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REVIEW ARTICLE

A Review on the Role of Lipid-Based Novel Drug Delivery Systems in Precision Medicine

Supriya Buderla*[1], Parimala Vudikala[2]

[1]*UG Scholar, Department of Pharmaceutics, Joginpally BR Pharmacy College, Moinabad, Telangana, India*
[2]*Assistant Professor, Department of Pharmaceutics, Joginpally BR Pharmacy College, Moinabad, Telangana, India*

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Abstract: Lipid-based novel drug delivery systems, especially Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs), play a vital role in the delivery of chemotherapeutic agents, offering a biocompatible alternative to polymeric and metallic systems. These third-generation colloidal carriers address the intrinsic limitations of conventional chemotherapy, including poor aqueous solubility, non-specific biodistribution, and systemic toxicity. These systems facilitate the encapsulation of hydrophobic bioactives by utilizing a lipid core matrix while protecting them from enzymatic degradation in the physiological environment. The structural evolution from the crystalline matrices of SLNs to the imperfect lattice structures of NLCs demonstrates how lipid composition directly influences drug loading capacity and expulsion kinetics. Moreover, surface functionalization strategies play a crucial role in modulating pharmacokinetics, enabling a transition from reliance on passive accumulation via the Enhanced Permeation and Retention (EPR) effect to active cellular targeting through ligand conjugation. Additionally, these carriers exhibit the capability to circumvent multidrug resistance (MDR) mechanisms via endocytic uptake pathways that bypass efflux pumps. Despite these therapeutic advantages, the actual practical implementation remains constrained by critical bottlenecks in scale-up and stability that currently hinder widespread clinical adoption.

Keywords: Solid Lipid Nanoparticles; Nanostructured Lipid Carriers; Tumor Targeting; Multidrug Resistance; Enhanced Permeation and Retention.

1. Introduction

The global burden of neoplastic diseases continues to drive the demand for therapeutic interventions that maximize cytotoxicity against malignant cells while preserving healthy tissue integrity. Conventional chemotherapy, despite its prevalence, remains plagued by suboptimal pharmacokinetic profiles, primarily due to the hydrophobic nature of many potent antineoplastic agents [1]. The systemic administration of free drugs often results in indiscriminate distribution, necessitating high dosages that precipitate severe off-target effects. Consequently, the field of pharmaceutics has pivoted toward nanomedicine, seeking to exploit the unique pathophysiology of solid tumors.

Lipid-based drug delivery systems have emerged as a superior class of nanocarriers owing to their physiological compatibility and biodegradability. Unlike polymer-based counterparts, which may generate toxic degradation byproducts, lipid carriers utilize physiological lipids such as triglycerides, fatty acids, and waxes that are well-tolerated by the human body [2]. The initial development of liposomes marked a significant milestone; however, issues regarding polymer instability and rapid leakage of encapsulated content necessitated further innovation. This led to the engineering of Solid Lipid Nanoparticles (SLNs) and subsequently, Nanostructured Lipid Carriers (NLCs), which combine the advantages of lipid emulsions and polymeric nanoparticles while mitigating their respective drawbacks [3].

The primary mechanism driving the utility of these nanocarriers in oncology is the Enhanced Permeation and Retention (EPR) effect. Rapidly proliferating tumor vasculature exhibits fenestrations ranging from 200 to 800 nm, coupled with defective lymphatic drainage, allowing nanoparticles to accumulate preferentially within the tumor interstitium [4]. However, reliance on passive targeting alone often proves insufficient due to heterogeneity in tumor vascularization and elevated interstitial fluid pressure. Thus, recent research has focused on the structural refinement of lipid matrices and surface engineering to facilitate active uptake and overcome cellular barriers.

* Corresponding author: Supriya Buderla

2. Structural Dynamics and Matrix Evolution

The efficiency of a lipid-based nanocarrier depends heavily on the physical state of the lipid core, which dictates drug loading capacity, release kinetics, and long-term stability.

