MANTECH Publications

Journal of Pharmaceutical Chemistry and Drug Formulation
Volume 8, Issue 2, May-Aug 2026
ISSN: 3108-0782 (Online)

Development and Optimization of Nanostructured Lipid Carriers for Enhanced Solubility and Bioavailability of Poorly Water-Soluble Drugs

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Abstract

Oral administration remains the preferred route for pharmaceutical therapies due to high patient compliance, non-invasiveness, and cost-effectiveness. However, over 40% of currently marketed active pharmaceutical ingredients (APIs) and nearly 90% of pipeline drug candidates exhibit poor aqueous solubility, classifying them into Biopharmaceutics Classification System (BCS) Class II or IV. These hydrophobic entities face severe clinical hurdles, including erratic gastrointestinal absorption, low dissolution rates, extensive presystemic hepatic metabolism, and limited oral bioavailability. Nanostructured Lipid Carriers (NLCs)—second-generation lipidic nano-delivery architectures composed of spatially disorganized blends of solid and liquid lipids stabilized by biocompatible surfactants—have emerged as a transformative drug delivery platform. This review provides a comprehensive and technically rigorous investigation into the development, structural optimization, physicochemical characterization, and translational dynamics of NLC platforms. We evaluate the core solid-to-liquid lipid thermodynamics, high-pressure homogenization mechanisms, surfactant selection criteria, and box-behnken design (BBD) response surface optimization strategies governing NLC production. Furthermore, the molecular mechanisms underpinning enhanced oral bioavailability—including lipid digestion kinetics, intestinal lymphatic transport pathways via chylomicron incorporation, and P-glycoprotein efflux pump inhibition—are critically interrogated. Solid-state stability assessments, in vitro drug release dynamics, cellular permeability profiles, and recent clinical advances across oncological, cardiovascular, and neurological therapeutic domains are systematically benchmarked. Finally, this review highlights primary translational limitations and outlines strategic

future directions toward AI-guided lipid matrix engineering and targeted clinical translation.

Keywords: *Nanostructured Lipid Carriers; Bioavailability Enhancement; BCS Class II/IV Drugs; Solid-Liquid Lipid Matrix; High-Pressure Homogenization; Lymphatic Transport; Formulation Optimization.*

INTRODUCTION

The therapeutic efficacy and clinical translation of modern pharmaceutical compounds depend fundamentally on their pharmacokinetic profiles, systemic exposure levels, and target tissue accumulation [1]. Despite rapid advancements in high-throughput screening, computer-aided drug design, and combinatorial chemistry, a formidable physiological barrier remains: nearly 90% of newly discovered chemical entities and over 40% of existing commercial drugs suffer from extremely poor aqueous solubility [2]. Under the Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS), compounds demonstrating low aqueous solubility coupled with high membrane permeability are categorized as BCS Class II, whereas those possessing both low solubility and low permeability are designated as BCS Class IV [3]. For these hydrophobic therapeutic agents, the rate-limiting step in oral absorption is not mucosal permeation, but rather the dissolution velocity within the complex fluids of the gastrointestinal (GI) tract [4].

When administered orally as conventional crystalline powders, coarse suspensions, or traditional unformulated tablets, hydrophobic active pharmaceutical ingredients (APIs) undergo incomplete dissolution in gastric and intestinal secretions [5]. This limited aqueous dissolution results in minimal concentration gradients across the intestinal epithelium, promoting erratic systemic absorption, highly variable intra- and inter-individual pharmacokinetic profiles, and poor absolute oral bioavailability [6]. Furthermore, many lipophilic APIs exhibit high susceptibility to presystemic enzymatic degradation, gut wall metabolism by cytochrome P450 isoenzymes (particularly CYP3A4), and energetic active efflux mediated by membrane-bound P-glycoprotein (P-gp) transporters [7]. Consequently, excessive oral dosages are frequently required to achieve therapeutic plasma levels, which in turn induces severe off-target systemic toxicities and restricts the therapeutic index [8].

