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Recent Advances and Challenges in Lipid-Polymer Hybrid Nanocarriers for Oral Drug Delivery

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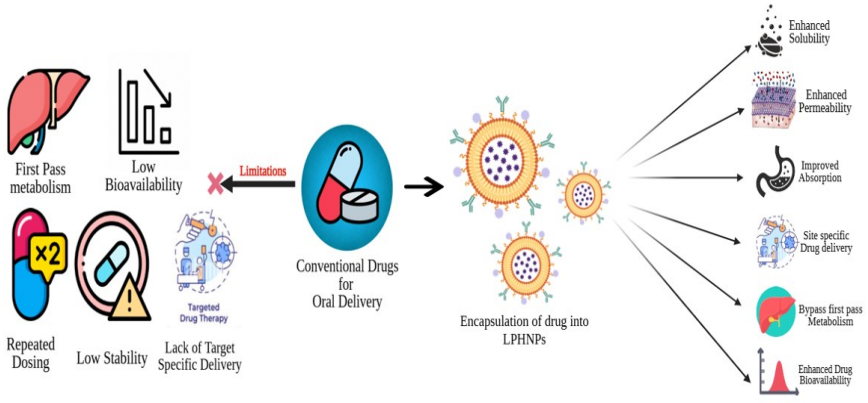
ABSTRACT

Lipid-polymer hybrid nanocarriers (LPHNPs) have gained significant attention in oral-drug delivery due to their ability to combine polymeric nanoparticles' structural integrity with the biocompatibility and enhanced permeability of lipid-based carriers. These hybrid nanocarriers offer improved drug stability, controlled release, and enhanced bioavailability, making them a promising platform for delivering a wide range of therapeutic agents. Despite these promising features, several challenges prevent their clinical translation. Further studies should focus on developing scalable and reproducible fabrication techniques, optimizing surface functionalization strategies, and conducting in-depth toxicological studies to confirm the effective and safe clinical application of LPHNPs. Addressing these limitations will successfully translate LPHNPs into clinical practice, offering a revolutionary approach to oral drug delivery. This review provides a comprehensive overview of the structural elucidation and classification of LPHNPs, with various fabrication methods and recent advances in LPHNP synthesis and surface functionalization in enhancing drug targeting, mucoadhesion, and circulation time. Additionally, recent advancements in the therapeutic applications of LPHNPs for improving oral bioavailability are highlighted, showcasing their potential to address solubility and permeability challenges.

Graphical Abstract



INTRODUCTION

Oral drug delivery is the most convenient and widely used administration route, offering high patient compliance, cost-effectiveness, and a simplified regulatory approval process [1]. Despite its benefits, oral drug delivery is unsuitable for all therapeutic agents due to low bioavailability, enzymatic degradation, first-pass metabolism, and poor solubility, which can hinder its effectiveness [2]. In recent decades, nanotechnology has been considered one of the most proficient systems for biomedical and drug delivery applications. It has witnessed significant growth, enabling various nanocarriers to overcome biological barriers and achieve targeted drug delivery of numerous

medications, including genes, RNAs, peptides, proteins, small molecules and theranostic agents [3]. These nanocarriers have significant potential for improving the therapeutic index by enabling controlled and sustained drug delivery, thereby minimizing the frequency of dosing and systemic toxicity. Among the several nanocarriers designed for drug delivery applications, "Liposomes" and "Polymeric Nanoparticles" (PNPs) have evolved as a promising platform [4]. PNPs, consisting of non-toxic and eco-friendly - biodegradable polymers such as polycaprolactone (PCL), poly (lactic-co-glycolic acid) (PLGA) and chitosan, offer exceptional structural integrity, stability, and versatility in encapsulating a broad range of therapeutic agents. Their surface can be easily altered with ligand targeting to enhance site-specific drug delivery [5]. However, PNPs also have some limitations, such as potential toxicity from polymer degradation (impurities), limited surface functionalization for targeted delivery and a limited ability for effective drug loading and controlled release [6]. On the contrary, liposomes have been widely utilized as drug delivery platforms because of their excellent biocompatibility and favourable safety profile. Surface functionalization with polyethylene glycol (PEG) improves the therapeutic agents' half-life[7]. The first nanocarrier-based drug delivery systems to receive regulatory approval were liposomes. The Food and Drug Administration (FDA) approved two liposomal formulations of doxorubicin, Doxil, in 1995 and Myocet in 1999 [8]. Since then, numerous liposomal formulations have entered the clinical landscape. Currently, around 16 liposomal drugs have received clinical approval, with several being actively marketed, including AmBisome (amphotericin B), DaunoXome (daunorubicin), DepoCyt (cytarabine), DepoDur (morphine), and Visudyne (verteporfin) [9]. Despite this, liposomes exhibit structural instability, short circulation time due to rapid immune clearance, drug leakage, limited drug loading capacity for hydrophobic molecules, and challenges in large-scale production [10].

To utilize the distinctive advantages of the both PNPs and liposomes, while overcoming their inherent limitations, LPHNPs have been developed as an advanced drug delivery system, integrating the robustness and regulated drug release characteristics of PNPs with the biocompatibility and prolonged circulation time of liposomes [11]. The graphical representation of drug-loaded LPHNP is shown in Figure 1. The polymeric core of LPHNPs enhances the structural integrity of drug release and prevents drug leakage. At the same time, the lipid shell improves biocompatibility, extends circulation time, and allows for surface modifications such as PEGylation for targeted delivery [12]. Additionally, this hybrid system achieves better drug loading efficiency for hydrophobic and hydrophilic drugs, minimizes polymer toxicity, and enhances scalability for clinical applications. This hybrid system is a robust drug delivery platform, particularly in oral drug delivery offering improved encapsulation efficiency, mucoadhesion, enhanced stability and effective targeting at the tissue, cellular, and molecular levels [13]. The current review discusses the recent advancements in LPHNPs, emphasizing strategies of preparation methods, their applications, challenges in clinical translation, and future perspectives for their application in oral drug administration.

