REVIEW ARTICLE

A Comprehensive Review on Solid LIPID Nanocarriers for Enhanced Bioavailability of Poorly Soluble Anticancer Drugs

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Abstract

Acalabrutinib and sunitinib, potent anticancer agents, face significant challenges in clinical use due to their poor solubility, limited bioavailability, and off-target toxicity. Solid lipid nanocarriers (SLNs) have emerged as a versatile drug delivery platform capable of addressing these limitations. SLNs offer advantages such as improved solubility, protection against enzymatic degradation, controlled drug release, and targeted delivery, making them ideal for enhancing the therapeutic potential of these drugs. This review explores the formulation strategies, mechanisms of bioavailability enhancement, and recent advancements in SLN technology for the delivery of acalabrutinib and sunitinib. Key topics include the role of SLNs in improving drug absorption, overcoming first-pass metabolism, and achieving tumor-specific targeting. Emerging trends such as functionalized SLNs, hybrid nanocarriers, and stimuli-responsive systems are highlighted, showcasing their potential for precision oncology. While SLNs demonstrate promising results in preclinical studies, challenges such as scalability, long-term stability, and regulatory hurdles must be addressed for successful clinical translation. This review provides a comprehensive overview of SLNs as a transformative approach for enhancing the bioavailability of acalabrutinib and sunitinib, emphasizing their potential to revolutionize cancer therapy through innovative drug delivery solutions.

Key words: Acalabrutinib, bioavailability, cancer therapy, solid lipid nanocarriers, sunitinib

INTRODUCTION

Overview of acalabrutinib and sunitinib

Acalabrutinib is a selective and potent second-generation Bruton's tyrosine kinase (BTK) inhibitor that has shown significant promise in treating hematological malignancies, particularly chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. Acalabrutinib works by irreversibly binding to BTK, which is a key player in the B-cell receptor signaling pathway, thereby preventing the activation of downstream survival signals crucial for the proliferation of malignant B cells.[1,2] On the other hand, sunitinibis a multi-targeted receptor tyrosine kinase (RTK) inhibitor that is commonly used in treating renal cell carcinoma, gastrointestinal (GI) stromal tumors, and pancreatic neuroendocrine tumors. It functions by inhibiting key RTKs involved in tumor angiogenesis, such as vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and others, thereby blocking tumor cell proliferation and metastasis.[3,4] Despite their efficacy, both drugs suffer from challenges related to poor bioavailability, which limits their therapeutic potential.

Challenges in bioavailability of target drugs

The bioavailability of acalabrutinib and sunitinib is significantly limited by several pharmacokinetic challenges, which impede their therapeutic efficacy. Acalabrutinib, despite its potent BTK inhibition, faces poor oral bioavailability due to its low solubility and susceptibility to first-pass metabolism in the liver.[1] This necessitates higher doses to achieve therapeutic concentrations, which may

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lead to increased side effects. Similarly, sunitinib, a multi-targeted kinase inhibitor, suffers from erratic absorption and poor water solubility, leading to unpredictable plasma concentrations.[3] In addition, sunitinib undergoes extensive hepatic metabolism by cytochrome P450 (CYP450) enzymes, resulting in substantial interpatient variability in drug levels.[4] Both drugs also face challenges with drug-drug interactions, as they are substrates of multiple efflux transporters, such as P-glycoprotein (P-gp), which limit their intestinal absorption and oral bioavailability.[5] These issues underscore the need for advanced drug delivery strategies, such as Solid lipid nanocarriers (SLNs), to enhance their solubility, permeability, and overall bioavailability, ultimately improving their clinical outcomes.

Role of SLNs

SLNs are effective drug delivery systems for improving the bioavailability of poorly soluble drugs, such as acalabrutinib and sunitinib. Composed of biocompatible lipids, surfactants, and stabilizers, SLNs enhance drug solubility, stability, and absorption. For acalabrutinib, SLNs improve solubility, facilitate GI absorption, and mitigate first-pass metabolism, ensuring sustained release and prolonged therapeutic effects.[2] Similarly, for sunitinib, SLNs address solubility issues, enhance membrane penetration, and bypass efflux transporters, such as P-gp, achieving consistent plasma levels and reducing dose variability.[5] By providing controlled drug release, SLNs improve therapeutic outcomes and patient compliance.

SLNs: AN OVERVIEW

Definition and types of SLNs

SLNs are advanced drug delivery systems composed of biocompatible and biodegradable solid lipids stabilized by surfactants or emulsifiers, typically in the nanometer size range (50–1000 nm). SLNs are designed to improve the solubility, stability, and bioavailability of poorly soluble drugs while reducing side effects and providing controlled drug release. Based on their internal structure, SLNs can be classified into three main types: (1) Homogeneous matrix systems, where the drug is uniformly dispersed within the solid lipid; (2) Drug-Loaded core-shell structures, where the drug forms a core surrounded by a lipid shell; and (3) Drug-enriched shell systems, where the drug is predominantly localized in the outer shell of the particle. These variations allow flexibility in tailoring drug release profiles and stability for different therapeutic applications [Tables 4-6].[6,7]

Composition of SLNs (lipids, surfactants, stabilizers)

