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# Lipid–Polymer Hybrid Nanoparticles as Emerging Carriers for Antihypertensive Drugs: Advances in Formulation, Characterization, and Bioavailability Enhancement

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## Abstract

Hypertension remains a predominant global health burden, significantly contributing to cardiovascular morbidity and mortality. While oral pharmacotherapy is the cornerstone of management, the clinical efficacy of many potent antihypertensive agents—ranging from calcium channel blockers to angiotensin II receptor blockers—is compromised by biopharmaceutical limitations. These include poor aqueous solubility (BCS Class II drugs), extensive hepatic first-pass metabolism, and short biological half-lives, necessitating frequent high-dose administration and resulting in erratic bioavailability and patient non-adherence. To address these challenges, nanomedicine has evolved toward "next-generation" delivery systems. Among these, Lipid–Polymer Hybrid Nanoparticles (LPHNs) have emerged as a superior platform, synergistically combining the structural integrity and controlled release properties of polymeric nanoparticles with the high biocompatibility and biomimetic characteristics of liposomes. This review provides a comprehensive analysis of LPHNs as a transformative strategy for antihypertensive drug delivery. We critically examine the unique core-shell architecture of LPHNs, wherein a polymer core encapsulates the drug for sustained release, while a lipid shell confers stability and enhances cellular interaction. Detailed attention is given to advanced formulation techniques, including single-step nanoprecipitation and two-step emulsification, alongside critical characterization parameters such as particle size, zeta potential, and drug entrapment efficiency. Furthermore, the review consolidates recent in vitro and in vivo evidence demonstrating the capability of LPHNs to significantly enhance the oral bioavailability of hydrophobic antihypertensives, prolong systemic circulation, and improve therapeutic outcomes compared to conventional dosage forms. Finally, we discuss the current regulatory landscape, scalability challenges, and future perspectives for the clinical translation of LPHN-based antihypertensive therapies.

**Keywords:** Lipid–Polymer Hybrid Nanoparticles (LPHNs), Hypertension, Oral Bioavailability, Sustained Release, Nanomedicine, Core-Shell Nanostructure..

## 1. Introduction

### 1.1. The Global Epidemiology of Hypertension: A Silent Crisis

Hypertension, as defined clinically by a persisting elevation in human arterial blood pressure (systolic blood pressure > or = 140 mmHg and/or diastolic blood pressure > or = 90 mmHg), is perhaps one of the most critical public health concerns of the 21st century. Commonly known as the "silent killer" because of its often-asymptomatic presentation, hypertension is a major modifiable risk factor for a wide range of cardiovascular diseases (CVDs). The estimated number of adults between 30 and 79 years old worldwide suffering from hypertension, as stated by the WHO, is an astonishing 1.28 billion, of whom two-thirds reside in low- and middle-income countries (1). In addition, there is an alarmingly low rate of therapeutic control, as an estimated 46% of all individuals worldwide suffering from hypertension are unaware of their illness, and fewer than half (42%) of all hypertensive patients are diagnosed and treated accordingly. The financial burden of hypertensive-induced illness cannot be overlooked and arises not only from direct financial expenses but also from lost productivity caused by disabilities and premature deaths.

## 1.2. Current Pharmacotherapy: Classes of Antihypertensive Drugs

The pharmacological treatment of hypertension usually utilizes the stepped-care method, which employs the varying antihypertensive drugs as monotherapy or a combination of the drugs within the same class. The drugs have been classified depending on their mechanisms of action:

- Diuretics (Thiazides, Loop, Potassium-sparing): These agents stimulate sodium and water excretion, hence decreasing
- Angiotensin-Converting Enzyme (ACE) Inhibitors (Ramipril, Enalapril): Inhibit the enzyme converting Angiotensin I to
- Angiotensin II Receptor Blockers (ARBs) - e.g., Telmisartan, Candesartan. This type of antihypertensive blocks
- Calcium Channel Blockers (CCBs) (e.g., Amlodipine, Nifedipine): These drugs block the influx of calcium ions in vascular smooth muscles,
- Beta-Blockers (e.g., Atenolol, Carvedilol):

Despite their efficacy, the clinical use of these agents is always marred by certain biopharmaceutical limitations. Most of the modern antihypertensive drugs, especially in the CCB and ARB groups, belong to Class II of the Biopharmaceutics Classification System (BCS), which includes compounds with poor aqueous solubility and high permeability, leading to variable absorption and bioavailability. In addition, the antihypertensive drugs propranolol and nifedipine are subject to first-pass metabolism in the liver and require larger doses of the drug to produce the desired plasma concentrations, thereby enhancing the risk of dose-related side effects (2).

## 1.3. The Shift from Conventional Dosage Forms to Nanomedicine

Generally speaking, the oral dosage forms that are routinely used will result in peak and trough blood drug concentration profiles. Such blood level variation is potentially undesirable in hypertension therapy, where the peak blood levels will cause episodes of hypotension with side effects, and the trough blood levels might result in suboptimal blood pressure control, predisposing the patient to episodes of cardiovascular complications. Furthermore, the need to dose the patient frequently—e.g., 2 to 3 times daily for short-half-life drugs—robs the regimen of compliance, which is an integral part of the management of essentially asymptomatic chronic diseases (3).

To overcome these shortcomings, the focus in the research field of pharmaceuticals has begun to shift toward nanotechnology-based research, specifically nanomedicine. Nanotechnology-based drug delivery systems, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and dendrimers, have tremendous potential for the revolutionization of hypertension treatment. Considering the various nanotechnology-based delivery platforms, the focus has recently shifted to the novel approach termed "Lipid-Polymer Hybrid Nanoparticles" (LPHNs), which have demonstrated tremendous potential in developing a potent 'next-generation' drug delivery system with the ability to surmount the particular biopharmaceutical problems faced in the treatment of hypertension using antihypertensive agents (4).

