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Solid lipid nanoparticles in precision oncology: Mechanistic design, manufacturing innovations, and translational perspectives

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ABSTRACT

Solid lipid nanoparticles (SLNs) have emerged as an adaptable nanocarrier system for cancer treatment due to their biocompatible lipid matrix, capacity to encapsulate chemically diverse therapeutics, and ability to protect drugs from premature degradation. Their nanoscale dimensions support passive tumor accumulation through the enhanced permeation and retention (EPR) effect, while surface engineering allows ligand-mediated targeting to improve cellular internalization and reduce off-target toxicity. The performance of SLNs is strongly influenced by the manufacturing approach, as process parameters dictate particle size, polymorphic behavior, drug loading efficiency, and release kinetics. Conventional and advanced preparation strategies including high-pressure homogenization, ultrasonication, solvent emulsification, membrane-assisted techniques, and supercritical fluid processing continue to evolve to meet requirements for scalability, structural stability, and improved pharmacological performance. Post-processing approaches further enhance the shelf-life and handling suitability of SLN formulations through conversion into solid dosage forms without compromising colloidal behavior after redispersion. Extensive research has demonstrated that rationally developed SLNs enhance therapeutic efficacy across multiple cancer types, including lung, liver, colorectal, breast, prostate, cervical, melanoma, and bladder malignancies. These systems have shown improved drug solubility, superior intracellular uptake, stronger induction of apoptosis, enhanced tumor-site accumulation, and reduced systemic toxicity compared with conventional formulations. Co-delivery of synergistic agents, tumor-microenvironment-responsive release, and targeted surface modifications further elevate their potential as precision-oriented delivery systems. This review consolidates advancements in SLN manufacturing technologies and evaluates their application in diverse cancer models. By linking fabrication principles to biological performance, it highlights current opportunities and challenges in expanding SLN-based therapeutics as promising platforms for more effective and safer cancer treatment.

1. Introduction

The clinical outcomes of conventional anticancer drug therapy are frequently limited by poor aqueous solubility, rapid systemic elimination, multidrug resistance mechanisms, and toxicity arising from nonspecific biodistribution. These challenges are further compounded by the structural heterogeneity of solid tumors, including disordered vasculature, dense extracellular matrix components, and elevated interstitial pressure [1,2]. Such barriers restrict effective drug penetration and reduce the fraction of therapeutic agents reaching malignant cells at sufficient concentrations. Consequently, nanomedicine-based formulations have gained significant attention for cancer treatment, as they can improve pharmacokinetics, enhance tissue accumulation, and promote intracellular drug retention [3,4].

Among nanoscale delivery systems, SLNs have emerged as versatile carriers due to their use of physiologically compatible lipids, ability to encapsulate diverse therapeutic molecules, and adaptability to multiple administration routes. SLNs protect encapsulated drugs from chemical degradation and enable modulation of release kinetics, which is particularly advantageous for hydrophobic or instability-prone anticancer agents [5]. Their nanoscale dimensions support prolonged circulation and passive tumor localization via the enhanced permeation and retention (EPR) effect, while surface functionalization strategies can further enhance receptor-mediated cellular uptake and therapeutic efficacy [6].

In the context of precision oncology, SLNs offer distinct advantages

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over conventional nanocarriers by enabling controlled and tunable design at multiple levels, including lipid composition, surface engineering, and stimuli-responsive behavior. While many nanocarriers rely primarily on passive accumulation mechanisms, SLNs can be engineered to achieve spatiotemporally controlled drug release, selective cellular uptake, and modulation of intracellular pathways. This design flexibility allows SLNs to better address tumor heterogeneity and biological barriers. Therefore, the concept of "precision" in SLN-based systems arises from the integration of manufacturing control, physicochemical optimization, and disease-specific targeting, rather than passive delivery alone.

The pharmaceutical performance of SLNs is strongly influenced by the selected preparation method, as manufacturing processes govern key attributes such as particle size, surface charge, crystallinity, dispersity, and stability. Techniques including high-pressure homogenization, ultrasonication, solvent-based emulsification, membrane-assisted methods, and supercritical fluid processing represent the primary routes for SLN production [7]. Optimization of these approaches enables the generation of particles with controlled size distribution, enhanced encapsulation efficiency, and improved physicochemical stability. In addition, post-processing strategies such as spray drying and lyophilization are increasingly employed to convert dispersions into stable solid forms, facilitating long-term storage and large-scale handling [8,9].

The therapeutic potential of SLNs has been demonstrated across multiple cancer types, including lung, liver, colorectal, breast, prostate, cervical, melanoma, and bladder cancers. SLN-based formulations have consistently shown improvements in drug solubility, intracellular uptake, and induction of apoptosis, while reducing systemic toxicity associated with conventional therapies. Advanced formulation strategies, such as co-delivery of synergistic agents, ligand-mediated targeting, and tumor microenvironment-responsive release, have further enhanced their anticancer performance [10,11].

This review moves beyond conventional descriptive summaries by adopting a mechanism-driven and translation-oriented framework to analyze SLN systems in oncology. Specifically, it establishes explicit relationships between manufacturing processes, physicochemical properties, and biological performance, providing a structured understanding of how formulation design influences therapeutic outcomes. In contrast to existing reviews that primarily catalogue studies, this work emphasizes critical analysis, comparative evaluation, and identification of current limitations. Furthermore, it integrates key considerations related to scalability, stability, and clinical translation, offering practical insights to bridge the gap between laboratory research and real-world application. Through this integrated approach, the manuscript provides a comprehensive and actionable framework for the rational design and translation of next-generation SLN systems in precision oncology.

