Journal of Pharmacology, Genetics and Molecular Biology (JPGMB)
ISSN: 3049-3757 | Vol. 02, Issue-02, March-April, 2026

Lipid-Based Nanocarriers in Drug Delivery: Pharmacokinetic Modulation and Clinical Perspectives

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Abstract:

Lipid-based nanocarriers (LNCs) have emerged as a cornerstone in modern drug delivery, offering innovative solutions to the limitations of conventional formulations such as poor solubility, low stability, and limited bioavailability. Comprising biocompatible lipids like phospholipids, triglycerides, and cholesterol, these nanocarriers—encompassing liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanocapsules (LNCs)—enable precise control over drug release and targeted delivery. Their unique composition facilitates enhanced drug solubilization, protection from enzymatic degradation, and improved absorption through lymphatic transport and membrane fusion mechanisms. By modulating key pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to reach peak concentration (Tmax), area under the curve (AUC), and half-life (t½), LNCs significantly improve systemic exposure and therapeutic efficacy. Clinically, lipid nanocarriers have demonstrated transformative outcomes in oncology (*Doxil®, Onivyde®*), antifungal therapy (*AmBisome®, Fungisome®*), and vaccine technology (mRNA–LNP platforms for COVID-19), highlighting their translational success. Despite existing challenges in large-scale manufacturing, stability, and regulatory approval, continuous advancements—especially the integration of AI-driven pharmacokinetic modeling and stimuli-responsive lipid systems—promise to accelerate their evolution toward personalized and precision nanomedicine.

Keywords: Lipid-based nanocarriers, pharmacokinetics, bioavailability, drug delivery, clinical translation, nanomedicine

Received: Jan. 08, 2026 **Revised: Feb. 16, 2026** **Accepted: March. 23, 2026** **Published: April 10, 2026**

DOI: https://doi.org/10.64062/JPGMB.Vol2.Issue2.3

https://jpgmb.com/1/issue/archive

1. 1. Introduction

Conventional drug delivery systems have long been constrained by a range of physicochemical and biological challenges that limit their therapeutic potential [1]. Many promising drug candidates suffer from poor aqueous solubility, chemical instability, and inadequate permeability across biological barriers, resulting in suboptimal absorption and reduced bioavailability. These shortcomings often necessitate higher or more frequent dosing, which can increase systemic toxicity and diminish patient compliance [2-3]. Moreover, conventional formulations frequently lack site-specific targeting, leading to non-selective drug distribution and off-target effects that compromise treatment efficacy and safety.

To overcome these limitations, nanocarrier-based drug delivery has emerged as a revolutionary approach in modern pharmaceutics. Nanocarriers provide the means to encapsulate, protect, and deliver therapeutic agents in a controlled and targeted manner [4]. By manipulating the physicochemical properties of nanoparticles—such as size, surface charge, and composition—scientists can tailor drug release profiles, enhance bioavailability, and achieve sustained therapeutic concentrations [5]. Among the various nanocarrier systems developed, lipid-based nanocarriers have garnered particular attention due to their inherent biocompatibility, ability to encapsulate both hydrophilic and lipophilic drugs, and physiological similarity to biological membranes.

The evolution of lipid-based nanocarriers has given rise to several advanced formulations, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid nanocapsules (LNCs), and self-emulsifying drug delivery systems (SEDDS) [6]. Each of these systems brings unique advantages in terms of stability, controlled release, and biodistribution. Liposomes, the earliest of these systems, pioneered the concept of vesicular delivery and demonstrated the potential of lipid vesicles in encapsulating and delivering therapeutic molecules effectively [7]. The subsequent development of SLNs and NLCs addressed key issues such as drug leakage and limited loading capacity, paving the way for next-generation lipid nanocarrier platforms with improved performance and scalability.

A critical determinant of therapeutic efficacy in drug delivery is pharmacokinetic (PK) modulation—the capacity to control the absorption, distribution, metabolism, and excretion (ADME) of drugs [8]. Lipid-based nanocarriers excel in modulating these pharmacokinetic parameters by improving solubility, prolonging circulation time, reducing premature metabolism, and enabling targeted delivery to specific tissues or cells. Such PK advantages translate into enhanced therapeutic outcomes, reduced dosing frequency, and minimized side effects, thereby offering significant clinical value across various therapeutic domains, including oncology, infectious diseases, and neurology [9-10].

The objective of this review is to provide a comprehensive understanding of lipid-based nanocarriers in drug delivery, with an emphasis on their role in pharmacokinetic modulation

and clinical translation [11]. It explores the structural diversity, mechanisms of PK enhancement, and therapeutic implications of different lipid-based systems, while also discussing the challenges associated with their formulation, scale-up, and regulatory approval. Ultimately, this review aims to highlight how lipid nanotechnology is reshaping the pharmacokinetic landscape of modern therapeutics and paving the way for more effective and personalized drug delivery strategies [12-13].

