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LIPID–POLYMER HYBRID NANOPARTICLES: ADVANCED PLATFORMS FOR ORAL CHEMOTHERAPY AND ENHANCED DRUG BIOAVAILABILITY

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ABSTRACT

Cancer remains a major global health challenge, and although chemotherapy is widely used for its treatment, the oral administration of anticancer drugs is often limited by poor bioavailability. Factors such as low aqueous solubility, limited intestinal permeability, extensive first-pass metabolism, and active efflux mechanisms significantly reduce the amount of drug reaching systemic circulation. These limitations lead to inconsistent therapeutic outcomes and reduced clinical efficacy. Despite these challenges, oral drug delivery is highly desirable due to improved patient compliance, convenience, and reduced healthcare burden. Recent advancements in nanotechnology have introduced lipid–polymer hybrid nanoparticles (LPHNs) as an effective strategy to overcome these barriers. LPHNs combine the structural stability and controlled-release properties of polymeric nanoparticles with the biocompatibility and solubilization capacity of lipid-based systems. Their core–shell architecture enables efficient drug encapsulation, protection from gastrointestinal degradation, enhanced solubility, and improved intestinal absorption. Additionally, LPHNs can facilitate lymphatic transport, thereby reducing first-pass metabolism and enhancing systemic availability. Surface modification of LPHNs with targeting ligands further improves tumor-specific drug delivery while minimizing off-target toxicity. Preclinical studies have demonstrated significant improvements in pharmacokinetic profiles, bioavailability, and therapeutic efficacy of various anticancer agents when delivered through LPHNs. Although challenges such as large-scale production and long-term stability remain, LPHNs represent a promising platform for oral cancer therapy. Continued research in formulation optimization and clinical translation is essential to fully realize their potential in improving anticancer treatment outcomes.

KEYWORDS: Lipid–polymer hybrid nanoparticles (LPHNs), Oral bioavailability, Anticancer drug delivery, Nanocarrier systems, and Targeted chemotherapy.

INTRODUCTION

Cancer continues to be one of the leading causes of mortality worldwide, and chemotherapy remains a cornerstone in its treatment. Despite the effectiveness of many anticancer agents, their oral administration is often hindered by several pharmacokinetic limitations. These include poor aqueous solubility, limited intestinal permeability and substantial first-pass metabolism in the liver and rapid systemic clearance. Collectively, these challenges lead to subtherapeutic plasma drug concentrations and reduced bioavailability, limiting the clinical efficacy of orally administered chemotherapeutics.[1] Oral drug delivery, however, offers substantial advantages, such as improved patient convenience, higher adherence to therapy, reduced need for hospital visits, and better quality of life.[2] To address these limitations, lipid–polymer hybrid nanoparticles (LPHNs) have emerged as an innovative nanocarrier system. These hybrid nanoparticles integrate the mechanical strength and controlled-release properties of polymeric nanoparticles with the biocompatibility and solubilization advantages of lipid-based carriers.[3] Structurally, LPHNs consist of a biodegradable polymeric core that encapsulates the drug, surrounded by a lipid shell that enhances stability, protects the drug from enzymatic degradation, and promotes intestinal absorption.[4] The hybrid architecture of LPHNs allows multiple strategies to improve oral bioavailability. The lipid layer supports lymphatic transport, partially bypassing hepatic first-pass metabolism, while also improving the solubilization of hydrophobic drugs.[5] Simultaneously, the polymeric core safeguards the therapeutic molecule against the harsh gastric environment and enzymatic breakdown, while enabling sustained drug release.[6] Surface modification strategies, including conjugation with ligands or mucoadhesive polymers, further enhance intestinal absorption and tumor-targeted delivery, simultaneously reducing systemic toxicity.[7] Preclinical studies have demonstrated the potential of LPHNs in improving oral bioavailability for various anticancer drugs. For instance, paclitaxel-loaded hybrid nanoparticles exhibited superior absorption and enhanced anticancer efficacy.[8] Similarly, LPHN formulations of doxorubicin and docetaxel showed improved pharmacokinetic profiles, better tumor targeting, and reduced adverse effects compared to conventional formulations.[9,10] Hydrophobic phytochemicals, such as curcumin, also displayed increased solubility, prolonged plasma half-life, and higher therapeutic potential when delivered via LPHNs.[11]

Additionally, LPHNs can be surface-functionalized with ligands targeting receptors overexpressed on cancer cells, such as folate, transferrin, or monoclonal antibodies. This targeted approach improves drug accumulation at tumor sites while minimizing off-target toxicity.[12] Overall, LPHNs represent a promising oral drug delivery platform for anticancer therapeutics, bridging the gap between preclinical research and potential clinical application due to their biocompatibility, biodegradability, and tunable surface properties.[13] Future research should focus on optimizing formulation parameters, elucidating absorption mechanisms, and assessing long-term safety to translate these systems effectively into clinical use.[14]

Anti cancer drugs with limited bioavailability issues

Factors Influencing Oral Bioavailability of Anti-Cancer Drugs

Oral bioavailability refers to the proportion of an orally administered drug that reaches the systemic circulation intact and is available to exert its therapeutic effects. It is a critical pharmacokinetic parameter that reflects how efficiently a drug can achieve its desired plasma concentration and, consequently, its clinical efficacy.[32] For anticancer medications, oral bioavailability is a particularly complex issue because it is influenced by multiple physicochemical, biochemical, and physiological factors. These include the drug's solubility in aqueous environments, chemical stability in the gastrointestinal tract, rate of dissolution, permeability across the intestinal epithelium, susceptibility to

metabolism by intestinal and hepatic enzymes, and the activity of efflux transporters such as P-glycoprotein.[33,34] Many anticancer agents exhibit poor oral bioavailability, often due to the combined effects of low solubility and active efflux mechanisms. P-glycoprotein, an ATP-dependent efflux pump located on the apical membrane of enterocytes, plays a significant role in limiting the intestinal absorption of various chemotherapeutic drugs. By actively transporting the drug back into the intestinal lumen, P-glycoprotein reduces net drug absorption and contributes to interpatient variability in systemic exposure. Drugs such as camptothecin, topotecan, etoposide, teniposide, doxorubicin, certain anthracyclines, and vinca alkaloids are all susceptible to these limitations, resulting in reduced oral bioavailability and inconsistent therapeutic outcomes.[35]