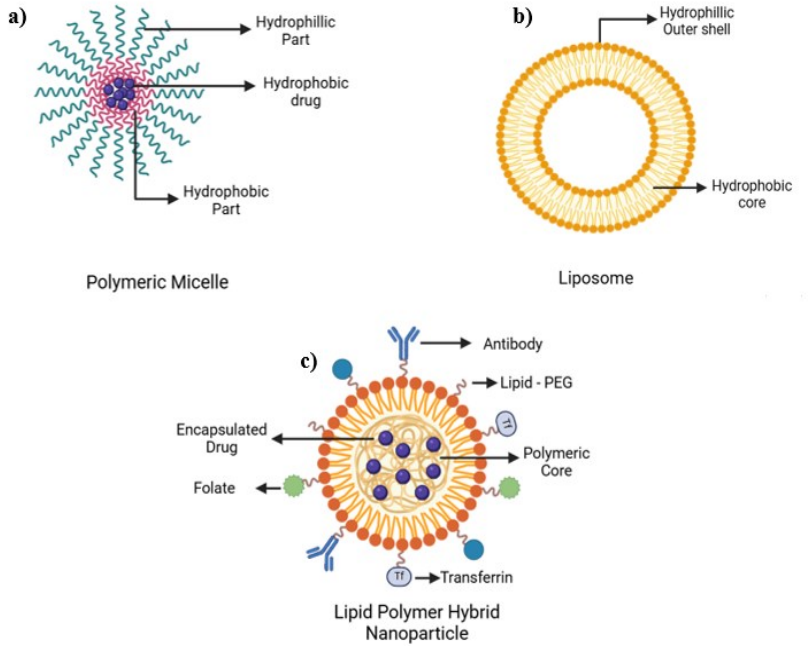


Figure 1: Schematic representation of (a) Polymeric Micelle, (b) Liposome and (c) Lipid Polymer Hybrid Nanoparticles (LPHNPs); LPHNPs consists of a polymer core incorporated with drug, surrounded by an external phospholipid membrane and a lipid-PEG coating.

1. Structural Elucidation and Classification of LPHNPs

Structurally, LPHNPs are composed of three key components (Figure 1)

(1) A polymeric core designed to incorporate the drug, ensuring protection and controlled release,

(2) A surrounding phospholipid monolayer that acts as a shell to minimize drug leakage and protect the core from degradation and

(3) An outer lipid-PEG layer that enhances systemic circulation by preventing immune recognition and clearance [14].

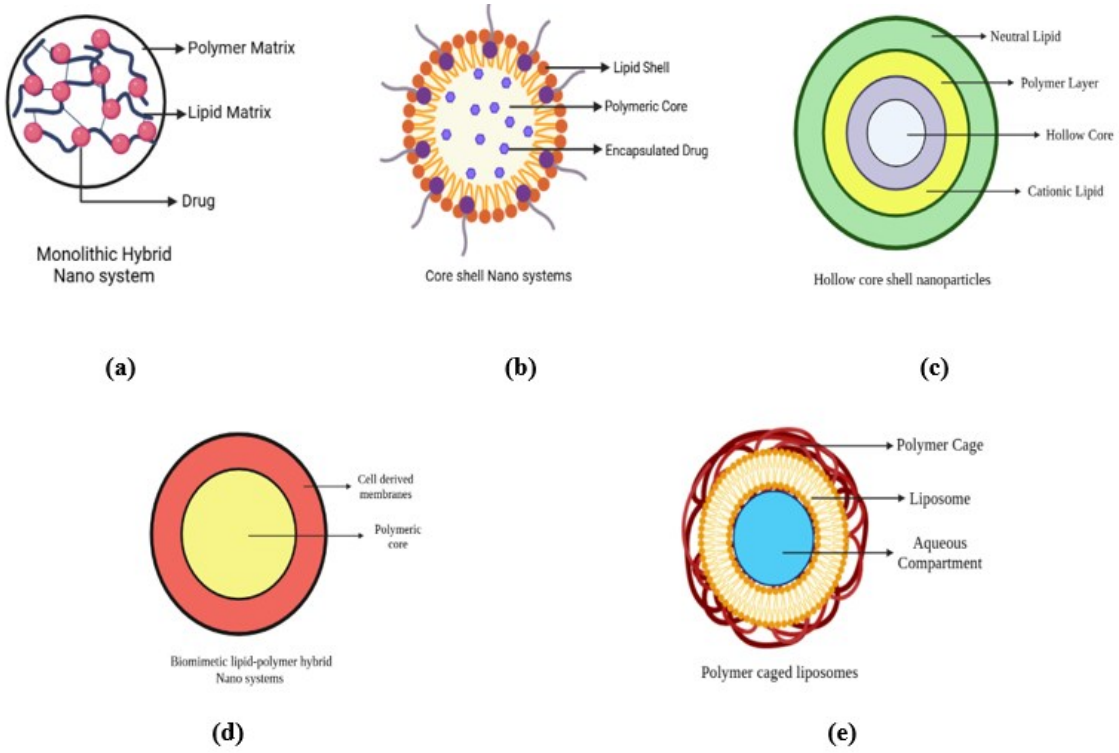


Figure 2: Schematic Illustration of Various LPHNP Designs. (a) Monolithic hybrid nano system; (b) Core shell Nano systems; (c) Hollow core shell nanoparticle; (d) Biomimetic lipid-polymer hybrid nano systems; (e) Polymer caged liposomes

1.1. Types of LPHNPs

Based on their structural composition and structural differences, LPHNPs are categorized as:

(a) Monolithic Hybrid Nanosystems (Figure 2 (a)), contain a polymeric core matrix where lipid components are randomly dispersed [15]

(b) Core-shell Nanosystems (Figure 2 (b)) contain a polymeric core enclosed by a highly compatible lipid shell, enhancing stability and controlled drug release [16].

(c) Hollow core-shell nanoparticles (Figure 2 (c)) containing a hollow inner aquatic core enclosed by a polymer layer, surrounded by PEG-lipids, neutral lipids, and a cationic lipid layer [17]

(d) Biomimetic lipid-polymer hybrid Nanosystems (Figure 2 (d)), consist of a polymer core enveloped with cell-derived membranes, enhancing cellular integrity [18]

(e) Polymer caged liposomes (Figure 2 (e)) contain liposomes enclosed within a polymer core matrix [19].