2. Classification of Lipid-Based Nanocarriers

Lipid-based nanocarriers (LNCs) encompass a broad and versatile class of nanosystems engineered to enhance the delivery, stability, and bioavailability of therapeutic compounds [14]. Their structural diversity, compositional flexibility, and biological compatibility make them highly effective vehicles for both hydrophilic and hydrophobic drugs. These nanocarriers are primarily classified based on their lipid composition, internal structure, and method of preparation [15-16]. The major categories include liposomes**,** solid lipid nanoparticles (SLNs)**,** nanostructured lipid carriers (NLCs)**,** lipid nanocapsules (LNCs)**,** and other lipid-based systems such as micelles, nanoemulsions, and self-emulsifying drug delivery systems (SEDDS).

2.1. Liposomes

Liposomes are spherical, vesicular structures composed of one or more concentric phospholipid bilayers surrounding an aqueous core. Their composition typically includes natural or synthetic phospholipids, cholesterol (which stabilizes the bilayer), and other surfactants or lipids that enhance membrane fluidity and encapsulation efficiency [17]. Due to their amphiphilic nature, liposomes can simultaneously encapsulate hydrophilic drugs in their aqueous interior and lipophilic drugs within the lipid bilayers, offering a dual delivery advantage [18].

Based on their surface characteristics and structural modifications, liposomes can be categorized into several types. Conventional liposomes are the simplest form, offering basic encapsulation and protection but suffering from rapid clearance by the mononuclear phagocyte system (MPS) [19-20]. To overcome this, PEGylated liposomes—also known as “stealth liposomes”—are coated with polyethylene glycol (PEG), which provides steric stabilization, prolongs circulation time, and reduces opsonization. Immunoliposomes, on the other hand, are functionalized with antibodies or ligands that enable active targeting of specific cells or receptors, enhancing site-specific drug delivery and minimizing systemic side effects [21-22].

Liposomes have demonstrated remarkable versatility across various applications, including anticancer therapy (e.g., Doxil® for doxorubicin delivery), antifungal therapy (e.g., AmBisome® for amphotericin B), and gene delivery (liposomal mRNA vaccines). Their advantages include biocompatibility, controlled release potential, and improved pharmacokinetics; however, limitations such as high production costs and stability concerns during storage still pose formulation challenges [23].

2.2. Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles represent the first generation of lipid-based nanocarriers that combine the advantages of polymeric nanoparticles with the biocompatibility of lipids. SLNs are composed of physiologically safe lipids that remain solid at both room and body temperatures, such as triglycerides, fatty acids, or waxes, stabilized by surfactants [24-25]. The mechanism of drug incorporation involves embedding the drug molecules within the crystalline lipid matrix, which controls the release profile through diffusion or erosion.

SLNs offer several advantages**,** including protection of labile drugs from degradation, controlled drug release, excellent biocompatibility, and suitability for large-scale production. Moreover, they eliminate the use of potentially toxic organic solvents common in polymeric systems [26-27]. However, SLNs face notable limitations such as limited drug loading capacity due to the tight lipid lattice and the potential for drug expulsion or burst release during storage as the lipid matrix undergoes polymorphic transitions. These drawbacks have driven the evolution toward more advanced lipid systems such as NLCs.

2.3. Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers represent the second generation of lipid nanoparticles, designed to overcome the limitations of SLNs [28]. Unlike SLNs, NLCs are formulated using a hybrid matrix of solid and liquid lipids, which introduces structural imperfections that prevent drug expulsion and enhance loading capacity [29-30]. This combination disrupts the highly ordered crystalline structure of solid lipids, creating more space for drug molecules and improving encapsulation efficiency.

NLCs offer superior control over drug release and greater physical stability compared to SLNs. They can be fine-tuned for sustained or targeted delivery by varying the solid-to-liquid lipid ratio and surfactant composition [31-32]. Additionally, NLCs exhibit improved bioavailability and enhanced permeation through biological membranes, making them ideal for oral, topical, and parenteral drug delivery. Their versatility and scalability have led to increasing interest in clinical and industrial applications, particularly in dermal formulations and oral delivery of poorly soluble drugs [33-34].

2.4. Lipid Nanocapsules (LNCs)

Lipid nanocapsules are hybrid systems that combine the characteristics of polymeric nanoparticles and liposomes, forming a core–shell structure consisting of an oily core surrounded by a rigid surfactant shell [35-36]. Unlike traditional liposomes, LNCs do not rely on a bilayer structure but rather on a stable, surfactant-stabilized interface between the aqueous and lipid phases. The lipid core often comprises medium-chain triglycerides, while the shell includes surfactants such as lecithin or polyethylene glycol derivatives [37-38].

This unique configuration grants LNCs high physical stability, protection against enzymatic degradation, and excellent biocompatibility [39]. They are particularly advantageous for both oral and parenteral delivery, as they facilitate lymphatic uptake and can bypass hepatic first-pass metabolism, enhancing systemic bioavailability. LNCs have been successfully explored for the delivery of anticancer agents, vaccines, and CNS-targeted therapeutics, offering controlled release and improved biodistribution [40-41].

2.5. Other Lipid-Based Systems

Beyond the major categories, several other lipid-based delivery platforms have been developed to meet specific therapeutic needs. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oils, surfactants, and co-solvents that spontaneously form fine oil-in-water emulsions upon contact with gastrointestinal fluids, enhancing the oral absorption of poorly water-soluble drugs [42-43]. Micelles, formed by amphiphilic surfactants, are particularly useful for solubilizing hydrophobic molecules, improving dissolution rates, and facilitating targeted delivery. Nanoemulsions, another closely related system, are kinetically stable emulsions with droplet sizes typically below 200 nm, known for their transparency, stability, and versatility in both topical and parenteral formulations [44-45].Each of these systems provides unique benefits in drug solubilization, stability enhancement, and targeted delivery. However, their successful implementation depends on careful optimization of formulation parameters, lipid selection, and compatibility with the drug molecule.Table 1. Comparative Characteristics of Different Lipid-Based Nanocarriers [46].