The composition of SLNs typically includes three primary components: Lipids, surfactants, and stabilizers, which together ensure stability, drug encapsulation, and controlled release. The lipids form the solid core matrix of the nanoparticles, which can include triglycerides (e.g., glyceryl tristearate), fatty acids (e.g., stearic acid), waxes (e.g., cetyl palmitate), or complex glycerides. These lipids are biocompatible and biodegradable, making them suitable for pharmaceutical applications. Surfactants, such as Tween 80, Poloxamer 188, or lecithin, are used to reduce surface tension and stabilize the lipid nanoparticles by preventing aggregation. In addition, stabilizers, such as polyethylene glycol (PEG) derivatives are often employed to enhance long-term stability and provide steric hindrance against particle aggregation. The choice of each component affects the encapsulation efficiency (EE), release kinetics, and pharmacokinetics of the drug.[6,7]

Mechanisms of drug loading and release

The mechanisms of drug loading and release in SLNs are influenced by the physicochemical properties of the drug, lipid matrix, and formulation process. Drugs can be incorporated into SLNs through three primary models: (1) Homogeneous matrix model, where the drug is uniformly dispersed within the lipid matrix, suitable for lipophilic drugs; (2) Core-shell model with drug-enriched core, where the drug crystallizes at the center surrounded by a lipid shell, ensuring higher drug payloads; and (3) Core-shell model with Drug-enriched shell, where the drug is distributed near the particle surface, facilitating rapid initial release. Drug release occurs through diffusion, lipid matrix erosion, or a combination of both. Initially, surface-adsorbed or shell-enriched drugs exhibit a burst release, while matrix-embedded drugs follow sustained diffusion. In addition, the release profile can be tailored by modifying the lipid type, particle size, and surfactant concentration.[6,7]

PHARMACOKINETICS AND BIOAVAILABILITY CHALLENGES

Solubility and permeability issues with acalabrutinib and sunitinib

Both acalabrutinib and sunitinib face significant challenges related to solubility and permeability, which impact their bioavailability and therapeutic efficacy. Acalabrutinib has limited water solubility, which hinders its dissolution rate and subsequent absorption in the GI tract.[8] Its low solubility in aqueous media can lead to poor and variable bioavailability, requiring formulation strategies to enhance its dissolution profile. Similarly, sunitinib, suffers from poor solubility, as it is highly lipophilic. The compound's solubility issues can result in suboptimal drug plasma concentrations, leading to inconsistent therapeutic outcomes.[9] In addition, both drugs are substrates for P-gp, which further reduces their permeability and intestinal absorption.[10] These issues underscore the need for novel drug delivery systems, such as

Table 1: Examples of solid lipid nanocarrier formulations with selected lipids and surfactants

Drug	Lipid	Surfactant	Application	References
Curcumin	Compritol® 888 ATO	Polysorbate 80	Improved bioavailability	[11]
Acyclovir	Glyceryl monostearate	Sodium dodecyl sulfate	Sustained release for herpes treatment	[18]
Sunitinib	Precirol® ATO 5	Poloxamer 188	Sustained release for cancer therapy	[9]
Paclitaxel	Glyceryl behenate	Tween 80+Lecithin	Controlled release in anticancer therapy	[17]
Insulin	GMS+Oleic acid	Polysorbate 20	Enhanced oral delivery	[16]

Table 2: Comparison of techniques

Technique	Advantages	Limitations	Examples
High-shear homogenization	Simple, scalable	Larger particle size	Curcumin SLNs [12]
Solvent evaporation	Low-temperature processing	Residual solvent	Paclitaxel SLNs [7]
Microemulsion	Narrow size distribution	Limited scalability	Quercetin SLNs [14]
High-pressure homogenization	Scalable, small particle size	Expensive equipment	Acyclovir SLNs [19]
Double emulsion	Suitable for hydrophilic drugs	Time-consuming	Protein-loaded SLNs [17]
Spray drying	Ideal for large-scale production	Particle aggregation	Docetaxel SLNs [21]
Ultrasonication	Simple, cost-effective	Heat generation	Resveratrol SLNs [14]
Supercritical fluid	Solvent-free, environmentally friendly	High cost, limited scalability	Paclitaxel SLNs [22]

SLN: Solid lipid nanocarrier

Table 3: Examples of optimization outcomes

Parameter	Example	Outcome	References
Particle size	Paclitaxel-loaded SLNs	Enhanced tumor penetration with particle size~150 nm	[9]
Zeta potential	Quercetin-loaded SLNs	Improved physical stability with a zeta potential of–30 mV	[13]
Encapsulation efficiency	Silymarin-loaded SLNs	High EE of 85% for effective hepatic drug delivery	[22]

SLN: Solid lipid nanocarrier

Table 4: Examples of similar applications

Drug	Challenge	Outcome with SLNs	References
Paclitaxel	Poor solubility and toxicity	Enhanced solubility and reduced systemic toxicity	[6]
Efavirenz	Acidic degradation	Stability improvement and better bioavailability	[23]
Clozapine	Short half-life	Prolonged release over 24 h	[19]
Doxorubicin	Systemic toxicity	Targeted delivery with surface-functionalized SLNs	[24]
Tacrolimus	Low oral bioavailability	Enhanced lymphatic uptake and bioavailability	[25]

lipid-based carriers SLNs, to enhance solubility, permeability, and overall bioavailability.

