REVIEW ARTICLE

Lipid-Based Drug Delivery Systems for Antihypertensive Therapy: Emerging Concepts, Formulation Advances, and Future Clinical Potential

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Abstract

Hypertension still represents one of the most prevalent global health burdens with sustained hurdles for achieving sufficient long-term control, because of poor compliance, dosing complexity, and oral drug pharmacokinetic fluctuations. Lipid-based drug delivery systems (LBDDS) can be a potential solution to these problems for effective treatment of hypertension by enhancing solubility, protection against pre-systemic metabolism, and promotion of intestinal lymphatic transport, as well as the possibility of prolonged or site-specific release. Here, we offer a synthesis of the current knowledge about the most important lipidic drug delivery platforms, respectively, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, lipid–polymer hybrid nanoparticles, and nanoemulsions, addressing their structural aspects for antihypertensive therapeutic strategies, formulation constraints, and activity potential against representative hypertensive drugs. Key formulation variables (lipid selection, surfactant type, particle size, polydispersity index, and encapsulation efficiency) and stability challenges (lipid oxidation, polymorphic transitions, surfactant hydrolysis, and drug expulsion) are examined alongside common excipients and mitigation strategies such as antioxidants, mixed lipid matrices, and cryoprotectants. Translational barriers, such as manufacturing scale-up, reproducibility, long-term safety, regulatory characterization requirements, and economic considerations, are discussed, as are opportunities from microfluidic manufacturing, targeted surface functionalization, and alternative administration routes (transdermal, buccal, and intranasal) to enable precision dosing and rapid onset where needed. The review concludes that while robust pre-clinical data support the pharmacokinetic and compliance advantages of LBDDS for antihypertensives, coordinated efforts in standardizing characterization, validating *in vitro–in vivo* correlations, and conducting comparative clinical trials are essential for clinical translation and adoption, particularly in resource-limited settings.

Key words: Antihypertensive drugs, lipid-based drug delivery, liposomes, nanoemulsions, nanostructured lipid carriers, solid lipid nanoparticles

INTRODUCTION

Over 1.4 billion adults worldwide suffer from hypertension, with almost a third living in low- and middle-income nations.[1] Hypertension persists as a substantial cause of morbidity and mortality worldwide. Many people still struggle to control their high blood pressure despite years of advancements in medicine. Approximately 29.8% of adults in India suffer from high blood pressure, frequently with inadequate long-term management and poor medication adherence.[2] Lifelong treatment is required because high blood pressure is frequently asymptomatic, but it is still challenging to maintain steady, adequate plasma levels of antihypertensive medications.[3]

Lifestyle modification and oral tablets are mainly used for hypertension prevention. Although these regimens are effective, their efficacy may be diminished or adverse

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effects may arise due to variable absorption, first-pass liver metabolism, and fluctuating plasma levels.[1,4] Due to extensive pre-systemic metabolism, medications such as losartan, verapamil, and propranolol have low bioavailability. Furthermore, complicated dosing regimens and polypharmacy eventually reduce patient adherence.[5]

New drug delivery platforms, particularly lipid-based drug delivery systems (LBDDS), have gained significant interest as potential solutions to limitations such as poor pharmacokinetic profiles (including low bioavailability and variable absorption) and reduced patient adherence associated with conventional antihypertensive therapies. In addition to encouraging intestinal lymphatic transport and regulated drug release, these systems use natural lipids to encapsulate, improve solubility, and protect medications from degradation.[6] They are particularly appropriate for lipophilic antihypertensive drugs with low water solubility due to their biocompatibility and adaptability.[7] Liposomes, immobilized lipid nanoparticles, nanostructured lipid carriers (NLCs), nanoemulsions, and growing lipid-polymer hybrid systems are examples of such formulations. When combined, they allow for the customization of release profiles, increase absorption, and reduce systemic variability, all of which are significant benefits for treating chronic illnesses which rely on oral pharmacotherapy.[6,7]

This review provides a current, systems-oriented overview of lipid-based targeted delivery strategies for antihypertensive medications.

ADVANTAGES AND CONCEPTUAL UNDERPINNINGS OF LIPID-BASED SYSTEMS

Lipid-based transport systems take advantage of lipids' inherent ability to work with organic membranes. Low oral bioavailability and unpredictable absorption are common characteristics of drugs that are poorly soluble in water (log P > 2, indicated by a slow dissolution rate). By keeping the drug dissolved or in a colloidal system created during digestion, their inclusion in lipid matrices improves their apparent solubility.[8] By generating mixed micelles that quickly interact with enterocytes and increase permeability across organic membranes, lipid excipients facilitate intestinal lipolysis.[9]

