**Journal of Biomedical and Pharmaceutical Research**
**Available Online at www.jbpr.in**
**CODEN: - JBPRAU (Source: - American Chemical Society)**
**NLM (National Library of Medicine): ID: (101671502)**
**Index Copernicus Value 2024: 84.28**
**Volume 15, Issue 3; 2026, 33-42**

**ISSN (Online): 2279-0594**
**ISSN (Print): 2589-8752**

**Review Article**

# A Review on Solid Lipid Nanoparticles: Preparation Methods, Evaluation, and Therapeutic Potential

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**Article Info: Received: 20-03-2026 / Revised: 09-04-2026 / Accepted: 22-04-2026**
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**DOI: https://doi.org/10.32553/jbpr.v15i3.1457**
**Conflict of interest statement: No conflict of interest**

**Abstract:**
Solid Lipid Nanoparticles (SLN) have emerged as a promising nanocarrier system in modern drug delivery, offering improved bioavailability, controlled drug release, and enhanced therapeutic efficacy. These colloidal carriers, composed of biocompatible solid lipids stabilized by surfactants, overcome the limitations associated with traditional delivery systems such as liposomes and polymeric nanoparticles. SLN provide advantages including reduced toxicity, enhanced stability, and the ability to encapsulate both hydrophilic and lipophilic drugs. This review comprehensively discusses the structural models, formulation components, preparation techniques, and physicochemical characterization of SLN. It further highlights their wide-ranging therapeutic applications in oncology, infectious diseases, central nervous system disorders, cosmetics, and gene delivery. Despite challenges such as drug expulsion, limited drug loading, and scale-up issues, recent advancements including nanostructured lipid carriers (NLC), stimuli-responsive systems, and AI-driven formulation design have significantly improved their performance. Overall, SLN represent a versatile and efficient platform for next-generation drug delivery and translational nanomedicine

**Keywords:** Solid Lipid Nanoparticles (SLN), Nanostructured Lipid Carriers (NLC), Controlled Drug Delivery, Nanotechnology, Drug Loading, Targeted Drug Delivery, Biocompatible Lipids, Pharmacokinetics.

## Introduction

The emergence of nanotechnology has fundamentally transformed drug delivery science, enabling the engineering of carriers at the nanoscale (1–1000 nm) capable of precise spatiotemporal drug release, improved pharmacokinetics, and reduced systemic toxicity. Among the diverse nanocarrier platforms developed over the past three decades, solid lipid nanoparticles (SLN) have garnered exceptional attention from pharmaceutical researchers, clinicians, and the industry alike [1]. SLN were first reported independently by Müller et al. and Gasco in the early 1990s as a colloidal delivery system composed of physiologically tolerable solid lipids stabilized by surfactants. Unlike earlier nanocarrier systems such as liposomes, which suffered from poor physical stability and phospholipid oxidation, or polymeric nanoparticles, which required potentially toxic organic solvents

during fabrication, SLN offered a pragmatic solution: they combined the advantages of multiple colloidal systems while minimizing their individual drawbacks [2].

The solid lipid matrix provides a sustained and controlled release depot for entrapped drugs, while the nanoscale dimensions confer enhanced bioadhesion, prolonged circulation time, and passive targeting via the enhanced permeability and retention (EPR) effect in tumor tissues. The biocompatibility of natural or synthetic lipids such as glycerides, fatty acids, and waxes ensures a favorable toxicological profile, making SLN suitable across a broad spectrum of drug classes—hydrophilic, lipophilic, macromolecular biologics, and nutraceuticals.

This review comprehensively examines SLN: their structural variants, formulation strategies, physicochemical characterization, pharmacokinetic advantages, therapeutic applications across multiple routes of administration, regulatory landscape, and future directions in translational nanomedicine [3,4].

