Studies have shown that certain biodegradable polymers may trigger immune responses or accumulate in reticuloendothelial organs like the liver and spleen.[139] Dedicated toxicological evaluation using preclinical models is essential, including data on chronic toxicity, immunogenicity, and polymer degradation products. Moreover, potential local toxicities due to high local concentrations of cytotoxic drugs in the GI tract should be assessed, especially in regions with prolonged nanoparticle residence.

The manufacturing and industrial scalability of PNPs also presents considerable obstacles. Production challenges include achieving consistent particle size, high drug loading, and batch-to-batch reproducibility.[140] Techniques such as nanoprecipitation, emulsification, and spray drying have demonstrated feasibility; however, comparative evaluations of these methods in terms of cost-efficiency, drug loading capacity, and process yield are necessary. For instance, while nanoprecipitation offers simplicity and scalability, it may suffer from low drug encapsulation efficiency.[141] Additionally, GMP (Good Manufacturing Practice) compliance, sourcing pharmaceutical-grade excipients, and polymer cost significantly impact commercial translation.[142] From a regulatory perspective, the clinical approval of PNPs requires a comprehensive understanding of their pharmacokinetics, safety, and efficacy. Regulatory agencies such as the U.S. FDA and EMA have issued guidelines on NPs-based drug formulations, emphasizing the need for robust characterization, toxicity data, and evidence of therapeutic benefit over existing standards of care.[143] Regulatory approval pathways often involve additional scrutiny due to the complexity of nanomaterials, including their surface properties, interaction with biological systems, and long-term biocompatibility.[144]

Furthermore, interindividual variability remains a critical factor affecting therapeutic outcomes. Patient-specific factors such as age, gut microbiota composition, nutritional status, comorbidities, and genetic polymorphisms (e.g., in metabolizing enzymes or transporter proteins) can significantly influence the pharmacokinetics and pharmacodynamics.[145] Incorporating precision medicine approaches, such as pharmacogenomics and biomarker-guided therapy, may improve the efficacy and safety profile of PNP-based chemotherapy. Personalized nanomedicine is an emerging strategy wherein PNP formulations are tailored based on individual patient characteristics, such as genetic profile, disease stage, and metabolic status. Such approaches may enhance therapeutic precision, reduce off-target effects, and improve treatment adherence.[146,147] Lastly, there is a need to integrate real-world data and clinical evidence to support the application of oral PNPs in oncology. While numerous preclinical studies exist, few clinical trials have fully validated the long-term safety, tolerability, and effectiveness of PNPs in cancer chemotherapy.[148,149] Examples of marketed products and clinical trials are represented in Table 3.

Conclusion

PNPs have revolutionized the landscape of oral chemotherapy by addressing critical biopharmaceutical challenges that hinder drug stability, absorption, and therapeutic efficacy. Through advanced engineering strategies, PNPs have demonstrated a remarkable ability to improve the bioavailability of anticancer drugs by enhancing GI stability, promoting mucoadhesion, bypassing hepatic first-pass metabolism, and inhibiting efflux transporters. Furthermore, functionalized PNPs enable targeted drug delivery, reduce systemic toxicity, and enhance therapeutic outcomes. Despite these advancements, the clinical translation of PNPs remains challenging due to concerns regarding large-scale production, batch-to-batch variability, and long-term safety. Future research should focus on refining PNPs formulations through personalized medicine approaches and integrating precision targeting strategies to maximize clinical success. By overcoming these challenges, PNPs have the potential to establish a new paradigm in oral chemotherapy.

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Figs. 1-3 were created with BioRender.com (https://biorender.com/).

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Table 3. Clinical trials of different polymer-based NPs for cancer chemotherapy

Name	Company	NPs type	Drug	Application	Status	Clinical Trial No.
Ambraxane	Ambraxis Bioscience	Albumin NPs	Paclitaxel	Metastatic breast cancer	Approved	NCT00748553
Oncaspar	Enzon	Polymer-protein conjugate	L-asparaginase	Leukaemia	Approved	NCT01574274
Genexol-PM	Samyang Biopharmaceuticals	Polymeric micelles	Paclitaxel	Breast cancer	Approved	NCT00912639
NC-6004	NanoCarrier Co., Ltd.	Polymeric micelles	Cisplatin	Pancreatic cancer	Phase III	NCT02043288
NK105	Nippon Kayaku Co.	PNPs	Paclitaxel	Breast and gastric cancer	Phase III	NCT01644890
BIND-014	BIND Therapeutics	PNPs	Docetaxel	Prostate cancer	Phase II	NCT02479178
Docetaxel-PM	Samyang Biopharmaceuticals	Polymeric micelles	Docetaxel	Head and neck cancer	Phase II	NCT02639858
CRLX101	Newlink Genetics Corporation	PNPs	Camptothecin	Renal cancer	Phase II	NCT02187302
CRLX301	Cerulean Pharma Inc.	Polymer-drug conjugate	Docetaxel	Advanced solid tumors	Phase II	NCT02380677
AZD2811	AstraZeneca	PNPs	Aurora B kinase inhibitor	Advanced solid tumors	Phase I	NCT02579226

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Competing Interests
The authors declare that they have no competing interests.

Data Availability Statement
Not applicable to this manuscript.

Ethical Approval
Not applicable.

Review Highlights

What is the current knowledge?

- Oral chemotherapy provides improved patient compliance and convenience compared to intravenous administration.
- Major challenges limiting oral chemotherapy include poor drug solubility, enzymatic degradation, P-gp-mediated efflux, and extensive first-pass metabolism.
- PNPs are a promising strategy to enhance oral bioavailability by improving drug stability, controlled release, and targeted delivery.

What is new here?

- This review highlights the recent advancements in PNPs-based strategies for oral chemotherapy.
- Highlights novel strategies like mucoadhesion, P-gp inhibition, receptor-mediated uptake, and co-delivery of multiple drugs for enhanced therapeutic outcomes with reduced systemic toxicity.
- Identifies key challenges that hinder clinical translation and proposes future directions for optimizing PNPs-based systems for effective oral chemotherapy.

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