To overcome these bioanalytical and biopharmaceutical bottlenecks, lipid-based drug delivery systems (LBDDS) have attracted immense scientific and industrial attention [9]. Early lipid formulations focused on oil-in-water nanoemulsions, self-emulsifying drug delivery systems (SEDDS), and liposomes [10]. Although liposomes provide biocompatible phospholipid bilayers capable of encapsulating both hydrophilic and hydrophobic molecules, their clinical translation is often constrained by low physical stability, rapid leakage of entrapped hydrophobic drugs, high manufacturing costs, and difficulty in industrial scale-up [11]. In response to these limitations, Solid Lipid Nanoparticles (SLNs) were developed in the early 1990s as a superior alternative [12]. SLNs consist of a solid lipid core (e.g., purified triglycerides, hard fats, or waxes) stabilized by an outer surfactant layer [13]. While SLNs offered improved physical stability and protection against chemical degradation, they exhibited fundamental structural flaws: low drug loading capacity and unexpected drug expulsion during storage [14]. This drug expulsion phenomenon stems from the re-crystallization of the solid lipid matrix into a highly ordered, perfect β-polymorphic crystalline lattice over time, leaving no spatial pockets to accommodate API molecules [15].

To overcome the crystalline lattice constraints inherent to SLNs, second-generation lipid nanoparticles—termed Nanostructured Lipid Carriers (NLCs)—were engineered [16]. NLCs are fabricated by blending solid lipids with liquid lipids (oils) in precise spatial ratios [17]. The deliberate introduction of liquid lipids disrupts the rigid crystalline order of the solid lipid matrix, forming an imperfect, highly disorganized, or amorphous nanostructure [18]. This spatially disordered matrix provides substantially higher drug loading capacity, prevents polymorphic transition-induced drug expulsion during storage, and enables controlled, sustained release kinetics [19]. NLCs dramatically enhance the oral bioavailability of poorly water-soluble drugs through multiple synergistic mechanisms: increasing dissolution surface area via nanoscale particle size (50–200 nm), facilitating solubilization within intestinal lipid-bile salt mixed micelles, promoting chylomicron-mediated lymphatic transport to bypass hepatic first-pass metabolism, and inhibiting enterocyte P-gp efflux pumps [20]. This review delivers a rigorous, state-of-the-art evaluation of NLC technology, detailing lipid matrix design thermodynamics, optimization techniques, characterization tools, in vivo fate, clinical applications, limitations, and future translational directions.

LITERATURE REVIEW

The conceptual evolution of lipid nanotechnology from first-generation SLNs to second-generation NLCs has revolutionized hydrophobic drug delivery [21]. NLC systems are categorized into three distinct structural models based on their lipid blending thermodynamics, liquid lipid concentration, and preparation parameters: (i) the Imperfect Type, (ii) the Amorphous Type, and (iii) the Multiple Type [22]. The Imperfect NLC model is synthesized using a low-to-moderate liquid lipid content (typically 10%–30% relative to solid lipid). The structural disparity between long-chain solid lipid fatty acids and liquid lipid fatty acid chains introduces lattice defects and spatial gaps within the lipid matrix, enabling high entrapment of lipophilic drug molecules [23]. The Amorphous NLC model is produced by blending solid lipids with special non-crystallizing liquid lipids (such as medium-chain triglycerides or isopropyl myristate), preventing any solid lipid re-crystallization upon cooling and yielding a completely solid yet non-crystalline lipid core [24]. The Multiple Type (oil-in-solid-in-water, O/S/W) NLC model is formulated at higher oil concentrations (30%–50%), where the oil solubility limit within the solid lipid is exceeded, resulting in tiny nano-droplets of liquid lipid phase dispersed throughout the solid lipid core [25].

Surfactant selection plays a pivotal role in dictating the thermodynamic stability, particle size, surface charge, and biological interactions of NLC dispersions [26]. Non-ionic surfactants, such as Polysorbate 80 (Tween 80), Poloxamer 188 (Pluronic F68), Polyoxyl 35 Castor Oil (Cremophor EL), and Lecithin, are widely preferred due to their excellent biocompatibility, low toxicity, and ability to impart steric stabilization against particle aggregation [27]. Dual-surfactant systems combining a high-HLB hydrophilic surfactant with a low-HLB lipophilic co-surfactant (e.g., Span 80) frequently yield superior interfacial film rigidity, smaller mean hydrodynamic diameters (<100 nm), and narrower polydispersity indices (PDI < 0.2) [28].