Nanocarrier Type	Structural Composition	Typical Size Range (nm)	Advantages	Limitations	Representative Drugs	Reference
Liposomes	Phospholipid bilayer with aqueous core	50–500	Biocompatible, versatile, controlled release	Costly, storage instability	Doxil®, AmBisome®	47
SLNs	Solid lipid matrix with surfactant	50–300	Protects labile drugs, controlled release	Low drug loading, burst release	Paclitaxel SLNs	48
NLCs	Solid + liquid lipid hybrid	50–250	Higher drug loading, stable release	Complex formulation	Curcumin NLCs	49
LNCs	Lipid core with surfactant shell	20–100	Stable, suitable for oral/parenteral use	Limited large-scale data	Docetaxel LNCs	50

SEDDS/Nanoemulsions	Oil–surfactant–co-solvent system	50–200	Enhanced solubility, oral bioavailability	Stability issues, surfactant toxicity	Cyclosporine, Ritonavir	51

Table 1: *Comparative characteristics of different lipid-based nanocarriers (composition, particle size, stability, advantages, limitations, and drug examples).*

3. Mechanisms of Pharmacokinetic Modulation

Lipid-based nanocarriers exert a profound influence on the pharmacokinetic (PK) behavior of drugs by altering their absorption, distribution, metabolism, and excretion (ADME) profiles [52]. Through their unique structural and physicochemical attributes, these nanocarriers enable solubilization of poorly water-soluble compounds, sustain release for prolonged activity, and facilitate targeted delivery to specific tissues—all while protecting the drug from premature degradation [53-54]. The following sections outline the major mechanisms by which lipid-based nanocarriers modulate pharmacokinetics to enhance therapeutic efficacy.

3.1. Enhancement of Drug Solubility and Absorption

One of the primary advantages of lipid-based nanocarriers lies in their ability to improve the solubility and gastrointestinal absorption of hydrophobic drugs [55]. A significant proportion of new chemical entities (NCEs) discovered today fall under the Biopharmaceutics Classification System (BCS) Class II and IV, characterized by low aqueous solubility and poor permeability. Lipids act as solubilizing agents by forming micellar or vesicular structures that can encapsulate hydrophobic molecules within their lipid core or bilayer, thereby increasing their apparent solubility in biological fluids [56-57].

Additionally, lipid nanocarriers can facilitate lymphatic transport**,** effectively bypassing the hepatic first-pass metabolism that often limits oral bioavailability [58]. When administered orally, these carriers promote the formation of chylomicron-like structures within intestinal enterocytes, directing the absorbed drug into the lymphatic system rather than the portal vein [59]. This mechanism is particularly advantageous for lipophilic drugs such as cyclosporine, curcumin, and paclitaxel, which undergo extensive first-pass metabolism when delivered in conventional formulations [60].

Overall, lipid-based nanocarriers not only enhance solubility and absorption but also improve the overall bioavailability and therapeutic consistency of poorly soluble compounds, addressing one of the most persistent challenges in drug development [61-62].

3.2. Controlled and Sustained Drug Release

Controlled and sustained release is a key feature of lipid-based nanocarrier systems, allowing drugs to maintain therapeutic concentrations over extended periods while minimizing peak–

trough fluctuations [63-64]. The mechanism of drug release from these systems depends on both diffusion through the lipid matrix and degradation or erosion of the lipid shell. In liposomes, drug release occurs via diffusion across the phospholipid bilayer or through vesicle destabilization, while in SLNs and NLCs, it is governed by the physicochemical properties of the lipid matrix and the solubility of the encapsulated drug [65-66].

The composition of the lipid—including its melting point, chain length, and degree of saturation—plays a crucial role in determining the release kinetics. For instance, incorporating liquid lipids in NLCs can introduce structural imperfections that facilitate a more uniform and sustained drug release compared to the highly crystalline matrix of SLNs. Similarly, the addition of cholesterol in liposomes modulates bilayer fluidity, influencing both drug entrapment efficiency and release behaviour [67-68].

Such controlled release characteristics enable precise dosing schedules, reduce the frequency of administration, and minimize systemic toxicity, making lipid-based systems ideal for chronic therapies and drugs with narrow therapeutic windows [69].

3.3. Modulation of Distribution and Targeting

Another major pharmacokinetic advantage of lipid nanocarriers is their ability to modulate drug distribution and tissue targeting**.** Upon systemic administration, lipid nanoparticles can exploit both passive and active targeting mechanisms to deliver drugs selectively to diseased tissues [70-71].

Passive targeting primarily relies on the enhanced permeability and retention (EPR) effect**,** a phenomenon observed in tumor and inflamed tissues characterized by leaky vasculature and poor lymphatic drainage [72-73]. Nanocarriers within the size range of 50–200 nm can preferentially accumulate in these regions, enhancing local drug concentration while minimizing exposure to healthy tissues [74].