## Structure of SLN

SLN are spherical colloidal particles with a solid lipid core dispersed in an aqueous medium containing emulsifier. The core is composed of solid lipid(s) or a mixture of solid and liquid lipids that remain in the solid state at both physiological temperature (37 °C) and room temperature (25 °C). The drug is dissolved, dispersed, or adsorbed within this lipid matrix. The hydrophilic shell, formed by surfactant molecules oriented at the particle surface, provides colloidal stability and modulates the release profile.

The arrangement of drug within the SLN matrix can follow three distinct models:

- Drug-enriched shell model: Drug is concentrated at the outer lipid shell. This occurs when drug solubility is higher in the liquid state during preparation and is expelled upon solidification. Results in a pronounced initial burst release.
- Drug-enriched core model: Drug is concentrated in the particle core, surrounded by a drug-free lipid shell. Achieved by precise temperature manipulation during homogenization. Results in sustained, controlled release.
- Homogeneous matrix model: Drug is uniformly distributed throughout the lipid matrix. Occurs with molecularly dispersed drugs. Provides intermediate release kinetics [4,5].

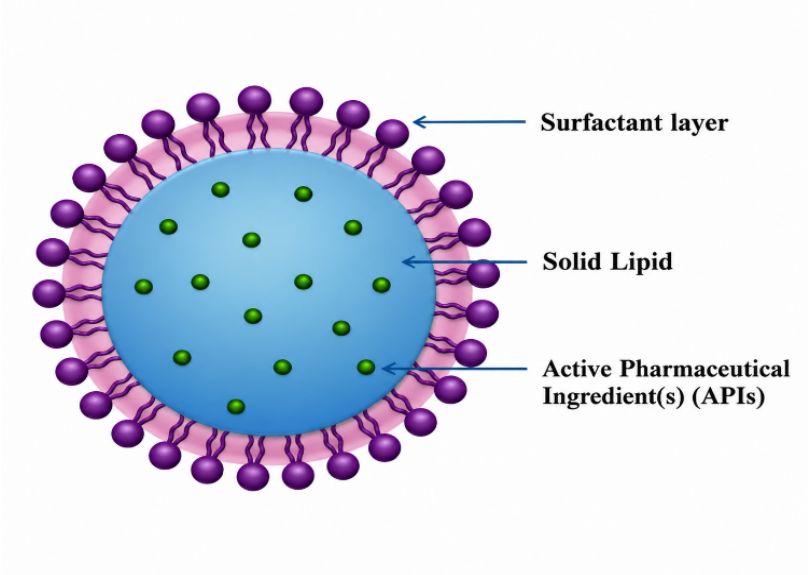


**Figure 1: Structure of Solid Lipid Nanoparticle**

### SLN vs. Nanostructured Lipid Carriers (NLC)

A key limitation of SLN is the polymorphic transition of the lipid from the alpha (amorphous) form, which forms immediately after preparation, to the thermodynamically stable beta form over time. This crystallization expels the drug from the lattice, causing drug leakage during storage. To overcome this, Nanostructured Lipid Carriers (NLC) were developed as a second-generation SLN by incorporating liquid lipid (oils) into the solid lipid matrix, creating a disordered crystal structure that retards polymorphic transitions and accommodates more drug.

The three NLC types are: (i) imperfect type, with blends of spatially different lipids; (ii) amorphous type, with drugs remaining in the amorphous state within the matrix; and (iii) multiple type, an oil-in-solid-lipid-in-water (O/SL/W) structure resembling a reverse emulsion within the particle [6].