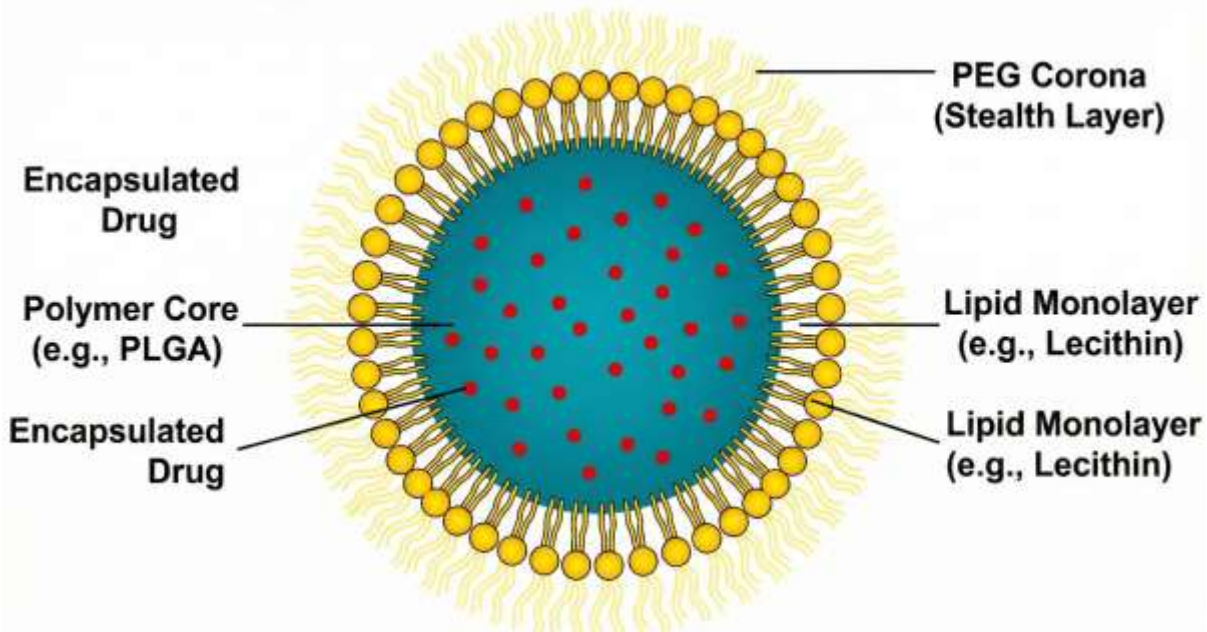


**Fig 1.** Structure & Anatomy of a Lipid-Polymer Hybrid Nanoparticle

## 2. Biopharmaceutical Challenges in Antihypertensive Therapy

## 2.1. Solubility Issues (BCS Class II and IV Drugs)

Most practiced and desired route of drug administration remains the oral route because of its convenience, cost-effectiveness, and high patient compliance. Nevertheless, the efficacy of an orally administered drug entirely hinges upon its ability to dissolve in the stomach fluids and permeate the membrane. A considerable percentage of newly identified chemical entities and a number of existing antihypertensive drugs have been found to possess a low solubility in aqueous media (5). Telmisartan, Candesartan cilexetil, Nifedipine, and also Felodipine present examples of typical BCS Class II drugs. In this set of drugs, the absorption process faces a major constraint in terms of the solubility of the drugs. While these drugs fail to show a desired absorption profile while given in the conventional dosage forms, the inability also extends to the "food effect," in which the presence of food vastly influences the absorption process and, in turn, results in an inconsistent outcome.

### 2.2. Hepatic First-Pass Metabolism and Low Bioavailability

Even if a drug is capable of dissolving in and moving through the intestinal walls, its ability to withstand the liver's metabolic processes prior to entering the circulation is critical to its absorption rate (6). This is exemplified by what is called the first-pass effect, and a number of antihypertensives, such as Propranolol, Carvedilol, and Verapamil, undergo extensive metabolism by cytochrome P450 enzymes, especially CYP3A4, in the liver. This limits an oral dose to as low as 10% to 30% because, to minimize the first-pass effect, high oral doses must be used—a factor that not only unnecessarily burdens the liver in metabolizing the drugs, making them less effective, but also increases the probability of systemic toxicity and side effects such as dizziness, fatigue, and gastrointestinal problems.

### 2.3. Short Half-Life and the Burden of Frequent Dosing

The maintenance of drug plasma concentrations within a critical "therapeutic window" is critical to effective blood pressure control. However, a significant percentage of these antihypertensive agents, such as "Captopril" and "Nifedipine," have relatively low "elimination half-lives"—defined as less than 4 to 6 hours (7). This in turn requires multiple daily doses to maintain drug efficacy. Considered in the context of a lifelong, asymptomatic condition, adherence to these complicated dosage regimens is notoriously variable. "Missing doses" allows for potentially life-threatening fluctuations in blood pressure, which may trigger "rebound hypertension." Therefore, in a critical clinical sense, there exists a need for delivery systems which extend the drug half-life in order to accommodate a "once daily schedule."

## 3. Lipid–Polymer Hybrid Nanoparticles (LPHNs): Architecture & Rationale

### 3.1. The Core-Shell Structure: Bridging Liposomes and Polymeric Nanoparticles

Lipid-Polymer Hybrid Nanoparticles (LPHNs) is a cutting-edge technology in the field of nanomedicine, developed with the definite purpose of circumventing the limitations inherent in the two earlier generations of drug delivery systems: liposomes and polymeric nanoparticles (8). In their structure, Lipid-Polymer Hybrid Nanoparticles comprise a novel robust core-shell structure with the following elementary constituents:

Polymeric Core: The central core of the nanoparticles consists of a biodegradable hydrophobic polymer, such as PLGA, PLA, or PCL. The role of this common scaffold of the drug-delivery mechanism is that it provides a matrix that can entrap poorly soluble drugs belonging to the antihypertensive class, such as Telmisartan or Nifedipine. The more rigid polymeric structure ensures that the drug is released over an extended period through sustained release.

Lipid Shell: This consists of a monolayer or bilayer of lipids, typically phospholipids, for example, lecithin and DSPC. This mimics the cell membrane and improves the biocompatibility of the nanoparticle considerably. It functions as a "glue" that holds the drug particles together and assists in their membrane interaction.

The lipid-PEG conjugate, Outer Steric Layer: This often represents the functionalization of the lipid shell with PEG. This outer corona gives "stealth" properties: such a layer forms a hydration barrier that prevents plasma protein adsorption (opsonins). Thus, due to evasion of RES recognition, the nanoparticles can circulate in the bloodstream for extended periods, thereby increasing the opportunity for reaching the target site (9).

**Table 1: Comparative Analysis of Lipid-Polymer Hybrid Nanoparticles (LPHNs) vs. Conventional Nanocarriers**

| Feature / Characteristic | Liposomes | Polymeric Nanoparticles (PNPs) | Lipid-Polymer Hybrid Nanoparticles (LPHNs) |
|---|---|---|---|
| **Structure** | Phospholipid bilayer enclosing an aqueous core. | Solid matrix of biodegradable polymer (e.g., PLGA). | **Core-Shell:** Polymer core + Lipid shell. |
| **Drug Loading Capacity** | Low for hydrophobic drugs; drug often leaks. | Moderate to High; depends on polymer-drug interaction. | **High:** Polymer core efficiently traps hydrophobic drugs. |
| **Structural Stability** | Low; prone to leakage and fusion in storage. | High; rigid structure but can aggregate. | **Excellent:** Polymer core provides rigidity; Lipid shell prevents aggregation. |
| **Release Kinetics** | Often rapid or "burst" release; difficult to control. | Tunable (diffusion/erosion controlled), but initial burst is common. | **Sustained & Controlled:** Lipid shell acts as a barrier, slowing diffusion from the core. |
| **Circulation Time** | Short (unless PEGylated); rapidly cleared by RES. | Variable; hydrophobic surface attracts opsonins (rapid clearance). | **Prolonged:** Lipid-PEG shell provides "stealth" properties, evading immune system. |
| **Biocompatibility** | Excellent (mimics cell membrane). | Good (if using PLGA/PLA), but degradation products can be acidic. | **Superior:** Combines biocompatibility of lipids with the safety of biodegradable polymers. |
| **Scale-Up Potential** | Difficult; batch-to-batch variability. | Moderate; requires extensive purification. | **Moderate to High:** One-step methods are scalable; highly reproducible. |

### 3.2. Advantages of LPHNs over Single-Component Carriers

The rationale for the design of LPHNs is the capability to unify the advantages of liposomes and polymeric nanoparticles via the compensation of their limitations.