In contrast, active targeting involves the surface modification of lipid nanocarriers with ligands such as antibodies, peptides, or small molecules that bind specifically to overexpressed receptors on target cells [75]. Immunoliposomes and ligand-functionalized NLCs are examples of such systems that have demonstrated superior selectivity and therapeutic performance in cancer, neurological disorders, and infectious diseases [76].

Through these targeting strategies, lipid-based nanocarriers can achieve site-specific drug accumulation, reduce systemic side effects, and significantly improve therapeutic outcomes, marking a major advancement over traditional delivery systems [77].

3.4. Reduction in Drug Metabolism and Elimination

The lipid matrix surrounding a drug in nanocarrier form serves as a protective barrier against premature degradation by metabolic enzymes and harsh physiological environments. Many

drugs—especially peptides, proteins, and nucleic acids—are highly susceptible to enzymatic hydrolysis in the gastrointestinal tract or rapid metabolism in the liver [78]. Encapsulation within lipid nanocarriers shields these molecules from such degradation, enhancing their chemical and metabolic stability.

Additionally, the surface modification of lipid nanoparticles (for example, PEGylation) can extend the plasma half-life by reducing recognition and clearance by the mononuclear phagocyte system (MPS). This prolonged circulation time allows the drug to remain in the bloodstream longer, increasing the likelihood of reaching its target site and maintaining effective concentrations. Consequently, this pharmacokinetic modulation results in higher bioavailability, reduced dosing frequency, and improved patient adherence [79-80].

3.5. Impact on Cellular Uptake and Transport Mechanisms

At the cellular level, lipid-based nanocarriers facilitate efficient cellular uptake and intracellular delivery through multiple mechanisms. Their lipidic composition closely resembles biological membranes, promoting membrane fusion and endocytosis-mediated uptake. Once internalized, these nanocarriers can escape endosomal compartments, releasing their cargo directly into the cytoplasm or targeting specific organelles [81].

The uptake pathway—whether clathrin-mediated, caveolae-mediated, or macropinocytosis—depends on the carrier's size, surface charge, and lipid composition. For example, cationic liposomes interact strongly with negatively charged cell membranes, enhancing internalization, whereas neutral or PEGylated systems offer a stealth profile suitable for prolonged circulation and targeted delivery [82].

This ability to modulate cellular transport mechanisms significantly improves drug bioavailability at the intracellular level, ensuring that therapeutic agents reach their intended targets within cells or tissues. The combined effects of enhanced uptake, controlled release, and prolonged circulation make lipid-based nanocarriers one of the most efficient systems for overcoming pharmacokinetic barriers in modern therapeutics [83].

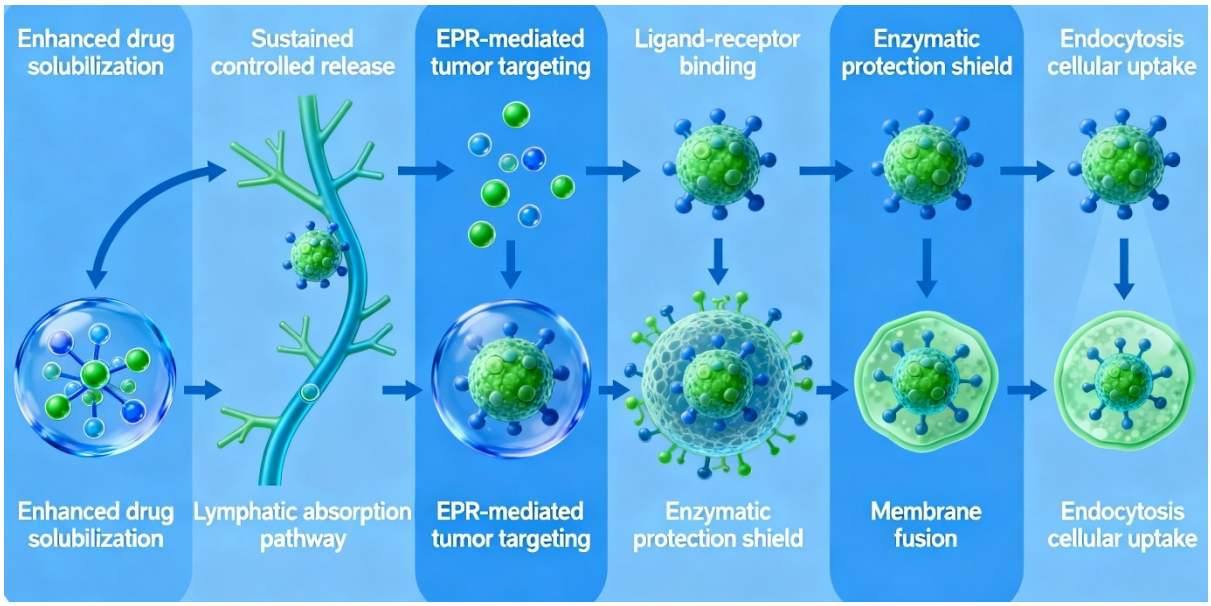

Figure 1. Schematic Representation of Pharmacokinetic Modulation by Lipid-Based Nanocarriers. *The figure illustrates key pharmacokinetic processes influenced by lipid-based nanocarriers, including enhanced solubilization, lymphatic absorption, sustained release, targeted distribution via EPR and ligand-mediated mechanisms, protection from enzymatic degradation, and improved cellular uptake through membrane fusion and endocytosis.*

4. Pharmacokinetic Parameters and Evaluation

Pharmacokinetic (PK) evaluation plays a crucial role in understanding how lipid-based nanocarriers influence the absorption, distribution, metabolism, and elimination of therapeutic agents. By modulating these parameters, lipid nanocarriers can profoundly alter the drug's systemic exposure, duration of action, and overall therapeutic index. The assessment of PK profiles provides vital insight into the efficiency and performance of these nanocarriers compared to conventional formulations [84].

