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Review article

Solid lipid nanoparticle-based approaches for improving the bioavailability of low-solubility drugs: a detailed review

Nikita Mahadev Ghadage*, Ankita Barshile, Pranit Kale

Late Laxmibai Phadtre College of Pharmacy, Kalamb, Maharashtra, India

Corresponding author: Nikita Mahadev Ghadage, ✉ ghadagenikita3555@gmail.com, **Orcid Id**: https://orcid.org/0009-0001-9971-3590

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ABSTRACT

Poor aqueous solubility continues to be a critical barrier in the development of effective oral drug delivery systems, particularly for compounds classified under BCS Class II and IV. Although these molecules possess strong therapeutic promise, their clinical performance is often compromised by inadequate dissolution, restricted gastrointestinal absorption, and extensive first-pass metabolism. Solid lipid nanoparticles (SLNs) have gained considerable attention as an advanced nanocarrier platform capable of overcoming these limitations by improving drug solubilization, stabilizing chemically sensitive molecules, enhancing membrane permeability, and enabling controlled or site-specific release.

This review provides a comprehensive overview of the fundamental concepts underlying SLN technology, including formulation principles, key preparation methods, and current characterization techniques. In addition, recent therapeutic applications of SLNs for enhancing the bioavailability of poorly soluble drugs are critically examined. The discussion also addresses existing challenges such as stability issues, drug expulsion, and scale-up complexities, along with potential safety considerations. Emerging innovations—such as targeted SLN systems, hybrid lipid matrices, and the integration of artificial intelligence in formulation design—are highlighted as promising directions for future development. Overall, SLNs represent a biocompatible and versatile nanotechnology platform with substantial potential to improve the clinical translation of poorly water-soluble therapeutic agents.

Keywords: Solid lipid nanoparticles, Poorly soluble drugs, Bioavailability enhancement, Lipid-based nanocarriers, Solubility improvement, Nanotechnology.

INTRODUCTION

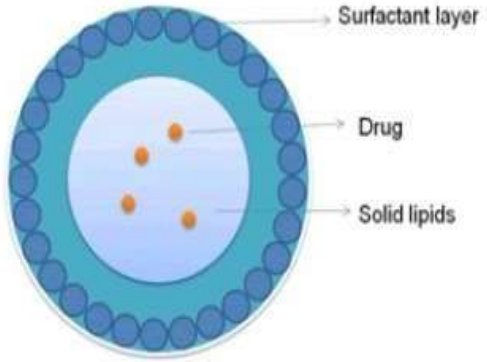
A large proportion of newly developed therapeutic candidates exhibit poor aqueous solubility, which substantially limits their ability to achieve meaningful clinical outcomes despite strong intrinsic pharmacological activity. Current estimates suggest that nearly half of the molecules emerging from drug discovery pipelines fall into Biopharmaceutics Classification System (BCS) Class II or IV, where restricted solubility, inadequate permeability, or a combination of both hinder effective absorption. As a result, these compounds often display slow dissolution rates, unpredictable gastrointestinal uptake, and reduced systemic exposure, presenting major challenges in formulation design and development [1].

A wide range of solubility-enhancement strategies—such as solid dispersions, cyclodextrin complexes, particle size reduction, and surfactant-based techniques—have been explored to improve the delivery of poorly soluble drugs. Although these methods offer certain advantages, issues related to physical instability, limited drug-loading capacity, and scale-up complexity frequently restrict their practical application in commercial formulations. Against this backdrop, lipid-based nanocarriers, particularly solid lipid nanoparticles (SLNs), have emerged as a promising alternative due to their intrinsic biocompatibility, favorable safety profile, structural robustness, and capacity to modulate pharmacokinetic behavior [2].

SLNs integrate the benefits of conventional colloidal systems with the physicochemical stability of solid lipids, enabling improved solubilization, sustained drug release, enhanced permeation, and protection of labile molecules against environmental or enzymatic degradation. Considering these distinctive advantages, this review provides a comprehensive and human-style discussion of SLN formulation principles, mechanisms of bioavailability enhancement, key production methods,

therapeutic applications, and the evolving prospects of this technology in modern drug delivery.

Figure 1: General Structure of Solid Lipid Nanoparticles (SLNS)



Challenges associated with poorly soluble drugs

Drugs with poor aqueous solubility encounter several interconnected physiological and physicochemical barriers that collectively limit their therapeutic effectiveness. One of the primary concerns is the slow dissolution rate, as a drug must first dissolve in gastrointestinal (GI) fluids before it can permeate the intestinal membrane. For compounds with high lipophilicity, dissolution frequently becomes the rate-determining step, resulting in delayed or incomplete absorption [3].

A second challenge involves restricted membrane permeability. Some molecules exhibit high solubility but limited permeability, while others show adequate permeability but insufficient solubility. In either case, the imbalance creates a significant obstacle to efficient oral bioavailability.