2. Manufacturing techniques of solid lipid nanoparticles

The therapeutic efficiency of SLNs is strongly controlled by the manufacturing process, because the way lipid droplets are created and solidified determines particle size, crystallinity, drug retention, surface properties, and storage stability. Factors such as lipid melting behavior, type of emulsification force, shear intensity, and cooling rate dictate how the lipid matrix recrystallizes and how effectively the encapsulated drug remains protected during processing and administration [12]. Therefore, manufacturing technologies must be carefully selected based on the physicochemical profile of the therapeutic compound and the clinical requirements of the cancer treatment strategy. A diverse set of preparation routes is available, including high-pressure homogenization, ultrasonication, high-shear mixing, solvent emulsification–diffusion, microemulsion dilution, double-emulsion processing, membrane-contactor techniques, and supercritical fluid–assisted methods (Fig. 1). Each technique offers unique technical advantages with respect to scalability, energy consumption, particle-size distribution, control of polymorphic transitions, and compatibility with heat-sensitive or hydrophilic drugs [13]. For example, solvent-free approaches are preferred for clinically relevant parenteral formulations due to higher regulatory acceptability, while solvent-based methods allow processing of high-melting-point lipids and sensitive anticancer molecules under mild thermal conditions. Following dispersion formation, post-processing transformations such as spray-drying or lyophilization convert colloidal SLNs into stable dry powders suitable for long-term storage, transportation, and ease of administration. These drying techniques must be optimized to avoid irreversible aggregation, crystallinity changes, and drug leakage caused by alterations in lipid microstructure [14]. Careful tuning of cryoprotectant concentrations, drying kinetics, and reconstitution conditions ensures preservation of

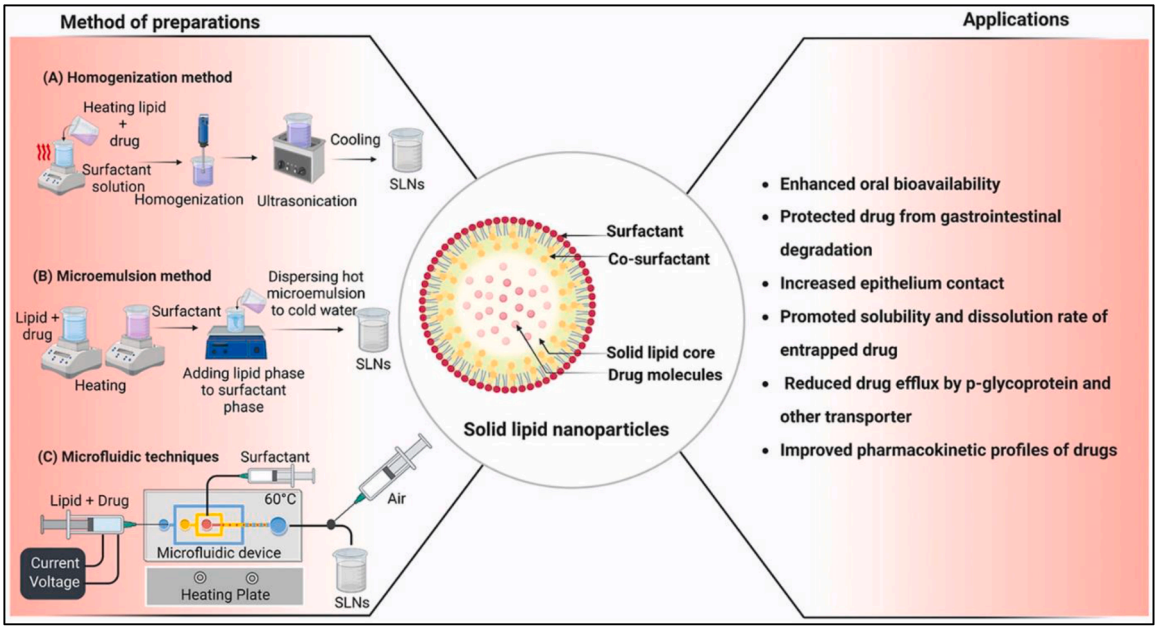

Fig. 1. Overview of solid lipid nanoparticles, highlighting key preparation methods and their pharmaceutical applications (reproduced with permission from Ref [16].).

nanoparticle attributes and reliable therapeutic function. Overall, manufacturing-driven control of particle architecture represents the foundation of successful SLN-based oncology therapy. The subsequent subsections critically analyze each preparation route, emphasizing the relationship between process variables, resulting physicochemical characteristics, and performance outcomes in cancer management [15].

In this section, SLN manufacturing techniques are discussed within a process–structure–performance framework. Each method is evaluated in terms of how processing conditions influence physicochemical properties such as particle size, polydispersity, and crystallinity, and how these attributes subsequently affect biological performance and therapeutic outcomes. This structured approach provides a systematic understanding of SLN design and facilitates rational selection of fabrication strategies for oncology applications.