In addition to efflux pumps, drug-metabolizing enzymes in both the intestinal mucosa and liver significantly affect oral bioavailability. For instance, etoposide, a topoisomerase II inhibitor used in treating small-cell lung cancer, lymphomas, and germ-cell tumors, demonstrates a variable oral bioavailability ranging between 47% and 76% [36][37]. This variability arises from metabolism by CYP3A4 enzymes, as well as degradation in the acidic and enzymatically active environment of the stomach and intestines. Similarly, topotecan, a topoisomerase I inhibitor, has an oral bioavailability of approximately 40%, reflecting both poor solubility and substantial first-pass metabolism.[38] Certain targeted therapies also face severe bioavailability challenges due to their physicochemical properties. Exemestane, an irreversible aromatase inhibitor commonly used as a first-line treatment for estrogen receptor-positive breast cancer, exhibits an oral bioavailability of less than 10%. Its limited absorption arises from poor solubility and extensive first-pass metabolism, which restrict its systemic exposure and therapeutic potential.[39] Fluorouracil (5-FU), an antimetabolite widely used to treat solid tumors, presents another challenge. Although both oral and intravenous formulations exist, oral absorption of 5-FU is highly variable and unpredictable, making therapeutic monitoring and dose optimization difficult.[40] Small-molecule tyrosine kinase inhibitors (TKIs) such as pazopanib, vemurafenib, and lapatinib also demonstrate poor oral bioavailability due to their low aqueous solubility. Moreover, co-administration with antacids or acid-suppressing agents can further reduce their absorption. For example, the area under the plasma concentration–time curve (AUC) for drugs like erlotinib, gefitinib, and pazopanib can decrease by nearly 50% when taken alongside antacids, highlighting the importance of gastrointestinal pH in modulating oral drug exposure.[41]

Ibrutinib, a Bruton's tyrosine kinase inhibitor, exhibits an exceptionally low oral bioavailability of approximately 2.7%. This extreme limitation leads to significant interpatient variability in systemic drug levels, complicating dosing strategies and clinical management.[42] The collective challenges posed by these chemotherapeutic agents underscore the urgent need for innovative drug delivery approaches capable of enhancing solubility, stabilizing the drug in the gastrointestinal environment, and overcoming efflux and metabolism-related barriers. Advanced delivery systems such as lipid–polymer hybrid nanoparticles, polymer-coated nanocarriers, and other nanoformulations offer promising solutions to these limitations. By improving solubility, protecting the drug from degradation, facilitating intestinal absorption, and bypassing first-pass metabolism, these delivery platforms can significantly enhance the oral bioavailability of poorly soluble anticancer drugs, reduce interpatient variability, and improve clinical outcomes.

The oral bioavailability of anticancer drugs is influenced by a complex interplay of factors including physicochemical properties, enzymatic metabolism, efflux transport, and gastrointestinal stability. Drugs with poor solubility, high metabolic turnover, or susceptibility to efflux transporters exhibit significantly reduced systemic exposure when administered orally. These limitations not only compromise therapeutic efficacy but also contribute to interpatient

variability, highlighting the critical need for advanced delivery strategies to improve the oral administration of anticancer therapies. The development of such technologies is essential for achieving more predictable, effective, and patient-friendly chemotherapeutic regimens.

Strategies for Oral Formulation to Enhance Bioavailability

Developing oral formulations of anticancer drugs poses significant challenges due to multiple physiological and biochemical barriers that limit absorption and systemic exposure. Many chemotherapeutic agents exhibit poor water solubility, reducing their dissolution in gastrointestinal fluids and decreasing the fraction available for absorption. Additionally, the gastrointestinal tract presents a hostile environment, including acidic gastric conditions and digestive enzymes, which can degrade sensitive drugs before they reach systemic circulation. First-pass metabolism, primarily via hepatic cytochrome P450 enzymes such as CYP3A4, further decreases the amount of active drug entering the bloodstream. Efflux transporters like P-glycoprotein actively pump certain drugs back into the intestinal lumen, while poor epithelial permeability also restricts absorption, especially for hydrophilic or high-molecular-weight molecules.[43] Nanotechnology-based oral delivery systems have emerged as an effective strategy to overcome these barriers. Nanoscale carriers, such as lipid–polymer hybrid nanoparticles (LPHNs), solid lipid nanoparticles (SLNs), polymeric micelles, and nanoemulsions, can encapsulate anticancer drugs, protecting them from enzymatic degradation and gastric acidity while enhancing solubility and intestinal transport.[44,45] These carriers can also reduce drug recognition by efflux transporters, prevent premature release, and stabilize drugs in gastrointestinal fluids. Beyond protection, nanocarriers provide controlled and sustained release, maintaining therapeutic plasma concentrations. Surface functionalization with targeting ligands enables selective delivery to tumor tissues, increasing efficacy and minimizing systemic toxicity. LPHNs, for example, utilize a polymeric core for stability and a lipid shell to enhance solubilization, intestinal absorption, and lymphatic transport, effectively bypassing first-pass metabolism. SLNs and micelles improve solubility and epithelial uptake, while nanoemulsions enhance dissolution and absorption due to their ultra-small droplet size.[46]

Overall, nanotechnology-enabled oral formulations offer a comprehensive approach to overcome solubility, stability, metabolism, and permeability challenges, improving bioavailability, reducing systemic side effects, and enhancing therapeutic outcomes and patient compliance.