The capability of lipid-based formulations to avoid the liver's first-pass metabolism is a significant pharmacokinetic advantage. When taken orally, the intestinal lymphatic system can absorb digestive agents and lipid particles without going through the portal vein. For lipophilic antihypertensive medications such as carvedilol and nifedipine, which would otherwise undergo significant metabolic breakdown, this method is particularly beneficial.[10] Lymphatic absorption increases bioavailability and prolongs the half-life of the drug. Another key advantage of LBDDS is controlled and sustained release. Formulators can modify membrane permeability and lipid crystallinity by adjusting the solid–liquid ratio and lipid composition, resulting in an optimal release profile for a 12–24-h antihypertensive action. The naturally biocompatible and biomimetic nature of lipids also reduces the risk of irritation and can be administered by both oral and parenteral methods of drug delivery.[10,11] Continuous-dose therapy is recommended for chronic conditions such as high blood pressure to prevent fluctuations that could result in episodes of hypotension or rebound hypertension. LBDDS simplifies dosage and boosts compliance by offering continuous medication production with little patient involvement. Single-dose sustained-release formulations should considerably lower dosing frequency and side effects in older people with polypharmacy.[12]

Four interrelated concepts – metabolic protection, sustained systemic exposure, improved patient compliance, and bioavailability enhancement through solubilization form the conceptual foundation for the use of lipid-based structures in antihypertensive drug delivery. All of these benefits make LBDDS a desirable alternative to well-known tablets in the best delivery systems intended for long-term treatment.[7,10]

MAJOR LIPID-BASED DELIVERY SYSTEMS

A number of well-known lipidic carrier systems have shown promise for the creation of antihypertensive medication [Figure 1]. Both hydrophilic and lipophilic medications are traditionally transported by liposomes, which are made of phospholipid bilayers encasing aqueous compartments.[13] To achieve targeted vascular delivery and prolonged release, they can encapsulate antihypertensive medications such as amlodipine or captopril. Polyethylene glycol surface modification can reduce opsonization and increase circulation half-life. Physical instability brought on by phospholipid oxidation and leakage, however, continues to be a major problem that calls for the use of antioxidants and carefully monitored storage conditions.[14]

Solid lipids stabilized by surfactants make up solid lipid nanoparticles (SLNs), which are submicron carriers. Because of their crystalline core matrix, they provide controlled release and high drug loading for moderately lipophilic drugs. SLNs loaded with nimodipine and valsartan have shown enhanced bioavailability and lower degradation in antihypertensive studies.[15] The second generation of lipid nanocarriers, known as NLCs, combines liquid and solid lipids to form a less ordered internal matrix that improves drug accommodation and lowers the risk of expulsion. NLC systems provide better intestinal uptake and stability for medications such as losartan or nebivolol, both *in vitro* and *in vivo*. Their scalability and

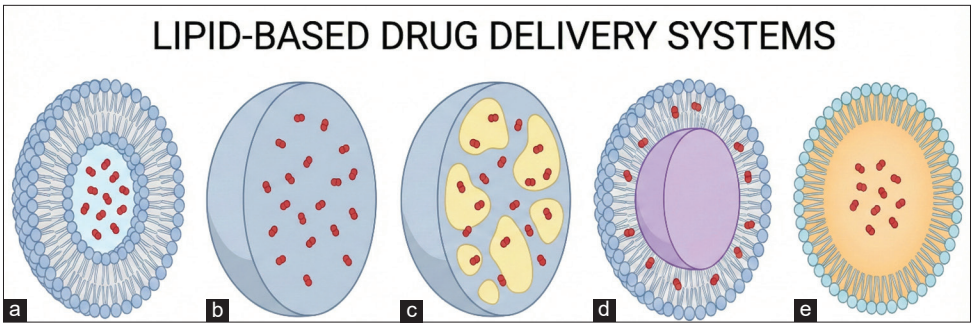

Figure 1: Structural representation of major lipid-based drug delivery systems used in antihypertensive therapy: (a) Liposome, (b) solid lipid nanoparticle, (c) nanostructured lipid carrier, (d) lipid–polymer hybrid nanoparticle, and (e) nanoemulsion droplet

physical flexibility make them particularly attractive for oral and transdermal antihypertensive formulations.[11,15]

Lipid-polymer hybrid nanoparticles (LPHNs) combine the advantages of lipid systems (biocompatibility and cellular interaction) and polymeric nanoparticles (mechanical robustness and controlled release). Usually, a lipid shell is applied to a polymeric core to regulate drug diffusion and improve *in vivo* stability. Dual-release tuning and surface functionalization of antihypertensives encapsulated in LPHNs can provide opportunities for targeted delivery to endothelial or cardiac tissue.[16]

Another important role is played by nanoemulsions, which are finely dispersed water-in-oil or oil-in-water systems. High kinetic stability and optical transparency are produced by their tiny droplet size (<200 nm). Nanoemulsions greatly improve intestinal absorption and dissolution for lipophilic antihypertensive drugs such as felodipine, sometimes leading to a 3–5-fold increase in bioavailability. Formulation simplicity, however, contrasts with challenges in long-term stability and surfactant sensitivity to temperature and pH.[17]