2.1. Solid Lipid Nanoparticles (SLNs)

SLNs were introduced as the first generation of lipid nanoparticles, consisting of a solid lipid core stabilized by surfactants in an aqueous phase. The lipid matrix remains solid at both room and body temperatures, which restricts the mobility of the encapsulated drug and retards its leakage compared to liquid emulsions [5]. The solid state is achieved by using lipids with high melting points, such as glyceryl behenate or stearic acid. Despite their advantages, SLNs exhibit specific thermodynamic limitations. During storage, the lipid matrix tends to undergo polymorphic transitions, typically shifting from a high-energy α-form or β-form to a more thermodynamically stable, highly ordered β-modification. This crystallization process results in a perfect lattice structure with minimal imperfections, leading to the expulsion of the encapsulated drug a phenomenon known as "drug expulsion" [6]. Moreover, the densely packed crystal lattice limits the available space for drug accommodation, often resulting in low drug loading capacities (DLC).

Table 1. Physicochemical Functionality of Common Excipients in SLN/NLC Formulations

Component Class	Examples	Function & Physicochemical Role
Solid Lipids	Glyceryl behenate (Compritol® 888 ATO), Stearic acid, Cetyl palmitate	Forms the structural core; determines particle size and controlled release profile. High melting point ensures solid state at body temperature.
Liquid Lipids (Oils)	Oleic acid, Caprylic/capric triglycerides (Miglyol® 812), α-Tocopherol	Creates lattice imperfections in NLCs to increase drug payload; modulates viscosity and crystallization kinetics.
Surfactants	Poloxamer 188, Polysorbate 80 (Tween 80), Lecithin	Reduces interfacial tension to facilitate emulsification; provides steric or electrostatic stabilization to prevent particle aggregation.
Charge Modifiers	Stearylamine (Positive), Dicetyl phosphate (Negative)	Modifies Zeta potential to influence cellular uptake interaction and physical stability (prevention of flocculation).
Cryoprotectants	Trehalose, Mannitol, Sorbitol	Prevents particle aggregation and fusion during the lyophilization (freeze-drying) process; aids in redispersibility.

2.2. Nanostructured Lipid Carriers (NLCs)

NLCs were developed as second-generation carriers to overcome the limitations of SLNs. The fundamental modification in NLCs involves the incorporation of liquid lipids (oils) into the solid lipid matrix. The presence of liquid lipids, such as oleic acid or Capryol™, creates a "mass imperfection" within the crystal lattice [7].

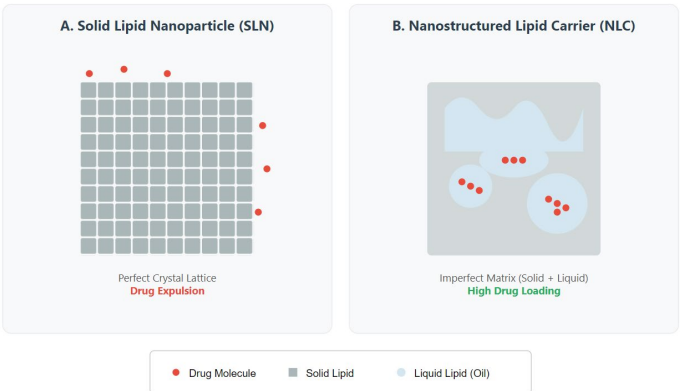

Figure 1. Comparison of SLN and NLC matrices. (A) Solid Lipid Nanoparticles (SLN) form a highly ordered crystalline lattice during storage. This tight packing reduces free volume, leading to the expulsion of drug molecules (red dots) to the particle surface or dispersion medium. (B) Nanostructured Lipid Carriers (NLC) incorporate liquid lipids (oils) to create imperfections and amorphous regions within the solid matrix. These "voids" accommodate a higher payload of drug molecules and prevent expulsion during storage

This imperfect matrix structure prevents the formation of a highly ordered crystal lattice, thereby maintaining distinct voids and vacancies where drug molecules can reside. The resulting amorphous structure significantly enhances Drug Loading Capacity (DLC) and Entrapment Efficiency (EE). Moreover, the inclusion of liquid lipids reduces the melting point of the matrix slightly but maintains solid integrity at body temperature, preventing the rapid polymorphic transitions observed in SLNs [8]. Consequently, NLCs demonstrate superior storage stability and a minimized risk of drug expulsion, making them the preferred architecture for delivering high-payload hydrophobic chemotherapeutics.