Lipid–Polymer Hybrid Nanoparticles (LPHNs)

Basic Formulation Concept

Lipid–polymer hybrid nanoparticles (LPHNs) represent a cutting-edge strategy in nanomedicine for enhancing the oral delivery of poorly water-soluble anticancer drugs. These hybrid nanoparticles integrate the benefits of both lipid-based and polymeric drug delivery systems, forming a multifunctional carrier capable of addressing several limitations of conventional oral chemotherapy. Structurally, LPHNs are composed of three distinct yet synergistic layers: a lipid monolayer surrounding the polymeric core, a hydrophilic polymer coating over the lipid shell, and a biodegradable hydrophobic polymeric core that encapsulates the therapeutic agent (Figure 1).[47,48] The lipid layer plays a central role in ensuring compatibility with biological membranes, enhancing particle stability in physiological environments, and providing a protective shield against harsh gastrointestinal (GI) conditions, including enzymatic degradation and acidic pH. Phospholipids, the primary lipid component, also facilitate the penetration of nanoparticles through the intestinal epithelium due to their structural similarity to biological membranes. Commonly used lipids include zwitterionic,

cationic, anionic, and neutral phospholipids such as lecithin, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, and 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine. Additional lipids such as cholesterol, myristic acid, and PEG-lipid conjugates are incorporated to modulate particle stability, circulation time, and drug release profiles.[49,50]

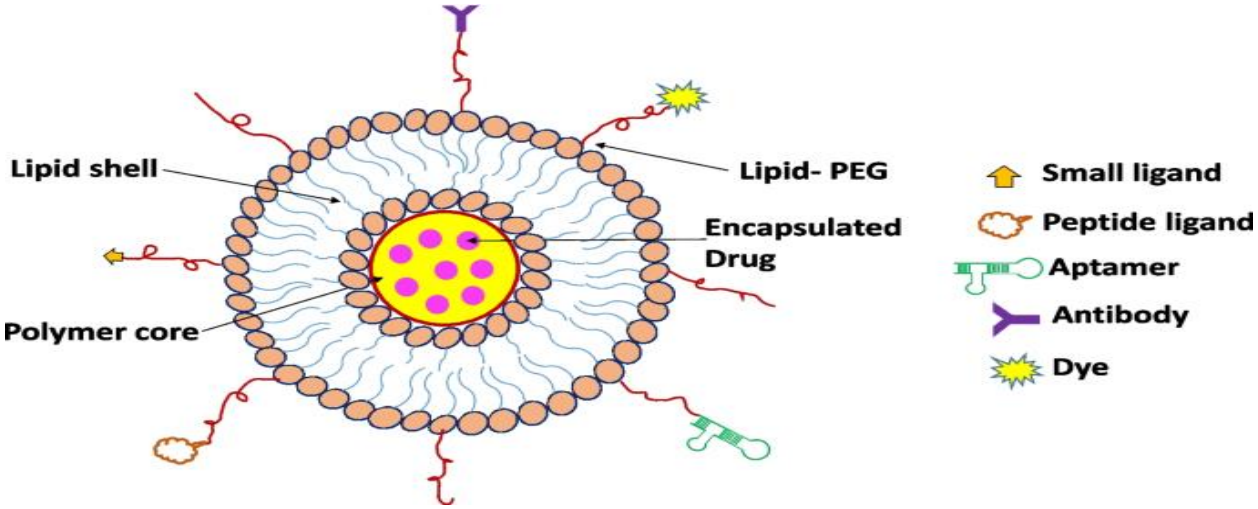

Fig. 1: Structure of Lipid polymer hybrid nanoparticle.

The hydrophilic polymer shell surrounding the lipid layer enhances colloidal stability, prevents aggregation, and prolongs circulation by reducing protein adsorption and RES clearance. It also improves mucoadhesion, increasing intestinal residence and drug absorption. The polymeric core, typically PLGA or PCL, encapsulates hydrophobic drugs and protects them from early degradation; PLGA offers tunable degradation and regulatory approval, while PCL provides sustained release.[47,48] Formulation factors, including ionic strength, lipid charge, vesicle size, and lipid-to-polymer ratio, govern particle size, zeta potential, and encapsulation efficiency.[51–53] LPHNs can be prepared via two-step assembly or single-step nanoprecipitation and functionalized with targeting ligands for selective drug delivery.[29,53]

Preparation Methods

Single-Step Approach

The single-step preparation method is highly favored for its simplicity, reproducibility, and ability to produce uniform lipid-polymer nanoparticles. In this process, lipids and PEG-lipid conjugates are dissolved in an aqueous medium, while hydrophobic polymers and the therapeutic drug are solubilized in a water-miscible organic solvent, such as acetonitrile. To facilitate complete dissolution of lipid molecules, a small portion of the organic solvent may be added to the aqueous solution. The polymer-drug solution is gradually introduced into the lipid-containing aqueous phase, inducing rapid diffusion of the organic solvent and precipitation of polymer nanoparticles. Hydrophobic interactions drive the self-assembly of the lipid monolayer around the polymeric core, with PEG chains extending into the aqueous medium to provide steric stabilization (Figure 2A).[54,55] During the self-assembly process, the hydrophobic regions of the lipid molecules embed into the polymer core, stabilizing the encapsulated drug, while the hydrophilic portions face outward to interact with the surrounding biological environment. This technique is particularly advantageous for producing LPHNs with controlled particle size, narrow size distribution, and high encapsulation efficiency. It is also economically viable and scalable for potential clinical translation.[56] As an example, folic acid-functionalized palbociclib-loaded LPHNs prepared using this method demonstrated a particle size of 143.36 ± 5.24 nm, a zeta

potential of −16.84 ± 0.27 mV, and an encapsulation efficiency of 93.12 ± 0.43%. These nanoparticles significantly enhanced cytotoxicity against breast cancer cell lines, reducing IC50 values approximately nine- to eleven-fold compared to free palbociclib in MCF-7 and MDA-MB-231 cells at 48 hours.[57]

Classical Two-Step Approach

The classical two-step approach is often employed for small-scale preparation of LPHNs. Initially, polymeric nanoparticles are generated via nanoprecipitation, solvent evaporation, or high-pressure homogenization. Simultaneously, lipid vesicles are prepared either by forming thin lipid films in organic solvents followed by hydration or by other vesicle-forming methods. The preformed polymeric nanoparticles are then combined with the lipid vesicles to form hybrid nanoparticles. Differential centrifugation is commonly used to remove unencapsulated lipids and separate free nanoparticles, ensuring a uniform product (Figure 2B).[58,59]

Modern Two-Step Approach

For large-scale production, advanced two-step methods employ technologies such as spray drying and soft lithography. In spray drying, polymeric nanoparticles are suspended in an organic solvent containing lipids, which is then converted into a dry powder through controlled spray processes. Soft lithography involves coating a polymer solution onto a substrate (e.g., polyethylene terephthalate), molding nanoparticles in microfabricated templates, and then coating with lipids. Freeze-drying finalizes the nanoparticles, producing uniform, needle-shaped particles approximately 200 nm in size with favorable surface charge.[60–63]