FORMULATION PROPERTIES AND STABILITY ISSUES

It is necessary to take into consideration the lipid composition, surfactant type, and processing conditions carefully in order to design potent LBDDS. Lipids need to remain compatible with the physiological environment of the body and the drug. Because they balance fluidity and melting point, medium-chain triglycerides and glyceryl behenate are frequently utilized lipid matrices. Lipids such as phytantriol or stearic acid help ensure uniform encapsulation of highly hydrophobic antihypertensive molecules while preventing leakage caused by crystallization.[19] The general formulation workflow for lipid-based antihypertensive nanocarriers is illustrated in [Figure 2].

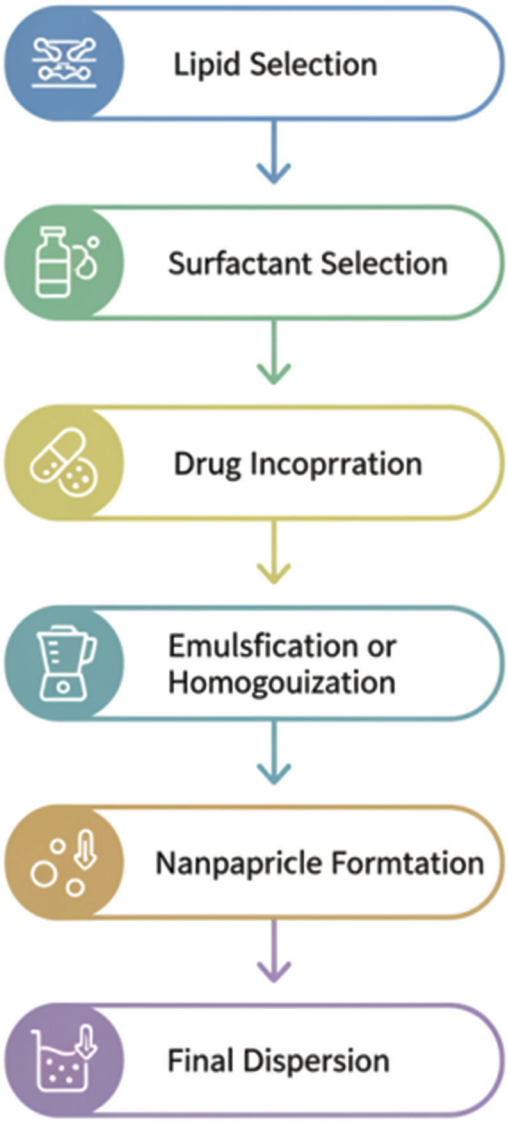

Figure 2: General formulation steps involved in the preparation of lipid-based drug delivery systems for antihypertensive therapy

Particle size, stability, and polydispersity index (PDI) are all significantly impacted by the choice of surfactant. Due to low toxicity, non-ionic surfactants such as polysorbate 80, poloxamer 188, or lecithin are preferred for oral or intravenous applications. Optimizing formulation is necessary to reduce micellar solubilization, which could cause the drug to release too soon. Reproducibility is

Table 1: Comparative features of lipid-based systems for antihypertensive drug delivery

System	Principal structure	Representative advantages	Common issues	Typical antihypertensive examples	References
Liposomes	Phospholipid bilayers enclosing an aqueous core	Versatile for hydrophilic/lipophilic drugs; biocompatible	Oxidation, leakage	Amlodipine, captopril	[13,14]
SLNs	Solid lipid core+ surfactant layer	Controlled release; physical stability	Drug expulsion, polymorphic transitions	Nimodipine, valsartan	[11,15]
NLCs	Blend of solid and liquid lipids	High loading, better stability	Complexity of lipid ratio optimization	Losartan, nebivolol	[17,18]
LPHNs	Polymeric core–lipid shell	Dual control, surface functionalization	Multi-step fabrication	Carvedilol, enalapril	[16]
Nanoemulsions	Oil–water dispersed phase	Solubilization, rapid absorption	Surfactant sensitivity, storage instability	Felodipine, nifedipine	[17]

SLNs: Solid lipid nanoparticles, NLCs: Nanostructured lipid carriers, LPHNs: Lipid-polymer hybrid nanoparticles

impacted by the way surfactant and lipid phases interact to control droplet formation energy during high-pressure homogenization or ultrasonication.[20,21]

The solubility of the active molecule in the lipid phase and process variables such as homogenization cycles and cooling rate determine encapsulation efficiency. For instance, because of its affinity for lipid matrices, carvedilol shows 80–90% encapsulation efficiency in optimized NLC formulations. Stability concerns remain a practical concern.[22]