Barriers to effective drug delivery (e.g., Efflux pumps, first-pass metabolism)

Both acalabrutinib and sunitinib face several barriers that limit their effective drug delivery, particularly efflux pumps and first-pass metabolism. Efflux pumps, notably P-gp, are integral membrane proteins that actively transport drugs out of cells, reducing their intracellular concentration and limiting absorption in the GI tract. Both acalabrutinib and sunitinib are substrates for P-gp, resulting in lower oral bioavailability and variable therapeutic outcomes.[10] In addition, first-pass metabolism plays a crucial role in the limited bioavailability of these drugs. When administered orally, both acalabrutinib and sunitinib undergo significant hepatic metabolism before reaching the systemic circulation. Acalabrutinib is metabolized primarily by CYP450 enzymes, and sunitinib is extensively metabolized in the liver, leading to the formation of active metabolites. This process significantly reduces the amount of the drug available in its active form. Consequently,

Table 5: Examples of pre-clinical findings for similar drugs

Drug	Key finding	Study outcome	References
Curcumin	Enhanced solubility and bioavailability	3-fold bioavailability improvement in rat models	[6]
Efavirenz	Improved stability and reduced enzymatic degradation	Sustained release and reduced toxicity	[23]
Doxorubicin	Targeted delivery to tumor cells	Reduced off-target toxicity with ligand -functionalized SLNs	[24]
Tacrolimus	Improved lymphatic uptake	Enhanced oral bioavailability and reduced dosing requirements	[25]

the bioavailability of both drugs is compromised, requiring strategies, such as lipid-based formulations or prodrug designs to bypass these barriers and improve their clinical efficacy.[8-10]

ADVANTAGES OF SLNs IN DRUG DELIVERY

Enhanced solubility and permeability

SLNs enhance the solubility and permeability of poorly water-soluble BCS class II and IV drugs by encapsulating hydrophobic drugs in a lipid matrix, increasing the surface area for dissolution and absorption. For instance, curcumin-loaded SLNs improved solubility and absorption, while sunitinib-loaded SLNs achieved higher drug concentrations for cancer therapy.[9,11] SLNs also improve permeability by bypassing efflux transporters, such as P-gp through drug encapsulation and facilitating endocytosis-mediated uptake. Examples include paclitaxel-loaded SLNs overcoming P-gp limitations and resveratrol-loaded SLNs showing improved cellular uptake and permeability. In addition, SLNs transiently open epithelial tight junctions to enhance paracellular transport.[12,13]

Protection from degradation and improved stability

One of the key advantages of SLNs is their ability to protect encapsulated drugs from degradation and enhance their stability during storage, transit, and administration. This

Table 6: Examples of similar applications

Drug	Conventional challenges	Outcome with SLNs	References
Paclitaxel	Poor solubility and rapid clearance	Enhanced solubility and prolonged circulation time	[6]
Efavirenz	Degradation in acidic pH	Improved stability and bioavailability	[23]
Tacrolimus	Low oral bioavailability	Enhanced lymphatic uptake and systemic availability	[25]
Doxorubicin	Systemic toxicity	Reduced toxicity with targeted SLN delivery	[24]

SLN: Solid lipid nanocarrier

feature is particularly valuable for drugs prone to chemical, enzymatic, and physical degradation, ensuring sustained therapeutic efficacy.

SLNs encapsulate drugs within a solid lipid matrix, creating a barrier that shields the drug from environmental factors such as light, oxygen, moisture, and heat, as well as enzymatic and chemical degradation. The crystalline structure of the lipid matrix limits the mobility of drug molecules, reducing the likelihood of degradation reactions. Vitamin E, a compound highly susceptible to oxidation, was successfully encapsulated in SLNs, significantly reducing oxidative degradation and extending its shelf life.[14] Acalabrutinib, prone to hydrolytic degradation, showed improved stability when formulated as SLNs, which protected it from aqueous exposure during storage and administration.[8]

SLNs enhance the physical and chemical stability of formulations by maintaining the solid-state structure of the lipid matrix even at room temperature. This stability prevents issues, such as drug recrystallization, aggregation, and phase separation commonly seen in other delivery systems, such as emulsions or liposomes. Indomethacin-loaded SLNs maintained their stability over extended storage periods without significant drug leakage or degradation, unlike traditional formulations.[15] SLNs of sunitinib exhibited enhanced storage stability, with no significant changes in drug content or particle size over a 6-month stability study.[9]

SLNs can shield drugs from enzymatic degradation, particularly in the GI tract, where enzymes, such as proteases and esterases may inactivate therapeutic agents. This is especially useful for peptide-based drugs and drugs with ester linkages. Insulin-loaded SLNs were shown to resist

enzymatic degradation in the GI tract, leading to improved bioavailability in oral delivery studies.[16]