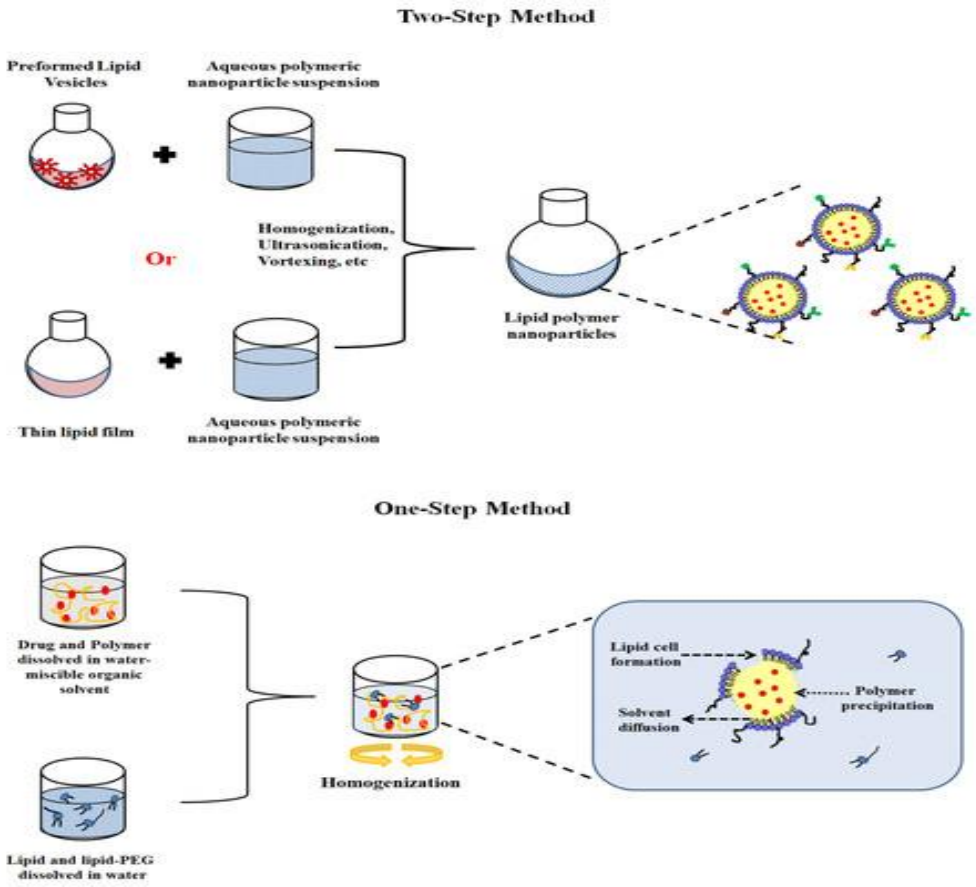

Fig. 2: Self-Assembled Nanoprecipitation Method.

The self-assembled nanoprecipitation method enables the production of LPHNs smaller than 100 nm with high encapsulation efficiency. In this technique, the polymeric core and lipid shell are prepared separately and then combined to form a hybrid structure. Hydrophobic interactions drive the self-assembly of the lipid monolayer around the polymeric core, providing structural stability and controlled release properties. This method has been effectively employed for encapsulating vincristine sulfate with dextran sulfate to improve oral bioavailability.[64,65].

Single Emulsification Solvent Evaporation

In this technique, the polymer and drug are dissolved in an organic solvent (oil phase) and gradually added to a lipid-water dispersion under ultrasonic stirring, forming an oil-in-water emulsion. The organic solvent is removed via rotary evaporation, allowing lipid-PEG conjugates to self-assemble around the polymer core. This method is particularly suitable for hydrophobic drugs and nucleic acids, providing high encapsulation efficiency and stable nanoparticles.[18,66]

Dual Emulsification Solvent Evaporation

The double emulsification (water/oil/water) method is ideal for encapsulating hydrophilic and hydrophobic drugs within core-shell LPHNs. Initially, the drug is dispersed in an aqueous polymer solution, which is emulsified with an organic lipid-containing phase to form a primary (w/o) emulsion. This is then emulsified in a secondary aqueous phase to form a (w/o/w) emulsion, followed by solvent evaporation to generate the final nanoparticles. This method ensures high drug loading and encapsulation efficiency and is widely used for chemotherapy drugs and nucleic acids.[61,67]

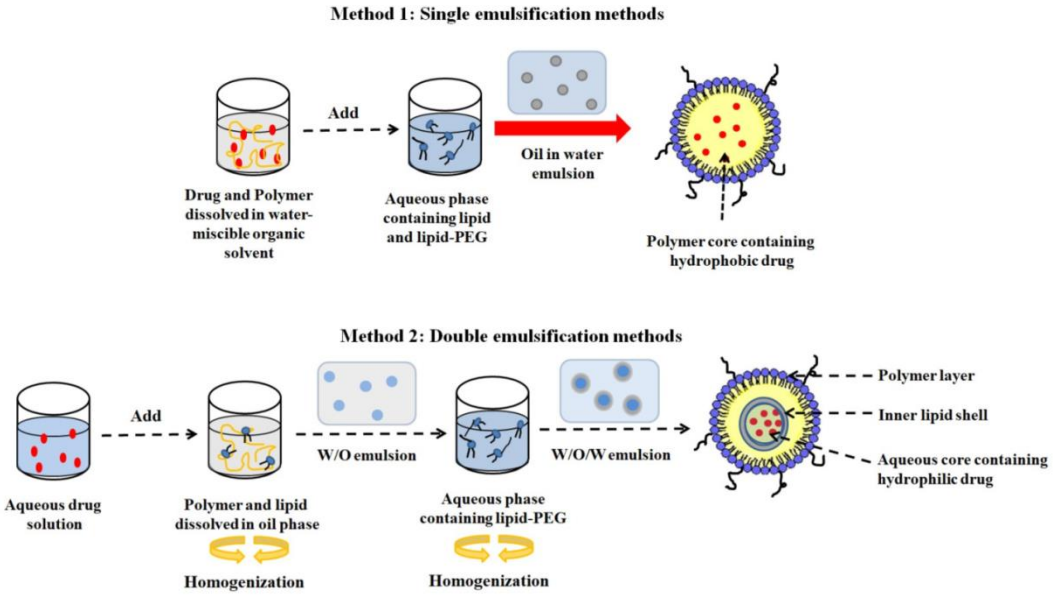

Fig 3: Preparation of LPHNs using the emulsification solvent evaporation technique.