Table 2. Comparison of Lipid-Based Nanocarrier Generations

Feature	Solid Lipid Nanoparticles (SLN)	Nanostructured Lipid Carriers (NLC)	Liposomes (Reference)
Core Structure	Solid crystalline lipid matrix (Highly ordered lattice)	Solid matrix with liquid lipid nanocompartments (Imperfect lattice)	Aqueous core enclosed by phospholipid bilayer(s)
Drug Loading Capacity (Hydrophobic)	Low to Moderate (Limited by crystal packing density)	High (Mass imperfections create voids for drug accommodation)	Moderate (Restricted to the bilayer membrane)
Storage Stability	Moderate; prone to polymorphic transition (α to β)	High; liquid lipids inhibit crystallization and lattice ordering	Low; susceptible to hydrolysis, oxidation, and fusion
Drug Expulsion Risk	High (Due to lattice tightening during crystallization)	Minimal (Amorphous structure prevents drug exclusion)	High (Leakage of encapsulated content)
Release Kinetics	Biphasic (Initial burst release + sustained release)	Modulated controlled release (Tunable by solid:liquid lipid ratio)	Often rapid unless surface-modified (e.g., PEGylation)

3. Surface Engineering for Site-Specific Delivery

While the lipid core governs drug retention and release, the surface characteristics of the nanocarrier dictate its interaction with the biological environment. Unmodified lipid nanoparticles are prone to opsonization the adsorption of serum proteins (opsonins) that mark the particles for rapid clearance by the Reticuloendothelial System (RES), primarily in the liver and spleen [9].

3.1. Stealth Effect and PEGylation

To extend systemic circulation time, the surface of SLNs and NLCs is frequently modified with hydrophilic polymers, most notably Polyethylene Glycol (PEG). This process, termed "PEGylation," creates a steric hydration barrier around the nanoparticle.