1.2. Applications of LPHNPs:

LPHNPs are highly versatile nanocarriers with broad applications, including drug delivery, gene therapy, immunotherapy, imaging, and stimuli-responsive treatments. In drug delivery, LPHNPs enhance the targeted and controlled release of various therapeutic agents, including antibiotics and cardiovascular medications, ensuring improved bioavailability and reduced side effects [20]. Their role in gene delivery involves transporting siRNA and DNA to treat genetic disorders and metabolic conditions by protecting genetic material from enzymatic degradation. Immune activation is another key area where LPHNPs serve as vaccines and receptor agonist carriers, stimulating immune responses for infectious diseases and autoimmune disorders [21]. An overview of the main applications of LPHNPs is shown in Figure 3.

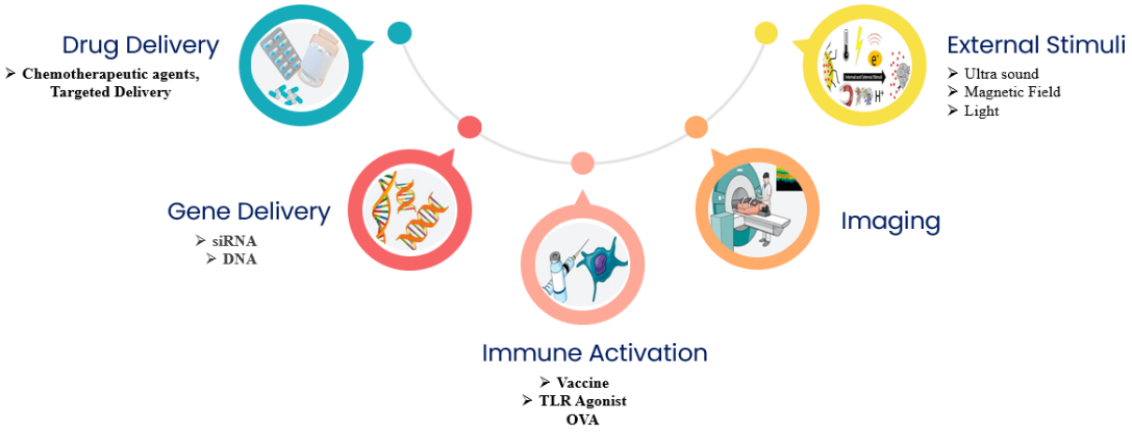


Figure 3: Overview of main applications of LPHNPs

Additionally, in imaging applications, LPHNPs functionalized with gadolinium (Gd), manganese (Mn), and gold (Au) enhance contrast in MRI, CT, and fluorescence imaging, aiding in the early detection of various diseases, including carcinomas, cardiovascular conditions and inflammatory disorders [22]. Additionally, LPHNPs are utilized in stimuli-responsive therapies, responding to

external factors for controlled drug release and precision treatment in different medical conditions [23].

2. Fabrication of LPHNPs

The fabrication of LPHNPs can be broadly categorized into two main strategies (Figure 4): (i) Two-step method: Phospholipid membrane & polymeric core were formulated separately and later merged to produce a bilayer structure; (ii) One-step method: Drug, lipids and polymers are simultaneously combined into a monolayer of self-assembled nanoparticles [24].

2.1. Two-step Method

2.1.1. Two-step - Conventional method

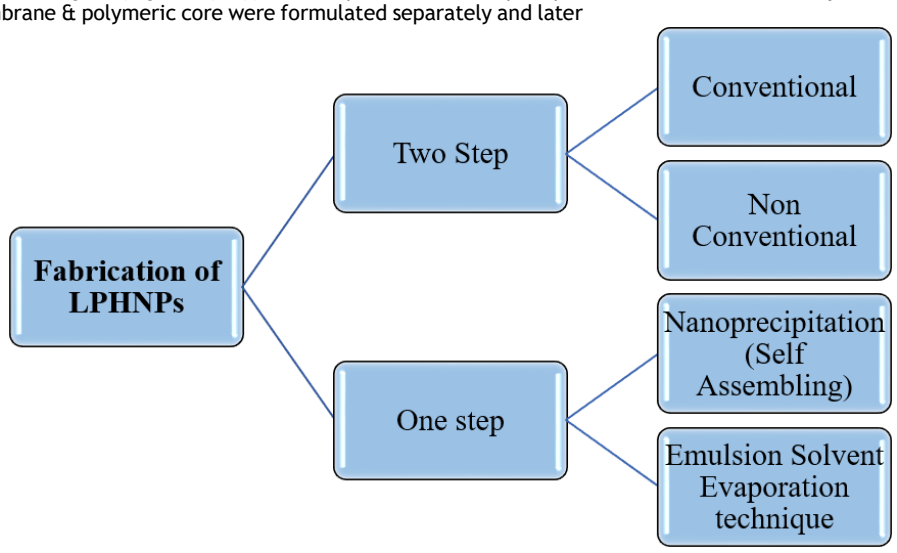


Figure 4: Different Methods for Fabricating LPHNP System.

This approach played a significant role in the initial development of LPHNPs. Typically, a two-step process is employed to formulate a bilayer or multilayer structure of lipid membranes (Figure 5). This traditional method involves integrating pre-synthesized PNPs with preformed lipid vesicles, relying on electrostatic forces to facilitate their adhesion [25]. This method is furthermore sub-classified into - (A) Subsequent incorporation of preformed PNPs to a dehydrated lipid layer or (B) Integration of pre-synthesized PNPs into lipid vesicles formed through the hydration of a thin lipid layer. In both instances, hybrid nanoparticles are fabricated using external energy stimuli such as vortexing, ultrasonication, or heating beyond the lipid's phase transition temperature. During filtration, non-adsorbed free-lipid and fabricated LPHNPs are isolated by centrifugation [26].