Characterization of LPHNs involves evaluation of particle size, morphology, surface charge, drug loading, release kinetics, and biocompatibility. Particle size and zeta potential are typically measured using dynamic light scattering (DLS), while morphology is examined via electron microscopy. Drug loading (DL) and encapsulation efficiency (EE) are quantified using analytical techniques such as high-performance liquid chromatography (HPLC) or spectrophotometry. DL represents the proportion of drug loaded per unit weight of nanoparticles, whereas EE reflects the percentage of the initial drug successfully entrapped within the nanoparticles. High DL and EE are critical indicators of formulation efficiency. For example, paclitaxel-loaded LPHNs showed a DL of 27.71% and an EE of

92.24%, demonstrating their ability to effectively encapsulate hydrophobic anticancer drugs.[19] LPHNs loaded with curcumin, docetaxel, 5-FU, and other chemotherapeutic agents have reported EE values ranging from 20% to 96%, depending on the composition, preparation method, and nature of the drug.[69–77]

Drug Release Mechanisms in LPHNs

Lipid–polymer hybrid nanoparticles (LPHNs) release drugs primarily through polymer degradation and diffusion processes. Hydrophobic agents can either be encapsulated within the polymer core or chemically linked to the polymer chains. The lipid monolayer surrounding the core acts as a protective barrier, reducing water penetration, slowing polymer breakdown, and preventing early drug leakage.[78] The release profile is influenced by factors such as polymer composition, particle size, and environmental conditions. Some LPHNs are designed to respond to external stimuli, such as magnetic fields, allowing controlled and targeted drug release. For example, camptothecin-loaded magnetic LPHNs have demonstrated long-term stability and stimulus-responsive release when exposed to remote radiofrequency magnetic fields. Drug release kinetics are typically studied in vitro using dialysis-based methods, with drug concentrations quantified over time using HPLC or mass spectrometry.[79]

Passive Targeting

Passive targeting utilizes the inherent differences between tumor and normal tissues to promote selective drug accumulation. Tumor blood vessels are often irregular, highly permeable, and disorganized, facilitating the extravasation of nanoparticles into the tumor interstitium. Tumor vasculature typically contains endothelial gaps of 400–600 nm, allowing nanoparticles of 10–500 nm to penetrate efficiently. Additionally, impaired lymphatic drainage in tumors limits the clearance of nanoparticles, resulting in prolonged retention, a phenomenon known as the enhanced permeability and retention (EPR) effect. Features such as abnormal blood flow, hypervascular structures, and high angiogenesis rates further enhance nanoparticle accumulation.[100]

Optimizing nanoparticle properties, including size, surface charge, and hydrophilic coatings like PEG, can significantly improve passive targeting by prolonging circulation time and reducing recognition by the reticuloendothelial system. Clinically, PEGylated liposomal doxorubicin (Doxil) and poly(ethylene oxide)-modified nanoparticles have demonstrated enhanced tumor accumulation and retention. Passive targeting also provides a foundation for active targeting strategies, where ligands on nanoparticle surfaces recognize tumor-specific receptors, enabling precise intracellular delivery and enhanced therapeutic outcomes.[101,102]

Mechanistic Insights into Passive Targeting

Passive targeting efficiency depends on both nanoparticle design and tumor microenvironment characteristics. Tumors often have irregular blood vessels, uneven blood flow, and leaky vasculature due to rapid cell growth, allowing nanoparticles to accumulate in the tumor tissue. This accumulation is enhanced by the enhanced permeability and retention (EPR) effect, which is influenced by nanoparticle surface properties. Hydrophilic coatings like polyethylene glycol (PEG) reduce immune clearance, prolong circulation, and increase tumor accumulation. Nanoparticle size and charge are also critical; particles smaller than 200 nm penetrate tumor tissue effectively, while slightly positive charges enhance interactions with negatively charged extracellular matrix components, improving retention and uptake.[103,104,105]

Integration with Active Targeting

Passive targeting provides initial localization, but functionalizing nanoparticles with ligands such as antibodies, folate, or peptides enables receptor-mediated uptake into tumor cells. Combining passive and active targeting enhances intracellular drug delivery, maximizes therapeutic efficacy, and minimizes systemic toxicity, offering a precise and effective strategy for cancer treatment.[105,106,107]

Lipid-based nanoparticles (LBNPs) target tumors through passive and active mechanisms. Passive targeting exploits leaky tumor vessels and poor lymphatic drainage for selective accumulation, enhanced by optimized size, charge, and hydrophilic coatings. Active targeting involves attaching ligands that recognize tumor-specific receptors, promoting receptor-mediated uptake. Combining these strategies improves intracellular drug delivery, therapeutic efficacy, pharmacokinetics, and reduces off-target toxicity, offering a precise and efficient approach for cancer treatment.