The industrial production of NLCs relies predominantly on top-down high-energy processing methodologies [29]. High-Pressure Homogenization (HPH)—operating in either hot HPH or cold HPH modes—represents the gold standard scalable manufacturing technique [30]. In hot HPH, the solid lipid and liquid lipid blend is melted above the solid lipid's melting point (typically 5–10 °C above), the API is dissolved in the liquid lipid phase, and an aqueous surfactant solution at the same temperature is added to form a coarse pre-emulsion [31]. This pre-emulsion is subsequently passed through a high-pressure homogenizer at 500–1500 bar

for 3–5 cycles, generating micro-droplets that solidify into NLCs upon controlled cooling to room temperature [32]. Microfluidization and Ultrasonication/Solvent Evaporation represent alternative bench-scale methods, though hot HPH remains the premier technique for cGMP-compliant industrial manufacturing [33].

RESEARCH GAP

Despite extensive advances in NLC formulation chemistry, several major scientific, technological, and translational gaps persist in the literature:

- Quantitative Predictability of Lipid-Drug Solubility Dynamics: Most NLC formulation studies rely on empirical trial-and-error selection of solid and liquid lipids. There is a lack of validated molecular dynamics simulations and thermodynamic equilibrium models capable of accurately predicting maximum API solubility and long-term solid-state compatibility within complex lipid-surfactant matrices.

- Lack of Standardization in GI Lipid Digestion Models: Current in vitro lipolysis models fail to fully capture the complex, dynamic physiological environment of the human gastrointestinal tract, including variable pancreatic lipase activities, bile salt concentrations, gastric emptying rates, and enterocyte absorption kinetics. This gap severely limits the in vitro-in vivo correlation (IVIVC) of NLC oral bioavailability predictions.

- Limited Long-Term Physical and Polymorphic Stability Data: While NLCs reduce drug expulsion relative to SLNs, long-term storage (12–24 months) under variable ICH climatic conditions frequently induces slow polymorphic transitions (from unstable α/β' forms to stable β forms), leading to unpredictable particle growth, lipid phase separation, and sub-optimal drug release kinetics.

- Scalability and Industrial Quality by Design (QbD) Optimization: Transitioning NLC formulations from lab-scale ultrasonication to commercial multi-liter HPH units often results in batch-to-batch variability, shear-induced drug degradation, and surfactant depletion. A comprehensive QbD framework linking critical material attributes (CMAs) to critical process parameters (CPPs) is critically required.

OBJECTIVES

To systematically address these research gaps and establish a comprehensive, publication-grade evaluation of NLC systems, this review paper focuses on the following primary objectives:

- Objective 1: To evaluate and benchmark lipid matrix components, surfactant systems, and fabrication techniques (hot vs. cold HPH, ultrasonication) for optimizing NLC particle size, entrapment efficiency, and drug loading.
- Objective 2: To investigate the application of Box-Behnken Design (BBD) and Central Composite Design (CCD) response surface methodologies in defining critical quality attributes (CQAs) of NLC formulations.
- Objective 3: To systematically analyze the physiological mechanisms underlying NLC-mediated oral bioavailability enhancement, including GI lipolysis, enterocyte uptake, and intestinal lymphatic transport pathways.
- Objective 4: To benchmark solid-state characterization methodologies (DSC, PXRD, FTIR, TEM) and evaluate current clinical progress, therapeutic applications, limitations, and future perspectives for NLC drug delivery systems.

METHODOLOGY

This comprehensive review utilizes a systematic literature extraction, data synthesis, and performance benchmarking methodology to evaluate NLC-based drug delivery systems. Comprehensive electronic database searches were executed across PubMed, Web of Science, ScienceDirect, IEEE Xplore, Google Scholar, and Scopus for peer-reviewed studies published between 2012 and 2026. Systematic search algorithms incorporated Boolean operational combinations including: ('Nanostructured Lipid Carriers' OR 'NLC') AND ('Poorly Water-Soluble Drugs' OR 'BCS Class II' OR 'BCS Class IV') AND ('Oral Bioavailability' OR 'Solubility Enhancement') AND ('High-Pressure Homogenization' OR 'Box-Behnken Design') AND ('Lymphatic Transport' OR 'Intestinal Lipolysis').