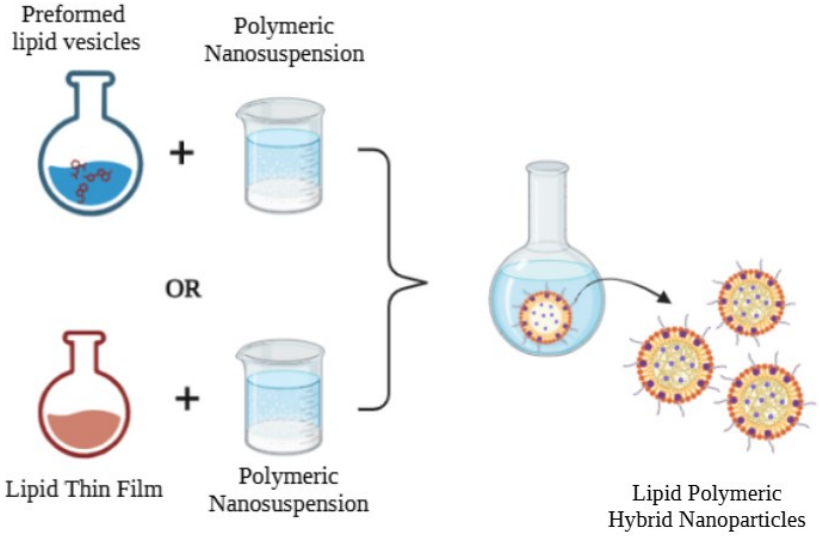


Figure 5: Graphical Representation of Conventional Two-step Method for Fabrication of LPHNPs

Suksiriworapong et al. fabricated LPHNPs functionalized with hyaluronic acid (HYA) to enhance targeted drug delivery. This enabled the selective delivery of *Cordyceps militaris* herbal extract to breast cancer cells using a conventional two-step method. A preformed poly (glycerol adipate) (PGA) polymer core, grafted with cholesterol and vitamin E (PGA-VE), was used for LPHNP preparation. The HYA-decorated LPHNPs enhanced CME's anticancer effects by enhancing cellular internalization via CD44 receptor-facilitated uptake. These findings highlight the potential of PGA-based LPHNPs for targeted drug delivery for cancer therapy [27].

2.1.2. Non-conventional method

Spray drying and soft lithographic particle moulding have been utilized to fabricate LPHNPs using a non-conventional method. Hitzman et al. used spray drying to fabricate polymeric nanoparticles (polylysine and polyglutamic acid), which are then dispersed in dichloromethane solution containing phospholipids. The lipid-polymer mixture was spray-dried to form polymeric nanoparticles coated with lipids [28]. Researchers have recently investigated a soft lithography-based particle moulding technique called Particle Replication in Nonwetting Templates (PRINT) for fabricating LPHNPs designed to deliver genetic materials. [29].

Table 1: Comparison of one-step and two-step approaches in fabrication of LPHNPs.

Method	Principle	Advantages	Disadvantages	Ref
One-Step Method	Polymers and lipids are processed together in a single step, typically using nanoprecipitation, high-pressure homogenization, or melt emulsification.	Simple and time efficient. Reduces processing steps and solvent use. Suitable for large-scale production.	The usage of organic solvents limits the applicability of this method for fabrication of LPHNPs.	[29]
Two-Step Method	Polymers and lipids are prepared separately before being combined to form hybrid nanoparticles by emulsification solvent evaporation or double emulsion methods.	Greater control over nanoparticle properties. Allows better drug encapsulation and stability. Suitable for both hydrophilic and hydrophobic drugs.	More complex and time-consuming. Risk of phase separation. Increased risk of process variability.	[30]

2.2. One Step Method

This method of fabricating LPHNPs is an alternative and more efficient conventional two-step method, which involves individual synthesis of PNPs and lipids before incorporating them. In contrast, the one-step method eliminates the need for preformed PNPs and lipid vesicles by relying on the direct mixing of lipid and polymer solutions under controlled conditions, leading to the self-assembly of LPHNPs, while avoiding multiple intermediate steps that are typically time-consuming and energy-intensive[31]. Nanoprecipitation and Emulsion Solvent Evaporation (ESE) are generally used to prepare LPHNPs.

2.2.1. Nanoprecipitation technique

This method includes dispersion of drug and polymer in a hydrophilic organic solvent such as ethanol while lipids are dispersed in an aqueous phase [32]. The phospholipid or lipid-PEG mixture needs to be heated above its gel-to-liquid transition point to ensure the formation of a homogeneously dispersed liquid crystalline phase (Figure 6). The polymeric solution was then added drop by drop to the aqueous lipid suspension under continuous stirring, facilitating polymer nanoparticle formation. As the polymer chains cool and solidify into nanoparticles, lipids instantly self-assemble around the polymer core through hydrophobic interactions. In this self-assembly process, the hydrophobic tails of the lipids adjust inward toward the nanoparticle core, whereas the hydrophilic head groups face outward into the surrounding aqueous medium[33] [34].

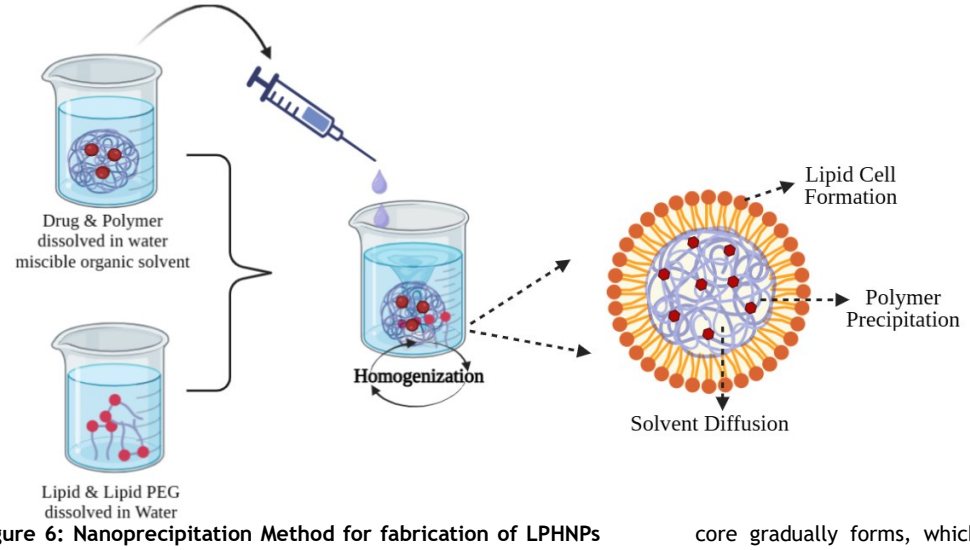


Figure 6: Nanoprecipitation Method for fabrication of LPHNPs by One-Step Approach.