**Table 1: Comparative Overview of Nanocarrier Systems**

| Parameter | SLN | NLC | Liposomes | Polymeric NP |
|---|---|---|---|---|
| Particle Size (nm) | 50–1000 | 50–500 | 80–300 | 100–500 |
| Drug Loading | Moderate | High | Moderate | Moderate–High |
| Stability | High | High | Low | High |
| Toxicity | Very Low | Very Low | Low | Low–Moderate |
| Scalability | Easy | Easy | Difficult | Moderate |
| Organic Solvents | Not required | Not required | Required | Required |

### Composition: Lipids, Surfactants, and Other Excipients

#### Solid Lipids

The solid lipid matrix is the structural backbone of SLN. Ideal lipid candidates must be solid at body temperature (>37 °C melting point), biocompatible, biodegradable, chemically stable, and capable of forming colloidal dispersions with high drug loading. Commonly employed solid lipids include [7]:

- Glycerides: Glyceryl monostearate (GMS), glyceryl behenate (Compritol 888 ATO), glyceryl palmitostearate (Precirol ATO 5)
- Fatty acids: Stearic acid, palmitic acid, behenic acid
- Waxes: Beeswax, carnauba wax, cetyl palmitate
- Hard fats: Witepsol series (W35, E85, H35)

#### Liquid Lipids (for NLC)

Liquid lipids incorporated in NLC formulations include medium-chain triglycerides (Miglyol 812), squalene, oleic acid, capric/caprylic acid, and soybean oil. The ratio of solid to liquid lipid is critical—typically 70:30 to 99.9:0.1 to maintain solid matrix integrity.

#### Surfactants and Co-surfactants

Surfactants stabilize the nanoparticle dispersion by adsorbing at the lipid-water interface and preventing Ostwald ripening and particle aggregation. Selection depends on the route of administration:

- Non-ionic: Polysorbate 80 (Tween 80), Poloxamer 188, Poloxamer 407, Brij 78, Span 85 — preferred for parenteral and oral routes
- Anionic: Sodium dodecyl sulfate (SDS) — used in topical formulations
- Lecithins (Phospholipids): Soy lecithin, egg phosphatidylcholine — provide biocompatible, biomimetic surface
- Co-surfactants: Sodium glycocholate, Taurocholate — reduce surface tension further and improve stability [8,9].

**Table 2: Commonly Used Lipid Excipients in SLN and NLC Formulations**

| Lipid | Type | Melting Point (°C) | Common Applications |
|---|---|---|---|
| Glyceryl Monostearate | Solid Lipid | 54–64 | Oral, topical SLN |
| Compritol 888 ATO | Solid Lipid | 69–74 | Sustained release |
| Precirol ATO 5 | Solid Lipid | 50–60 | Oral, parenteral |
| Stearic Acid | Solid Lipid | 69–70 | Topical, oral |
| Beeswax | Solid Lipid | 60–67 | Topical formulations |
| Cetyl Palmitate | Solid Lipid | 45–54 | Dermal delivery |
| Miglyol 812 | Liquid Lipid (NLC) | Liquid at RT | NLC formulations |
| Oleic Acid | Liquid Lipid (NLC) | Liquid at RT | NLC, self-emulsifying |

## Preparation Methods

SLN can be prepared by a variety of techniques. The choice of method depends on the physicochemical properties of the drug, intended route of administration, scale of production, and available equipment. All methods generally involve melting the solid lipid, dispersing the drug within the lipid melt, and then emulsifying the lipid melt in an aqueous surfactant solution followed by cooling.

### High-Pressure Homogenization (HPH)

HPH is the most widely employed and industrially scalable method for SLN preparation. The technique operates on the principle of high turbulence, cavitation, and shear forces generated when the premix is forced through a narrow gap at pressures of 100–2000 bar. Two variants exist:

**Hot HPH:** The lipid is melted above its melting point, drug is dissolved/dispersed in the melt, and the resulting hot premix is emulsified in hot aqueous surfactant solution at the same temperature. Multiple homogenization cycles (3–5 passes) are applied, followed by cooling to room temperature to form solid nanoparticles. Suitable for heat-stable drugs [10].

**Cold HPH:** The drug-lipid melt is rapidly cooled using liquid nitrogen to form solid lipid microparticles, which are then milled and dispersed in cold aqueous surfactant solution before homogenization. Suitable for heat-labile drugs and hydrophilic molecules.