Extensive first-pass metabolism further complicates drug delivery. Drugs absorbed through the GI tract often undergo enzymatic degradation in the intestinal wall or liver before reaching systemic circulation, leading to a substantial reduction in their effectiveleading to a substantial reduction in their effective dose [4].

Additionally, many poorly soluble drugs experience instability within biological fluids. Exposure to acidic gastric conditions, enzymatic activity, or oxidative processes may degrade the drug before it can be absorbed. Collectively, these challenges highlight the need for advanced delivery strategies capable of improving solubility, enhancing permeability, and protecting drugs from premature breakdown.

Overview of solid lipid nanoparticles (SLNs)

Concept and evolution

Solid lipid nanoparticles (SLNs) represent a class of submicron colloidal carriers formulated using physiologically acceptable lipids that remain solid at both ambient and physiological temperatures. They were introduced in the 1990s as an improved alternative to earlier lipid- and polymer-based delivery systems such as liposomes, Nano emulsions, and polymeric nanoparticles. Traditional carriers often faced issues including drug leakage, cytotoxicity associated with synthetic polymers, and limited long-term stability. SLNs were conceptualized to combine the advantages of these systems while minimizing their drawbacks, offering a more stable, biocompatible, and scalable platform for delivering both conventional drugs and complex bioactive [5].

Structure and characteristics

The structural framework of SLNs consists of a solid lipid core in which the drug may be molecularly dispersed, embedded within the lipid matrix, or adsorbed onto the particle surface. This lipid core is coated and stabilized by suitable surfactants that prevent aggregation and ensure colloidal stability. The solid state of the lipid at body temperature provides a rigid matrix that can slow down drug diffusion, thereby enabling controlled or sustained release. Furthermore, the crystalline nature of the lipid matrix enhances physical stability, reduces the risk of drug leakage, and helps protect sensitive molecules from degradation during storage and physiological transit [6].

Advantages of SLNS

Solid lipid nanoparticles offer several noteworthy advantages that have accelerated their adoption in modern drug delivery research. Their use of biodegradable and biocompatible lipids ensures excellent safety and tolerability, making them suitable for a wide range of administration routes. Owing to their lipophilic core, SLNs can effectively encapsulate hydrophobic drugs that typically struggle with solubility and stability. The particles also provide substantial protection against chemical, photolytic, and enzymatic degradation, which is particularly beneficial for unstable or labile molecules. In addition, SLNs enable controlled and sustained release, potentially improving patient compliance and reducing dosing frequency. Another important attribute is their suitability for large-scale production using established techniques such as high-pressure homogenization, making them attractive for industrial translation [7].

Limitations of SLNS

Despite their advantages, SLNs are associated with certain formulation challenges that must be addressed for successful product development. A major limitation is the potential for drug expulsion during lipid recrystallization, as the lipids may transition into more thermodynamically stable polymorphic forms over time, reducing drug retention within the matrix. The rigid crystalline structure of solid lipids also inherently restricts drug loading capacity, particularly for molecules that do not readily integrate into the lipid lattice. Additionally, polymorphic transitions and crystal growth can compromise long-term stability, affecting particle size, drug distribution, and overall performance. These limitations highlight the need for optimized lipid combinations and advanced hybrid systems such as nanostructured lipid carriers (NLCs) to enhance stability and loading efficiency [8].

Components of SLNs:

Solid lipid nanoparticles (SLNs) are formulated using a combination of solid lipids, surfactants, and co-surfactants, each contributing to the stability and performance of the system. Solid lipids such as glyceryl monostearate, stearic acid, Precirol®, and Compritol® form the core matrix and determine key attributes like

melting point, crystallinity, particle size, and drug-loading capacity. Surfactants—including Poloxamers, Tweens, lecithin, and sodium cholate—stabilise the dispersion by lowering interfacial tension and preventing particle aggregation. Co-surfactants such as ethanol or propylene glycol further enhance dispersion stability and support the formation of uniform nanoparticles. Selection of these components depends on factors such as drug–lipid compatibility, lipid melting behaviour, desired stability profile, and regulatory acceptability to ensure the development of an efficient and biocompatible SLN formulation.

Table 1: Common lipids and surfactants used in SLN formulations

Component	Examples	Role
Solid Lipids	Compritol 888 ATO, Glyceryl Monostearate	Matrix formation
Surfactants	Poloxamer 188, Tween 80	Stabilization
Co-surfactants	Ethanol, Propylene glycol	Reduce interfacial tension

Methods of preparation

High-pressure homogenization

This is one of the most commonly employed techniques for producing SLNs and can be carried out using either hot or cold processing. The method generates uniform nanoparticles through intense shear forces and is well suited for large-scale manufacturing.

Ultrasonication

A straightforward and cost-effective approach that uses ultrasonic energy to reduce particle size. Despite its simplicity, it may result in a wider size distribution and carries the risk of metal contamination from the ultrasonic probe.