4.1Measurement of Key PK Parameters (Cmax, Tmax, AUC, t½, Bioavailability)

The performance of any drug delivery system, including lipid-based nanocarriers, is primarily evaluated using standard PK parameters such as Cmax (maximum plasma concentration), Tmax (time to reach Cmax), AUC (area under the plasma concentration-time curve), t½ (elimination half-life), and bioavailability (F%)**.**

- **Cmax** reflects the peak concentration achieved in systemic circulation, indicating the extent of drug absorption. Lipid nanocarriers often result in a *moderate Cmax* with a *delayed Tmax*, signifying sustained release and controlled absorption.
- **AUC**, which represents the total drug exposure over time, is significantly higher for lipid-based formulations, demonstrating enhanced bioavailability due to improved solubility and reduced first-pass metabolism.

- **t½** is typically prolonged because of the protective lipid shell and surface modifications such as PEGylation that slow down clearance.
- **Bioavailability**, the fraction of the administered dose reaching systemic circulation, increases substantially when drugs are encapsulated in lipid-based nanocarriers—especially for poorly water-soluble and lipophilic molecules.

For instance, oral administration of paclitaxel in a lipid-based system shows a several-fold increase in bioavailability compared to traditional formulations, illustrating the dramatic pharmacokinetic improvements achievable through lipid nanotechnology [85-86].

4.3In Vitro–In Vivo Correlation (IVIVC)

Establishing an in vitro–in vivo correlation (IVIVC) is vital for predicting the in vivo behavior of lipid nanocarriers based on laboratory-based release studies. It helps in understanding how in vitro dissolution or drug release kinetics correspond to in vivo absorption and bioavailability.

In lipid-based nanocarriers, IVIVC can be complex due to the involvement of physiological factors such as lipolysis, digestion of lipid components, and lymphatic uptake mechanisms. Nevertheless, using biorelevant media that mimic gastrointestinal conditions has improved the reliability of IVIVC for oral lipid systems like SEDDS and NLCs. A strong IVIVC not only reduces the dependency on animal testing but also aids in optimizing formulation design, predicting therapeutic outcomes, and satisfying regulatory requirements for bioequivalence studies [87-88].

4.4Role of Lipid Composition and Particle Size on PK Behavior

The lipid composition and particle size of nanocarriers are fundamental determinants of their pharmacokinetic performance. The type of lipid used—whether solid, liquid, or a combination—directly affects drug solubility, encapsulation efficiency, and release rate.

- **Solid lipids** (e.g., glyceryl monostearate, stearic acid) tend to form rigid matrices that provide sustained release but may limit drug loading.
- **Liquid lipids** (e.g., oleic acid, medium-chain triglycerides) introduce structural imperfections, enhancing drug encapsulation and facilitating faster release.
- **Hybrid systems** like NLCs combine both types, achieving an optimal balance between stability and controlled delivery.

Particle size also exerts a significant influence on PK properties. Smaller particles (<200 nm) exhibit improved solubility, surface area, and interaction with biological membranes, resulting in faster absorption and enhanced tissue penetration. Conversely, larger particles (>200 nm) are more suitable for sustained release applications and passive targeting via the enhanced permeability and retention (EPR) effect in tumors. Furthermore, surface charge impacts systemic circulation time—positively charged nanoparticles may enhance cellular uptake but risk rapid clearance, while neutral or PEGylated systems prolong plasma retention [89-90].

4.5 Case Studies Highlighting PK Improvements for Different Drugs

Numerous studies have demonstrated how lipid nanocarriers dramatically enhance the pharmacokinetic profiles of various therapeutic agents.

- **Doxorubicin (Liposomes – Doxil®):** Liposomal encapsulation increased plasma half-life from less than 0.5 hours to over 50 hours and reduced cardiotoxicity by controlling tissue distribution.
- **Amphotericin B (AmBisome®):** The liposomal formulation provided higher AUC and improved tissue targeting, minimizing nephrotoxicity while maintaining potent antifungal activity.
- **Curcumin (NLCs):** Oral administration via nanostructured lipid carriers improved bioavailability by more than 10-fold compared to free curcumin, attributed to enhanced solubilization and lymphatic transport.
- **Cyclosporine A (SEDDS – Neoral®):** Self-emulsifying lipid systems increased oral bioavailability from 10% to approximately 35%, offering more predictable absorption.
- **Paclitaxel (SLNs):** Incorporation into solid lipid nanoparticles prolonged systemic exposure and reduced clearance, achieving better therapeutic outcomes at lower doses.