Vs. Liposomes: Liposomes are highly biocompatible nanostructures, but they suffer the limitation of structural instability, leakage of the drug in the presence of serum, and the ability to encapsulate limited amounts of hydrophobic drugs. This is dealt with in LPHN with the use of the solid drug matrix.

Vs. Polymeric Nanoparticles: Generally, the drawback associated with polymeric nanoparticles is that the water uptake by the particles is low, limiting the extent to which the rate of the drug administered in the nanoparticles can be adjusted. Another drawback is that the hydrophobic nature of the surface makes them susceptible to rapid clearance in the immune system. LPHNs, being hydrophilic, are less cleared by the immune system, and their cell uptake is enhanced (10).

### 3.3. Mechanisms of Drug Loading and Stability

In LPHNs, the drug is primarily retained within the hydrophobic polymeric core through hydrophobic interactions and physical entrapment. The lipid monolayer at the interface reduces the surface tension between the polymer core and the aqueous environment, stabilizing the system during synthesis and storage (11). This architecture allows for high encapsulation efficiency (often >80%) for hydrophobic antihypertensive drugs, ensuring that a therapeutic dose can be delivered in a small volume of nanoparticles.

## 4. Materials and Excipients in LPHN Formulation

Therefore, the formulation of effective LPHNs as antihypertensive therapy relies heavily on the selection of proper polymeric and lipid vehicles that can control the size, rate of release, and stability of the compounds.

### 4.1. Choice of Polymers (Biodegradable)

The polymer acts as the backbone structure for the LPHN. In antihypertensive drug delivery, besides being a biodegradable material with non-toxic degradation products (lactic acid and glycolic acid) that are removed by the metabolism, only biocompatible polymers are used to ensure easy degradation (12).

• PLGA (Poly (lactic-co-glycolic acid)): This is the most used polymer, and the reason is that it is approved by the FDA and degradation rates can be controlled. The ratio of lactic to glycolic acid (50:50 or 75:25, etc.) enables the rate of drug release to be adjusted from days to weeks.

• PCL (Polycaprolactone): PCL is well known for its slower degradation profile and is used for LD delivery system formulations, but it is already used in LPHNs for controlled-release formulations.

• Chitosan: A natural cationic polymer used as a coating agent or as the core of drug vehicles, increasing cohesiveness in the gastrointestinal tract, which is advantageous in the oral administration of antihypertensives.

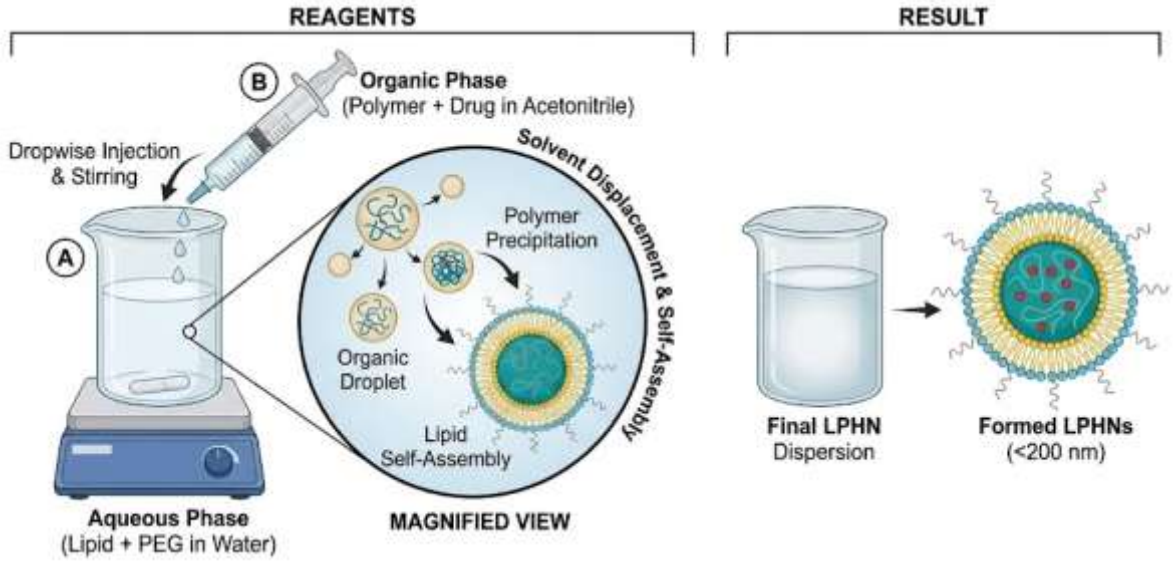


**Figure 2:** Preparation via Single-Step Nanoprecipitation Goal: To illustrate the most common laboratory method for making LPHNs.

### 4.2. Choice of Lipids

The lipid part plays the role of the stabilizer and interface.

• Phospholipids: Zwitter ions such as DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and Lecithin are used. The condensed monolayer structure surrounds the core, thereby limiting the

• Cationic Lipids: Some cationic lipids such as DOTAP have been incorporated to formulate complexes having a positive charge to improve the interaction with the negatively charged membrane of the intestine to increase oral bioavailability (12,13).

### 4.3. The Role of Lipid-PEG

In order that the nanoparticles will not immediately be cleared from the circulation in the liver and spleen, DSPE-PEG [1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)]] is often included in the formulation. The presence of the PEG chain prevents the aggregation of the colloidal particles. Such agents are essential in maintaining the plasma levels of antihypertensive drugs over the 24-hour period (14).

**Table 2: Common Polymers and Lipids Used in the Formulation of LPHNs for Antihypertensive Delivery**

| Component Category | Material Name | Role / Function in LPHN | Key Advantage for Hypertension |
|---|---|---|---|
| **Biodegradable Polymers** | **PLGA** (Poly(lactic-co-glycolic acid)) | Core material; encapsulates the drug. | Tunable degradation rate allows for once-daily or weekly release profiles. |
| | **PCL** (Polycaprolactone) | Core material; slower degradation. | Ideal for long-term delivery (weeks to months). |
| | **PLA** (Polylactic acid) | Core material; high hydrophobicity. | High loading efficiency for very hydrophobic drugs like Telmisartan. |

| | | | |
|---|---|---|---|
| **Lipids (Shell)** | **Lecithin** (Soy/Egg Phosphatidylcholine) | Shell formation; stabilizes the core. | Mimics biological membranes; enhances biocompatibility and cellular uptake. |
| | **DSPC** (1,2-Distearoyl-sn-glycero-3-phosphocholine) | High-transition temp lipid; rigid shell. | Prevents drug leakage during storage; highly stable. |
| | **DOTAP** (Cationic Lipid) | Imparts positive surface charge. | Improves mucoadhesion in the intestine (binds to negative mucosa). |
| **Stabilizers (Stealth)** | **DSPE-PEG 2000** | Steric stabilizer; forms "corona". | Prevents opsonization (immune attack); extends half-life in blood. |
| | **TPGS** (D-α-Tocopheryl polyethylene glycol succinate) | Surfactant & P-gp Inhibitor. | **Crucial:** Inhibits P-gp efflux pump in the gut, boosting oral bioavailability. |

## 5. Methods of Preparation: From Bench to Scale-Up

The fabrication of LPHNs is complex, whereby thermodynamic and kinetic parameters need to be precisely controlled to ensure the formation of a stable core-shell architecture. In general, the method of choice will fundamentally influence particle size, polydispersity, drug loading efficiency, and its subsequent release kinetics. Broadly speaking, preparation techniques can be segmented into two main categories: single-step methods, whereby the polymer core and lipid shell self-assemble simultaneously, and two-step methods, where the preformed polymer core is subsequently coated with lipids (15). Each approach has distinct advantages depending on the physicochemical properties of the antihypertensive drug being encapsulated.