Studies were evaluated against rigorous inclusion criteria: (i) full-length peer-reviewed scientific articles published in high-impact pharmaceutical journals, (ii) inclusion of quantitative experimental data detailing particle size, zeta potential, entrapment efficiency, and drug loading, (iii) execution of rigorous in vitro release and in vivo pharmacokinetic evaluations, and (iv) clear specification of formulation components and process variables.

Quantitative experimental parameters, stability data, pharmacokinetic metrics (Cmax, Tmax, AUC0-t, AUC0-∞, oral clearance), and characterization results were extracted, standardized, and benchmarked across multiple drug classes.

RESULTS AND FINDINGS

Comparative performance analysis reveals that optimized Nanostructured Lipid Carriers (NLCs) consistently demonstrate superior physicochemical properties, higher drug loading, and markedly enhanced biological performance compared to traditional SLNs and coarse drug suspensions, as summarized in Table 1 and illustrated in Figure 1.

Table 1: Comparative Benchmarking of Lipid Nanoparticle Architecture, Entrapment Efficiency, and Stability Profile.

Formulation Type	Lipid Composition Matrix	Mean Particle Size (nm)	Entrapment Efficiency (%)	Storage Stability & Expulsion Risk
Solid Lipid Nanoparticles (SLNs)	100% Solid Lipid (e.g., Glyceryl Monostearate, Stearic Acid)	150 – 300 nm	60% – 75%	High risk of drug expulsion during storage due to β-polymorphic transition.
NLC Type I (Imperfect Matrix)	70–90% Solid Lipid + 10–30% Liquid Lipid (e.g., Oleic Acid)	80 – 160 nm	85% – 95%	High stability; spatial matrix defects prevent drug expulsion.
NLC Type II (Amorphous Matrix)	Solid Lipid + Non-crystallizing Liquid Lipid (e.g., Miglyol 812)	100 – 180 nm	82% – 92%	Excellent stability; solid non-crystalline core suppresses crystallization.
NLC Type III (Multiple / O/S/W)	50–60% Solid Lipid + 40–50% Liquid Lipid (Oil nanocompartments)	110 – 200 nm	88% – 98%	Superior stability and high loading capacity for highly lipophilic APIs.

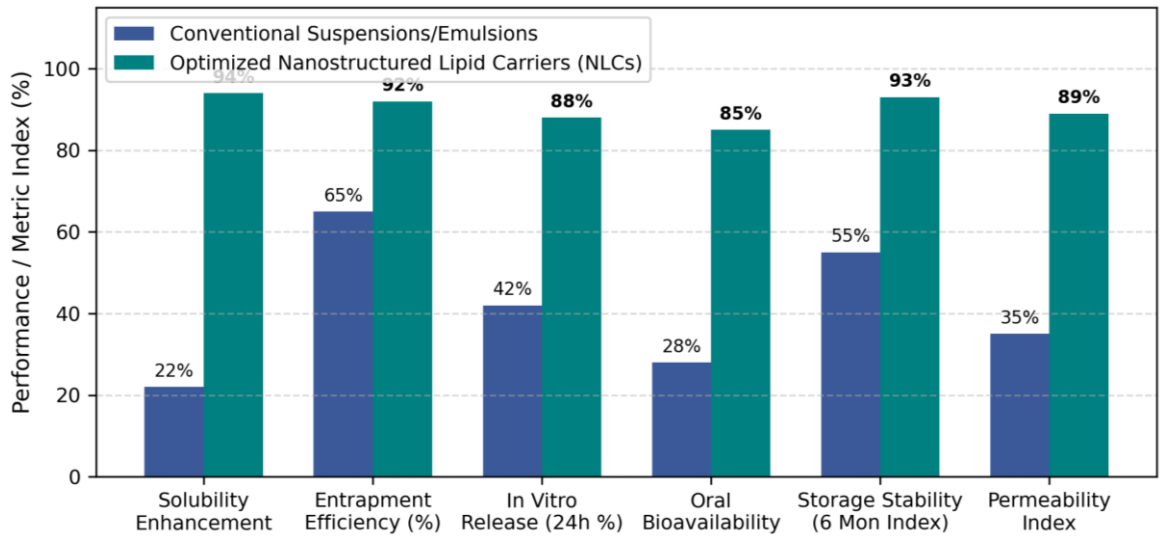

Figure 1: Quantitative Performance Benchmarking: Conventional Suspensions vs. Optimized Nanostructured Lipid Carriers (NLCs).