These examples underscore how lipid-based nanocarriers offer a robust strategy for overcoming the pharmacokinetic challenges associated with conventional formulations, ensuring improved patient safety, efficacy, and compliance.

Table 2. Summary of Pharmacokinetic Enhancement Using Lipid Nanocarriers for Representative Drugs

Drug	Nanocarrier Type	Pharmacokinetic Impact	Findings / Benefits	Reference
Doxorubicin	Liposomes (Doxil®)	↑ t½ (50 h vs. 0.5 h), ↓ clearance	Prolonged circulation, reduced cardiotoxicity	91
Amphotericin B	Liposomes (AmBisome®)	↑ AUC, ↓ renal toxicity	Targeted delivery, improved safety profile	92

Paclitaxel	SLNs	↑ t½, ↓ clearance	Sustained release, enhanced tumor accumulation	93
Curcumin	NLCs	↑ Bioavailability (10×)	Enhanced solubility and absorption	94
Cyclosporine A	SEDDS (Neoral®)	↑ Oral F (35% vs. 10%)	Reduced variability, improved absorption	95
Docetaxel	LNCs	↑ Plasma concentration, prolonged release	Improved therapeutic index	96

Lipid-based nanocarriers thus represent a transformative approach in pharmacokinetics, enabling precise control over drug behavior within the body. By tailoring lipid composition, particle characteristics, and formulation design, these systems can optimize absorption, distribution, metabolism, and elimination profiles—ultimately leading to safer, more effective, and patient-friendly therapies.

5. Clinical Applications and Approved Products

Lipid-based nanocarriers have made remarkable contributions to modern therapeutics, with several formulations achieving regulatory approval and clinical success. Their ability to modulate pharmacokinetics, improve drug stability, and enable targeted delivery has transformed the treatment landscape for cancer, infectious diseases, and neurological disorders [97-98]. This section highlights key therapeutic areas where lipid nanocarriers have proven their clinical potential.

5.1. Anticancer Therapy

Lipid-based nanocarriers have become integral in oncology due to their ability to enhance the selective accumulation of chemotherapeutic agents in tumors while reducing systemic toxicity. *Doxil*® (PEGylated liposomal doxorubicin) is one of the most successful examples, offering a prolonged circulation time and reduced cardiotoxicity compared to conventional doxorubicin. Similarly, *Myocet*®, a non-PEGylated liposomal formulation, provides comparable efficacy with improved safety. *Onivyde*® (liposomal irinotecan) has shown superior pharmacokinetic stability, sustained drug release, and enhanced tumor targeting through the enhanced permeability and retention (EPR) effect. These formulations demonstrate that lipid nanocarriers can balance efficacy and tolerability, achieving a higher therapeutic index through controlled pharmacokinetic modulation [99-100].

5.2. Antifungal and Antiviral Therapy

The clinical adoption of lipid-based formulations in antifungal and antiviral therapy has been equally transformative. *AmBisome®* (liposomal amphotericin B) revolutionized antifungal therapy by drastically reducing the nephrotoxicity associated with conventional amphotericin B formulations. *Fungisome®*, another liposomal antifungal preparation, provides enhanced tissue distribution and reduced infusion-related reactions. In the context of antiviral therapy, lipid nanoparticles have been used to deliver antiviral agents with improved stability and targeted cellular uptake. Lipid-based carriers for antiretroviral drugs such as zidovudine and lamivudine have shown enhanced bioavailability and reduced dosing frequency, contributing to better patient compliance [101-102].

5.3. Vaccines and Immunotherapy

Lipid nanoparticles (LNPs) have gained global recognition as critical delivery vehicles for nucleic acid–based vaccines and immunotherapies. The mRNA vaccines developed against COVID-19, such as *BNT162b2* (Pfizer–BioNTech) and *mRNA-1273* (Moderna), rely on LNPs to encapsulate and protect the mRNA, facilitate cellular uptake, and promote efficient antigen expression. These systems demonstrate controlled release, immune activation, and excellent safety profiles. Beyond COVID-19, similar LNP systems are being evaluated for influenza, cancer immunotherapy, and personalized vaccines, underscoring the versatility and scalability of lipid-based delivery platforms in immunological applications [103-104].

5.4. Neurological and Cardiovascular Disorders

Lipid-based nanocarriers have shown promise in overcoming the formidable challenge of delivering drugs across the blood–brain barrier (BBB). Liposomes and nanostructured lipid carriers (NLCs) have been engineered with surface ligands such as transferrin or apolipoproteins to enhance BBB penetration and target neural tissues. This strategy has been explored for delivering drugs in Alzheimer's disease, Parkinson's disease, and brain tumors. In cardiovascular therapy, lipid nanocarriers have improved the delivery of antihypertensive, anti-inflammatory, and anticoagulant agents. Their controlled release and prolonged circulation contribute to steady therapeutic plasma concentrations, minimizing dose fluctuations and improving clinical outcomes [105-106].