2.1. High-pressure homogenization (HPH)

High-pressure homogenization (HPH) is one of the most widely adopted and industrially accepted technologies for the fabrication of SLNs. In this process, a coarse pre-emulsion of molten lipid dispersed in an aqueous surfactant solution is forced through a narrow homogenization gap under high pressure. The intense shear forces, hydraulic turbulence, and cavitation occurring inside the valve rapidly break down micron-sized droplets into nanoscale particles, which subsequently solidify during cooling to form stable SLNs. The technique is inherently solvent-free, supports short processing times, and offers direct scalability to pharmaceutical production through piston-gap homogenizers.

Ultrahigh-pressure homogenization (UHPH), a high-energy variant of HPH, has been applied for preparing SLNs using Otoba wax, a lipid rich in lauric and myristic acids with a required HLB value of approximately 9. The resulting nanoparticles exhibited sizes below 200 nm, polydispersity indices below 0.3, and high zeta-potential values, indicative of strong physical stabilization. Notably, variations in internal phase concentration did not significantly affect physicochemical or microbiological quality attributes, demonstrating robustness of this method and its suitability for formulations where process reproducibility is essential [17].

The scalability of HPH was further demonstrated using piston-gap homogenizers across batch volumes ranging from 40 mL to 50 L without compromising product quality. Larger batch sizes even produced narrower particle-size distributions and superior storage stability, confirming batch-to-batch uniformity. Homogenization pressure in the range of 300–500 bar had only moderate influence on mean particle size, whereas processing temperature and cooling rate exerted a more dominant effect. Rapid cooling resulted in unstable polymorphic transitions and increased risk of drug expulsion, while controlled cooling at approximately 18 °C favored formation of uniform, stable lipid matrices. These observations highlight that, in addition to pressure and cycle number, precise control of thermal history is critical to prevent unfavorable crystallization and to achieve long-term stability of SLN dispersions [18].

2.2. Ultrasonication and high shear homogenization

Ultrasonication and high-shear homogenization are widely employed laboratory-scale techniques for the preparation of SLNs, offering simpler operation and lower capital requirements compared with high-pressure homogenization. High-shear homogenization uses rotor–stator assemblies to generate intense mechanical shear, producing fine emulsions, while ultrasound applies acoustic cavitation to further reduce droplet size into the nanometer range. These approaches are particularly suited for early-stage formulation screening and rapid prototype development.

In one investigation, SLNs were fabricated using high-shear homogenization with various solid lipids and Poloxamer 188 as the surfactant. Incorporation of the cationic stabilizer cetyltrimethylammonium bromide (CTAB) markedly enhanced zeta-potential values, leading to superior electrostatic stabilization. The optimized dispersion exhibited nanometer-scale particle diameters, a narrow polydispersity index (PDI < 0.25), and zeta-potential values exceeding +60 mV, confirming strong colloidal stability. These results highlight the suitability of high-shear homogenization as a rapid and cost-effective method for preparing physically stable SLN formulations [19].

A combined high-shear and ultrasonication strategy has also been evaluated for fenofibrate-loaded SLNs to enhance solubility and dissolution of this BCS Class II drug. A coarse emulsion composed of glycerol monostearate and Tween 40 at 80 °C was subjected to pulse-mode ultrasonication for 15 min. The resultant particles exhibited sizes ranging from 490 to 2410 nm, spanning the nano-to-microscale range. Particles at the higher end of this range fall within the submicron/microparticle domain and may limit suitability for intravenous applications. The formulations showed PDI values between 0.02 and 0.65 and zeta potentials of 2.8–8.8 mV. Although the particle-size distribution was relatively broad, encapsulation efficiencies remained high (77.23–87.82%), demonstrating successful drug incorporation. The enhanced dissolution performance indicated that this combined approach can improve the biopharmaceutical properties of poorly soluble drugs, even when ultra-small particle sizes are not achieved [20].

Overall, ultrasonication and high-shear homogenization provide accessible and flexible processing routes for small-scale SLN development. However, careful optimization of energy input is necessary to prevent overheating, degradation of thermosensitive actives, and excessive particle-size variability. These techniques are therefore advantageous for formulation feasibility studies and early-stage optimization, while scale-up generally requires transition to more robust manufacturing platforms.

2.3. Solvent-Based production approaches

Solvent-based methods are widely employed when lipids possess high melting points or when thermosensitive drugs cannot tolerate elevated processing temperatures. In these approaches, the lipid and drug are dissolved in an organic solvent, emulsified into an aqueous phase, and subsequently transformed into solid nanoparticles upon solvent removal. These techniques can produce narrow particle-size distributions and high encapsulation efficiencies, but they require efficient solvent elimination and strict control of residual solvent content to comply with pharmaceutical regulations [21].