### Microemulsion Technique

Developed by Gasco (1993), this technique involves preparation of a hot oil-in-water microemulsion (thermodynamically stable, isotropic, transparent system) composed of melted lipid, water, surfactant, and cosurfactant at elevated temperatures (65–70 °C). The microemulsion is then dispersed in cold water (2–3 °C) under gentle stirring. Rapid cooling induces lipid precipitation as nanoparticles. The method yields particles of 50–300 nm but requires high concentrations of emulsifiers and produces dilute dispersions [9,10].

### Solvent Emulsification–Evaporation and Solvent Injection

In solvent emulsification–evaporation, the solid lipid is dissolved in a water-immiscible organic solvent (e.g., cyclohexane), which is then emulsified in an aqueous surfactant phase. Evaporation of the organic solvent under reduced pressure precipitates the lipid nanoparticles. The solvent injection method involves injection of a lipid-containing ethanol or acetone solution into a hot aqueous surfactant phase. The rapid diffusion of solvent induces spontaneous nanoparticle formation without high shear. Both methods are mild but carry residual solvent risk and are better suited to small-scale manufacturing.

### Other Methods

- **Ultrasonication:** Probe sonication disperses the lipid melt into nanoparticles. Simple but limited scalability and risk of metal contamination.

- **Membrane Contactor:** Lipid melt pressed through a glass membrane into aqueous phase. Gentle and continuous but limited industrial uptake.
- **Spray Drying & Lyophilization:** Used to convert SLN dispersions into dry powders for improved stability, oral solid dosage form development, and inhalation delivery. Cryoprotectants (trehalose, mannitol) are added prior to lyophilization to prevent aggregation [11,12].

**Table 3: Comparative Summary of SLN Preparation Methods**

| Method | Advantages | Limitations |
|---|---|---|
| High-Pressure Homogenization (Hot/Cold) | Scalable, no organic solvents, narrow size distribution | High energy input, potential drug degradation at high temperature |
| Microemulsion Technique | Simple, mild conditions, high reproducibility | Requires large amounts of surfactants and cosurfactants |
| Solvent Emulsification-Evaporation | Suitable for heat-labile drugs | Residual solvent traces, dilute dispersions |
| Solvent Injection Method | Simple, rapid, mild conditions | Use of organic solvents, limited to lipophilic drugs |
| Ultrasonication / Probe Sonication | Simple equipment, small batch production | Potential metal contamination, scale-up challenges |
| Membrane Contactor Method | Gentle, continuous process | Limited industrial adoption |
| Spray Drying | Converts to solid form for oral delivery | Heat exposure, loss of drug during processing |

## Physicochemical Characterization

Comprehensive characterization is essential to understand the quality, stability, and performance of SLN formulations.

A battery of analytical techniques is employed to evaluate critical quality attributes (CQAs).

### Particle Size and Polydispersity Index (PDI)

Particle size is the most fundamental CQA of SLN, directly influencing drug release, cellular uptake, tissue distribution, and immunological response.

Dynamic Light Scattering (DLS) is the standard technique, measuring hydrodynamic diameter via autocorrelation of scattered laser light.

PDI is a dimensionless measure of size distribution breadth, where values below 0.25 indicate a monodisperse, homogeneous population acceptable for pharmaceutical use.

Nanoparticle Tracking Analysis (NTA) provides complementary size and concentration data by tracking individual particles in solution [13].

### Zeta Potential

Zeta potential reflects the electrokinetic potential of the particle surface and serves as a predictor of colloidal stability. Particles with zeta potentials greater than ±30 mV are considered stable due to sufficient electrostatic repulsion between particles. Values below this threshold suggest aggregation tendency. Phospholipid-stabilized SLN typically exhibit negative zeta potentials (−20 to −40 mV), while cationic lipid-coated SLN display positive values (+20 to +50 mV), which are advantageous for nucleic acid delivery and mucoadhesion.