Table 3: Clinically Approved Lipid-Based Nanocarrier Formulations and Their Pharmacokinetic Advantages

Formulation (Brand Name)	Drug Encapsulated	Therapeutic Area	Type of Lipid Nanocarrier	Pharmacokinetic Benefits	Clinical Outcome	Reference
Doxil®	Doxorubicin	Cancer	PEGylated Liposome	Prolonged circulation, reduced cardiotoxicity, enhanced tumor targeting	Improved safety and efficacy	107
Myocet®	Doxorubicin	Cancer	Conventional Liposome	Controlled release, reduced plasma peak concentration	Comparable efficacy, fewer side effects	108
Onivyde®	Irinotecan	Pancreatic Cancer	Liposomal	Sustained release, increased tumor accumulation	Extended progression-free survival	109
AmBisome®	Amphotericin B	Fungal Infections	Liposomal	Reduced nephrotoxicity, improved tissue targeting	Better tolerability	110
Fungisome®	Amphotericin B	Fungal Infections	Liposomal	Enhanced bioavailability, reduced infusion reactions	Clinical safety improvement	111
BNT162b2 (Pfizer–BioNTech)	mRNA encoding spike protein	COVID-19 Vaccine	Lipid Nanoparticle (LNP)	Efficient cellular uptake, mRNA protection, rapid immune activation	High efficacy, global impact	112
mRNA-1273 (Moderna)	mRNA encoding spike protein	COVID-19 Vaccine	Lipid Nanoparticle (LNP)	Enhanced stability, robust immunogenicity	Proven clinical success	113
Cleviprex®	Clevidipine	Hypertension	Lipid Emulsion	Rapid onset, controlled clearance	Precise BP control	114
DepoDur®	Morphine sulfate	Pain Management	Liposome	Extended release, reduced dosing frequency	Improved analgesic duration	115

This growing list of clinically validated lipid-based nanocarrier systems reflects their broad adaptability across therapeutic domains. They exemplify how rational nanocarrier design and pharmacokinetic modulation can bridge the gap between laboratory innovation and clinical success.*Figure 2*

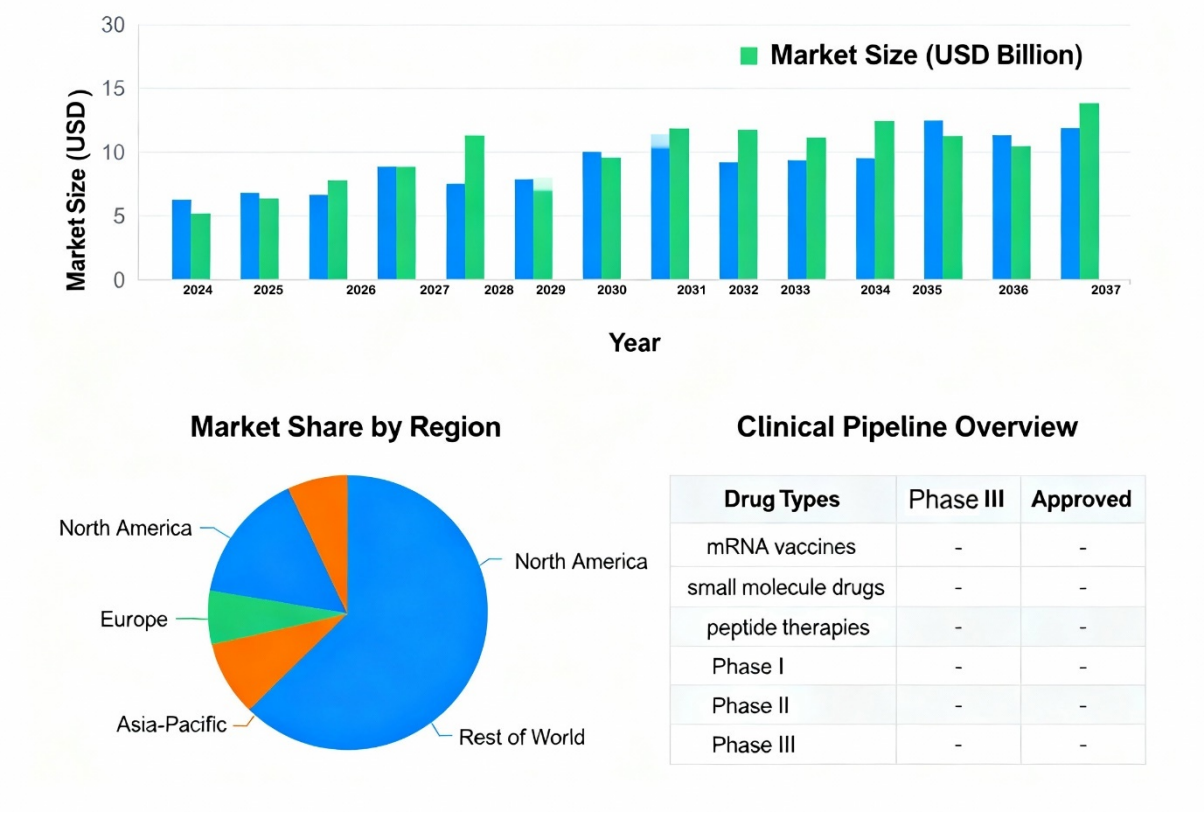

Figure 2: Global market and clinical pipeline overview of lipid nanocarriers.