The hydrophobic lipid tails are incorporated into the inner lipid shell for lipid-PEG. At the same time, the PEG chains extend outward into the surrounding aqueous environment, providing steric stabilization to the hybrid nanoparticle [35]. Once nanoprecipitation is complete, the organic solvent is evaporated, and the resulting LPHNPs are typically purified via centrifugation. Additionally, a recent advancement in mRNA-based vaccine delivery incorporates a post-insertion technique, where PEGylated lipid vesicles are introduced after nanoprecipitation, further enhancing the stability and efficacy of the nanoparticle system [36].

2.2.2. Emulsion Solvent Evaporation technique

This method represents an alternative approach for fabricating LPHNPs, categorized as single emulsification (SE) and double emulsification techniques (DE) (Figure 7). In the single emulsification solvent evaporation (ESE) method, a polymer and lipophilic drugs are initially solubilized in a non-aqueous solvent and thereafter combined with a hydrophilic phase containing lipids, resulting in the fabrication of an oil-in-water (O/W) emulsion. As the non-aqueous solvent evaporates, a polymeric core gradually forms, which is encapsulated by a lipid layer. Alternatively, the phospholipid component can be incorporated into the organic phase next to the polymer to facilitate self-assembly [37]. The double ESE method is utilized for hydrophilic drugs to form water-in-oil-in-water (W/O/W) emulsions. First, the hydrophilic phase is emulsified within a nonpolar solvent containing polymers and lipids, forming a water-in-oil (W/O) emulsion. The initial emulsion undergoes a secondary emulsification process in an aqueous phase enriched with lipid-PEG, ultimately forming a water-in-oil-in-water (W/O/W) emulsion. The final step involves solvent evaporation, leading to the formation of LPHNPs [38]. The LPHNPs synthesized using the double emulsification method exhibit distinct structural characteristics, including:

- An aqueous core encapsulated within a lipid membrane.
- A polymeric coat arranged between the aqueous core and lipid shell
- An outer lipid-PEG shell provides additional stability and surface modification [39].

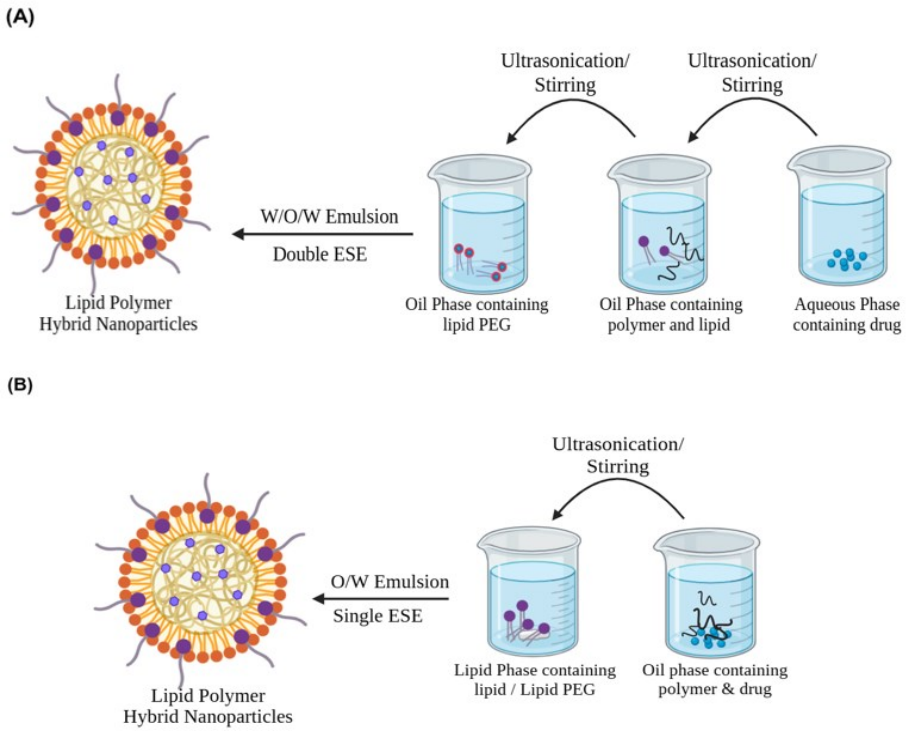


Figure 7: Fabrication of LPHNPs using ESE method - (A) Double ESE method (B) Single ESE method.

A critical advantage of the one-step method is the essential role of lipids and lipid-polyethylene glycol (PEG-lipids) as stabilizing agents, ensuring better nanoparticle integrity and biocompatibility [40]. Additionally, ionic or non-ionic surfactants such as polyvinyl alcohol (PVA), dimethyl ammonium bromide (DMAB), and poloxamers are often incorporated to enhance stability and dispersibility further. These stabilizers contribute to the physicochemical properties of LPHNPs and improve their interaction with biological systems, making them suitable for various drug delivery applications. Moreover, the one-step approach offers better scalability and reproducibility, making it a more feasible option for industrial translation [41].

2.3. Advances in the fabrication of LPHNPs

The manufacturing process significantly influences the physicochemical properties of the LPHNPs. Lab-scale manufacturing methods can lead to production variability, potentially impacting the quality, uniformity and *in vivo* efficacy of the LPHNPs. Recent developments in microfluidic rapid mixing techniques provide a significant advantage by enabling the production of uniformly sized LPHNPs [42]. Successive designs incorporating high-speed convective and micro vortex mixing have enhanced productivity to 3 g/h while ensuring improved repeatability and consistency. Additionally, the turbulence and vortex effects generated by high-speed mixing reduce mixing time and result in smaller nanoparticle sizes [43]. Table 2 presents an overview of the latest developments in LPHNP formulation techniques.