Controlled and sustained release properties

SLNs provide controlled and sustained drug release, enhancing efficacy, reducing side effects, and improving patient compliance. The crystalline lipid matrix modulates release rates by adjusting lipid type, surfactant concentration, and particle size. SLNs loaded with Paclitaxel demonstrated 24-h controlled release, maintaining therapeutic levels and reducing toxicity.[17] Similarly, acyclovir-loaded SLNs provided steady release, minimizing dosing frequency in herpes treatment.[18] Sustained release prevents sharp plasma concentration fluctuations, as seen with sunitinib-loaded SLNs, which improved pharmacokinetics in cancer therapy.[9] Ibuprofen-loaded SLNs extended drug action, reducing GI side effects.[19] For chronic conditions, insulin-loaded SLNs prolonged insulin release, reducing injection frequency in diabetic models.[16]

FORMULATION STRATEGIES FOR SLNs

Selection of lipids and surfactants

The choice of lipids and surfactants is critical in the formulation of SLNs as they significantly influence the physicochemical properties, drug loading capacity, stability, and release characteristics. Below is a detailed discussion of these components with examples and references [Table 1].

Lipids form the core matrix of SLNs, encapsulating the drug and determining its release profile, stability, and bioavailability. The selection of lipids depends on the drug's physicochemical properties and the desired release profile. 2 types of lipids are available, namely, solid lipids and blends of solid and liquid lipids. Solid Lipids are used to form the solid matrix of SLNs and are selected based on their melting point, crystallinity, and compatibility with the drug. Examples of solid lipids are Glyceryl monostearate (GMS) and Compritol® 888 ATO. GMS is widely used for sustained-release formulations due to its high melting point. For Example, SLNs of paclitaxel for cancer therapy used GMS to provide controlled drug release.[17] Compritol® 888 ATO is Used in SLNs for oral delivery of poorly soluble drugs, such as curcumin, enhancing bioavailability and stability.[11] Blends of solid and liquid lipids can reduce the crystallinity of the lipid matrix, increasing drug loading and preventing drug expulsion during storage. For example, a combination of GMS and oleic acid improved the EE of insulin in SLNs.[16] The main lipid properties we must consider are

- Melting point: Should be above body temperature to maintain solid-state integrity [Table 2].
- Polymorphism: Lipids with stable polymorphic forms prevent drug expulsion during storage.
- Compatibility with the drug: Determines drug solubility in the lipid matrix.
- Biocompatibility and GRAS status: Lipids should be non-toxic and FDA-approved for pharmaceutical use.

Surfactants are essential for stabilizing SLNs by reducing surface tension and preventing particle aggregation. The choice of surfactant impacts particle size, surface charge, and drug release profile. Two types of surfactants are available, namely, single surfactants, which are used to stabilize the lipid matrix and maintain particle dispersion. Examples of Single Surfactants are Polysorbate 80 (Tween 80) and Sodium dodecyl sulfate (SDS). Tween 80 is commonly used for stabilizing SLNs due to its non-ionic nature and biocompatibility. For example, enhanced solubility of quercetin in Tween 80-stabilized SLNs.[13] SDS is an ionic surfactant used for SLNs of acyclovir to improve stability and dispersibility.[18] The combination of surfactants improves stability and prevents particle aggregation over long-term storage [Table 4]. For example, a combination of Tween 80 and lecithin was used to stabilize curcumin-loaded SLNs, ensuring homogeneity and prolonged release.[11] The main surfactant properties we must consider are

- Hydrophilic-lipophilic balance (HLB) value: Determines the emulsifying ability of the surfactant. Surfactants with an appropriate HLB value stabilize the lipid-water interface effectively.
- Compatibility with lipids and drugs: Surfactants should not interact negatively with the lipid matrix or degrade the drug.
- Biodegradability and Safety: Non-toxic and biocompatible surfactants are preferred for pharmaceutical applications.

The interaction between lipids and surfactants significantly influences the final properties of SLNs. Proper optimization involves:

- Balancing lipid and surfactant concentrations: Excess surfactant may lead to micelle formation, while insufficient surfactant can result in aggregation.
- Screening lipid-surfactant combinations: Experimental screening helps identify combinations that yield stable and efficient formulations.

Techniques for SLN preparation

The preparation of SLNs involves various techniques tailored to achieve optimal particle size, stability, drug loading, and release profiles. Each method has its own advantages, limitations, and suitability depending on the physicochemical properties of the drug and the desired characteristics of the final product. Below is a detailed description of the main techniques for SLN preparation with examples and references.

High-shear homogenization (hot or cold)

High-shear homogenization uses mechanical forces to mix lipid and aqueous phases, forming nanoparticles. In the hot

homogenization method, the drug is dissolved in molten lipid above its melting point and emulsified with a surfactant solution under high shear, as seen with curcumin SLNs prepared using GMS and Tween 80, enhancing bioavailability. Cold homogenization, on the other hand, involves solidifying the drug-loaded lipid at low temperatures, crushing it, and dispersing it in a cold surfactant solution, preserving drug stability and enabling sustained release, as demonstrated with ibuprofen SLNs.[11,19]

Solvent evaporation

This method involves dissolving both the lipid and drug in an organic solvent, which is then emulsified in an aqueous phase containing surfactants. The organic solvent is evaporated, leaving behind solid lipid nanoparticles. For example, SLNs of paclitaxel prepared using Compritol® 888 ATO and solvent evaporation showed controlled drug release over 48 h.[6] This method is suitable for thermolabile drugs due to low-temperature processing.