6. Challenges and Limitations

Despite the remarkable clinical and technological advancements of lipid-based nanocarriers, several challenges continue to hinder their large-scale translation and widespread adoption. One of the foremost issues lies in scale-up and manufacturing complexity. While laboratory-scale synthesis allows precise control over particle size and composition, industrial-scale production demands reproducibility and compliance with Good Manufacturing Practices (GMP). Processes such as high-pressure homogenization or microfluidization often face difficulties in maintaining batch-to-batch consistency, particularly when dealing with thermolabile or sensitive bioactive compounds [116].

Another critical limitation is stability and shelf-life**.** Lipid nanocarriers are inherently prone to physicochemical degradation, including lipid oxidation, hydrolysis, and particle aggregation. These processes can alter drug release kinetics and compromise therapeutic performance over time. Maintaining long-term stability requires optimization of lipid composition, cryoprotectants, and storage conditions—factors that significantly affect formulation cost and feasibility.

Regulatory and safety concerns also remain substantial barriers. Although lipids used in nanocarriers are often biocompatible and recognized as safe, the introduction of synthetic lipids, surfactants, or PEGylated coatings introduces complexity in regulatory evaluation.

Concerns about immunogenicity, accumulation in reticuloendothelial organs, and the long-term fate of nanocarriers necessitate comprehensive toxicological assessments. Moreover, the lack of harmonized regulatory guidelines for nanomedicines further delays product approval and commercialization [117-118].

In addition, high production costs and limited reproducibility present economic hurdles. The cost of specialized equipment, sterile manufacturing environments, and quality control testing increases the financial burden, particularly for developing countries. Reproducibility issues, especially during formulation scaling or when switching lipid sources, can affect quality assurance and regulatory compliance. Collectively, these limitations underline the need for innovative formulation techniques, standardized production protocols, and global regulatory alignment to fully harness the therapeutic potential of lipid-based nanocarriers [119-120].

7. Future Perspectives

The future of lipid-based nanocarriers in drug delivery is promising, driven by advances in formulation science, material innovation, and computational modeling. One of the emerging directions involves the design of hybrid nanocarriers**,** which combine lipids with polymers, inorganic nanoparticles, or biomolecules to achieve multifunctionality. Such systems can offer enhanced drug stability, stimuli-responsive behavior, and tunable pharmacokinetics. For example, lipid–polymer hybrid nanoparticles exhibit the biocompatibility of lipids and the mechanical strength of polymers, making them suitable for complex therapeutic payloads [121-122.]

Another exciting development is the emergence of stimuli-responsive lipid nanocarriers**,** which can release drugs in response to specific biological or external triggers such as pH, temperature, redox potential, or light. These smart systems enable spatiotemporal control over drug delivery, maximizing therapeutic efficacy while minimizing systemic side effects. Coupled with this is the growing potential of personalized nanomedicine**,** where lipid nanocarriers are tailored based on patient-specific pharmacogenomics, disease phenotype, and metabolic profile [123-124].

The integration of artificial intelligence (AI) and pharmacokinetic (PK) modeling represents a paradigm shift in nanocarrier design. AI-driven algorithms can predict how modifications in lipid composition, particle size, and surface charge affect absorption, distribution, metabolism, and excretion (ADME) profiles. This accelerates formulation optimization, reduces trial-and-error experimentation, and improves clinical predictability. AI-based PK modeling can also facilitate virtual screening of lipid combinations for specific therapeutic applications.

Looking ahead**,** next-generation lipid platforms for gene and protein delivery are expected to dominate the nanomedicine landscape. The success of mRNA-based vaccines has validated lipid nanoparticles (LNPs) as efficient vectors for nucleic acid therapeutics, paving the way for siRNA, CRISPR-Cas9, and protein-based treatments. Innovations in ionizable lipids, biolipids, and microfluidic synthesis will further improve delivery precision, targeting specificity, and biocompatibility. Ultimately, the convergence of nanotechnology, biotechnology, and

computational science is set to transform lipid-based drug delivery from a formulation tool into a precision-engineered therapeutic platform, defining the future of personalized and predictive medicine [125-126].

8. Conclusion

Lipid-based nanocarriers have undeniably reshaped the landscape of modern drug delivery by addressing long-standing pharmacokinetic barriers such as poor solubility, rapid metabolism, and limited bioavailability. Through rational design and lipid composition optimization, these systems provide enhanced solubilization, controlled release, targeted distribution, and improved therapeutic index across a diverse range of drugs. The clinical success of formulations like *Doxil*®, *AmBisome*®, and lipid nanoparticle-based mRNA vaccines has proven that such technologies are not just experimental concepts but powerful, real-world therapeutic tools.

Their ability to fine-tune pharmacokinetic behavior—extending plasma half-life, reducing off-target toxicity, and achieving site-specific delivery—has made lipid-based nanocarriers central to the evolution of next-generation medicine. However, the path toward widespread adoption still requires overcoming key obstacles, including large-scale manufacturing consistency, long-term stability, and regulatory harmonization.

The continued advancement of this field will rely heavily on interdisciplinary collaboration—uniting expertise from pharmaceutical sciences, materials chemistry, bioengineering, and computational modeling. Integration of AI-driven pharmacokinetic modeling and personalized nanomedicine approaches will further refine formulation design and therapeutic precision. In essence, lipid-based nanocarriers represent not just a solution to current drug delivery challenges but a transformative platform driving the future of nanotherapeutics, where treatment is smarter, safer, and tailored to individual patient needs.

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