### Crystallinity and Polymorphism

The crystalline state of the solid lipid matrix profoundly influences drug incorporation and release. Lipids exist in three polymorphic

forms—alpha (α), beta-prime (β'), and beta (β)—in order of increasing thermodynamic stability and crystalline perfection.

The alpha form, obtained immediately after rapid cooling, has the least ordered structure, the lowest melting point, and accommodates the highest drug loading. Transition to the β form over time leads to a more ordered lattice with fewer defects, reducing drug capacity and causing drug expulsion.

Differential Scanning Calorimetry (DSC) measures melting enthalpy and onset temperature; a reduction in melting point and recrystallization index (RI) relative to the bulk lipid indicates imperfect crystallization and greater drug accommodation.

X-ray Powder Diffraction (XRPD) and Small-Angle X-ray Scattering (SAXS) provide detailed polymorphic analysis.

**Entrapment Efficiency and Drug Loading:** Entrapment efficiency (EE%) quantifies the fraction of total drug successfully incorporated into the nanoparticle matrix, expressed as:

$$\text{EE}\ (\%)\ \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

The free (unentrapped) drug is separated by ultracentrifugation, dialysis, or ultrafiltration before quantification by UV-Visible spectrophotometry or HPLC.

$$\text{Drug loading capacity (DL\%)} = \frac{\text{Drug in nanoparticles}}{\text{Total nanoparticle mass}} \times 100$$

High DL% reduces the quantity of excipient needed per drug dose and lowers the risk of excipient-related toxicity.

**Drug Release Studies**

In vitro drug release from SLN is typically evaluated using dialysis membrane methods or Franz diffusion cells with appropriate release media (phosphate-buffered saline, simulated intestinal or gastric fluid) at physiological temperature (37 ± 0.5 °C).

SLN typically exhibit biphasic release: an initial burst effect (surface-associated drug) followed by prolonged, sustained release from the lipid matrix. Mathematical models including zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell are fitted to release data to elucidate the release mechanism [13,14].

**Table 4: Characterization Parameters and Techniques for SLN**

| Parameter | Technique | Significance |
|---|---|---|
| Particle Size & PDI | Dynamic Light Scattering (DLS), NTA | Determines distribution and colloidal stability |
| Zeta Potential | Electrophoretic Light Scattering | Indicates surface charge and physical stability (>±30 mV preferred) |
| Morphology | TEM, SEM, AFM, Cryo-TEM | Visual confirmation of spherical shape and surface characteristics |
| Crystallinity | DSC, X-ray Powder Diffraction (XRPD) | Determines polymorphic form; lower crystallinity = better drug loading |
| Entrapment Efficiency (%) | Ultracentrifugation, dialysis, ultrafiltration | Ratio of entrapped drug to total drug added |
| Drug Release | Dialysis bag, Franz diffusion cell | Release kinetics: burst effect, controlled release profile |
| Lipid Polymorphism | Synchrotron X-ray, SAXS/WAXS | Identifies alpha/beta-prime/beta polymorphs affecting release |

## Therapeutic Applications

**Oncology:** Cancer nanomedicine is among the most actively pursued applications of SLN. The physicochemical versatility of SLN enables encapsulation of diverse anticancer agents—hydrophobic taxanes (paclitaxel, docetaxel), anthracyclines (doxorubicin), platinum compounds (cisplatin), camptothecins, and vinca alkaloids. SLN-encapsulated drugs demonstrate reduced systemic toxicity (e.g., doxorubicin-induced cardiotoxicity), overcoming multidrug resistance (MDR) by bypassing P-glycoprotein efflux pumps, and enhanced tumor accumulation via the EPR effect. Surface functionalization with tumor-targeting ligands (folate, transferrin, RGD peptides, antibodies) further improves tumor selectivity. Co-encapsulation of two anticancer agents in a single SLN enables synergistic drug combinations with precise molar ratios.