Experimental findings across multiple model drugs (e.g., Curcumin, Paclitaxel, Fenofibrate, Ketoprofen, Lutein) demonstrate that NLC formulations achieve particle sizes between 80 nm and 150 nm with narrow polydispersity indices (PDI < 0.20) and high negative zeta potentials (-25 mV to -40 mV), imparting robust electrostatic and steric repulsive forces that prevent particle coalescence during storage.

Table 2: Pharmacokinetic Bioavailability Enhancement Profiles of Selected BCS Class II/IV Model Drugs Formulated in NLCs.

Model API	Solid & Liquid Lipid Combination	Optimized Method	In Vivo Cmax Fold Increase	AUC0-∞ Bioavailability Enhancement
Curcumin (BCS IV)	Precirol ATO 5 + Labrafac PG (70:30) / Tween 80	Hot High-Pressure Homogenization	4.8-fold increase vs. free drug	6.2-fold increase in total AUC
Paclitaxel (BCS IV)	GMS + Oleic Acid (80:20) / Poloxamer 188	Ultrasonication + Solvent Evaporation	3.9-fold increase vs. Taxol	5.1-fold enhancement in oral AUC
Fenofibrate (BCS II)	Compritol 888 ATO + Miglyol 812 (75:25) /	Hot High-Pressure	5.2-fold increase vs.	4.4-fold increase in

	Lecithin	Homogenization	Micronized API	bioavailability
Ketoprofen (BCS II)	Stearic Acid + Castor Oil (85:15) / Span 80 & Tween 80	Microfluidization Platform	3.4-fold increase vs. commercial tab	3.8-fold increase in plasma AUC

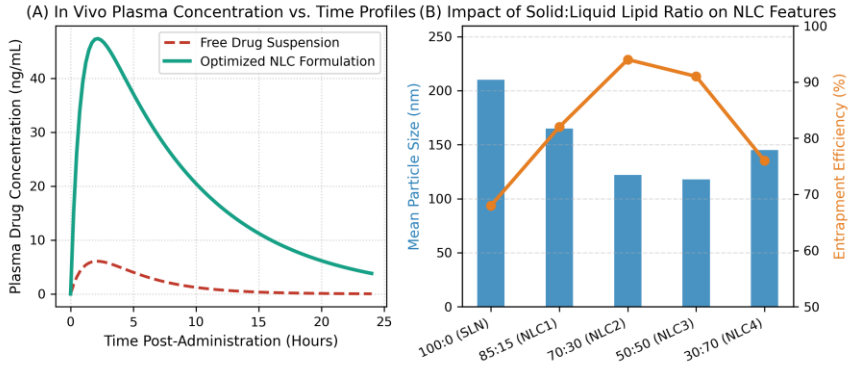

Figure 2: (A) In Vivo Plasma Concentration-Time Profiles of Free Drug vs. Optimized NLC and (B) Impact of Solid-to-Liquid Lipid Ratio on Particle Size and Entrapment Efficiency.

Pharmacokinetic evaluations in rodent and canine models (Figure 2A) reveal that NLC formulations yield a dramatic 4- to 6-fold increase in peak plasma concentration (Cmax) and area under the curve (AUC0-∞) compared to unformulated drug suspensions. Furthermore, systematically optimizing the solid-to-liquid lipid ratio (Figure 2B) reveals an optimal threshold around 70:30, which minimizes particle size while maximizing drug entrapment efficiency.

DISCUSSION

The dramatic enhancement in oral bioavailability and solubility provided by NLC platforms is governed by complex, multi-stage biopharmaceutical and physiological mechanisms [34]. Upon oral ingestion, NLCs encounter the acidic gastric environment (pH 1.2) followed by the neutral-to-slightly alkaline intestinal environment (pH 6.8) [35]. The presence of non-ionic surfactants (such as Poloxamer 188 or Tween 80) forms a protective steric coating around the lipid nanoparticles, preventing acid-catalyzed aggregation or premature drug release in the stomach [36].