2.3.1. Emulsification–evaporation technique

In the emulsification–evaporation method, the lipid and drug are dissolved in a water-immiscible organic solvent and emulsified into an aqueous surfactant solution. Subsequent solvent removal by evaporation leads to lipid solidification and formation of SLNs. This method enables precise control over particle size and drug loading, making it suitable for encapsulating poorly water-soluble anticancer agents. In oncology-focused applications, SLNs prepared using this technique have demonstrated improved delivery efficiency and targeting potential. For example, formulations containing bioactive compounds have shown particle sizes in the nanoscale range (~180 nm) with favorable surface charge, supporting enhanced cellular uptake and stability in biological environments [22]. In another study, SLNs loaded with 18β-glycyrrhetinic acid were optimized using a Box–Behnken experimental design by varying lipid and surfactant concentrations. The optimized formulation exhibited an encapsulation efficiency of 68.81%, mean particle size of 414 nm (approaching the upper nanoscale/submicron boundary), and a broad and highly heterogeneous particle-size distribution (PDI = 0.76), indicating poor uniformity and potential multimodality. The release profile showed an initial burst followed by sustained release, suggesting potential applicability in controlled drug delivery systems

[23]. Despite these advantages, the use of organic solvents in this method requires careful removal to ensure safety, particularly for parenteral administration. Residual solvent toxicity and scalability considerations remain important challenges in translating this technique for clinical use in anticancer therapy.

2.3.2. Emulsification–Diffusion technique

The emulsification–diffusion approach uses a partially water-miscible solvent to dissolve the lipid, forming an oil-in-water emulsion that solidifies into nanoparticles as the solvent diffuses into an excess aqueous phase. To improve solvent removal efficiency, supercritical CO_2 (SC—CO_2) has been integrated into this process. A hybrid emulsion–diffusion–SC—CO_2 method enabled preparation of stearic-acid nanoparticles with mean diameters of 30–50 nm, low aggregation tendency, and residual benzyl alcohol levels below 100 ppm. The dispersions remained physically stable for two weeks at 4 °C, demonstrating improved solvent elimination and size control [24]. A spontaneous emulsification solvent-diffusion (SESD) configuration has also been investigated using tocopheryl polyethylene glycol succinate (TPGS) to enhance emulsification efficiency. Systematic variation of formulation parameters produced nanoparticles with controlled morphology, improved drug entrapment, and modulated release behavior. Although many SESD studies use polymeric matrices, their principles are transferable to lipid systems, highlighting this method's potential for high-payload nanocarrier design [25].

2.3.3. Solvent-displacement (Injection) technique

The solvent-displacement technique involves dissolving lipid in a water-miscible organic solvent and rapidly injecting it into an aqueous phase under stirring. The immediate diffusion of solvent into water induces lipid precipitation, forming nanoparticles. This method is simple, requires no specialized equipment, and can be performed at relatively low temperatures, making it advantageous for incorporating drugs with thermal sensitivity.

Particle size, PDI, and encapsulation efficiency can be controlled by adjusting injection rate, solvent type, lipid concentration, temperature, and stirring speed. The process has been consistently applied to both SLNs and nanostructured lipid carriers (NLCs), providing reproducible, easily scalable formulations and compatibility with continuous manufacturing concepts. Nevertheless, appropriate solvent selection and validated solvent-removal steps remain critical considerations for regulatory approval in parenteral products [26].

2.4. Emulsion-based methods

Emulsion-based techniques utilize thermodynamically stable or metastable emulsions as precursors for solid lipid nanoparticle (SLN) formation. Lipid droplets dispersed in an aqueous medium are solidified through cooling, dilution, or solvent removal, resulting in nanoparticles. These strategies are particularly advantageous for incorporating lipophilic drugs and for processing lipids with relatively low melting points under mild conditions.

2.4.1. Microemulsion dilution technique

The microemulsion dilution method involves forming a transparent or translucent oil-in-water microemulsion composed of lipid, surfactant, cosurfactant, and water. Subsequent dilution with chilled aqueous medium induces rapid precipitation of the lipid phase as nanostructured particles. Using this technique, repaglinide-loaded SLNs were produced employing lipids such as glyceryl monostearate, cetyl palmitate, and tristearin stabilized with Poloxamer 188. The resulting nanoparticles possessed an average size of approximately 339 nm with an entrapment efficiency of 82.20%. Dialysis-based release studies demonstrated controlled release behavior, with 88.4% drug release over 12 h. Differential scanning calorimetry suggested amorphous or molecular dispersion of the drug in the lipid matrix, while scanning electron microscopy confirmed spherical morphology. Storage at 2–8 °C for one month showed no significant change in size or release kinetics, indicating good short-term stability [27]. A cold-dilution microemulsion variant has been applied to prepare curcumin-loaded SLNs (SLN—CURC) using trilaurin as the lipid component. The system employed a partially water-miscible solvent saturated with water to create the microemulsion, followed by dilution to trigger nanoparticle formation. SLN—CURC exhibited mean diameters around 200 nm, negative surface charge, and high entrapment efficiencies (up to 90%), with preserved colloidal stability. Encapsulation markedly improved the aqueous dispersibility and chemical stability of curcumin. In vitro experiments showed concentration-dependent inhibition of pancreatic adenocarcinoma cell proliferation, while preliminary biodistribution studies in rodents suggested prolonged systemic circulation after intravenous administration. These results support microemulsion dilution as a promising approach for generating high-payload SLNs for systemic delivery of poorly soluble anticancer agents [28].

2.4.2. Double-emulsion (w/o/w) technique

The double-emulsion (water-in-oil-in-water, w/o/w) method enables incorporation of hydrophilic drugs, peptides, and nucleic acids within lipid matrices by maintaining internal aqueous compartments during nanoparticle formation. A primary w/o emulsion containing the hydrophilic drug in the internal aqueous phase is first generated, followed by emulsification into an external aqueous phase to produce w/o/w droplets. Subsequent solidification or solvent removal yields SLNs with entrapped aqueous microdomains [29].