## Anti-infective Therapy

SLN have shown substantial promise for delivering antibiotics (ciprofloxacin, rifampicin, isoniazid), antivirals (lopinavir, ritonavir, efavirenz), and antifungals (amphotericin B, itraconazole) to infected compartments inaccessible to conventional drugs. For tuberculosis, SLN facilitate lymphatic targeting and macrophage uptake—key to reaching the intracellular Mycobacterium tuberculosis reservoir. In HIV therapy, SLN improve the oral bioavailability of antiretroviral drugs, reduce pill burden, and may target lymphatic reservoirs. Amphotericin B-loaded SLN markedly reduce the nephrotoxicity of this antifungal while maintaining efficacy comparable to liposomal formulations [12].

## Central Nervous System (CNS) Disorders

SLN represent a compelling strategy for CNS drug delivery given their ability to cross the BBB through multiple mechanisms. They have been investigated for Alzheimer's disease (rivastigmine, galantamine, tacrine), Parkinson's disease (bromocriptine, ropinirole), schizophrenia (clozapine, olanzapine), epilepsy (phenytoin, carbamazepine), and depression (duloxetine). The nanoparticle surface can be engineered with apolipoprotein E or other brain-targeting moieties to dramatically enhance brain accumulation following intravenous administration.

**Cosmetics and Nutraceuticals:** The cosmetics industry has widely adopted SLN technology for anti-aging, sun protection, and skin hydration products. SLN encapsulate UV filters (avobenzone, octylmethoxycinnamate), retinol, coenzyme Q10, vitamin C and E, and plant extracts, protecting chemically labile actives from oxidative degradation and providing controlled dermal release. In the nutraceutical space, SLN improve the oral bioavailability of poorly water-soluble phytochemicals—curcumin, resveratrol, quercetin, piperine—that show promise in metabolic, inflammatory, and oncological conditions but exhibit poor in vivo efficacy in their free form.

## Vaccine and Gene Delivery

Cationic SLN (CSLN) prepared with cationic lipids (cetrimide, DOTAP, DOTMA) complex negatively charged nucleic acids (DNA, siRNA, mRNA, antisense oligonucleotides) through electrostatic interactions, forming lipoplexes that protect nucleic acids from nuclease degradation, facilitate cellular uptake via endocytosis, and promote endosomal escape. CSLN have demonstrated efficient gene transfection and siRNA-mediated gene silencing in vitro and in vivo. For vaccine delivery, SLN act as adjuvants and depot systems, protecting antigens from degradation and providing slow antigen release for enhanced and prolonged immune responses.

## Challenges, Limitations, and Strategies for Improvement

**Drug Expulsion during Polymorphic Transitions:** The most critical challenge with SLN is the time-dependent crystallization of the lipid matrix from the amorphous/alpha form to the thermodynamically stable beta crystalline form. The ordered β-lattice excludes drug molecules, leading to gel formation and drug expulsion upon storage. This is particularly

problematic for aqueous SLN dispersions stored at refrigerated or room temperatures. Strategies include: use of NLC formulations with liquid lipid incorporation to disrupt crystallinity; blending of lipids with different fatty acid chain lengths; use of surfactants with crystal modifier properties; and lyophilization or spray drying to convert dispersions to solid powders [12,13].

### Low Drug Loading Capacity

SLN typically achieve drug loading of 1–10%, lower than polymeric nanoparticles or microencapsulation systems, because the highly ordered lipid crystal lattice leaves little space for drug molecules. Strategies to improve drug loading include use of NLC with imperfect crystalline structures, selection of lipids with chemical affinity for the drug (like solubility parameter matching), use of co-emulsifiers that improve drug-lipid miscibility, and microemulsion-based preparation methods that achieve higher drug incorporation.

### Scale-Up and Regulatory Considerations

Despite the simplicity of HPH, scale-up from laboratory to industrial production requires careful optimization of homogenization parameters (pressure, cycle number, temperature) to maintain consistent particle size and distribution. Regulatory approval of SLN products requires extensive characterization, toxicological evaluation, and quality control data. Many of the lipid excipients and surfactants used in SLN are GRAS (Generally Recognized As Safe) by the FDA, facilitating regulatory acceptance. However, the lack of universally accepted, validated in vitro-in vivo correlation (IVIVC) models for nanoparticle formulations remains a bottleneck in clinical translation [15].