Lipid-Based Nanoparticles (LBNPs) for Drug Encapsulation

Lipid-based nanoparticles (LBNPs) have emerged as highly versatile drug delivery platforms due to their ability to improve the solubility, stability, and bioavailability of therapeutic agents. These nanoparticles consist of a lipid core, which can encapsulate drugs, and often a polymeric or surfactant coating, which stabilizes the particle and allows controlled release. The ability to tailor LBNPs for specific drugs makes them particularly suitable for both hydrophilic (water-soluble) and hydrophobic (water-insoluble) compounds.[108,109,110] The encapsulation of drugs into LBNPs provides several advantages. For hydrophilic drugs, it helps prevent rapid diffusion and loss into surrounding fluids, thereby maintaining therapeutic concentrations. For hydrophobic drugs, which typically suffer from poor solubility and limited bioavailability, LBNPs provide a protective lipid matrix that enhances absorption, prolongs circulation, and allows controlled release. In addition, LBNPs can be engineered to target specific tissues or cells, improving the drug's therapeutic index while reducing systemic toxicity.[111,112]

Encapsulation of Water-Soluble Drugs

Hydrophilic drugs, due to their strong affinity for water, are particularly challenging to encapsulate within lipid-based nanoparticles. Their high solubility often leads to rapid leakage from the nanoparticle core, limiting the ability to achieve effective loading and controlled release.[113,114] To overcome these challenges, researchers have developed specialized techniques such as microemulsions and double emulsions, which provide a means of trapping water-soluble drugs within a stable lipid matrix. Similarly, water-in-oil-in-water (W/O/W) double emulsions are frequently employed for encapsulating hydrophilic drugs. In this method, the drug is first dispersed in the internal aqueous phase, which is emulsified within a lipid or oil phase to form a primary W/O emulsion.[122,123] This emulsion is then further dispersed into a secondary aqueous phase, producing a stable double emulsion that traps the hydrophilic drug within the lipid layer. This approach is particularly advantageous for drugs that require sustained release, as the encapsulation reduces premature drug leakage and maintains therapeutic concentrations over time. Hydrophilic drug-loaded LBNPs have found applications in multiple therapeutic areas, including antimicrobial therapy, cancer treatment, and immunotherapy. By enabling controlled drug release, these nanoparticles can maintain effective drug concentrations in target tissues, reduce dosing frequency, and minimize systemic toxicity.[129]

Encapsulation of Water-Insoluble Drugs

Hydrophobic drugs account for a large proportion of both approved pharmaceuticals (around 40%) and drugs currently under development (up to 90%). Due to their poor water solubility, these drugs often suffer from low oral

bioavailability, poor absorption, and limited therapeutic efficacy. LBNPs provide a lipid matrix that protects these drugs from degradation, enhances solubility, and allows controlled release, making them an ideal delivery platform for hydrophobic compounds. One prominent example is the chemotherapeutic agent docetaxel (DTX), which is highly hydrophobic and requires solubilization for effective delivery. LBNPs formulated with DTX achieved an encapsulation efficiency of 86% and a drug loading of 2%, with a particle size of approximately 128 nm and a polydispersity index (PDI) of 0.2. These nanoparticles exhibited controlled drug release and demonstrated exceptional stability for up to 120 days, indicating their suitability for both storage and therapeutic applications. The sustained release profile also reduces the frequency of administration, enhancing patient compliance. In addition to conventional chemotherapeutics, LBNPs have been applied in theranostics, combining therapeutic and diagnostic functions. For example, IR-780 iodide, a near-infrared imaging agent with photothermal properties, was encapsulated in c(RGDyK)-conjugated LBNPs using a solvent-diffusion method. These nanoparticles achieved high encapsulation efficiency (85.34%) and demonstrated effective cytotoxicity against tumor cells with minimal side effects in animal models. This dual functionality enables simultaneous imaging and therapy, improving treatment monitoring and efficacy.[130] The versatility of LBNPs allows them to encapsulate a wide range of drugs with diverse physicochemical properties, making them highly adaptable for multiple clinical applications. Hydrophilic drugs benefit from controlled release and protection against rapid diffusion, while hydrophobic drugs gain improved solubility, extended circulation, and sustained therapeutic action. By modifying the lipid composition, particle size, and surface properties, LBNPs can be tailored to optimize drug loading, release kinetics, and tissue targeting.

Advantages and Applications

Encapsulation within LBNPs provides several key benefits

1. **Enhanced Bioavailability:** Hydrophobic drugs that normally exhibit poor solubility in biological fluids can be effectively solubilized, improving absorption and systemic exposure.
2. **Controlled Release:** Both hydrophilic and hydrophobic drugs can be formulated to release over extended periods, reducing dosing frequency and minimizing side effects.
3. Targeted Delivery: Surface modification of LBNPs with ligands, antibodies, or polymers allows for selective targeting of tumor cells or specific tissues, improving therapeutic index.
4. **Protection from Degradation:** The lipid matrix protects encapsulated drugs from chemical or enzymatic degradation in biological fluids, ensuring that more active drug reaches the target site.
5. **Versatility:** LBNPs can accommodate a wide range of drug types, including antibiotics, anticancer agents, photothermal agents, and imaging dyes.

Preclinical studies have demonstrated that LBNPs improve drug accumulation in target tissues while reducing systemic toxicity. For example, docetaxel- and cisplatin-loaded LBNPs have shown enhanced anticancer efficacy compared to free drug solutions, while IR-780-loaded LBNPs enabled both imaging and photothermal therapy with minimal side effects.

In conclusion, LBNPs provide a robust platform for drug delivery, capable of addressing the solubility, stability, and bioavailability challenges of both hydrophilic and hydrophobic therapeutic agents. Their ability to control drug release, improve targeting, and maintain long-term stability makes them highly suitable for clinical applications, particularly in oncology and infectious disease therapy. Continuous innovation in formulation techniques, such as microemulsion,

double emulsion, and solvent-diffusion methods, ensures that LBNPs remain a promising approach for enhancing the therapeutic potential of a wide array of drugs.

Oral Bioavailability Enhancement (Preclinical Studies)

LPHNs improve oral bioavailability through multiple mechanisms, including protection from GI degradation, enhanced solubility of hydrophobic drugs, improved intestinal absorption, and controlled release. Paclitaxel-loaded LPHNs increased oral bioavailability from 4.75% (conventional formulation) to 21.95%, and incorporation of CYP450 and P-gp inhibitors further enhanced it to 42.6%, representing an almost eight-fold improvement.[105]

Surface functionalization with ligands, such as folic acid, enables targeted delivery to cancer cells. Mucoadhesive properties extend intestinal residence time and facilitate enhanced absorption through interactions with mucin, a primary component of intestinal mucus. Cabazitaxel-loaded LPHNs increased bioavailability seven-fold compared with free drug [108]. Similarly, tamoxifen-loaded LPHNs exhibited over two-fold increased bioavailability, extended half-life, and prolonged mean residence time, highlighting the benefits of controlled and sustained drug release [86,96,109]. Positively charged LPHNs exhibit strong mucoadhesion due to electrostatic interactions with negatively charged mucins, allowing for better penetration of the intestinal mucus barrier and improved oral absorption, as observed with paclitaxel-loaded LPHNs.[105,110,111]

