

# Lipid-Based Nanocarriers in Targeted Drug Delivery: Current Status and Limitations

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## Abstract

## Review Article

Lipid-based nanocarriers (LBNs), namely liposomes, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have become cornerstones in targeted therapeutics. Their inherent biocompatibility, ability to encapsulate both hydrophilic and lipophilic cargos at the same time, and tunable surface chemistry makes them ideal vectors for bypassing physiological barriers. This mini-review summarises the current clinical and technological state of LBNs, and evaluates passive vs active targeting strategies and critically addresses primary formulation and manufacturing bottlenecks including polymorphic transitions, early payload leakage, immunogenicity, and industrial scalability.

**Keywords:** Lipid-based nanocarriers; Liposomes; Solid lipid nanoparticles; Nanostructured lipid carriers; Targeted drug delivery; Active targeting; Nanomedicine; Industrial scalability.

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## INTRODUCTION

Conventional chemotherapeutics and lipophilic small molecules often suffer from poor aqueous solubility, poor bioavailability, non-specific systemic biodistribution, and high off-target toxicity [1, 2]. By mimicking endogenous membrane architectures, colloidal lipid carriers overcome these basic pharmacokinetic bottlenecks, prolonging vascular circulation half-life and facilitating targeted accumulation at pathological sites [3]. The landmark clinical approval of platforms like Doxil (PEGylated liposomal doxorubicin) [4] and more recently ionisable lipid nanoparticle (LNP)-formulated mRNA vaccines against SARS-CoV-2 [5] has validated lipid nanotechnology as a major delivery modality for precision medicine.

### Classification of Lipid Nanocarriers Liposomes:

Unilamellar or multilamellar vesicular bilayers of natural or synthetic phospholipids enclosing an aqueous compartment. They can uniquely load both hydrophilic agents (in the core) and hydrophobic agents (in the lipid bilayer), but are sensitive to membrane fluidity fluctuations and chemical peroxidation [4, 6].

### Solid Lipid Nanoparticles (SLNs):

Submicron colloidal systems containing a solid lipid matrix (e.g. highly purified triglycerides, fatty acids or waxes) surrounded by an interfacial surfactant layer. They have better protection to labile compounds and avoid toxic organic solvents in preparation but have low drug loading capacity [7].

### Nanostructured Lipid Carriers (NLCs):

Second generation carriers that are prepared by mixing solid lipids with spatially incompatible liquid lipids (oils). The resultant structurally disordered, imperfect crystalline matrix prevents rapid polymorphism and greatly improves drug payload accommodation [8].

### Delivery & Targeting Mechanisms

**Passive Targeting:** Largely driven by the Enhanced Permeability and Retention (EPR) effect in defective tumour microvasculature with steric surface stabilisation by polyethylene glycol (PEGylation) for reducing opsonisation and rapid clearance by the reticuloendothelial system (RES) [2, 9].

**Active Targeting:** Accomplished via conjugation of carrier surfaces with selective affinity

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ligands such as folic acid, transferrin, cyclic RGD peptides or monoclonal antibodies that specifically bind to the corresponding receptors overexpressed on tumour cells or diseased tissue [1, 6].

**Stimuli-Responsive Release:** Platforms designed to experience controlled destabilisation in response to external triggers, such as focused ultrasound or localised hyperthermia, or endogenous pathological gradients, such as endosomal acidity pH < 6.0 and hyper-reductive intracellular glutathione levels [2, 3].

### Current Clinical Landscape & Ionizable LNPs

Targeted cancer, systemic antifungal treatment (AmBisome), and modern genetic therapies are all

dominated by lipid nanocarriers, which make up the single largest class of clinically authorised nanomedicines [3, 5]. Ionisable cationic lipids (such DLin-MC3-DMA and ALC-0315) are the focus of recent formulation innovations. These special lipids reduce non-specific cellular lysis and clearance by systemic macrophages by maintaining a nearly neutral surface charge at healthy bloodstream pH (~7.4). Tertiary amines are protonated upon endocytosis into acidic endosomes (pH 5.0–6.0), where they interact electrostatically with anionic endosomal phospholipids to produce an inverted hexagonal (HII) non-bilayer phase shift that facilitates the transport of cytosolic cargo [5, 10].