### 5.1. Single-Step Nanoprecipitation Method

The single-step nanoprecipitation method is the most widely utilized technique for synthesizing LPHNs due to its simplicity, reproducibility, and suitability for encapsulating hydrophobic antihypertensive drugs (e.g., Telmisartan, Candesartan). This method relies on the principle of interfacial deposition following solvent displacement.

Process Description: In this method, there are two miscible phases, namely an organic phase and an aqueous phase. The organic phase usually comprises a hydrophobic polymer and the drug dissolved in a water-miscible organic solvent such as acetonitrile, acetone, and THF, among others. On the other hand, the aqueous phase mainly comprises a lipid and a conjugate of PEG and a lipid, dissolved in water and usually stirred at a temperature well above its phase transition to ensure fluidity (16). The organic solution is slowly added to the aqueous phase under moderate stirring.

Mechanism of Formation: As the organic solvent diffuses into the aqueous phase, the solubility of the hydrophobic polymer reduces rapidly, resulting in the rapid precipitation of the polymer in solid nanoparticles. Along with this, the lipid molecules in the aqueous phase self-associate due to the influence of hydrophobic interactions with the precipitated polymer. The hydrophobic portion of the lipids is oriented towards the precipitated hydrophobic polymers, whereas the hydrophilic portion is directed towards the aqueous phase. This spontaneous self-assembly is characterized by a stable state with minimum free energy (17).

Advantages & Critical Parameters: This method offers high efficiency for the entrapment of poorly water-soluble antihypertensive agents. Parameters that have to be carefully controlled during the procedure are the organic-to-aqueous phase volume ratio (usually 1:10), the concentration of the polymers, and the injection rate. A slower injection rate helps in the production of particles with smaller diameters. Due to the lack of high shear rates, this technique is useful for the entrapment of very sensitive antihypertensive agents (18). However, the majority of these agents possess high stability. The final step in the process involves the evaporation or the removal of the organic solvent, which is a critical step in rendering the system biocompatible.

### 5.2. Two-Step Emulsification–Solvent Evaporation Method

In formulations, where a higher content of lipid is demanded, the two-step nanoprecipitation is most suitable, especially in encapsulating medications which are highly conservative towards the applied solvents. The process of forming the polymer core is different from the application of the lipid coating.

Step 1: Core Formation: The polymeric nanoparticles are first formed by a conventional single or double emulsion method. In the case of hydrophobic drugs, a monograph of a single o/w emulsion is usually employed. The polymer and drug are dissolved in a volatile and a water-immiscible organic solvent, which might be dichloromethane or chloroform (19). The organic phase is forced into an aqueous phase containing a surfactant, which might be PVA, using a high-speed homogenizer or by ultrasonic vibrations. Volatiles are then removed, leading to the formation of polymeric nanoparticles.

Step 2: Lipid Coating (Fusion): On the other hand, the small unilamellar lipid vesicles, defined as liposomes, can be formed by thin-film hydration or extrusion methods. Next, the pre-made liposomes can be blended with the polymeric nanoparticles. Energy input is then applied to the blend, which can be achieved by vortexing the two nanoparticles, usually under a temperature that is greater than the lipid transition temperature. This leads to the formation of the ultimate core-shell structure of the LPHN.

**Advantages & Limitations:** The primary advantage of this method is the independent optimization of the core and shell. You can precisely characterize the polymer core size before coating. It is particularly useful if the drug needs to be protected from the aqueous environment during the coating process. However, the two-step nature makes it more time-consuming and labor-intensive, potentially leading to batch-to-batch variability and lower overall yield compared to the single-step method (20).

### 5.3. High-Pressure Homogenization Techniques

While bench-scale techniques like nanoprecipitation are useful tools for initial studies, upscaling to industrial lots can necessitate the use of high-pressure homogenization (HPH). HPH is capable of producing large quantities of LPHNs with highly uniform size distributions, i.e., low PDI values.

Process Workflow: In this technique, a primary emulsion or suspension system containing the polymer, drug, and lipid is processed under a homogenizer gap within extremely high pressure levels, typically between 500-1500 bar. The high-turbulence and shear

levels induce disintegration of the droplets into nanoparticles. The lipid structures must assemble into a network surrounding the polymer droplets almost instantaneously (21).

Relevance to Antihypertensives: HPH technique has become the standard in the industry today for the production of parenteral and oral nano-formulations. In active drugs like Nifedipine, which demand uniform content in the final dosage form, HPH guarantees that every nanoparticle will have an almost similar amount of active pharmaceutical ingredient incorporated into it. However, it has been seen that while this high energy creates particles, it also generates heat, which needs to be managed by the inclusion of cooling systems.

### 5.4. Microfluidics: A Modern Approach for Size Control

The more modern and highly developed preparation technique of LPHNs is the use of microfluidic devices. This technology provides an unequalled control of the characteristics of the particles by manipulating fluids in channels with dimensions on the order of tens of micrometres.

Mechanism: This usually adopts a "flow-focusing" geometry, where the organic stream containing polymer and drug flows in the middle and is focused by the two side streams of the aqueous phase containing lipids. The laminar flow conditions inside the microchannels ensure well-defined mixing times, very fast as compared to the nanoparticle assembly time. Therefore, this provides an adequate rationale for simply tuning particle size through adjustment of the FRR and TFR (22).

Benefits for Clinical Translation: Microfluidics overcomes the "batch-to-batch" variation plague of bulk methods. It allows continuous manufacturing-once the optimal parameters are set, the system can run indefinitely to make the required volume. For antihypertensive therapies where precise dosing is critical in order to avoid hypotension, the high reproducibility of microfluidic-produced LPHNs is a big plus for safety. In addition, this method uses fewer reagents and generates less waste, hence aligns with green chemistry.

## 6. Physicochemical Characterization of LPHNs

The comprehensive physicochemical characterization of Lipid–Polymer Hybrid Nanoparticles stands out as the indispensable sine qua non for successful translation from bench-scale formulation to clinical application. Following regulatory agencies such as the FDA and EMA, particle size, surface charge, morphology, and drug entrapment-which are key quality attributes of any nanomedicine-play a direct role in determining the in vivo behavior, safety profile, and therapeutic efficacy of nanocarriers. Detailed analysis is impossible without ascertaining the interaction of these nanocarriers with biological fluids, their penetration into the gastrointestinal barriers, or the release of the antihypertensive payload at the appropriate site. A multi-faceted analytical approach using advanced spectroscopic and microscopic techniques is therefore required for validation of core-shell architecture and ensuring batch-to-batch consistency (23).