This technique is particularly relevant for the delivery of hydrophilic anticancer agents, including proteins, peptides, and genetic materials such as siRNA or mRNA, which require protection from degradation and controlled intracellular release. In addition, w/o/w systems have demonstrated the ability to enhance permeability and delivery efficiency of hydrophilic compounds by modulating their partitioning behavior across lipid phases [30].

In oncology applications, double-emulsion systems have been explored for encapsulating both diagnostic and therapeutic agents. For example, Rhodamine B-loaded systems have been investigated in glioblastoma multiforme (GBM), where encapsulation reduced cytotoxicity and improved formulation tolerability [31]. Similarly, enhanced encapsulation efficiency of resveratrol has been reported in w/o/w systems compared to conventional lipid nanoparticles, likely due to the presence of dual oil–water interfaces that improve protection of the drug core [32]. Incorporation of chemotherapeutic agents such as 5-fluorouracil (5-FU) has demonstrated reduced tumor cell proliferation and improved therapeutic performance relative to free drug formulations [33]. Furthermore, the versatility of this method allows co-encapsulation of hydrophilic and lipophilic drugs; for instance, a dual-drug system containing doxorubicin and erlotinib exhibited enhanced cellular uptake and tumor suppression due to improved intracellular drug retention [34].

Despite these advantages, a key limitation of the double-emulsion method is the tendency to produce particles in the submicron range, which may restrict their suitability for intravenous administration and limit tumor penetration efficiency [29]. To address these challenges, recent methodological developments have explored the use of osmolytes to ensure formation of droplets with a single aqueous core, thereby improving release predictability. Additionally, replacement of conventional surfactants with colloidal stabilizers has been investigated to reduce toxicity and enhance formulation stability. The incorporation of impermeable shell components has also been shown to minimize drug leakage and improve encapsulation efficiency [35]. Overall, the double-emulsion method represents a versatile and promising approach for engineering SLNs designed for the delivery of hydrophilic anticancer therapeutics, particularly in applications requiring controlled release, combination therapy, and protection of sensitive biomolecules.

2.5. Membrane-contactor assisted nanoparticle formation

The membrane-contactor method is a highly controlled alternative to conventional emulsification techniques for SLN production. In this continuous approach, the lipid phase is maintained above its melting point and pressurized through the pores of a membrane to generate uniform microdroplets, which are immediately swept away by a tangentially flowing aqueous phase circulating within the module. Cooling of these droplets leads to their solidification into nanoparticles. Process variables such as membrane pore size, lipid feed pressure, cross-flow velocity of the aqueous phase, and the temperature differential between both phases strongly influence droplet break-up dynamics, particle size distribution, and production throughput. The method has successfully generated SLNs with particle sizes ranging from 70 to 215 nm at lipid-phase fluxes between 0.15 and 0.35 $m^3/h{\cdot}m^2$, demonstrating reliable nanoscale production under well-regulated flow conditions [36]. Precise droplet formation enables narrow size distribution, while scalability can be achieved simply by increasing membrane surface area, making the approach compatible with continuous manufacturing strategies increasingly adopted in pharmaceutical industries. Despite these advantages, the requirement for suitably engineered membranes and continuous monitoring to prevent pore fouling or wetting failures represents important practical considerations for industrial implementation.

2.6. Supercritical fluid technology

Supercritical fluid (SCF)–based approaches leverage the enhanced mass-transfer, solvation, and diffusivity characteristics of fluids above their critical pressure and temperature to engineer nanostructured materials. Among SCFs, CO_2 is particularly preferred in pharmaceutical systems due to its low toxicity, mild critical conditions, and facile removal after processing. SCF techniques have been explored for producing lipid-based particles through mechanisms such as rapid expansion, gas-saturation–induced atomization, and antisolvent-driven precipitation.

2.6.1. Rapid expansion of supercritical solutions (RESS)

In RESS, the solute is first dissolved in supercritical CO_2 and subsequently expanded through a nozzle, resulting in abrupt supersaturation and precipitation of fine particles. Although its direct application to lipid nanoparticle production is limited by poor CO_2 solubility for many lipids, the approach has been adapted using lipid-containing organic solutions to generate SLNs. One industrial-scale concept described SCF-assisted injection into a liquid antisolvent, producing SLNs with particle sizes between 158 ± 53 nm and 462 ± 88 nm and stability over 30 days. Additional work demonstrated submicron griseofulvin particles by tuning nozzle geometry, pre-expansion temperature, and dissolution pressure. These studies emphasize that strict maintenance of supersaturation governs nucleation behavior and enables size tailoring, though improved solvation strategies are needed for broader SLN applicability [37].

2.6.2. PGSS: particle formation from gas-saturated solutions

The PGSS process saturates a molten lipid with supercritical CO_2, which behaves as a blowing agent. Rapid depressurization causes expansion of dissolved CO_2, atomizing and solidifying the melt into particles. For example, fully hydrogenated soybean oil (FHSO) was processed into hollow lipid micro-/nanoparticles, with pressure (100–300 bar), temperature (60–80 °C), and melt volume (10–50 mL) significantly impacting particle size and internal structure. Empirical modelling enabled prediction of nanoparticle yield as a function of operating conditions, with optimal parameters (≈300 bar, 60 °C, 20–30 mL melt) yielding 6.3–6.6 μm particles and up to 24.1% nanoparticle fraction [38]. While sizes reported are often in the micron range, PGSS continues to evolve as a scalable route for producing solid lipid powders with tunable morphology.