Lipid–Polymer Hybrid Nanoparticles in Anticancer Therapy

Lipid–polymer hybrid nanoparticles (LPHNs) have emerged as a cutting-edge platform in anticancer drug delivery, offering solutions to several limitations associated with conventional chemotherapeutics. Oral administration of chemotherapeutic agents is increasingly preferred due to its convenience, enabling patients to manage therapy at home and reducing the need for hospital visits. However, oral chemotherapy is often hindered by low and variable bioavailability, which can reduce treatment efficacy and introduce inconsistencies in drug absorption among patients. LPHNs address these challenges by combining the benefits of both lipid-based and polymer-based nanocarriers, enhancing drug solubility, stability, and systemic availability. The structural versatility of LPHNs allows for the co-encapsulation of multiple chemotherapeutic agents, improving synergistic therapeutic effects while overcoming solubility and cellular uptake limitations. For instance, combinations of drugs such as gemcitabine with paclitaxel, cisplatin with paclitaxel, and doxorubicin with camptothecin have shown increased cytotoxicity against pancreatic, ovarian, and breast cancer cell lines when delivered via LPHNs compared to free drug formulations. This enhanced activity is largely attributed to improved cellular internalization through endocytosis and the ability to bypass passive diffusion barriers. LPHNs are also effective in enhancing the delivery of poorly soluble bioactive compounds, such as plant-derived phytochemicals. Thymoquinone (THQ), which has limited clinical utility due to low water solubility, demonstrated a substantial increase in oral bioavailability—approximately 4.7-fold—when encapsulated in optimized LPHNs. These nanoparticles maintain structural integrity under gastrointestinal conditions, provide a controlled biphasic release pattern, and ensure prolonged systemic exposure. Pharmacokinetic studies further support the superiority of LPHNs over conventional drug formulations. Paclitaxel-loaded LPHNs, for example, exhibited a threefold increase in maximum plasma concentration and significantly higher tissue exposure compared to free paclitaxel. Additionally, nanoparticle-mediated delivery prolonged drug circulation, reduced rapid clearance, and facilitated targeted delivery. Functionalization with ligands such as folate or hyaluronic acid enhances tumor specificity, increases accumulation at the tumor site, and reduces off-target toxicity. Dual-drug encapsulation strategies

further potentiate antitumor effects, as evidenced by enhanced apoptosis and cancer cell death in preclinical studies. Overall, LPHNs provide a multifaceted strategy for improving anticancer therapy, combining enhanced oral bioavailability, protection from gastrointestinal degradation, sustained drug release, targeted delivery, and superior pharmacokinetics. These attributes underscore the potential of LPHNs as a promising platform for both oral and systemic administration of chemotherapeutic agents. Ongoing research into scale-up, long-term safety, and clinical translation is essential to fully exploit the therapeutic potential of this innovative nanocarrier system.

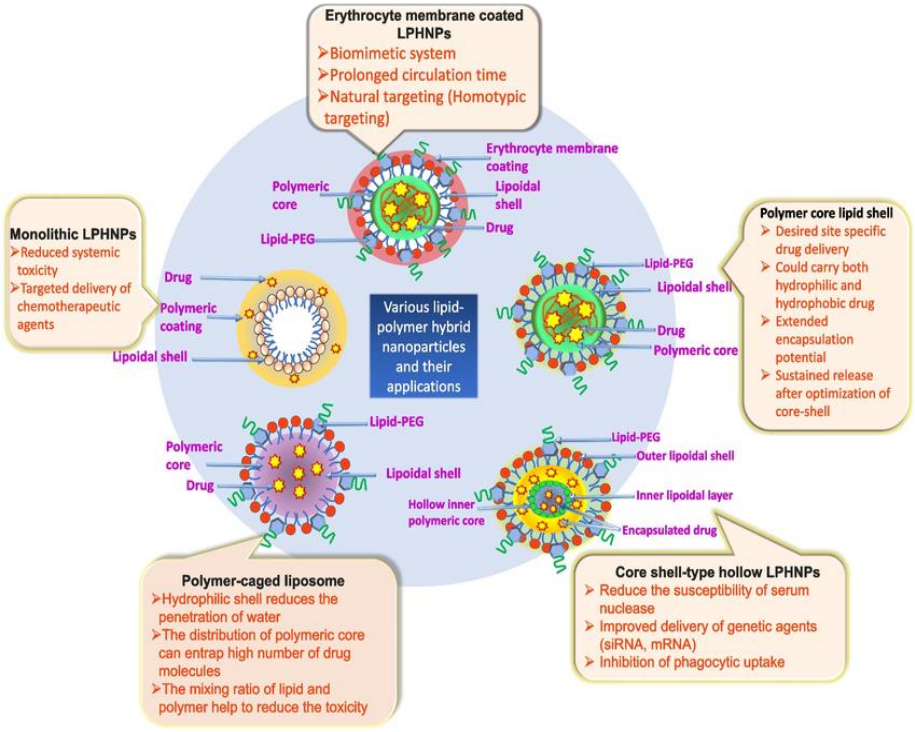

Fig 4: Schematic diagram showing different classes of lipid–polymer hybrid nanoparticles (LPHNPs) and their applications in drug delivery.