α-tocopherol or butylated hydroxytoluene reduces rancidity and drug degradation caused by lipid oxidation, particularly in unsaturated systems. Drug molecules may be expelled by crystallization transitions during storage, especially in SLNs made of high-purity lipids with monoform polymorphism.[23] Such challenges can be avoided by combining liquid and solid lipids or by employing amphiphilic polymers. Surfactants may, under humidity stress, hydrolyze or phase separate, requiring lyophilization or the addition of cryoprotectants to extend their shelf life.[24]

TRANSLATIONAL AND REGULATORY OBSTACLES

The clinical application of LBDDS in antihypertensive therapy is still limited, despite strong laboratory evidence. Characteristics of nanocarriers, including mean particle size, PDI (<0.3), zeta potential magnitude (>±30 mV preferred), drug loading efficiency, and repeatable release kinetics, are required by regulatory bodies such as the US Food and Drug Administration and European Medicines Agency.[25] Inconsistent product quality is oftentimes caused by variability in preparation techniques, such as solvent diffusion, melt emulsification, and microemulsion template.[26] One major manufacturing challenge is establishing scale-up procedures while preserving encapsulation performance and particle uniformity. Another regulatory obstacle is long-term safety. Concerns regarding accumulation, complement activation, and unanticipated effects on lipid metabolism are raised by long-term nanoparticle administration.[27] Excipient contaminants or surfactant residues can change biocompatibility, especially for parenteral use, even though lipids are physiologically tolerated. Approval is complicated by the absence of predictive *in vitro–in vivo* correlation models and standardized stability protocols. Due to complicated regulations and few commercial incentives, the majority of lipid-based antihypertensive formulations are still in pre-clinical evaluation; only a small number have progressed to human trials.[28]

Industrial uptake is also impacted by cost-benefit analysis and intellectual property landscapes. Lipid nanoparticle formulations are more expensive to produce and analyze than generic tablets.[29] However, new regulations pertaining to lipid carriers and nanomedicine are progressively simplifying developmental pathways. For antihypertensive LBDDS to be successfully translated into clinical use, characterization parameters and validated analytical techniques must be harmonized.[29]

CLINICAL SIGNIFICANCE AND PROSPECTS

Lipid-based systems have more potential for antihypertensive treatment than just improving solubility as summarized in [Table 1]. Patient-specific pharmacokinetics may be accommodated by customized dosing using modular lipidic systems as precision medicine develops. Vasodilators or renin-angiotensin modulators could be delivered directly to affected sites by long-circulating nanosystems designed to target vascular endothelium, lowering systemic exposure and adverse effects.[13,30]

Developing transdermal lipid vesicles for reliable systemic delivery, refining oral lipid nanocarriers for once-daily sustained release, and investigating intranasal or buccal lipid systems for quick onset in hypertensive emergencies are some of the future directions. Scalable production with high reproducibility is made possible by the integration of microfluidic technology, which offers exact control over particle size and composition.[6]

Translation, however, will depend on how safety, stability, and regulatory alignment are handled. Proof-of-concept should give way to comparative clinical evaluation that shows superiority or decreased variability in comparison to standard formulations. Adoption in resource-constrained areas where the prevalence of hypertension is rapidly rising will be supported by real-world pharmacoeconomic analyses.[31]

CONCLUSION

Lipid-based delivery systems are a clinically guided and explored option for promoting the therapeutic activity of antihypertensive agents. These systems circumvent some of the limitations or shortcomings associated with existing oral antihypertensive dosage forms, including the disadvantages that conventionally available organic salts have poor solubility in water, extensive first-pass metabolism leads to widely variable drug absorption, and variable plasma levels of drugs, by employing lipid excipients having good biocompatibility and physiologic compatibility. Lipid carriers ensure system exposure, facilitate lymphatic absorption from the intestine, and solubilize pharmacokinetics predictable. It may reduce dose-dependent variations.

Liposomes, SLNs, NLCs, nanoemulsions, and LPHNs offer unique structural advantages that could be tailored to the various groups of antihypertensive drugs. Higher drug loading, increased stability, and targeted tissue distribution allow them to better modulate therapeutic action with less systemic variance. These advantages are particularly beneficial in the treatment of chronic diseases, where sustainable adherence to medication over time is key to reducing future cardiovascular events.

The efficiency and consistency of such delivery systems can be improved in the future as lipid chemistry, microfluidic production methods, and targeted therapeutics are developed. In the future, attention should be directed toward scaling up the production technology that may accelerate the new drug approval process, standard stability analyses, and comparative studies such as clinical trials. If these challenges are overcome, LBDDS have the potential to provide safe, effective, and patient-friendly alternatives for long-term management of hypertension and will take liposomal drug delivery systems from just a concept in theory toward practiced possibilities.

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