Solvent emulsification evaporation

This technique is particularly advantageous for formulating thermosensitive drugs. The lipid and drug are dissolved in an organic solvent, emulsified into an aqueous phase, and the subsequent evaporation of the solvent causes the lipid to precipitate as nanoparticles.

Microemulsion method

A hot, thermodynamically stable microemulsion is initially prepared using lipid, surfactant, and co-surfactant. When this microemulsion is dispersed into cold water under controlled conditions, the lipid phase solidifies to form nanoparticles.

Supercritical fluid method

An environmentally friendly, solvent-free technique that utilizes supercritical fluids—typically CO_2—to produce SLNs. Although it offers high purity, the requirement for advanced and expensive equipment limits its widespread use.

Spray drying / Freeze drying

These post-processing techniques are used to convert liquid SLN dispersions into dry powders. Spray drying offers rapid conversion, while freeze drying provides enhanced stability, making the powders suitable for incorporation into tablets or capsules.

Characterization of SLNS

Particle size and PDI

Key indicators of stability and absorption. Smaller, uniformly distributed particles promote better bioavailability.

Zeta potential

Represents surface charge and predicts colloidal stability. Higher absolute values reduce aggregation.

Entrapment efficiency and drug loading

Determine the extent of drug incorporated within the lipid matrix and the formulation's payload capacity.

Surface morphology

TEM/SEM confirm particle shape, uniformity, and nanoscale dimensions.

Thermal and structural analysis

DSC, XRD, and FTIR assess lipid crystallinity, drug–lipid interactions, and potential polymorphic transitions.

In vitro release

Provides release profiles under simulated physiological conditions, guiding sustained/controlled delivery design.

Stability studies

Monitor changes in size, aggregation, and drug leakage during storage**.**

Mechanisms of bioavailability enhancement

Improved solubilization

Lipid matrices enhance the solubility of poorly water-soluble drugs.

Lymphatic uptake

Facilitates transport via lymphatics, helping bypass first-pass metabolism**.**

Protection from degradation

Encapsulation safeguards drugs from chemical and enzymatic breakdown.

Enhanced permeability

Nanoscale dimensions support improved membrane penetration.

Controlled release

Solid lipids enable gradual drug release, enhancing therapeutic efficiency and reducing fluctuations.

Therapeutic applications of SLNs

SLNs have been widely investigated for improving the delivery of poorly soluble drugs.

Anticancer agents

Formulations of paclitaxel, curcumin, and similar drugs show enhanced cellular uptake, improved efficacy, and reduced systemic toxicity.

Antifungal and antiviral drugs

SLNs increase solubility and targeting efficiency for agents such as itraconazole and acyclovir.

Anti-inflammatory and analgesic drugs

Incorporation of NSAIDs into SLNs improves gastrointestinal tolerability and provides prolonged therapeutic action.

Cardiovascular drugs

Molecules like atorvastatin and carvedilol demonstrate enhanced absorption through lipid-assisted transport.

CNS drugs

SLNs facilitate improved penetration across the blood–brain barrier, supporting better delivery of neurotherapeutics.

Herbal molecules

Phytochemicals including quercetin, berberine, and resveratrol show markedly improved bioavailability when formulated into SLNs [9, 10].

Toxicity and safety assessment

SLNs are composed of GRAS-status lipids, making them inherently safe. Toxicity issues, when observed, mainly arise from surfactants used in high concentrations. Hemolysis studies, cytotoxicity assays, and in vivo toxicity evaluations generally support their safety. Long-term effects remain an important area for future research.

Limitations of SLN technology

Risk of drug expulsion during storage

Limited drug payload due to crystalline lipid structure

Potential polymorphic transitions

Challenges in maintaining long-term stability

Scale-up complexities due to equipment requirement

Future perspectives

Research on SLNs is increasingly focused on developing more advanced and clinically relevant systems. Emerging approaches include ligand-targeted SLNs for site-specific delivery, PEGylated SLNs to extend systemic circulation, and hybrid SLN–NLC platforms designed to improve drug loading and stability. The exploration of thermoresponsive and stimuli-sensitive SLNs aims to enable on-demand drug release. Additionally, the integration of AI-based formulation prediction tools and personalized nanomedicine strategies is expected to accelerate optimization and enhance patient-specific therapeutic outcomes. Collectively, these advancements hold promise for improving the translational potential of SLN-based therapies [11].

CONCLUSION

Solid lipid nanoparticles have emerged as a versatile and efficient nanocarrier platform capable of overcoming many limitations associated with poorly soluble and unstable drug molecules. Their ability to enhance solubility, protect sensitive drugs from degradation, improve membrane permeability, and provide sustained release underscores their significance in contemporary drug delivery research. While issues such as limited drug loading, polymorphic transitions, and long-term stability continue to pose challenges, ongoing advancements in formulation strategies and lipid-based nanotechnology are steadily addressing these gaps. Overall, SLNs hold strong potential for future pharmaceutical development and are increasingly positioned for successful translation into clinical practice.

Conflicts of Interest: No conflict of interest

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