Limitations and Future Perspectives

While LPHNs have demonstrated remarkable potential in anticancer drug delivery, several challenges must be addressed to facilitate their clinical adoption. A major limitation lies in the technological precision required to ensure uniformity and reproducibility, especially during scale-up for large-scale production. Variability in particle size, surface charge, and functionalization can affect biodistribution, cellular uptake, and overall therapeutic efficacy. Achieving a consistent formulation is particularly critical for navigating multiple biological barriers, such as the gastrointestinal epithelium or lung tissue, which can limit nanoparticle penetration and drug delivery efficiency.[122] Drug loading capacity also remains a key constraint. The finite volume within each nanoparticle restricts the amount of drug that can be incorporated, potentially limiting effectiveness in cases of high tumor burden or for drugs requiring high systemic concentrations.[77] Furthermore, stability issues such as nanoparticle aggregation, premature drug leakage, or polymer degradation can compromise the integrity of LPHNs and diminish their delivery performance.[123,124] The targeting ability of LPHNs is influenced by particle size, surface chemistry, and ligand availability, which can limit selective accumulation at tumor sites.[125] Scaling up LPHN production for clinical use presents additional challenges. Manufacturing processes must maintain batch-to-batch consistency, particle uniformity, and encapsulation efficiency

while remaining economically feasible. These factors can impact the accessibility and widespread adoption of LPHNs in clinical oncology.[126]

Despite these challenges, numerous opportunities exist to optimize and expand LPHN applications. Advanced techniques, such as covalent drug conjugation, prodrug incorporation, and multistage delivery systems, can increase drug loading capacity while maintaining nanoparticle stability.[123] The development of novel polymers and protective coatings, including polymer-coated LPHNs, can enhance stability, prolong circulation time, and improve overall pharmacokinetic performance. Targeting efficiency can be enhanced through ligand-functionalization, stimuli-responsive surface coatings, and biomimetic approaches, enabling site-specific drug release and reducing off-target effects.[129] Modern imaging techniques, including fluorescence labeling and magnetic resonance imaging (MRI), provide real-time tracking of nanoparticles, facilitating precise delivery and personalized treatment strategies.[130,131] LPHNs also hold promise for combination therapies, including co-delivery with gene therapy, immunotherapy, or other novel anticancer modalities, potentially amplifying therapeutic efficacy.[131] Additionally, research is ongoing to develop scalable, cost-effective manufacturing protocols to enable broad clinical translation.[132]

Table 1: Applications of LBNPs in cancer therapy.

Cancer Type	LBNP Type	Drug/Compound Encapsulated	Targeting / Mechanism	Key Outcomes / Notes	References / Examples
Gastric Cancer (GC)	Liposomes, SLNs	SATB1 siRNA, RGD peptides, CD44 antibodies	Targeted delivery to CD44+ gastric cancer stem cells; improved tumor-specific accumulation	Enhanced gene silencing, reduced off-target liver accumulation; improved cytotoxicity in SGC7901 and MKN-45P cells	Preclinical studies; improved SATB1 silencing
Esophageal Cancer (EC)	188Re-labeled Liposomes	Radiotherapeutics	Combined with radiotherapy; enhanced retention in tumor tissue	Increased efficacy of radiation therapy; improved tumor targeting in BE-3 models	Preclinical studies
Pancreatic Cancer (PC)	Chitosan-coated LBNPs, Liposomes, NEs	Curcumin, Gemcitabine, Paclitaxel, PEG-EF24	Improved intracellular uptake, bypassing dense stroma; enhanced synergistic cytotoxicity	3-fold growth inhibition in PANC-1; improved activity in gemcitabine-resistant cells; improved in vivo tumor suppression	Phase III trial: nanoliposomal irinotecan (nal-IRI)
Liver Cancer (LC)	NLCs, SLNs	Paclitaxel, 5-FU, Sorafenib, SPIONs	Enhanced hepatic accumulation; protection from enzymatic degradation; dual therapy with imaging	Increased plasma stability; improved drug bioavailability; dual therapeutic and diagnostic functionality	Preclinical studies
Nervous System (Glioblastoma)	Non-PEGylated Liposomes, Liposomal IRI	Doxorubicin (DOX), Irinotecan	Crosses blood–brain barrier; improved tumor-specific accumulation	Increased drug delivery to high-grade gliomas; reduced systemic toxicity; phase I trials	Myocet®; nal-IRI clinical studies
Lung Cancer (LuC)	NEs, Liposomes	Docetaxel, Gemcitabine, PTX	Ligand-targeted delivery (glucose receptor); co-encapsulation	Selective cytotoxicity to tumor cells; improved intracellular accumulation;	Phase III clinical trial: PTX liposomal formulations

				synergistic effects (3:1 GEM/PTX)	
Breast Cancer (BreC)	NEs, NLCs, PEGylated Liposomes	Doxorubicin, Bromotetrandrine, Lapatinib	Overcomes P-gp resistance; targeted HER2 delivery	Enhanced tumor uptake; reduced GI and cardiac toxicity; improved therapeutic efficacy in resistant MCF-7/ADR cells	PEG-DOX + lapatinib (phase Ib); preclinical xenografts
Prostate Cancer (PrC)	NEs, Liposomes, SLNs	Docetaxel, Omega-3 Taxoids, Oleuropein, Gold nanorods	Folate-targeted, multifunctional nanoparticles; laser-assisted therapy	12-fold IC50 reduction; significant tumor volume reduction; enhanced apoptosis and survival	Preclinical studies: 22Rv1, PC-3 cells

CONCLUSION

In conclusion, the effectiveness of orally administered anticancer drugs is often limited by several biological and physicochemical barriers, including inadequate solubility, poor intestinal absorption, metabolic degradation, and active drug efflux. These factors collectively reduce the amount of drug reaching systemic circulation, leading to inconsistent therapeutic outcomes. Although oral chemotherapy provides significant benefits in terms of patient comfort and treatment adherence, these limitations necessitate the development of more efficient drug delivery systems. Lipid–polymer hybrid nanoparticles offer a promising approach to overcome these challenges by combining the advantages of lipid-based carriers and polymeric systems within a single structure. Their design allows for improved drug stability in the gastrointestinal environment, enhanced solubilization of poorly water-soluble drugs, and controlled release profiles.

In addition, these nanoparticles can promote better absorption and reduce metabolic losses, thereby increasing overall drug availability. The potential of these systems is further strengthened by their ability to incorporate targeting features, which help concentrate the drug at tumor sites while minimizing effects on healthy tissues. Their adaptability in carrying different types of therapeutic agents, including both hydrophilic and hydrophobic compounds, also makes them suitable for a wide range of anticancer applications. Despite encouraging findings from experimental studies, certain challenges such as large-scale production, long-term stability, and consistency between batches still need to be addressed. Continued research and technological advancements will be essential to translate these systems from laboratory studies to clinical practice. Overall, lipid–polymer hybrid nanoparticles represent a forward-looking strategy in oral cancer therapy, with the potential to improve treatment effectiveness, reduce side effects, and enhance patient quality of life.

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