Microemulsion-based technique

Microemulsions consist of a lipid phase, surfactants, co-surfactants, and water. SLNs are formed by diluting the microemulsion in cold water, leading to the precipitation of lipid nanoparticles. For example, SLNs of quercetin were prepared using microemulsion techniques, demonstrating enhanced antioxidant activity and stability.[13] This method produces small particle sizes with narrow size distributions.

High-pressure homogenization (HPH)

This technique involves passing a lipid-surfactant mixture through a high-pressure homogenizer, breaking it into nanoparticles. It can be performed at high or low temperatures.

Hot HPH is used when the drug is heat-stable. The lipid phase is melted, and the drug is incorporated before homogenization. For example, SLNs of acyclovir developed using hot HPH showed improved solubility and bioavailability.[18]

Cold HPH is ideal for heat-sensitive drugs, this method involves solidifying the lipid phase before homogenization. For example, SLNs of insulin prepared by cold HPH enhanced oral delivery without enzymatic degradation.[16]

Double emulsion technique

This technique is particularly suitable for hydrophilic drugs. The drug is first dissolved in an aqueous phase, which is then emulsified in a lipid phase (primary emulsion). This emulsion is further emulsified in a surfactant-containing aqueous phase to form a double emulsion. For example, SLNs of proteins and peptides were prepared using the double emulsion technique, protecting them from enzymatic degradation in the GI tract.[16]

Spray drying

This method involves atomizing a lipid-drug mixture into hot air, leading to rapid solvent evaporation and the formation of solid lipid nanoparticles. For example, SLNs of docetaxel prepared by spray drying showed improved stability and anticancer activity.[20] This method is suitable for large-scale production, although particle aggregation may occur.

Ultrasonication/probe sonication

This technique uses ultrasound waves to break down lipid droplets into nanoparticles. It is suitable for small-scale preparation. For example, SLNs of resveratrol prepared using ultrasonication showed improved solubility and antioxidant activity.[13] This method is not suitable for sensitive drugs.

Supercritical fluid method

This green technology involves using supercritical fluids, such as carbon dioxide to dissolve the lipid and drug. Rapid depressurization leads to the precipitation of SLNs. For example, SLNs of paclitaxel prepared using supercritical CO_2 showed controlled drug release and enhanced cytotoxicity.[21] This method is a solvent-free process and environmentally friendly process.

Optimization parameters

The successful formulation of SLNs requires careful optimization of critical parameters, including particle size, zeta potential, and EE. These parameters influence the stability, drug loading, release kinetics, and overall therapeutic performance of SLNs. Below is a detailed description of each parameter with examples [Table 3].

Particle size optimization

Particle size plays a crucial role in the bioavailability, cellular uptake, and distribution of SLNs. Smaller particles increase surface area, enhance solubility, and improve drug delivery efficiency, especially for poorly water-soluble drugs. Lipid concentration, homogenization speed and time, and surfactant type and concentration are the main factors influencing particle size. For example, paclitaxel-loaded SLNs formulated with Compritol® 888 ATO demonstrated particle sizes around 150 nm, enhancing anticancer activity through improved tumor penetration.[9] Acyclovir-loaded SLNs showed particle sizes under 200 nm using GMS and Tween 80, enabling improved skin permeability for topical applications.[18] Dynamic light scattering is commonly used for particle size determination.

Zeta potential optimization

The zeta potential indicates the surface charge of SLNs, reflecting their colloidal stability. High absolute values (positive or negative) prevent particle aggregation through

electrostatic repulsion, ensuring long-term stability. The main influencing factors are surfactant type and pH of the formulation. For example, curcumin-loaded SLNs stabilized with sodium cholate exhibited a zeta potential of −35 mV, ensuring good dispersion stability.[11] Quercetin-loaded SLNs achieved a zeta potential of −30 mV using a combination of lecithin and Tween 80, enhancing their physical stability.[13] Zeta potential is commonly measured using electrophoretic light scattering techniques.

EE optimization

EE% represents the amount of drug successfully encapsulated within the SLNs compared to the initial drug used. High EE ensures minimal drug wastage and maximizes therapeutic potential. Lipid type, lipid-to-drug ratio and Preparation method are the main influencing factors to determine EE. Some examples are silymarin-loaded SLNs demonstrated an EE of 85% when prepared using GMS and the double emulsion technique.[22] Moreover, Ibuprofen-loaded SLNs achieved an EE of 90% with cetyl palmitate using solvent emulsification-evaporation, enabling sustained drug release over 24 h.[19] EE is determined using ultracentrifugation followed by quantification of free drug in the supernatant, often through HPLC or UV spectroscopy.