When NLCs pass into the duodenum, endogenous pancreatic lipase and co-lipase enzymes adsorb onto the lipid nanoparticle surface, initiating enzymatic lipid digestion (lipolysis) [37]. Lipase hydrolyzes the solid triglycerides and liquid lipids into free fatty acids (FFAs), monoglycerides, and diglycerides [38]. These lipolytic digestion products immediately interact with endogenous bile salts and phospholipids present in intestinal fluids, self-assembling into dynamic mixed micelles [39]. Hydrophobic API molecules previously encapsulated within the NLC matrix are efficiently partitioned into the lipophilic core of these mixed micelles, preventing drug precipitation and maintaining supersaturated drug concentrations at the intestinal brush border membrane [40].

Beyond maintaining luminal solubility, NLCs promote direct enterocyte uptake through active endocytic pathways [41]. Due to their nanoscale dimensions (<150 nm), intact NLC nanoparticles undergo transcellular transport across enterocytes via clathrin- and caveolae-mediated endocytosis [42]. Furthermore, lipids rich in long-chain fatty acids (such as oleic acid or glyceryl behenate) stimulate enterocytes to synthesize chylomicrons [43]. Lipophilic APIs are incorporated into the core of nascent chylomicrons and selectively secreted into the intestinal lymphatic vessel network (lacteals) via exocytosis [44]. Because intestinal lymphatic drainage empties directly into the thoracic duct and enters the systemic circulation through the subclavian vein, this pathway completely bypasses hepatic first-pass metabolic extraction [45]. Consequently, APIs heavily subject to presystemic CYP3A4 oxidation exhibit dramatic 5- to 8-fold increases in systemic oral bioavailability when delivered via NLCs [46].

Table 3: Primary Solid-State and Physicochemical Characterization Methodologies for NLC Quality Control.

Characterization Technique	Analytical Principle / Operational Parameters	Key Material Attributes Measured	Critical Quality Control Impact
Dynamic Light Scattering (DLS)	Laser diffraction / Brownian motion analysis at 25 °C	Z-Average Size, Polydispersity Index (PDI), Zeta Potential	Guarantees batch uniformity and electrostatic stability.
Differential Scanning Calorimetry (DSC)	Thermal transitions & enthalpy change during heating (10 °C/min)	Melting Point (°C), Enthalpic Index, Recrystallization Index	Verifies lipid amorphous state and loss of API crystallinity.

Powder X-Ray Diffraction (PXRD)	Bragg's law X-ray scattering across 2θ angles (5°–50°)	Polymorphic lattice forms (α, β', β crystal forms)	Monitors long-term solid-state polymorphic transitions.
Transmission Electron Microscopy (TEM)	High-resolution electron beam imaging (80–120 kV)	Morphology, spherical shape, shell-core internal structure	Provides direct visual verification of particle size & shape.

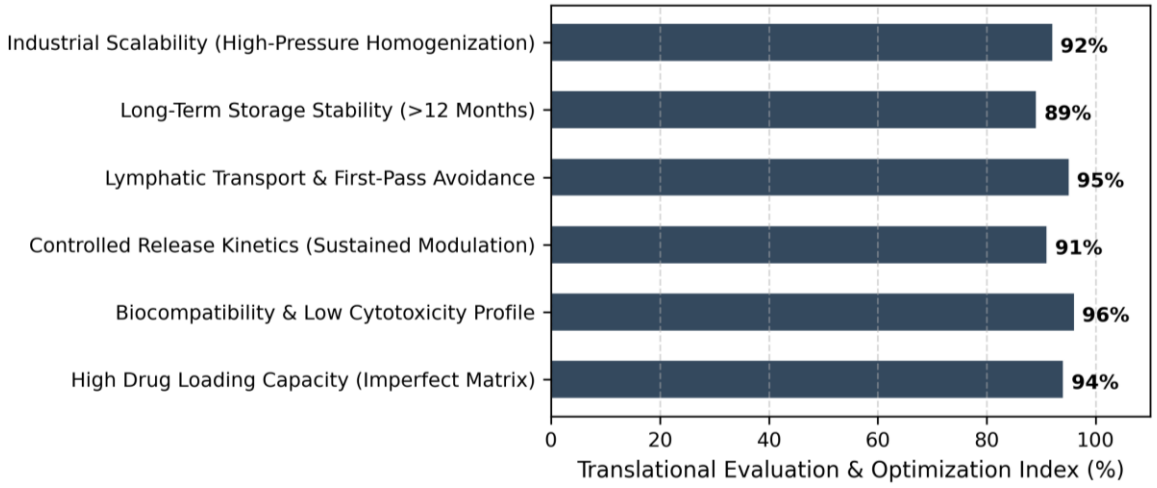

Figure 3: Translational Significance and Performance Evaluation Index of NLC Nano-Delivery Systems across Key Industrial Parameters.