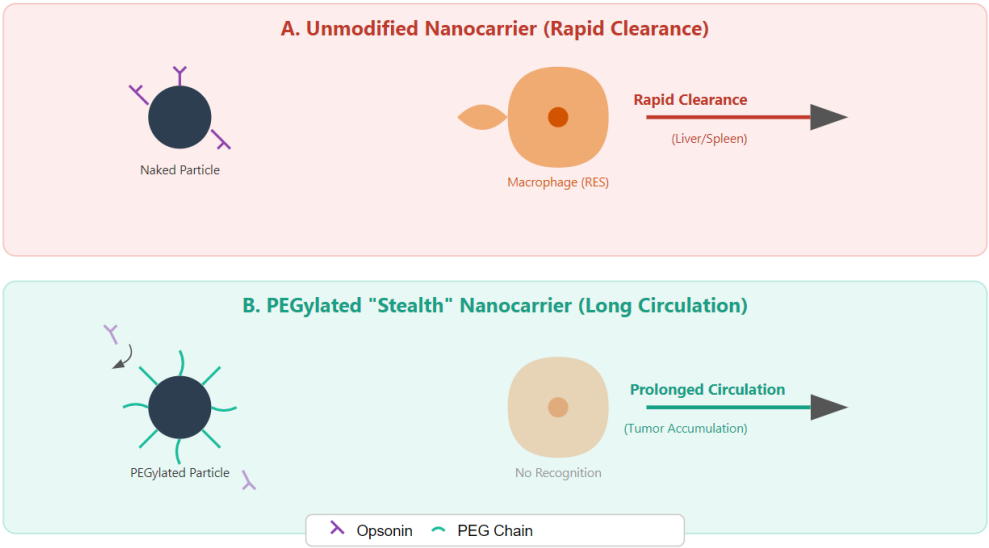

Figure 2. Impact of PEGylation on Pharmacokinetics. (A) Unmodified lipid nanoparticles are rapidly opsonized by serum proteins (opsonins) and recognized by macrophages of the Reticuloendothelial System (RES), leading to rapid clearance from the bloodstream. (B) Functionalization with Polyethylene Glycol (PEG) creates a hydrophilic steric barrier. This "Stealth" layer prevents opsonin adsorption, inhibits macrophage recognition, and significantly prolongs systemic circulation time, thereby increasing the probability of tumor accumulation via the EPR effect

The dense hydrophilic cloud prevents the adsorption of opsonins and inhibits recognition by macrophages, effectively rendering the particles "invisible" to the immune system [10]. Long-circulating "stealth" nanoparticles have a higher probability of reaching the tumor site via the EPR effect. However, excessive PEGylation can hinder cellular uptake by the tumor cells themselves, a trade-off often referred to as the "PEG dilemma."

3.2. Active Targeting Techniques

To enhance specificity beyond passive accumulation, active targeting involves the conjugation of ligands to the nanoparticle surface that specifically bind to receptors overexpressed on cancer cells.

3.2.1. Folate Targeting

The folate receptor is frequently overexpressed in ovarian, breast, and lung cancers. Functionalizing lipid carriers with folic acid facilitates receptor-mediated endocytosis, significantly increasing intracellular drug concentration relative to non-targeted formulations [11].

3.2.2. Transferrin and Lactoferrin

Rapidly dividing tumor cells require iron, leading to an upregulation of transferrin receptors. Lipid nanoparticles decorated with transferrin exploit this pathway for efficient internalization.

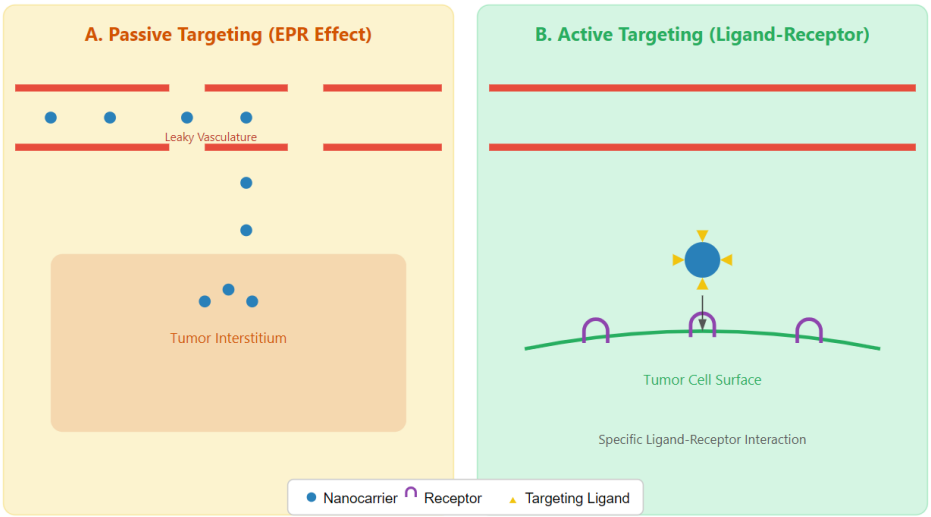

Figure 3. Tumor Targeting Techniques. (A) Passive Targeting utilizes the Enhanced Permeation and Retention (EPR) effect, where nanocarriers (blue) accumulate in tumor tissue through fenestrations in leaky angiogenic blood vessels. (B) Active Targeting involves modifying the nanocarrier surface with specific ligands (yellow triangles) that bind to receptors (purple) overexpressed on the tumor cell surface, facilitating specific cellular internalization