A recent study introduced a microfluidic platform that leverages ultra-fast sequential nanoprecipitation processes, facilitating the large-scale manufacturing of the LPHNPs, yielding around 700 g per day per device. This approach enhances drug payload capacity and ensures controlled drug release [44]. Furthermore, a flexible "coaxial turbulent jet mixer" has demonstrated the ability to scale up NP production to 3 kg/day while ensuring uniformity and reproducibility [45].

Table 2: Recent Advances in LPHNP Fabrication: Strategies and Key Benefits

Advance strategy	Key Benefits	Ref
PRINT technology facilitates the production of highly uniform HNPs with precise control over their characteristics.	Fabrication of monodispersed nanoparticles while allowing precise and independent control over key physicochemical parameters, including particle size, shape, and composition.	[29]
Microfluidic electroporation-assisted synthesis	Utilizes precise electrical pulses within microfluidic systems like erythrocyte membrane-coated magnetic nanoparticles.	[46]
Rapid fabrication of LPHNPs through a one-step sonication technique.	Enhances production efficiency by nearly 20-fold without altering physiochemical properties.	[47]
Bulk production of LPHNPs by multi-inlet vortex reactor	Enables large-scale synthesis of LPHNPs with vortex-driven mixing for uniform nanoparticle formation and improved reproducibility, ensuring consistent batch-to-batch quality.	[48]
Synthesis of ultra-small LPHNPs using nanoprecipitation techniques.	Facilitates the synthesis of ultra-small LPHNPs with sizes below 25 nm, offering selective drug delivery to cancer cells while minimizing off-target effects.	[49]
Coaxial turbulent Jet mixer	Reduces processing time by increasing LPHNP production capacity.	[45]

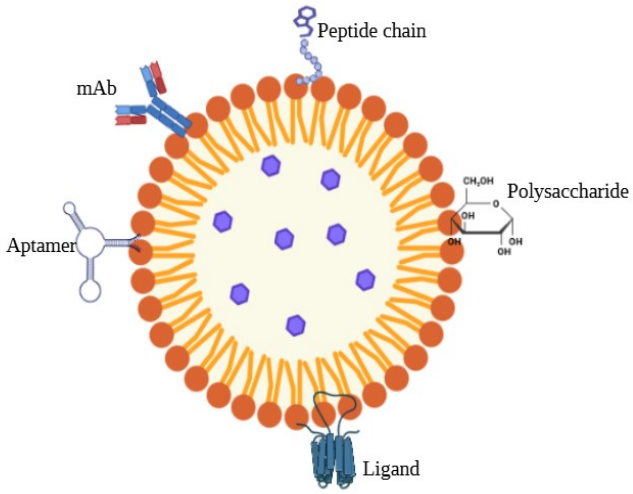


Figure 8: Illustration of various surface-anchoring strategies for LPHNPs.

3. Surface Functionalization of LPHNPs

Surface modification is essential for improving the pharmacokinetics (PK) and pharmacodynamics (PD) of the LPHNPs. Incorporating PEGylated phospholipids in the external layer extends the systemic retention time of LPHNPs in the bloodstream[50]. Modifying surface charge, zeta potential, and lipophilicity are vital in enhancing cellular internalization and modifying the PK-PD profile of various therapeutics. Functionalizing the surface of LPHNPs allows for target-specific intracellular delivery while reducing toxicity. This can be achieved by conjugating aptamers, small molecules, cell-penetrating peptides and antibodies, facilitating improved biodistribution and therapeutic efficacy (Figure 8) [51].

Clawson et al. designed pH-sensitive LPHNPs with PEG shedding by integrating a lipid-(succinate)-methoxy PEG (mPEG) conjugate, which exhibits increased susceptibility to acidic hydrolysis. This conjugate forms a hydrolyzable PEG stealth layer, ensuring pH sensitivity through diester succinate hydrolysis. The degree of pH responsiveness could be modified by altering the lipid-(succinate)-mPEG amount. A higher integration of this conjugate into the lipid layer enhances the stability of nanoformulation at lower pH levels. Modifying the PEG layer optimizes LPHNP across a broad pH spectrum, offering a valuable strategy for controlled drug delivery applications [52].

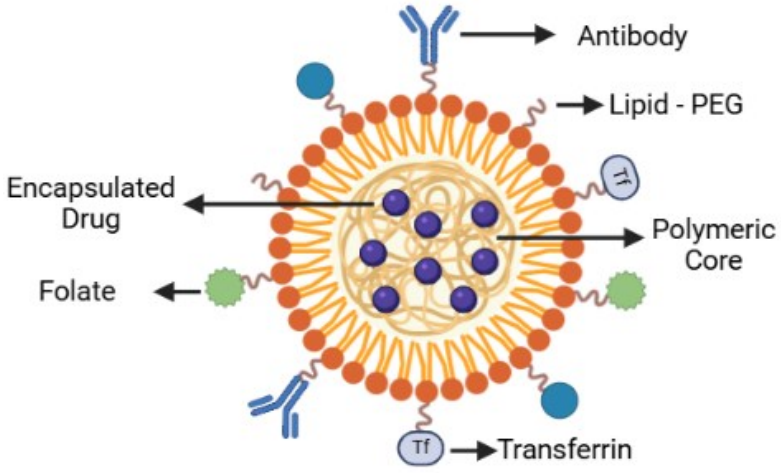


Figure 9: Schematic illustration of multifunctional LPHNPs, highlighting structural components and potential functionalities.

Various ligands and targeting moieties enhance cellular absorption through ligand-dependent uptake, enhancing the specificity of delivery systems. Among these, folic acid (FA) is broadly utilized in targeting ligands due to its ability to bind folate receptors (FRs) selectively, which are exaggerated in various tumour sites (Figure 9) [53]. Wu et al. enhanced the efficiency of LPHNPs by enabling their surface with FA, resulting in the development of folate-targeted lipid polymer hybrid nanoparticles (FLPHNPs). These FLPHNPs consisted of a PLGA matrix, a lecithin-coated layer, a reduction-sensitive monomethoxy-poly (ethylene glycol)-S-S-hexadecyl (mPEG-S-S-C16) membrane, a conjugated FA ligand. Designed for targeted doxorubicin (DOX) delivery, FLPNPs effectively suppressed the growth of human oral cavity squamous cell carcinoma (KB) cells while minimizing DOX-related toxicity. The nanoparticles demonstrated excellent stability and rapidly disassembled in a modelled reductive cancer cell environment [54].