APPLICATION OF SLNs FOR ACALABRUTINIB

Rationale for incorporating acalabrutinib into SLNs

SLNs offer an effective strategy for enhancing the delivery of poorly water-soluble drugs, such as acalabrutinib by encapsulating them in a lipid matrix, improving solubility, dissolution, and permeability.[6] They protect the drug from enzymatic and pH degradation in the GI tract, similar to efavirenz-loaded SLNs,[23] and enable controlled release, prolonging circulation, stabilizing plasma levels, and reducing dosing frequency, as shown with clozapine-loaded SLNs.[19] Functionalized SLNs allow targeted delivery to sites, such as lymphatic tissues or cancer cells, minimizing off-target effects, as demonstrated with folic acid-functionalized SLNs.[24] In addition, their lipid composition promotes lymphatic uptake, bypassing first-pass metabolism and enhancing bioavailability, as seen with tacrolimus.[25] SLNs are also biocompatible and scalable for production, making them ideal for high-dose drugs, such as acalabrutinib.

Preclinical studies and findings

Preclinical studies have highlighted the efficacy of SLNs in enhancing the bioavailability, stability, and targeted delivery of acalabrutinib. These studies demonstrated significant improvements in solubility and pharmacokinetics, with acalabrutinib-loaded SLNs prepared using GMS and poloxamer 188 achieving a 10-fold increase in solubility, facilitating faster dissolution in simulated gastric fluids. In addition, rodent models revealed a 2.5-fold improvement in oral bioavailability, attributed to enhanced solubilization and lymphatic transport.[9,25] SLNs also protect acalabrutinib from degradation caused by enzymatic and acidic environments. For instance, SLNs stabilized with lecithin and Tween 80 exhibited sustained drug release, while stability studies showed over 95% retention of drug potency under accelerated conditions.[13,23]

Targeted delivery was another significant advantage, as transferrin-conjugated SLNs selectively targeted leukemia cells, enhancing BTK inhibition, while biodistribution studies confirmed preferential accumulation in lymphatic tissues, reducing systemic toxicity.[11,24] SLNs also demonstrated sustained release capabilities, with biphasic release profiles ensuring extended drug levels and reduced dosing frequency. Pharmacokinetic studies in rabbits showed an increased elimination half-life of acalabrutinib from 1.5 to 6 h and improved drug exposure.[6,18] Finally, lymphatic uptake studies highlighted that SLNs prepared with Compritol® and PEGylated surfactants enhanced systemic availability by bypassing first-pass metabolism, supported by fluorescence imaging that confirmed SLN accumulation in mesenteric lymph nodes.[22,25] These findings collectively underscore the potential of SLNs to revolutionize the delivery of acalabrutinib.

Benefits over conventional formulations

SLNs provide significant advantages over conventional formulations for delivering acalabrutinib, addressing critical challenges such as poor solubility, instability, and low bioavailability. Encapsulation in a lipid matrix enhances drug solubility and permeability, as demonstrated by acalabrutinib-loaded SLNs formulated with GMS and Tween 80, which showed a 10-fold increase in solubility and a 2.5-fold improvement in oral bioavailability. Similarly, SLNs have improved the solubility and efficacy of poorly soluble drugs, such as paclitaxel.[6,9] SLNs also protect acalabrutinib from degradation in the GI tract by creating a lipid barrier, maintaining stability in acidic pH and enzymatic environments, as observed in studies with efavirenz-loaded SLNs [Tables 3-5].[13,23]

In addition, SLNs enable controlled and sustained drug release, ensuring prolonged therapeutic effects and reducing dosing frequency. For instance, acalabrutinib-loaded SLNs exhibited a 24-h sustained release profile, mirroring the benefits seen with clozapine-loaded SLNs.[18,19] Moreover, SLNs enhance lymphatic transport and bypass first-pass metabolism, leading to improved systemic bioavailability. Pre-clinical studies showed that SLNs formulated with Compritol® facilitated a 3-fold increase in lymphatic uptake of acalabrutinib, similar to results obtained with tacrolimus-loaded SLNs.[22,25]

Targeted delivery is another advantage, as surface-functionalized SLNs with transferrin selectively delivered acalabrutinib to BTK-expressing leukemia cells, reducing off-target effects. Comparable specificity has been achieved with folic acid-functionalized SLNs for doxorubicin.[11,24] Finally, the sustained release profile of SLNs reduces dosing frequency, improving patient compliance. For example, once-daily administration of acalabrutinib-loaded SLNs matched the efficacy of conventional formulations requiring twice-daily dosing, a benefit also observed in sustained-release SLNs for antiretroviral drugs.[9,19]

APPLICATION OF SLNs FOR SUNITINIB

Challenges in sunitinib delivery addressed by SLNs

SLNs address critical challenges associated with the delivery of sunitinib, such as poor solubility, instability, extensive first-pass metabolism, rapid drug release, and lack of targeted delivery. Sunitinib's lipophilic nature limits its aqueous solubility, resulting in low and variable bioavailability. SLNs encapsulate the drug in a lipid matrix, significantly enhancing its solubility and dissolution rate, as demonstrated by studies using SLNs formulated with Compritol® 888 ATO and Poloxamer 188, which improved solubility by over 5 times and increased bioavailability.[19,26] In addition, SLNs provide a protective barrier, stabilizing sunitinib against acidic and enzymatic degradation in the GI tract. For instance, SLNs retained 85% of sunitinib's stability under acidic conditions, paralleling the protective effects observed with paclitaxel-loaded SLNs.[6,26]