2.6.3. SAILA: SCF-assisted antisolvent precipitation

The supercritical assisted injection in a liquid antisolvent (SAILA) process involves spraying an organic solution into a liquid antisolvent under supercritical conditions to induce instantaneous supersaturation and coprecipitation. Originally established for polymeric matrices such as PLGA loaded with NSAIDs (diclofenac, piroxicam, indomethacin), the method achieved spherical microparticles (0.28–2.50 μm) with encapsulation efficiencies of 50–97%. Process variables including pressure, temperature, polymer/drug ratio, and concentration controlled particle size and release kinetics. Extensive morphological and physicochemical characterization (SEM, XRD, FT-IR) confirmed composite uniformity, while mathematical modelling (Hoffenberg equation) showed close correlation between experimental and predicted release profiles [39]. Though the approach predominantly yields micro-scale carriers in current studies, its versatile antisolvent mechanism provides a foundation for future adaptation to lipid-based nanocarriers. To facilitate direct comparison and improve interpretability of different SLN fabrication strategies, a summary of key physicochemical and performance-related parameters across major manufacturing techniques is presented in Table 1. As summarized in Table 1, different manufacturing techniques yield SLNs with distinct ranges of particle size, polydispersity index, and encapsulation efficiency, which directly influence stability, drug retention, and biological performance.

This comparison highlights differences in particle size distribution, encapsulation efficiency, scalability, and suitability for various drug types, enabling more rational selection of preparation methods for oncology applications. Although a wide range of SLN manufacturing techniques are available, no single method is universally optimal. High-pressure homogenization offers scalability and regulatory acceptance but may induce thermal stress and polymorphic instability. In contrast, solvent-based approaches provide better control over particle size and drug loading but raise concerns regarding solvent toxicity and regulatory compliance. Emerging techniques such as membrane-contactor systems and supercritical fluid processing show promise for precise control and continuous manufacturing; however, their industrial adoption remains limited due to equipment complexity and cost. Therefore, selection of an appropriate manufacturing strategy requires balancing physicochemical control, scalability, and clinical feasibility, rather than relying solely on particle-size optimization. Importantly, a well-recognized limitation of conventional SLNs is drug expulsion during storage, primarily caused by lipid crystallization into highly ordered polymorphic forms. To overcome this limitation, nanostructured lipid carriers (NLCs) have been developed by incorporating liquid lipids into the solid lipid matrix, resulting in a less ordered structure with higher drug accommodation capacity. Consequently, NLCs are often preferred over SLNs in applications requiring enhanced drug loading and long-term stability, whereas SLNs remain advantageous for simpler formulations with more controlled and predictable release profiles.

While several reviews have summarized SLN preparation techniques, most focus primarily on descriptive overviews of fabrication methods. In contrast, the present review integrates a process–structure–performance perspective, explicitly linking manufacturing conditions to physicochemical attributes and their subsequent impact on biological performance in oncology. In addition, comparative evaluation of different techniques and discussion of practical selection criteria are incorporated to provide a more application-oriented framework. This approach enables a deeper understanding of how formulation design influences therapeutic outcomes, thereby distinguishing this work from existing literature. These comparative insights highlight that rational selection of SLN or NLC systems depends not only on manufacturing feasibility but also on long-term stability and therapeutic requirements

It is important to note that particle size critically influences the biological performance and clinical applicability of SLNs. While particles below ~200–300 nm are generally preferred for intravenous

Table 1
Comparative analysis of SLN manufacturing techniques and their physicochemical characteristics.

Method	Particle Size (nm)	PDI Range	Encapsulation Efficiency	Key Advantages	Limitations	Precision / Translational Relevance	Ref
High-Pressure Homogenization (HPH)	50–300	0.1–0.3	High	Scalable, solvent-free, reproducible	Thermal stress, drug expulsion risk	Suitable for parenteral delivery; enables controlled nanoscale size (<200 nm) critical for tumor targeting and reproducibility	[17,18]
Ultrasonication / High-Shear	100–1000	0.2–0.5	Moderate–High	Simple, low cost	Broad size distribution, poor scalability	Useful for formulation screening; limited precision due to variability in size and reproducibility	[19,20]
Emulsification–Evaporation	100–500	0.1–0.3	Moderate–High	Good size control, mild conditions	Residual solvent issues	Enables controlled particle formation but requires strict solvent removal for clinical translation	[22,23]
Emulsification–Diffusion	30–200	0.1–0.25	High	Narrow size distribution	Complex processing	Produces uniform nanoparticles suitable for enhanced cellular uptake and precision delivery	[25]
Solvent Injection	100–300	0.1–0.3	Moderate	Simple, low temperature	Solvent removal needed	Suitable for thermolabile drugs; moderate control over size limits precision targeting	[26]
Microemulsion Dilution	100–400	0.2–0.4	High	High entrapment efficiency	Dilution instability	Effective for lipophilic drug loading; size variability may affect biodistribution consistency	[27,28]
Double Emulsion (w/o/w)	200–1000 (nano–submicron range)	0.3–0.6	Moderate	Suitable for hydrophilic drugs	Large size, instability	Limited precision for IV delivery due to larger size (>300 nm) and broad distribution	[29,35]
Membrane Contactor	70–200	0.1–0.2	High	Uniform particles, controlled production	Equipment complexity	High precision control over size and distribution; promising for reproducible and scalable manufacturing	[36]
Supercritical Fluid	100–500	0.1–0.3	Moderate–High	Solvent-free, tunable properties	Expensive, technical complexity	Enables tunable particle engineering; potential for precision design but limited industrial adoption	[37–39]

administration and efficient tumor penetration, systems exceeding 500 nm may exhibit altered biodistribution, reduced tumor accumulation, and increased risk of vascular complications. Therefore, accurate classification between nanoscale, submicron, and microparticle systems is essential to ensure proper interpretation of formulation behavior and therapeutic potential.