Omar et al. developed lipid polysaccharide surface-modified hybrid nanoparticles (LPNs) through the nanoprecipitation approach for CNS-targeted delivery of rivastigmine. Dextros-cholic acid (DxC) and a polysaccharide were incorporated to modify the surface of lipid-PLGA nanoparticles. The resulting surface-altered LPNs had a particle size of 111.6±11.4 nm and exhibited a high encapsulation efficiency. *In vivo studies* on albino rats revealed that these modified nanoparticles achieved more efficient and rapid brain penetration than free drug solutions. Notably, the surface-modified LPNs demonstrated approximately fivefold more significant blood-brain barrier (BBB) permeability than the drug solution, significantly enhancing brain retention time for up to 40 hours. These findings indicate that LNPs offer a promising strategy for overcoming the BBB, potentially minimizing systemic side effects while improving therapeutic efficacy in neurological disorders [55].

4. Mechanisms for Enhancing Oral Bioavailability of LPHNPs

The main purpose of developing the LPHNP system is to enhance lipid nanocarriers' storage stability and gastrointestinal (GI) resilience by employing a polymer coating to their lipid-in-

aqueous interface. Encapsulating drugs within the LPHNP system improves stability and prevents premature drug leakage. It also prolongs therapeutic effects while reducing potential toxicity, making it a highly effective drug delivery platform [56]. The latest advancements and unique mechanisms in the enhancement of oral therapeutic drug delivery of LPHNPs are:

4.1. Muco-adhesion and permeability: All oral drug delivery systems rely on effective interactions with the mucosal layers, as these interactions facilitate two key advantages:

(i) prolonged gastric retention, which enhances drug exposure at absorption spots, and (ii) efficient transport through epithelial barriers to reach the intestinal epithelium. Studies have shown that gastric residence time is influenced by both the length and type of lipid chains, which are crucial in optimizing drug absorption [57]. Mucoadhesive polymers can be utilized to coat LPHNP systems, enhancing their adhesion and permeability across mucus barriers. Chitosan and its derivatives, known for their strong mucoadhesive properties, have been widely utilized. Ana et al. demonstrated this by developing chitosan-coated solid lipid nanoparticles (SLNs) to deliver carbamazepine (CBZ). Their study showed a 100-fold increase in CBZ permeability compared to uncoated SLNs, emphasizing chitosan's role in enhancing drug absorption [58].

Similarly, alginate has been explored as an alternative mucoadhesive polymer. Shtenberg et al. developed alginate-lipid pastes and hydrogels for the controlled release of doxorubicin in the oral cavity. By adjusting the viscosity through varying concentrations of alginate and calcium as a cross-linker, they optimized mucoadhesion and drug release. These studies highlight the potential of chitosan and alginate in lipid-polymer hybrid nanoparticles for improving oral drug delivery efficiency [59].

4.2. Stealth properties: After oral administration, nanoparticles are taken up by M cells in the gastrointestinal tract and transported to the mononuclear phagocyte system (MPS), where they undergo phagocytosis [60]. However, their accumulation in macrophages and subsequent clearance by the MPS reduces systemic absorption, limiting oral bioavailability. To overcome this challenge, lipid phases can be coated with hydrophilic polymers such as PEG and PEGylated surfactants, which prevent opsonization [61].

Vonarbourg et al. demonstrated the stealth properties of PEG-coated lipid nanocapsules, revealing that smaller PEG-coated nanoparticles exhibited greater resistance to opsonization than larger ones. Specifically, phagocytosis of 20 nm PEG-coated nanoparticles was reduced to approximately 20% compared to uncoated counterparts, whereas 100 nm PEG-coated nanoparticles showed nearly 90% uptake of uncoated 20 nm particles. This study highlights the role of PEGylation in enhancing nanoparticle stability and prolonging circulation time for improved oral drug delivery [62].

4.3. Enhanced Gastrointestinal Residence time:

A significant challenge in oral drug delivery is the early and irregular gastric emptying, resulting in insufficient drug release and a narrow timeframe for absorption in the small intestine[63]. To address this, a commonly used strategy for prolonging gastrointestinal (GI) residence time in LPHNPs is to develop floating drug delivery systems that remain buoyant in the stomach without significantly affecting gastric emptying. Floating polymer-based LPHNPs are designed to remain buoyant in the stomach while enabling controlled drug release. This is typically achieved by coating lipid-based formulations with a hydrophobic polymer, which prevents rapid dispersion and facilitates sustained drug delivery [64].

Setthacheewakul et al. developed a floating self-emulsifying LPHNP (SE-LPHNPs) system by incorporating liquid lipid excipients into polymeric and colloidal carriers. The optimized SE-LPHNPs, containing 0.8% w/w sodium starch glycolate and 55% w/w glyceryl behenate, achieved 93% floating efficiency at 6 hours and sustained tetrahydro curcumin (THC) release over 8 hours. In contrast, the liquid self-emulsifying drug delivery system (SEDDS) released 80% of THC within just 2 hours, indicating a rapid burst release profile [65].

4.4. Improved solubility by inhibiting drug precipitation: The ability to solubilize lipid-based formulations for poorly aqueous soluble drugs decreases upon dispersion, potentially resulting in a transient supersaturated state. This state occurs when the initial drug concentration exceeds its equilibrium solubility and there is a high chance of drug precipitation. Polymeric precipitation inhibitors (PPIs) help stabilize this supersaturation, enhancing drug absorption and oral bioavailability. They increase nucleation activation energy by forming hydrogen bonds and hydrophobic interactions with drug molecules and altering bulk medium characteristics to delay crystal formation and growth in the gastrointestinal tract [66].