### Sterilization Challenges

For parenteral SLN formulations, terminal sterilization by autoclaving is incompatible with the lipid matrix, and filtration through 0.22 μm membranes is challenging for particles >220 nm. Gamma irradiation and UV irradiation have been evaluated but may alter lipid structure and degrade drugs. Aseptic manufacturing under laminar airflow conditions remains the preferred but costly approach.

### Recent Advances and Future Perspectives

**Stimuli-Responsive SLN:** Stimuli-responsive or 'smart' SLN release their drug payload in response to specific endogenous or exogenous triggers. Temperature-sensitive SLN with lipid matrices near body temperature allow accelerated drug release upon mild hyperthermia. pH-responsive SLN exploit the acidic microenvironment of tumors (pH 6.5–6.8) or lysosomes (pH 4.5–5.5) for selective drug release. Redox-responsive SLN incorporate disulfide linkers that cleave in the high glutathione environment of cancer cells. Light-activated and magnetic-responsive SLN are also under investigation for spatially controlled drug release [16,17].

### Theranostic SLN

The integration of diagnostic and therapeutic functionalities within a single SLN platform—so-called 'theranostics'—is an emerging frontier. Superparamagnetic iron oxide nanoparticles (SPIONs) or quantum dots incorporated within SLN enable MRI or fluorescence imaging-guided drug delivery. Gold nanoparticle-embedded SLN facilitate photothermal therapy alongside chemotherapy. Such multifunctional systems enable real-time monitoring of drug biodistribution and treatment response.

### mRNA and Nucleic Acid Delivery

The extraordinary global success of mRNA-lipid nanoparticle COVID-19 vaccines (BNT162b2, mRNA-1273) has catalyzed intense interest in lipid-based nucleic acid delivery. While the vaccines employ ionizable lipid nanoparticles, closely related to SLN principles, the mechanistic insights gained are directly applicable to SLN-based siRNA and mRNA delivery for cancer, rare genetic diseases, and infectious disease prevention. Cationic and ionizable SLN are being actively developed for efficient and safe nucleic acid delivery [17].

### Artificial Intelligence in SLN Development

Machine learning (ML) and artificial intelligence (AI) approaches are increasingly applied to optimize SLN formulation design. Algorithms trained on large datasets of formulation variables (lipid type, concentration, surfactant, drug properties) and CQAs (size, PDI, EE%) can predict optimal formulation compositions and preparation conditions, dramatically reducing experimental iterations. Quality by Design (QbD) combined with Design of Experiments (DoE) and ML offers a rational, systematic framework for SLN development and scale-up.

### Green and Sustainable SLN

Growing environmental consciousness is driving interest in sustainable SLN formulation approaches. These include use of plant-derived lipids (shea butter, cocoa butter, carnauba wax), supercritical CO2 fluid processing (eliminating organic solvents), and biodegradable polymeric coatings. Green synthesis methods align with principles of green chemistry and reduce the environmental and health burden of pharmaceutical manufacturing [18].

### Conclusions

Solid Lipid Nanoparticles represent a highly promising drug delivery system that combines the advantages of conventional colloidal carriers while minimizing their limitations. Their biocompatibility, scalability, and ability to provide controlled and targeted drug release make them suitable for a wide range of pharmaceutical and biomedical applications. However, challenges such as polymorphic transitions, drug expulsion, and limited drug loading still need to be addressed for successful clinical translation. Advances in formulation strategies, including the development of nanostructured lipid carriers, stimuli-responsive systems, and AI-assisted design, are paving the way for overcoming these limitations. With continued research and technological innovation, SLN are expected to play a crucial role in the future of personalized medicine, gene therapy, and advanced drug delivery systems.

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