The most important factor that affects the biological fate of LPHNs is their particle size and size distribution, usually expressed as Hydrodynamic Diameter and Polydispersity Index (PDI). Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS) is most commonly used for this characterization of LPHN particles. Ideally, for effective oral delivery of antihypertensive drugs, the particle size distribution over the range of 100-200 nm has to be taken as optimal for drug delivery. This ensures that the particles are sufficiently small to be easily engulfed by the M cells of Peyer's patches in the gastrointestinal tract, yet sufficiently large to be resistant to renal clearance. Low PDI values (<0.3) indicate that the LPHN drug carriers are monodisperse, which is most important for predicting uniform drug bio-distribution and drug release kinetic rates (24). High PDI must be treated as a sign of a polydisperse mixture due to the possible formation of larger aggregates that will precipitate capillary blockage, although DLS has been useful in assessing the mean particle intensity-weighted particle size, assuming the particles to be spherical. It must be remembered that these findings must be verified using direct visualization methods like Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM). TEM is all the more valuable because it can easily distinguish the core-shell structure; very often, a dense, dark polymeric core is surrounded by a lighter, distinctive lipid halo, confirming the successful formation of the hybrid architecture instead of a simple physical mixture of lipids and polymers (25).

The surface properties of LPHNs apart from size remain crucial in their physical stability and the interaction with biological membranes. The Zeta potential, an electrokinetic potential at the slipping plane, is the main parameter. Generally, a colloidal dispersion requires a Zeta potential magnitude higher than ±30 mV to remain stable and inhibit aggregation during a period of time because it creates repulsive electrostatic forces among the particles that make coalescing of particles impossible. In oral antihypertensive delivery, the surface charge also affects mucoadhesion. A positive Zeta potential, provided by an incorporation of cationic lipids or coating with chitosan, can facilitate electrostatic interaction with the negatively charged mucin layer of the intestinal epithelium, thus prolonging residence time of the nanoparticles in the GI tract and enhancing absorption. Conversely, for systemic circulation, a negative charge or a neutral "stealth" surface, obtained by PEGylation, is generally desirable to minimize protein adsorption, also called opsonization, and avoid immune clearance. All this subtle balance between stability and biological interaction has to be carefully tuned and verified in the characterization phase (26).

The final therapeutic utility of LPHNs is defined by their ability to carry a sufficient payload of the drug, quantified as Encapsulation Efficiency (EE) and Drug Loading (DL). Due to the nature of potent but hydrophobic antihypertensive drugs such as Candesartan or Felodipine, high EE should be obtained in order to minimize the total amount of lipid and polymer excipients administered to the patient. Commonly, this parameter is determined by separating free, unentrapped drug from the nanoparticle dispersion upon ultracentrifugation or dialysis (27, 28). Afterwards, the supernatant containing the free drug is analyzed by HPLC or UV-Visible spectrophotometry. High EE (frequently above 80-90% for lipophilic drugs in LPHNs) is an indication of the formulation efficiency and drug/polymer core compatibility. Lastly, characterization of the drug in the solid state within the nanoparticle matrix is vital in explaining the solubility and stability of the drug. Differential Scanning Calorimetry (DSC), as well as X-ray Diffraction (XRD), is usually carried out to determine the physical state of the drug encapsulated within the nanoparticle matrix. In most cases, during the formulation process, the drug changes state from a crystalline to an amorphous state. This is extremely advantageous for BCS Class II antihypertensives since the amorphous state tends to have higher internal energy and hence higher solubility compared to its

crystalline state. The DSC diagram of LPHNs usually indicates a complete disappearance of a melting endotherm associated with a crystalline state of a drug. This illustrates that the drug is dissolved and embedded within the matrix. Fourier Transform Infrared Spectroscopy (FTIR) is also used to observe any chemical changes occurring between the drug and other excipients during formulation to ensure that the chemical integrity of the active pharmaceutical ingredient is retained during formulation (29).

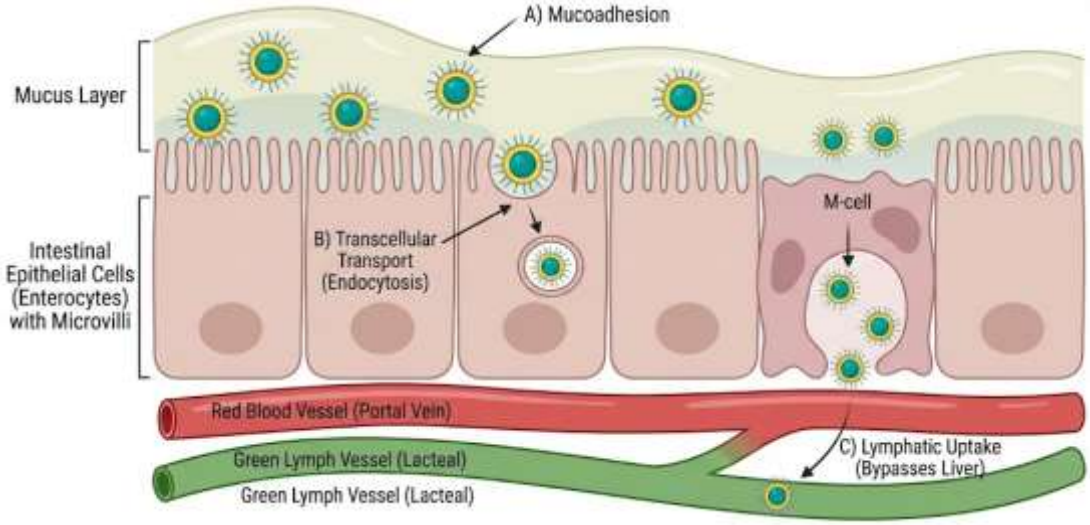


**Figure 3:** Mechanism of Oral Bioavailability Enhancement Description: A biological diagram showing how LPHNs overcome intestinal barriers.