The synergistic combination of lipids and PPIs is especially advantageous for delivering poorly soluble weak bases (PSWBs) that exhibit pH-dependent solubility. These compounds are highly soluble and protonated in the acidic gastric environmentleading to drug supersaturation [67]. However, upon gastric emptying and exposure to the neutral pH of the small intestine, solubility drastically decreases, resulting in rapid precipitation at the primary absorption site. This challenge can be mitigated by integrating lipid solubilization along with the effects of inhibiting precipitating, improving drug stability and enhancing oral bioavailability [68]. Rao et al. demonstrated that Pluronic F127 effectively inhibited pH-induced precipitation of cinnarizine in a solid lipid-based formulation. The oil phase maintained the drug in a solubilization state, while Pluronic F127 blocked its conversion to a more stable crystalline form, resulting in a 1.6-fold increase in oral bioavailability [69].

4.5. Stimuli Mediated drug release: Polymerized liposomes incorporating polydiacetylene can undergo structural distortion in response to pH and biorecognition, enabling stimuli-responsive drug release. Developing innovative PLH systems that react to external stimuli (e.g., light, magnetic field, ultrasound) and internal factors (e.g., temperature, pH and redox potential) or presents a promising strategy for enhancing drug formulation efficacy [70]. Magnetic field (M F)-mediated thermo-responsive release has emerged as an innovative mechanism for controlled drug release in LPHNP-based delivery systems. Kong et al. designed MF-excited LPHNPs incorporating Fe_3O_4 as a stimuli-responsive component. Upon exposure to a remote radio frequency magnetic field, Fe_3O_4 generates localized heat, disrupting the polymer matrix structure and facilitating the accelerated release of encapsulated anticancer drugs, such as camptothecin [71].

5. Limitations in Clinical Translation

While LPHNPs offer advantages over PNPs and liposomes, several limitations prevent their clinical translation. The practical clinical implementation of LPHNPs depends on overcoming key technical challenges, including improving drug loading efficiency, achieving sustained drug release, evading immune system recognition, and optimizing nanoparticle aggregation at specific sites[72]. One of the key challenges is optimizing the lipid-to-polymer ratio within the nanoparticles, as variations in this ratio can lead to instability and drug leakage during prolonged storage. Since phospholipids primarily contribute to the micellar phase while polymers form the nanoparticle core, lipid/polymer composition fluctuations can increase polydispersity, destabilization, aggregation, and phase separation [73].

Additionally, the encapsulation of hydrophilic drugs within the LPHNPs matrix is often ineffective. This issue can be addressed using the double emulsification technique, which enhances drug loading efficiency; however, this method is both time-intensive and energy-consuming. To prevent phase separation, carefully selecting phospholipids and polymers is crucial, ensuring that phospholipids form a stable monolayer over the polymeric nanoparticle surface[74].

Another challenge that could arise is the scale-up and large-scale production of LPHNPs. Currently, LPHNPs are primarily produced on a small scale in laboratory environments, and replicating their properties consistently on a large scale for industrial manufacturing remains a significant challenge[75]. The high production cost of LPHNPs is another concern, as it involves additional manufacturing processes and the combined use of phospholipids and polymers, which results in high manufacturing costs. Furthermore, a crucial consideration of LPHNPs is their notable adverse impact on biological systems, particularly due to using solvents and excipients, which must be carefully evaluated [76]. A limitation to regulatory approval is the lack of well-

established guidelines for the design, development and clinical use of LPHNPs. The rapid clinical translation of LPHNPs can be achieved by developing scalable techniques that ensure highly reliable *in-vivo* properties. Consequently, further research is essential to investigate their toxicity, biodistribution, clearance, and *in-vivo* therapeutic efficacy[77].

CONCLUSION

LPHNPs have emerged as innovative oral drug delivery models, offering a unique combination of polymeric nanoparticles' structural stability and lipid-based systems' biocompatibility. These hybrid carriers enhance drug solubility, bioavailability, and controlled release, making them a promising solution for overcoming the limitations of conventional oral drug delivery systems. Recent advancements in LPHNP fabrication techniques, surface functionalization, and therapeutic applications have further enhanced their potential in delivering a wide range of pharmaceutical compounds. Despite these advancements, several challenges remain in the clinical translation of LPHNPs. Difficulties such as large-scale manufacturing, storage stability, batch-to-batch reproducibility, and regulatory compliance must be addressed before these nanocarriers can be widely adopted in clinical settings. Additionally, in vivo toxicity, biodistribution, and long-term safety concerns require extensive preclinical and clinical evaluations.

Future research should optimize scalable and cost-effective fabrication techniques that ensure consistent LPHNP properties while maintaining high drug-loading efficiency and stability. The integration of advanced manufacturing technologies, such as microfluidics and 3D printing, could enhance the precision and reproducibility of these nanocarriers. Moreover, enhancing surface functionalization through ligand conjugation, stimuli-responsive coatings, and bio-adhesive polymers will facilitate precise and regulated drug release, reducing adverse effects and enhancing therapeutic effectiveness.

Another significant aspect to explore is enhancing surface functionalization strategies to achieve targeted and stimuli-responsive drug release. Functionalizing LPHNPs with ligands such as peptides, antibodies, or aptamers can improve site-specific drug delivery while minimizing adverse effects. Smart nanocarriers that respond to physiological triggers could enable more precise drug release, improving therapeutic outcomes. Comprehensive *in vivo* research is vital to evaluate the long-term safety, biodistribution, and clearance of LPHNPs. Standardized guidelines for evaluating the quality, safety, and efficacy of LPHNP formulations need to be established to facilitate their transition from research to clinical application. By addressing these challenges, LPHNPs could serve as a transformative system for oral drug administration, offering enhanced bioavailability for oral routes, reduced dosing frequency, and patient compliance, ultimately advancing the field of nanomedicine.

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Author contribution

Sanjay Sathiyamoorthy – Conceptualization, Methodology. Writing - original draft, Writing - review and editing. **Suriya Prakaash Kannan** - Visualization, Writing - review and editing. **Damodharan Narayanasamy** - Project administration, Supervision, Writing - review and editing.

Declaration of competing interest

The authors declare no competing interest.

Data availability

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