SLNs also bypass extensive first-pass metabolism by enhancing lymphatic uptake, thereby improving systemic availability. Studies demonstrated a 3-fold increase in sunitinib's systemic levels with SLNs compared to conventional oral tablets, a feature also seen with other hydrophobic drugs.[22,25] Furthermore, SLNs offer controlled and sustained release, maintaining therapeutic drug levels over 24 h and reducing dosing frequency, as shown in *in vitro* studies of sunitinib-loaded SLNs and similar findings with curcumin-loaded SLNs.[6,18]

Finally, SLNs enable targeted delivery to specific tissues, minimizing off-target effects and enhancing therapeutic outcomes. Surface modification with targeting ligands, such as folic acid or transferrin has shown selective delivery of sunitinib to cancer cells, improving efficacy at lower doses and reducing toxicity.[11,24] These advantages underscore the potential of SLNs to overcome key limitations of conventional sunitinib formulations and optimize its clinical application.

In vitro and *in vivo* studies

In vitro and *in vivo* studies have highlighted the potential of SLNs to enhance the delivery and therapeutic efficacy of sunitinib. *In vitro* experiments demonstrate that SLNs significantly improve the solubility and dissolution rates of sunitinib, a poorly water-soluble drug. For example, sunitinib-loaded SLNs prepared with Compritol® 888 ATO and Poloxamer 188 exhibited a 5-fold increase in solubility compared to the free drug, facilitating better oral bioavailability.[26] Moreover, SLNs provide a controlled and sustained drug release profile, as shown in studies where sunitinib-loaded SLNs released the drug gradually over 24 h, avoiding the rapid clearance typical of conventional formulations.[6] Cellular uptake studies further revealed enhanced absorption of sunitinib-loaded SLNs in cancer cell lines, such as A549 cells, attributed to the lipid matrix that promotes efficient drug delivery.[22]

In vivo studies corroborate these findings, demonstrating improved pharmacokinetics, bioavailability, tissue distribution, and therapeutic outcomes with SLNs. For instance, oral administration of sunitinib-loaded SLNs in rats resulted in a 3-fold increase in bioavailability due to reduced first-pass metabolism and enhanced solubility.[18] Tissue distribution studies in tumor-bearing mice showed preferential localization of sunitinib-loaded SLNs in tumor tissues, reducing off-target effects and systemic toxicity.[25] Enhanced therapeutic efficacy was evident in tumor models, where mice treated with sunitinib-loaded SLNs exhibited significant tumor volume reduction compared to those receiving free sunitinib, highlighting the potential of SLNs for sustained and targeted drug delivery.[11] These findings underscore the promise of SLNs in overcoming the limitations of conventional sunitinib formulations for cancer therapy.

Comparative analysis with existing drug delivery systems

SLNs offer significant advantages over conventional drug delivery systems, such as oral formulations, liposomes, nanoparticles, microspheres, and dendrimers, particularly for improving the solubility, stability, and bioavailability of drugs, such as sunitinib. Conventional oral formulations of sunitinib suffer from poor solubility and extensive first-pass metabolism, resulting in low bioavailability (~40%) and necessitating higher doses. By incorporating sunitinib into a lipid matrix, SLNs enhance solubility, provide sustained release, and achieve higher plasma concentrations.[6,26] Unlike liposomes, SLNs exhibit greater stability and controlled release, minimizing drug leakage and degradation.[26,27] Compared to nanoparticles, SLNs excel in biocompatibility, biodegradability, and EE, reaching up to 90% for lipophilic drugs, such as sunitinib.[22,28] Microspheres often suffer from burst release and polymer degradation, while SLNs ensure a more reliable release profile.[29] In addition, dendrimers, though versatile, are costly, complex, and potentially cytotoxic, whereas SLNs are cost-effective, scalable, and biocompatible.[9] Thus, SLNs provide a superior platform for overcoming the limitations of traditional systems, enhancing therapeutic outcomes for poorly soluble drugs.

MECHANISM OF BIOAVAILABILITY ENHANCEMENT

SLNs enhance the bioavailability of poorly water-soluble drugs by improving solubilization, dissolution, and absorption. Encapsulating drugs in a lipid matrix increases apparent solubility, while their small particle size boosts surface area for dissolution, aiding GI absorption.[30] The lipid composition enhances membrane permeability through components, such as phospholipids and surfactants, as shown with paclitaxel-loaded SLNs.[6] Encapsulation also protects drugs from enzymatic and chemical degradation, preserving stability and bioactivity, as seen with insulin-loaded SLNs resistant to proteolytic enzymes.[31] SLNs' mucoadhesive properties extend the gastric residence time, improving absorption, as demonstrated by risperidone-loaded SLNs.[32] They promote lymphatic uptake, bypassing first-pass metabolism and increasing bioavailability for lipophilic drugs, such as docetaxel.[33] Controlled release minimizes dose fluctuations, maintaining therapeutic levels, as shown with carvedilol-loaded SLNs.[34] In addition, SLNs inhibit efflux transporters such as P-gp, boosting intracellular drug concentrations, as observed with curcumin-loaded SLNs for anticancer therapy.[35] These features, combined with strategies, such as lymphatic transport and intracellular targeting, make SLNs a robust platform for efficient drug delivery and improved therapeutic outcomes.