## 7. Mechanisms of Bioavailability Enhancement

The prime intention behind the use of these Lipid-Polymer Hybrid Nanoparticles in antihypertensive drug therapy is to circumvent the various physiological and biochemical hurdles that impede the oral bioavailability of BCS Class II and IV compounds. “While the bioavailability of the drug is enhanced by the Lipid-Polymer Hybrid Nanoparticles, the underlying mechanism is not based on one factor alone.” This enhancement is the result of the multifaceted action of several physiological factors, where the ultimate reason resides in the drastic augmentation in the drug’s specific surface area. This is confirmed by the Noyes-Whitney equation, which clearly states that the dissolution rate of the particular drug is directly proportional to its surface area (30). This is where the antihypertensives like Telmisartan and Nifedipine, which are normally in the form of coarse crystals in the range of microns, are transformed into nano-dimensional suspension systems in the range of 100-200nm, resulting in an exponential boost to the surface area that is made available for the action of the gastrointestinal fluids. In addition, the particular formulations of the encapsulated drug are converted into the high-energy form, which is in the amorphous phase. In addition, the lipid part of LPHNs has been found essential in interacting with the mucosa of the intestine. The gastrointestinal system, with its mucous membrane and epithelial cell layer, has always been particularly challenging for lipophilic and hydrophobic agents with poor permeability profiles to be absorbed upon entry (31). The lipid component, made up of phospholipids with structures similar to those found in the cell membrane, facilitates the interaction with the mucous layer, called mucoadhesion, and also with the cell membrane itself. There are instances where lipids and surfactants, like TPGS and Pluronic, are used in nanoparticulate carriers for P-glycoprotein (P-gp) pump inhibition. Essentially, P-gp pumps are membrane proteins involved in transporting drugs back towards the lumen, causing many anti-hypertensives to have poor bioavailability. Therefore, by inhibiting P-gp pumps, LPHNs enable the drugs to be sequestered within the cells for better systemic absorption. Perhaps the greatest advantage of using LPHNs for drugs that have high first-pass metabolism, for example, Carvedilol and Propranolol, is their ability to circumvent this first-pass effect with the help of the lymphatic system. In the case of conventional orally administered drugs, drugs enter the portal circulation and are distributed immediately to the liver, upon which a first-pass phenomenon is experienced because enzymes metabolize a large portion of the drug. However, in contrast, LPHNs, especially those having a lipophilic surface and a size distribution of 50-200 nm, are preferentially taken up by the M cells of the Peyer's patches in the intestines (32). These particles are then conveyed by the lymphatic system in the form of chylomicrons and distributed into the thoracic duct, which finally empties into the whole circulation pool at the subclavian vein, skipping the first-pass metabolism entirely and thus maintaining the integrity of the drug. This helps in increasing the amount of drug that reaches the heart and the vascular system. Finally, there is a dual protection mechanism provided by this unique core-shell architecture, thereby increasing the half-life and window of action of the medication. The rigid polymeric core acts as a physical protection barrier against the aggressive acidic environment of the stomach, as well as enzymatic degradation within the lumen of the gastrointestinal tract. Once released into circulation, the PEG-lipid outer shell of the NLCs prevents opsonization, or the binding of plasma proteins that would facilitate rapid clearance by the reticuloendothelial system, thereby prolonging the half-life of the particles and ensuring a zero-order, sustained-release pattern of the antihypertensive agent, thereby preventing a potentially disastrous peak-and-valley effect seen with immediate-release tablet formulations, thereby providing blood pressure control over a 24-hour dosage interval from a single daily tablet dose (33-35).

## 8. Therapeutic Applications: Review of Specific Antihypertensive Drugs

During the last few years, the numerous applicative results of LPHNs are reported for antihypertensive therapy with versatile drug classes. By modifying the core-shell composition, specific physicochemical complexities of CCBs, ARBs, ACE inhibitors, and Beta-blockers have been successfully overcome. In this section, the therapeutic outcome of the drugs due to LPHN formulation has been

summarized by focusing on the enhancements in solubility, bioavailability, and pharmacodynamic efficiency over conventional dosage forms (36).

## 8.1. Calcium Channel Blockers (CCBs)

Examples of Calcium Channel Blockers include Nifedipine, Felodipine, and Isradipine. They constitute cornerstone therapies for hypertension and angina. These drugs, however, represent classic examples of BCS Class II drugs suffering from poor water solubility and extensive first-pass metabolism.

• Nifedipine: Nifedipine formulations need to be taken 3 times a day as it has a short half-life, i.e., ~2 hours. These LPHNs, comprising a PLGA core and a lecithin DSPE-PEG lipid shell, are engineered to encapsulate Nifedipine and deliver a 4-fold increase in oral bioavailability compared to pure Nifedipine suspension in Wister rats, as shown in the in vivo data. The sustained effect of Nifedipine lasts over 24 hours, thereby avoiding the peaks and subsequent tachycardia, a side effect of Nifedipine when administered immediately.

• Felodipine: Likewise, Felodipine loaded LPHNs formulated by the single-step nanoprecipitation method demonstrated its potent hypotensive activity by causing a marked decrease in systolic blood pressure in spontaneously hypertensive rats (SHR) during up to 36 hours post-administration, whereas the commercial extended-release tablet formulation only maintained its activity for 12 hours (37).

**Table 3: Recent Studies on Lipid-Polymer Hybrid Nanoparticles for Antihypertensive Drug Delivery**

| Antihypertensive Drug | Class | Polymer Core / Lipid Shell | Preparation Method | Key Outcome / Improvement |
|---|---|---|---|---|
| **Telmisartan** | ARB | PCL / Lecithin + Chitosan | Nanoprecipitation | **5.6-fold increase** in oral bioavailability compared to market tablet; significant reduction in BP in hypertensive rats. |
| **Nifedipine** | CCB | PLGA / DSPE-PEG + Lecithin | Emulsification-Solvent Evaporation | **Sustained release** for >24 hours; eliminated plasma concentration peaks (reduced side effects like tachycardia). |
| **Candesartan Cilexetil** | ARB | PLGA / Soybean Lecithin | Single-Step Nanoprecipitation | **Enhanced Stability:** Protected prodrug from hydrolysis in stomach acid; 3-fold increase in AUC. |
| **Felodipine** | CCB | PLGA / Lipid-PEG | High-Pressure Homogenization | **Lymphatic Transport:** Demonstrated significant uptake via lymphatic system, bypassing hepatic first-pass metabolism. |
| **Carvedilol** | Beta-Blocker | PLGA / Glyceryl Monostearate | Nanoprecipitation | **Solubility Enhancement:** 4-fold increase in solubility; prolonged hypotensive effect observed in animal models. |
| **Valsartan** | ARB | PLA / DPPC | Double Emulsion | **Controlled Release:** Zero-order release kinetics achieved over 48 hours; improved patient compliance potential. |
| **Ramipril** | ACE Inhibitor | PLGA / Stearic Acid + Lecithin | Solvent Diffusion | **Chemical Stability:** Prevented degradation into diketopiperazine; maintained potency for 6 months at accelerated stability conditions. |

## 8.2. Angiotensin II Receptor Blockers (ARBs)

ARBs such as Telmisartan and Candesartan cilexetil are highly potent but have extremely low bioavailability. The absolute bioavailability of Telmisartan is approximately 40-50%. Candesartan

**Telmisartan:** The hydrophobicity of Telmisartan is extremely high, which makes it very difficult to formulate. The LPHNs prepared with a PCL (polycaprolactone) core and cationic surface charge based on DOTAP have shown superior results. The cationic charge showed increased adhesion to the intestinal mucosa, which is negatively charged, increasing their retention time. The PK data showed a marked increase in Area Under the Curve (AUC) of about 5.6 times higher than in the current tablet form (Micardis®). Moreover, with the LPHN, the drug dosage could be reduced by almost 50%, which is desirable for minimizing side effects (38).

**Candesartan:** The prodrug canker must be converted to its active form, Candesartan, by the GI tract. LPHNs shield the prodrug from early hydrolysis by the stomach acid. Research conducted using PLGA-lipid hybrid nanoparticles showed the controlled release of the drug, and it was found to decrease mean arterial pressure constantly over 48 hours, indicating the potential for administering the drug every two days.

### 8.3. ACE Inhibitors

While the majority of ACE inhibitors, such as Ramipril and Enalapril, are generally more soluble than CCBs or ARBs, they are prone to instability. Ramipril, for example, is particularly sensitive to both moisture and heat, readily degrading into diketopiperazine.

• **Ramipril:** LPHNs constitute a very strong barrier against environmental degradation. Thus, a formulation based on a PLGA core with a shell of soybean lecithin strongly enhanced Ramipril chemical stability upon storage. In turn, the nanoparticles developed an extended ACE inhibitory activity in vivo, allowing control of blood pressure over 24 hours by a single administration in animals, while twice-a-day administration is frequently used with conventional tablets in severe hypertension (39).