Table 3. Active Targeting Ligands for Receptor-Mediated Endocytosis in Oncology

Targeting Ligand	Target Receptor	Primary Tumor Associations	Mechanism of Cellular Internalization
Folic Acid	Folate Receptor-α (FR-α)	Ovarian, Breast, Lung, Colorectal	Clathrin-independent endocytosis; bypasses lysosomal degradation in some pathways.
Transferrin	Transferrin Receptor (TfR)	Glioblastoma, Breast, Liver	Clathrin-mediated endocytosis; exploits iron demand of rapidly proliferating cells.
RGD Peptide	Integrin αvβ3	Angiogenic Endothelium, Melanoma, Glioma	Integrin-mediated internalization; targets both tumor cells and neovasculature.
Hyaluronic Acid	CD44 Receptor	Pancreatic, Breast, Lung	Ligand-receptor binding triggers internalization; targets cancer stem-like cells.
Anti-HER2 Ab	HER2/neu Receptor	HER2+ Breast Cancer	Antibody-dependent receptor-mediated endocytosis.

3.2.3. Peptide-Based Targeting

Ligands such as cRGD (cyclic Arginine-Glycine-Aspartic acid) bind to αvβ3 integrins, which are abundant on tumor endothelial cells, thereby targeting both the tumor vasculature and the malignant cells themselves [12].

4. Overcoming Biological Barriers and Multidrug Resistance

One of the most formidable challenges in oncology is Multidrug Resistance (MDR), often mediated by the overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp). These efflux pumps actively expel chemotherapeutic agents from the cytoplasm, reducing their therapeutic efficacy.

4.1. The "Trojan Horse" Mechanism

Lipid nanocarriers offer a distinct advantage in reversing MDR. Unlike free drugs, which enter cells via passive diffusion and are easily intercepted by efflux pumps, SLNs and NLCs enter cells primarily through endocytosis (clathrin- or caveolae-mediated) [13]. Once inside, the nanoparticles are localized within endosomes, bypassing the membrane-bound P-gp pumps. The lysosomal processing subsequently releases the drug deep within the cytoplasm or perinuclear region, effectively evading the efflux mechanism.

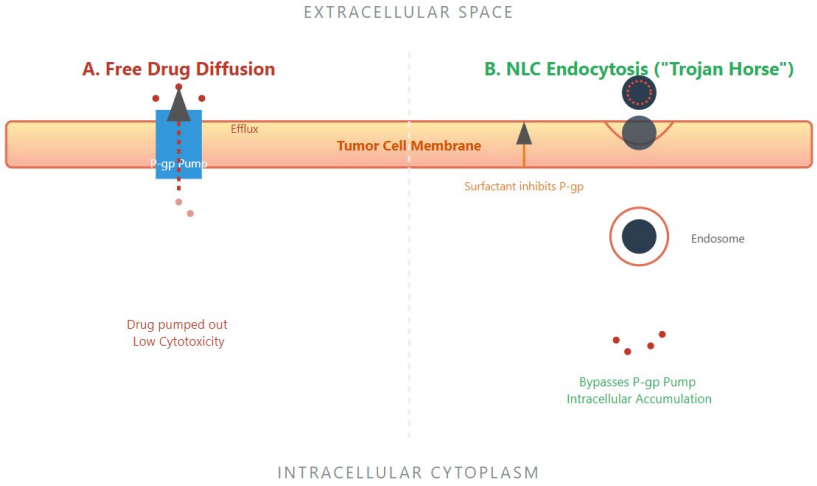

Figure 4. Mechanisms of Multidrug Resistance (MDR) Reversal. (A) Free chemotherapeutic agents (red dots) enter the cell via passive diffusion but are recognized by membrane-bound P-glycoprotein (P-gp) pumps and actively transported back into the extracellular space, resulting in sub-therapeutic intracellular concentrations. (B) Lipid nanocarriers (NLCs) enter the cell via endocytosis (The "Trojan Horse" effect), encapsulating the drug within a vesicle. This pathway bypasses the membrane-bound pumps. Surfactants in the lipid formulation can inhibit the ATPase activity of P-gp, preventing drug efflux