2.7. Post-processing strategies for solid-state stabilization

Post-processing approaches are employed to convert colloidal SLN dispersions into solid dosage forms that offer enhanced storage stability, ease of handling, and improved patient compliance. Among these, spray drying and lyophilization are widely used, although both techniques can significantly influence the physicochemical properties and release behavior of the final product if not carefully optimized.

Spray drying involves atomization of SLN dispersions into a heated airflow, enabling rapid solvent removal and particle solidification. This technique provides a scalable and continuous manufacturing approach and can influence drug release characteristics depending on process conditions. Studies have shown that spray-dried SLN formulations can exhibit modified release profiles and improved process efficiency, highlighting that post-processing methods can significantly impact performance, sometimes even more than upstream formulation parameters [40]. In addition, continuous spray-drying approaches, where active ingredients and excipients are molecularly dispersed prior to atomization, enable the formation of single- or multi-component particles and amorphous dispersions in a single step, offering flexibility in tailoring dissolution kinetics and bioavailability [41].

Conversely, lyophilization (freeze-drying) is preferred when maximum preservation of nanoparticle structure is required. However, its success is highly dependent on formulation composition and process conditions. For example, studies on drug-loaded SLNs have demonstrated that appropriate cryoprotectant selection particularly trehalose at optimized ratios combined with controlled freezing and drying parameters, can produce redispersible powders with minimal changes in particle size, polydispersity, and surface charge upon reconstitution. Stability studies further indicate that low-temperature storage preserves colloidal integrity, whereas higher temperature and humidity conditions can lead to particle growth and physicochemical instability [42].

From an oncology perspective, these post-processing strategies are particularly important for ensuring the long-term stability, reproducibility, and clinical applicability of SLN-based anticancer formulations. Spray drying supports scalable production and tunable release behavior, whereas lyophilization remains essential for maintaining structural integrity and stability of sensitive therapeutic payloads, including chemotherapeutics and nucleic acid-based agents.

3. Physicochemical characterization of solid lipid nanoparticles

Comprehensive physicochemical characterization is essential for establishing the performance, stability, and translational potential of SLNs. Rather than serving as isolated quality descriptors, these parameters collectively govern biological interactions, pharmacokinetics, and therapeutic outcomes.

Particle size and polydispersity index (PDI) are critical determinants of in vivo behavior. Nanoparticles with sizes below ~200 nm exhibit improved tumor penetration, enhanced cellular uptake via endocytosis, and reduced clearance by the reticuloendothelial system (RES), thereby prolonging systemic circulation. In contrast, larger or heterogeneous populations are more susceptible to opsonization and rapid elimination. PDI provides insight into formulation uniformity; values $\leq$0.25 indicate narrow distributions suitable for reproducible performance, whereas PDI $\geq$0.3 reflects heterogeneity that may compromise stability, biodistribution, and batch-to-batch consistency. Dynamic light scattering (DLS) is widely employed for size and PDI measurement, while nanoparticle tracking analysis (NTA) and electron microscopy (SEM/TEM)

provide complementary information on particle morphology and dispersion state [43].

Surface charge, expressed as zeta potential, plays a key role in colloidal stability and biological interactions. High absolute values ($\geq \pm 30$ mV) promote electrostatic stabilization, reducing aggregation during storage. However, in biological systems, surface charge also governs protein adsorption and formation of the protein corona, which in turn influences cellular uptake, immune recognition, and biodistribution. Neutral or slightly negative surfaces, often achieved through PEGylation or steric stabilization, can reduce nonspecific interactions and prolong circulation time, thereby enhancing tumor accumulation.

Lipid crystallinity and polymorphic transitions are central to drug incorporation and retention within the SLN matrix. Highly ordered crystalline structures tend to expel encapsulated drug molecules during storage, leading to reduced loading capacity and therapeutic inconsistency. Conversely, less ordered or metastable lipid arrangements improve drug accommodation and retention. Techniques such as differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier-transform infrared spectroscopy (FT-IR) are employed to monitor lipid phase behavior and drug–lipid interactions, ensuring structural stability and minimizing drug leakage [44].

Encapsulation efficiency and drug loading, typically quantified using high-performance liquid chromatography (HPLC) or UV–Vis spectroscopy, directly influence therapeutic dosing and efficacy [45]. However, high encapsulation alone is insufficient; it must be coupled with stable retention and controlled release to ensure consistent drug availability at the target site.