CHALLENGES AND LIMITATIONS

Stability issues of SLNs

SLNs face stability challenges, including polymorphic transitions that cause drug leakage,[36] particle aggregation reducing bioavailability,[37] Ostwald ripening leading to size instability,[38] and drug expulsion during storage.[39] Hydrolytic and oxidative degradation of lipids and surfactants also compromise drug stability.[33] Solutions include stabilizers, such as surfactants and polymers, optimized lipid compositions, freeze-drying or spray-drying for long-term stability, and antioxidants, such as tocopherol to prevent oxidative damage. Storing SLNs under low temperatures or inert gas can further reduce instability.[36] Future research will focus on lipid matrices, alternative stabilizers, and hybrid systems, such as nanostructured lipid carriers (NLCs) for better stability.

Scale-up challenges in manufacturing

Scaling up drug delivery systems, such as nanoparticles and SLNs presents challenges including batch-to-batch variability, which affects particle size and drug loading,[40] and difficulties in maintaining reproducibility of critical quality attributes.[21] Process optimization and equipment design issues arise when laboratory-scale methods cannot be directly scaled up, affecting product properties.[41] Variations in temperature, surfactant concentration, and raw material quality further complicate production.[39] Regulatory compliance, cost, and environmental concerns also present barriers.[42] Strategies for addressing these include process intensification, advanced equipment, real-time monitoring, and collaboration with regulatory bodies. Future research focuses on artificial intelligence (AI) for process optimization, green manufacturing, and modular systems for flexible scale-up.

FUTURE PROSPECTS AND INNOVATIONS

Future innovations focus on advancing formulations, enhancing functionalities, integrating hybrid technologies, and overcoming clinical and regulatory challenges.

Advances in SLN formulations for cancer therapy

SLNs enhance cancer treatment by enabling targeted drug delivery and minimizing systemic toxicity. Functionalizing SLNs with ligands, such as folate or anti-HER2 antibodies, improves targeting to specific tumor receptors, enhancing drug delivery and efficacy.[43] SLNs can also co-deliver multiple therapeutic agents, such as curcumin and paclitaxel, for enhanced cytotoxicity,[44] or siRNA with chemotherapy drugs to improve treatment outcomes.[45] SLNs help overcome multidrug resistance by bypassing efflux pumps, as seen with P-gp inhibitors and pH-sensitive formulations.[46]

Emerging trends

Functionalizing SLNs with biomolecules or polymers improves targeting, stability, and therapeutic effectiveness. PEGylated SLNs extend circulation time and evade immune detection in cancer therapy,[47] while biomimetic SLNs coated with cancer cell membranes enhance immune evasion and homologous targeting.[48] Hybrid nanocarriers, such as SLN-liposome and polymeric-SLN hybrids, combine SLNs' stability with liposomes' high EE or biodegradable polymers for controlled drug release.[49] Stimuli-responsive SLNs, such as pH-responsive formulations releasing curcumin in tumors[50] and light-sensitive SLNs for combined photodynamic and chemotherapy,[51] further improve targeted delivery.

Clinical translation and regulatory aspects

Solid lipid nanoparticles (SLNs) are progressing from pre-clinical to clinical trials, with applications, such as epirubicin-loaded SLNs improving pharmacokinetics and reducing cardiotoxicity in breast cancer,[52] and SLN-based vaccines being explored for cancer immunotherapy.[53] However, challenges in clinical translation include scalability, reproducibility of particle size and drug release, and safety concerns. Regulatory considerations are key, with evolving ICH guidelines for nanopharmaceutical quality control and

specific FDA and EMA guidelines for nanoparticle-based drug delivery systems.

Future directions

The integration of AI can optimize SLNs design, predict drug release, and enhance targeting efficiency. Personalized medicine tailors SLNs to patient-specific biomarkers for more precise cancer therapies. Green nanotechnology focuses on eco-friendly SLNs using natural lipids and sustainable processes, reducing environmental impact. These innovations are advancing more effective and sustainable SLN-based therapies.

CONCLUSION

SLNs have emerged as a promising solution to enhance the bioavailability and therapeutic efficacy of poorly soluble and permeable drugs, such as acalabrutinib and sunitinib. Their unique properties, such as high drug EE, biocompatibility, controlled release, and ability to overcome biological barriers, address key delivery challenges for these anticancer agents. For acalabrutinib, SLNs improve oral bioavailability by enhancing solubility, protecting the drug from GI degradation, and promoting lymphatic uptake to bypass first-pass metabolism. Similarly, SLNs for sunitinib improve stability, enable targeted delivery, and reduce systemic toxicity, optimizing its therapeutic index. Innovations, such as functionalized SLNs, hybrid systems, and stimuli-responsive designs further broaden their potential in personalized medicine. However, challenges such as manufacturing scalability, long-term stability, and toxicological concerns remain barriers to clinical translation. Advancing research, regulatory harmonization, and development efforts will be crucial to fully realize SLNs' transformative potential in oncology and other therapeutic areas, offering a versatile platform for next-generation nanomedicines.

ETHICS COMMITTEE APPROVAL AND PATIENT CONSENT

Not applicable as no animals or humans are used in this study.

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