4.2. Inhibition of Efflux Pumps

Beyond the "Trojan horse" effect, certain components of the lipid formulation can biologically inhibit P-gp activity. Surfactants commonly used in SLN/NLC fabrication, such as D- α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and Polysorbate 80, have been shown to deplete intracellular ATP levels or alter membrane fluidity, thereby inhibiting the function of efflux transporters [14]. This dual mechanism bypassing pumps via endocytosis and chemically inhibiting their function positions lipid nanocarriers as potent tools for treating refractory tumors.

4.3. Crossing the Blood-Brain Barrier (BBB)

The treatment of Glioblastoma Multiforme (GBM) is severely restricted by the BBB. Lipid nanoparticles, particularly those functionalized with ApoE or synthesized with specific surfactants like Polysorbate 80, can mimic Low-Density Lipoproteins (LDL). This allows them to interact with LDL receptors on the brain capillary endothelial cells, facilitating transcytosis across the BBB and enabling the delivery of therapeutics to central nervous system malignancies [15].

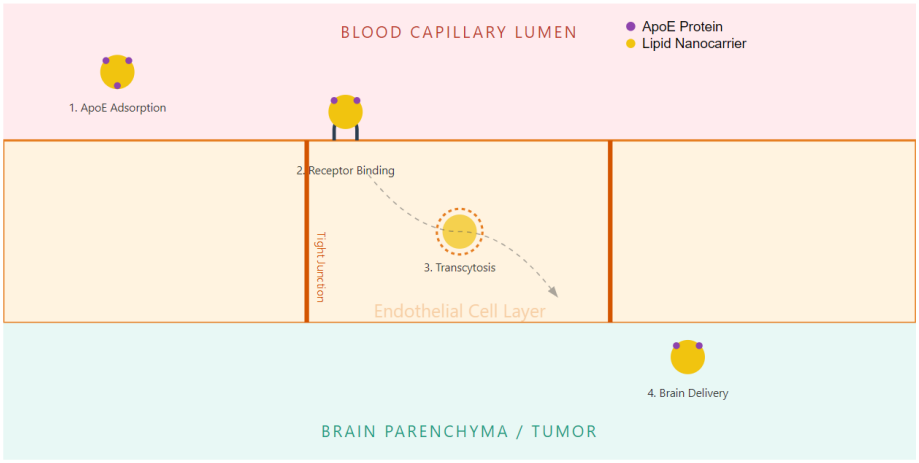

Figure 5. Receptor-Mediated Transcytosis across the Blood-Brain Barrier (BBB). To treat CNS malignancies like Glioblastoma, lipid nanocarriers are modified to mimic endogenous lipoproteins. Adsorption of Apolipoprotein E (ApoE) (purple dots) onto the nanoparticle surface enables recognition by LDL receptors on the brain capillary endothelial cells. This triggers receptor-mediated endocytosis, followed by transcytosis across the endothelial cytoplasm, and exocytosis into the brain parenchyma, bypassing the tight junctions that restrict paracellular transport

Table 4. Mechanisms of Multidrug Resistance (MDR) Reversal by Lipid Nanocarriers

Resistance Mechanism	Conventional Chemotherapy Limitation	Lipid Nanocarrier Strategy	Mechanism of Action
Efflux Transporters (e.g., P-gp, MRP1)	Substrates are actively pumped out of the cell, reducing intracellular concentration.	"Stealth" Entry / Trojan Horse	Nanocarriers enter via endocytosis, hiding the drug from membrane-bound efflux pumps.
P-gp ATPase Activity	High ATP levels fuel the efflux pumps.	Bio-inhibition	Surfactants (e.g., TPGS, Pluronic P85) inhibit P-gp ATPase and deplete intracellular ATP.
Membrane Rigidity	Altered lipid packing reduces drug permeability.	Membrane Fluidization	Lipid components merge with cell membranes, increasing fluidity and permeability.
Apoptosis Evasion	Upregulation of anti-apoptotic factors (e.g., Bcl-2).	Co-delivery	Simultaneous delivery of chemotherapeutics and siRNA/genes to silence resistance genes.