**Table 1: Comparative Profile of Major Lipid Nanocarrier Classes in Targeted Drug Delivery**

| System                 | Composition                                           | Profile of Payload                               | Merits                                                                  | Primary Limitations                                                                   |
|------------------------|-------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Liposomes [4, 6]       | Phospholipid bilayer + interior aqueous core          | Moderate to High (Dual hydrophilic & lipophilic) | High biomimicry; versatile surface engineering; proven clinical record  | Susceptible to lipid oxidation; high risk of premature drug leakage                   |
| SLNs [7]               | High-melting solid lipid core + surfactant coating    | Moderate (Predominantly lipophilic molecules)    | Excellent physical protection; solvent-free manufacturing (HPH)         | Polymorphic lipid crystallization causing drug expulsion during storage               |
| NLCs [8]               | Disordered blend of solid and liquid lipids           | High (Improved structural capacity)              | Suppressed polymorphic transitions; minimized active ingredient leakage | Complex excipient optimization; potential surfactant-mediated cytotoxicity            |
| Ionizable LNPs [5, 10] | Ionizable lipid, helper lipid, cholesterol, PEG-lipid | Very High (Nucleic acids & macromolecules)       | High endosomal escape efficiency; low systemic cationic toxicity        | Tight cold chain requirement for storage; Highly liver-specific requiring re-routing. |

### Important Restrictions & Translational Obstacles

Clinical translation beyond classical formulations is hampered by strict physical and immunological limitations, despite significant translational advances:

#### Polymorphic Transitions and Drug Expulsion:

Solid lipid cores change from metastable  $\alpha$  and  $\beta'$  forms to the densely packed, thermodynamically preferred  $\beta$ -crystalline lattice during storage. Encapsulated hydrophobic drug molecules are gradually expelled as a result of this compaction, which decreases the amount of available intermolecular free space [7, 8].

#### Early Payload Leakage:

During systemic dilution, adsorbed or outer-corona-associated medications often desorb before reaching the target tissue, resulting in systemic off-target exposure and reducing net therapeutic efficacy [4, 6].

#### Immunogenicity and Accelerated Blood Clearance (ABC):

Although PEGylation provides steric stability, repeated systemic treatment can cause anti-PEG IgM antibody reactions. After further dosing, this causes complement activation and speeds up the removal of nanocarriers by splenic and hepatic macrophages [11].

### Industrial Scalability & Quality by Design (QbD):

Strict parameter governance is necessary for microfluidic mixing and high-pressure homogenisation (HPH). Particle size distribution (polydispersity index, PDI) and encapsulation efficiency vary from batch to batch due to small changes in fluidic shear, flow rate ratios, or heat gradients [5, 10].

### Future Perspectives

The future direction of lipid nanocarrier engineering is focused on hybrid and biomimetic architectures in order to overcome the inherent limitations of conventional lipid systems. Promising methods to combine mechanical durability with natural biological stealth include lipid-polymer hybrid nanoparticles (LPHNs) and cell membrane-camouflaged lipid nanocarriers (using erythrocyte, platelet, or tumor-derived membranes) [1, 2]. Simultaneously, including Quality by Design (QbD) control parameters into microfluidics-on-a-chip technologies would enable robust, repeatable scale-up that complies with current Good Manufacturing Practice (cGMP) requirements and high-throughput parameter screening.

## CONCLUSION

Lipid-based nanocarriers have revolutionised macromolecular delivery and systemic cancer, making them indispensable in contemporary pharmacology. However, comprehensive solutions for crystalline polymorphism, off-target desorption, and repeat-dose immunogenicity are necessary to turn laboratory prototypes into effective treatments. Lipid nanocarriers are in a unique position to be the standard vehicle for next-generation precision medicine by balancing cutting-edge hybrid biomaterials with standardised continuous manufacturing platforms.

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