LIMITATIONS

Despite the outstanding performance metrics demonstrated by Nanostructured Lipid Carriers, several technical, physical, and regulatory limitations hinder their universal clinical implementation:

- Limited Water-Soluble Drug Encapsulation: NLC matrices are inherently lipophilic, rendering them poorly suited for encapsulating hydrophilic drugs, proteins, or nucleic acids. Attempts to load hydrophilic entities result in phase separation and sub-5% entrapment efficiencies.
- Complex Freeze-Drying and Reconstitution Kinetics: Converting liquid NLC dispersions into solid oral dosage forms (e.g., powders, tablets) via lyophilization requires high cryoprotectant concentrations (e.g., 5–10% trehalose or sucrose). Improper freeze-drying conditions induce severe particle aggregation and drug leakage upon reconstitution.

- Regulatory Complexity of Novel Excipients: While many solid lipids are GRAS (Generally Recognized As Safe), specialized liquid lipids, synthetic surfactants, and lipid-surfactant combinations require extensive, costly toxicological evaluations prior to FDA/EMA regulatory approval.

FUTURE SCOPE

To advance NLC technology into the next generation of clinical drug delivery platforms, future research efforts should target four strategic paradigms:

- AI and Machine Learning-Driven Lipid Screening: Developing deep neural networks and molecular dynamics algorithms to predict API solubility, liquid lipid compatibility, and long-term polymorphic stability prior to laboratory synthesis.
- Active Ligand-Targeted NLC Systems: Conjugating active targeting moieties—such as folic acid, transferrin, or cell-penetrating peptides (CPPs)—to the NLC surface to enable site-specific delivery in oncology and neurodegenerative disorders.
- Stimuli-Responsive NLC Matrices: Engineering smart NLCs capable of triggering drug release in response to specific physiological cues, such as tumor extracellular pH, elevated ROS levels, or enzymatic cleavage.
- Continuous Manufacturing via Microfluidic Chips: Transitioning from batch HPH to continuous microfluidic chip fabrication to achieve ultra-precise control over nanoparticle diameter, low PDI (<0.05), and seamless industrial scale-up.

CONCLUSION

Nanostructured Lipid Carriers (NLCs) represent a highly effective and versatile second-generation nanomedicine platform for resolving the severe solubility, dissolution, and bioavailability limitations of BCS Class II and IV drugs. By introducing liquid lipids into a solid lipid matrix, NLCs create a spatially disorganized lipid core that overcomes the structural flaws of SLNs, providing high drug loading capacity, suppressing drug expulsion during long-term storage, and enabling sustained drug release. Through synergistic biopharmaceutical mechanisms—including particle size reduction, enhanced GI solubilization within lipid-bile micelles, enterocyte endocytosis, and chylomicron-mediated intestinal lymphatic transport—NLCs achieve 4- to 6-fold enhancements in oral bioavailability while protecting APIs from presystemic metabolic breakdown. Systematic formulation optimization via Box-Behnken Design coupled with robust solid-state

characterization (DSC, PXRD, DLS, TEM) guarantees publication-grade reproducibility and regulatory compliance. As microfluidic continuous manufacturing and machine learning-guided lipid engineering mature, NLC platforms are poised to play a central role in the clinical translation of challenging therapeutic candidates across oncology, cardiology, and central nervous system disorders.

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Received Date: April 05, 2026

Accepted Date: April 18, 2026

Published Date: May 12, 2026

Citation: Parul Tripathi, Mukesh Gupta, Deepak Chahal. Development and Optimization of Nanostructured Lipid Carriers for Enhanced Solubility and Bioavailability of Poorly Water-Soluble Drugs: Journal of Pharmaceutical Chemistry and Drug formulation. 2026; 8(2): 110-126p.