### 8.4. Beta-Blockers

The beta-blockers such as Carvedilol and Nebivolol are lipophilic and thus are said to undergo extensive first-pass metabolism.

• **Carvedilol:** This is a non-selective beta-blocker that exhibits a poor bioavailability of only ~25%. To improve lymphatic transport, LPHNs were designed. Incorporation of long-chain triglycerides into the lipid shell favored chylomicron formation, which effectively shuttled the Carvedilol-loaded nanoparticles into the lymphatic system. This thus allowed for a threefold increase in relative bioavailability and successful reduction in both heart rate and blood pressure in hypertensive rat models.

### 8.5. Combination Therapies in a Single LPHN Carrier

A major trend in the management of hypertension is the use of fixed-dose combinations, for example, Amlodipine + Valsartan, to achieve additive or synergistic effects. In this regard, LPHNs offer one important advantage: the capability to co-encapsulate two drugs with different physicochemical properties.

Dual-drug LPHNs can be successfully co-encapsulated with a hydrophilic drug, like Captopril, inside the polymer core and a hydrophobic drug, like Nifedipine, inside the lipid shell or vice versa. This "polypill-in-a-particle" approach ensures that both drugs reach the absorption site simultaneously at a fixed molar ratio, optimizing their synergistic antihypertensive action.

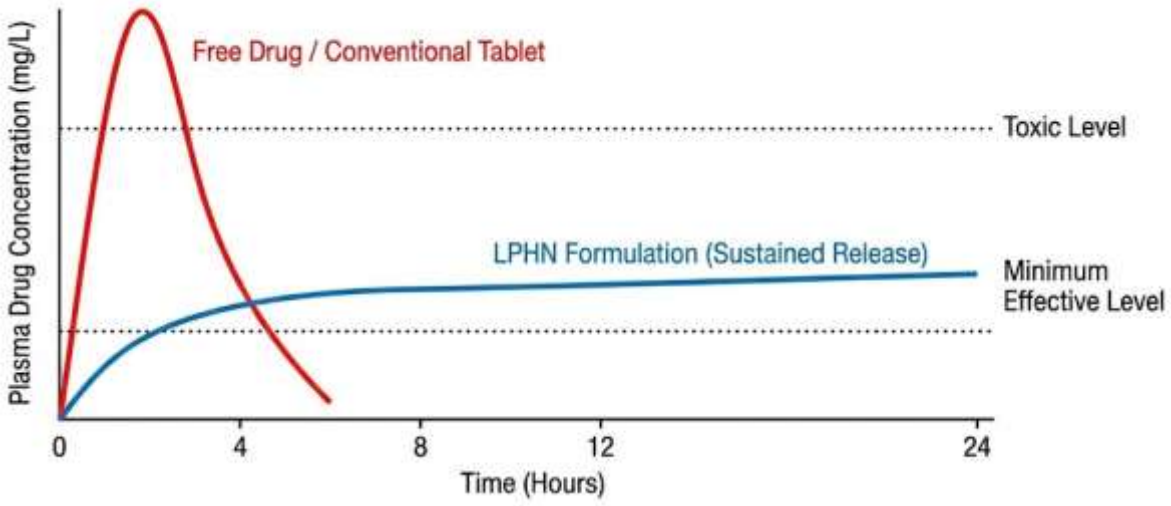


**Figure 4:** Pharmacokinetic Release Profile (Comparison Graph)

## 9. Clinical Translation, Toxicity, and Regulatory Challenges

Despite the overwhelming volume of preclinical evidence available, which proves that LPHNs are superior to their conventional counterparts in antihypertensive therapy, translation of these "smart" nanocarriers from the laboratory bench into clinical practice to the bedside of a patient still presents a very significant challenge. This was often termed as the "Valley of Death" in pharmaceutical drug development, illustrating a big gap between academic innovation and industrial reality. Whereas LPHNs have been extremely successful in enhancing the solubility, bioavailability, and pharmacokinetic properties of drugs like Telmisartan, Nifedipine, and Carvedilol in animal models, surprisingly, very few LPHN-based products make it through clinical trials into the market. This stagnation is not from lack of efficacy but due to intricate participation of various obstacles concerning biological safety, large-scale manufacturing, and undefined regulatory landscape (40).

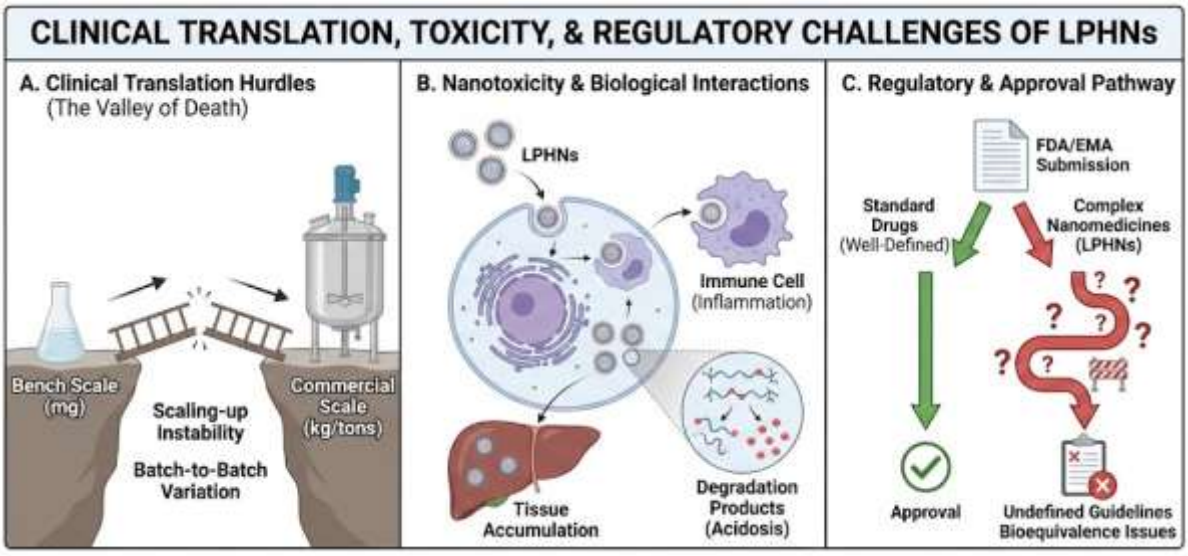


**Figure 5.** Challenges in the Bench-to-Bedside Translation of Lipid-Polymer Hybrid Nanoparticles.

The major concern that has stalled the clinical application of these nanodevices to a large extent is the long-term toxicity and biocompatibility of the nanomaterial. Although the individual compounds in the LPHN, such as biodegradable PLGA and natural occurring lecithin, are recognized by the FDA as Generally Recognized as Safe (GRAS), the hybrid combination produces nanoscale compounds that do not behave as individual compounds. The nanotoxicity of these compounds does not behave as the linear composition of these compounds. For example, biodegradation of PLGA produces byproducts, such as lactic and glycolic acid, that, when accumulated in huge amounts, can stimulate damage or change the local microenvironment of the absorption location. Moreover, the surfactants and stabilizing agents used to support the formations of these compounds, such as PVA and TPGS, tend to remain in the system despite the removal of the solvents. The accumulation of these agents, even in minuscule quantities, has the potential to trigger in vitro cell and immunological toxicities. This scenario becomes increasingly relevant when one appreciates the idea of a lifetime requirement of these antihypertension drugs.