5. Challenges for Implementation

Despite the extensive preclinical success of SLNs and NLCs, their transition from the bench to the bedside has been slower than that of liposomes or polymeric nanoparticles. Several factors contribute to this translational gap.

5.1. Scalability and Manufacturing

The laboratory-scale production of lipid nanoparticles typically involves high-pressure homogenization or microemulsion techniques, which are difficult to scale up while maintaining precise particle size distributions (polydispersity index < 0.3). Batch-to-batch variability in lipid crystallinity and drug loading remains a critical hurdle for industrial manufacturing [16]. Maintaining the delicate balance between the solid and liquid lipid phases in NLCs during large-scale production requires rigorous process control to prevent phase separation or supercooling phenomena.

5.2. Stability

While NLCs offer improved stability over SLNs, lipid-based systems are still susceptible to physical instability phenomena such as particle aggregation, gelation, and Ostwald ripening during long-term storage. Moreover, chemical stability, particularly lipid oxidation and hydrolysis, poses a challenge, necessitating the inclusion of antioxidants and stringent storage conditions. Regulatory agencies like the FDA and EMA have established guidelines for liposomal products, but specific guidance for complex multiphase

lipid nanoparticles like NLCs is still evolving. The complexity of characterizing the internal structure of NLCs specifically the degree of disorder and the precise localization of the drug within the lipid matrix complicates the quality control assays required for regulatory approval [17]. Current efforts are focused on defining Critical Quality Attributes (CQAs) specific to solid lipid nanocarriers to streamline the approval process.

5.3. Clinical Applications

Despite these challenges, several formulations are progressing through clinical pipelines. Lipid-based formulations are currently being evaluated for the delivery of paclitaxel, doxorubicin, and novel gene therapies (siRNA/mRNA). The success of lipid nanoparticles (LNPs) in COVID-19 mRNA vaccines has significantly bolstered interest and investment in lipid-based platforms, paving the way for accelerated approval pathways for oncological applications [18].

Table 5. Selected Lipid-Based Nanomedicines in Clinical Development or Market

Formulation Name	Active Pharmaceutical Ingredient (API)	Nanocarrier Type	Indication	Development Status
Doxil® / Caelyx®	Doxorubicin	PEGylated Liposome	Ovarian Cancer, Kaposi's Sarcoma	Marketed (FDA Approved)
Onpattro® (Patisiran)	siRNA (Transthyretin)	Lipid Nanoparticle (LNP)	hATTR Amyloidosis	Marketed (First FDA-approved siRNA LNP)
Comirnaty®	mRNA (BNT162b2)	Lipid Nanoparticle (LNP)	COVID-19 Prophylaxis	Marketed
Lipoplatin™	Cisplatin	Liposome	NSCLC, Pancreatic Cancer	Phase III
EndoTAG®-1	Paclitaxel	Cationic Lipid Complex	Pancreatic Cancer, Triple Negative Breast Cancer	Phase III

6. Conclusion

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers are a drug delivery technology, that can address the fundamental solubility and specificity issues of conventional chemotherapy. The transition from the crystalline matrix of SLNs to the imperfect lattice of NLCs has significantly improved drug loading and stability, making these systems viable candidates for commercial development. Through surface engineering, these carriers can actively target tumor cells and penetrate formidable biological barriers like the BBB, while their endocytic uptake mechanism offers a robust strategy for overcoming multidrug resistance. However, the path to widespread clinical use requires addressing the engineering challenges of scale-up and long-term stability.

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