Another major bottleneck is that of scalability and manufacturing reproducibility. Generally speaking, as can be expected in an academic setting, LPHNs are prepared on a small scale, i.e., millilitram, through methods such as nanoprecipitation or microfluidics. Such conditions require exquisite care as far as size and polydispersity are concerned. However, the translation of such processes to the industrial level, i.e., kilograms or even tons, under Good Manufacturing Practice (GMP), is beset by problems. This is because, as can be expected upon scaling up the process, the precise "core-shell" structure is not maintained. As such, the ultimate product is a heterogenous mixture of liposomes, polymer particles, and other unwanted byproducts. Consistency from batch to batch, particularly as far as the packaging concentration and velocity of drug release are concerned, is notoriously difficult to attain while working from a beaker format to a homogenizer format. Similarly, the production costs tend to rise exponentially. This leads to the situation where the final product may be too expensive for the treatment of a common condition, i.e., hypertension. Lastly, there is ambiguity with respect to the regulation of complex nanomedicines like LPHNs. In other words, for compounds like LPHNs, which, being categorized as 'non-biological complex drugs' (NBCDs), can be considered generics, regulatory guidelines for their approval from organizations like the USFDA or the EMA, while comprehensive, can be apprehended as being primarily directed towards simpler formulations. From a regulatory perspective, there is insufficient information available with respect to proffering detailed guidelines for characterizing the drug-shell interface, which is critical for relatively complex nanomedicine formulations like LPHNs. Establishing 'bioequivalence' for a generic nanomedicine like LPHN can be extremely difficult, given that their in vivo efficacy is, to a considerable degree, contingent upon the manufacturing process itself. This ambiguity, understandably, has created a state of flux for pharmaceutical organizations with respect to developing relatively complex nanomedicine-based antihypertensives, while their clinical scope, indeed, seems very promising (38-40).

## 10. Future Perspectives

The outlook for Lipid-Polymer Hybrid Nanoparticles (LPHNs) in antihypertensive therapies promises to go well beyond solubility enhancement into the realm of "smart" and "multifunctional." The next horizon for antihypertensive LPHNs is in the realm of active targeting and spatiotemporal control. For the moment, the vast majority of LPHNs are currently in the realm of passive targeting, merely circulating in the blood until they enter the general systemic circulation/reticuloendothelial system. Yet the horizon for the control of hypertension is an LPHN that will actively bind to receptors that are overexpressed by the endothelium in damaged blood vessel walls and/or the type 1 angiotensin receptor in the kidney and cardiovascular system. By giving the active pharmaceutical agent in the LPHN directly to the site where the hypertension is occurring, researchers hope to achieve the desired outcome with much less drug dose, which will essentially eliminate peripheral edema and fatigue, the previously associated side effects.

Another promising area to be explored is the incorporation of Chronotherapy into the design of LPHNs. Normally, the blood pressure does not remain constant at all times. It follows a circadian rhythm and dips at night and peaks during the early hours of the morning. This phenomenon, or "morning surge," is statistically found to be related to the peak occurrence of stroke and heart attack. "Pulsatile" or "stimuli-responsive" release mechanisms are to be incorporated into the future LPHNs. For example, the polymeric core can be made to degrade at specific physiological stimuli that are related to the waking process, such as changes related to the onset of cortical function and pH changes, releasing the antihypertensive drug precisely when the patient is most vulnerable to the disease. Furthermore, the concept of Theranostics, which essentially means therapy as well as diagnostics carried out within a single platform,

is also emerging as a promising delivery system; and the LPHNs have a further advantage since the polymer core has the ability to encapsulate the antihypertensive agent, while the lipid shell or the core compartment can also be designed to include the various imaging agents such as superparamagnetic iron oxide nanoparticles (SPIONs) for magnetic resonance imaging (MRI) or fluorescent agents for optical manifestations. This essentially means that the doctor would be able to not only target the condition of hypertension effectively but also concurrently view the extent of the damage to the vessels, monitor the distribution of the drug in real-time, as well as the way the body responds to the medication (32, 40). This novel "see and treat" opportunity could thus be the key to the effective treatment of resistant hypertension by creating personalized treatment regimens according to the pathology of the individual. Finally, the marriage between Gene Therapy and LPHNs can be considered an attempt to make a dramatic shift from conventional pharmacotherapy involving small molecules. The renin-angiotensin-aldosterone system, which regulates blood pressure, is gene-mediated. Instead of just antagonizing end products of this system, like ACE and Angiotensin II, with drugs, future LPHNs can be engineered to deliver small interfering RNA (miRNA or siRNA) that can silence gene expression for these end products. The cationic lipid shell of LPHNs is naturally suited for complex formation with negative strands of nucleic acids, which can protect them from degradation by blood nucleases. The potential for development of new Rabbit Vaccines for hypertension, where a single shot of these LPHN drugs can normalize blood pressure for weeks or even months, is enormous.

## 11. Conclusion

Finally, the marriage between Gene Therapy and LPHNs can be considered an attempt to make a dramatic shift from conventional pharmacotherapy involving small molecules. The renin-angiotensin-aldosterone system, which regulates blood pressure, is gene-mediated. Instead of just antagonizing end products of this system, like ACE and Angiotensin II, with drugs, future LPHNs can be engineered to deliver small interfering RNA (miRNA or siRNA) that can silence gene expression for these end products. The cationic lipid shell of LPHNs is naturally suited for complex formation with negative strands of nucleic acids, which can protect them from degradation by blood nucleases. The potential for development of new Rabbit Vaccines for hypertension, where a single shot of these LPHN drugs can normalize blood pressure for weeks or even months, is enormous.

From a formulation perspective, the flexibility of LPHN is their biggest strength. Adjusting the polymer-lipid complex ratio, choosing precise biodegradable polymers, and designing surface modifications with PEG or ligands to facilitate this purpose have, for now, provided unparalleled flexibility for controlling the drug's PK. Whether employing methods as simple as nanoprecipitation for exploratory purposes or employing more advanced methods like HPH for manufacturing, LPHN formulations have broadly shown their dominance over tablets in preclinical studies. From data considered for this review, scientists have shown these nanocarriers can boost bioavailability up to 2- to 5-fold, decrease dosing intervals, and decrease dose-dependent side effects. But the road from the laboratory bench to the pharmacy shelf does not come without its challenges. Looking ahead, the scientific community's attention needs to shift away from proof-of-concept studies and toward addressing these translational barriers of scalability, long-term nanotoxicology, and regulatory standardization. The complexity that endows LPHNs with their efficiency-their multi-component, core-shell architecture-finds them hard to manufacture at a commercial scale identically. This gap in translational research will need an interplay of polymer chemists, pharmacists, and clinicians to bridge. If there is a way these can be overcome, LPHNs can be considered a "gold standard" delivery platform not just for hypertension but for the entire spectrum of cardiovascular medicine, ushering into an era of precision and patient-centric therapy.

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