Drug-release kinetics provide mechanistic insight into delivery performance. Diffusion-controlled and erosion-based release profiles are commonly analyzed using models such as Higuchi, Korsmeyer–Peppas, zero-order, and first-order kinetics. An initial burst release may enhance early therapeutic action but can also increase systemic toxicity, whereas sustained release profiles are desirable for maintaining therapeutic concentrations over extended periods. Therefore, tuning release kinetics is essential for optimizing efficacy–toxicity balance in cancer therapy.

Stability assessment under accelerated and long-term conditions is critical for predicting shelf life and clinical applicability. Phenomena such as lipid recrystallization, particle aggregation, and Ostwald ripening can significantly alter physicochemical properties and compromise performance. Techniques including DLS monitoring, Turbiscan analysis, and visual inspection are employed to evaluate colloidal robustness and detect instability [46].

Importantly, these physicochemical parameters are highly interdependent and must be considered collectively. For example, particle size, surface charge, and lipid crystallinity together determine biodistribution, cellular uptake, and drug-release behavior. Consequently, characterization of SLNs should be viewed as an integrated framework linking formulation design with biological performance, safety, and translational feasibility. Such a structure–function–performance approach is essential for the rational development of SLNs as precision nanomedicine platforms in oncology.

4. Solid lipid nanoparticles in cancer therapy: strategies and applications

Cancer remains one of the leading causes of global mortality, and its treatment is often hindered by multidrug resistance, nonspecific drug distribution, and dose-limiting systemic toxicities. Conventional chemotherapeutics frequently suffer from poor aqueous solubility, rapid clearance, insufficient tumor accumulation, and lack of selectivity, resulting in suboptimal therapeutic indices and treatment failure. Moreover, the complex tumor microenvironment (TME) characterized by abnormal vasculature, acidic pH, hypoxia, dense extracellular matrix, and elevated efflux transporter expression significantly restricts drug penetration and intracellular retention, particularly in solid tumors. SLNs have emerged as a promising class of nanocarriers capable of addressing these barriers through a combination of physicochemical stability, biocompatibility, and controlled drug-release properties. Their lipid-based composition facilitates improved solubilization of hydrophobic anticancer agents while promoting enhanced cellular uptake through membrane integration, endocytosis, and TME-mediated retention. The nanoscale dimensions of SLNs can exploit the enhanced permeability and retention (EPR) effect for passive tumor targeting, while surface functionalization with ligands such as antibodies, peptides, folate, hyaluronic acid, or amino acids enables active, receptor-specific delivery. These features not only increase intracellular drug bioavailability but also minimize off-target toxicity.

In addition to single-drug loading, SLNs are particularly advantageous for co-delivery of multiple chemotherapeutics or adjuvant phytochemicals, thereby enabling synergistic action, overcoming drug resistance mechanisms, and reducing required dosages. Their structural flexibility allows incorporation of imaging agents or magnetic components for theranostic applications, where visualization and treatment are combined within a single platform. Furthermore, scalable manufacturing technologies such as high-pressure homogenization and emulsification-based systems support translational development toward clinical use. As evidence continues to expand, SLN-based formulations have demonstrated improved outcomes across major solid tumor types, including lung, liver, colorectal, breast, cervical cancer, melanoma, and prostate cancer. Collectively, these advances highlight the critical role of SLNs in enhancing pharmacokinetic performance, tumor selectivity, and overall therapeutic efficacy, positioning them as a leading nanotechnology candidate for next-generation precision oncology. These strategies highlight that the therapeutic success of SLNs is not solely dependent on drug selection but is strongly influenced by formulation design, surface engineering, and manufacturing conditions, reinforcing the need for an integrated approach in SLN development. Zeta potential values reported in this review are typically measured in aqueous media under near-physiological pH conditions; however, variations in buffer composition and pH can influence measured values and should be considered when comparing studies. The mechanistic framework of SLN-mediated drug delivery, including design, tumor targeting, intracellular trafficking, and stimuli-responsive release, is illustrated in Fig. 2.

4.1. Solid lipid nanoparticle–based strategies for lung cancer therapy

Solid lipid nanoparticles are increasingly investigated for lung cancer therapy due to their ability to enhance the solubility of poorly water-soluble drugs, improve dispersion stability, and promote intracellular uptake in tumor cells. Their nanoscale size and lipid composition enable efficient interaction with biological membranes and support both passive and active targeting of lung tumors, offering advantages over conventional formulations.

Encapsulation of 4-hexylresorcinol (4-HR) into SLNs has been explored to overcome hydrophobicity-induced aggregation and improve anticancer efficacy. Using hot-melt homogenization followed by sonication, particles with sizes ranging from 169.4 to 644.8 nm and zeta potentials between −19.8 and −40.3 mV were obtained. While smaller particles fall within the optimal nanoscale range, those approaching ~600 nm lie in the submicron domain and may exhibit altered biodistribution profiles. Entrapment efficiencies between 75.0% and 96.5% confirmed effective drug incorporation. Cytotoxicity studies in HeLa, A549, and CT-26 cancer cells demonstrated enhanced antiproliferative activity compared to free 4-HR, with performance influenced by particle size, drug retention, and cellular model. However, these findings are primarily based on in vitro systems, and the mechanistic basis of enhanced cytotoxicity requires further validation through detailed cellular uptake and intracellular trafficking studies [47].

Co-encapsulation of paclitaxel (PAC) and curcumin (CUR) within SLNs has been explored as a synergistic strategy for non-small cell lung

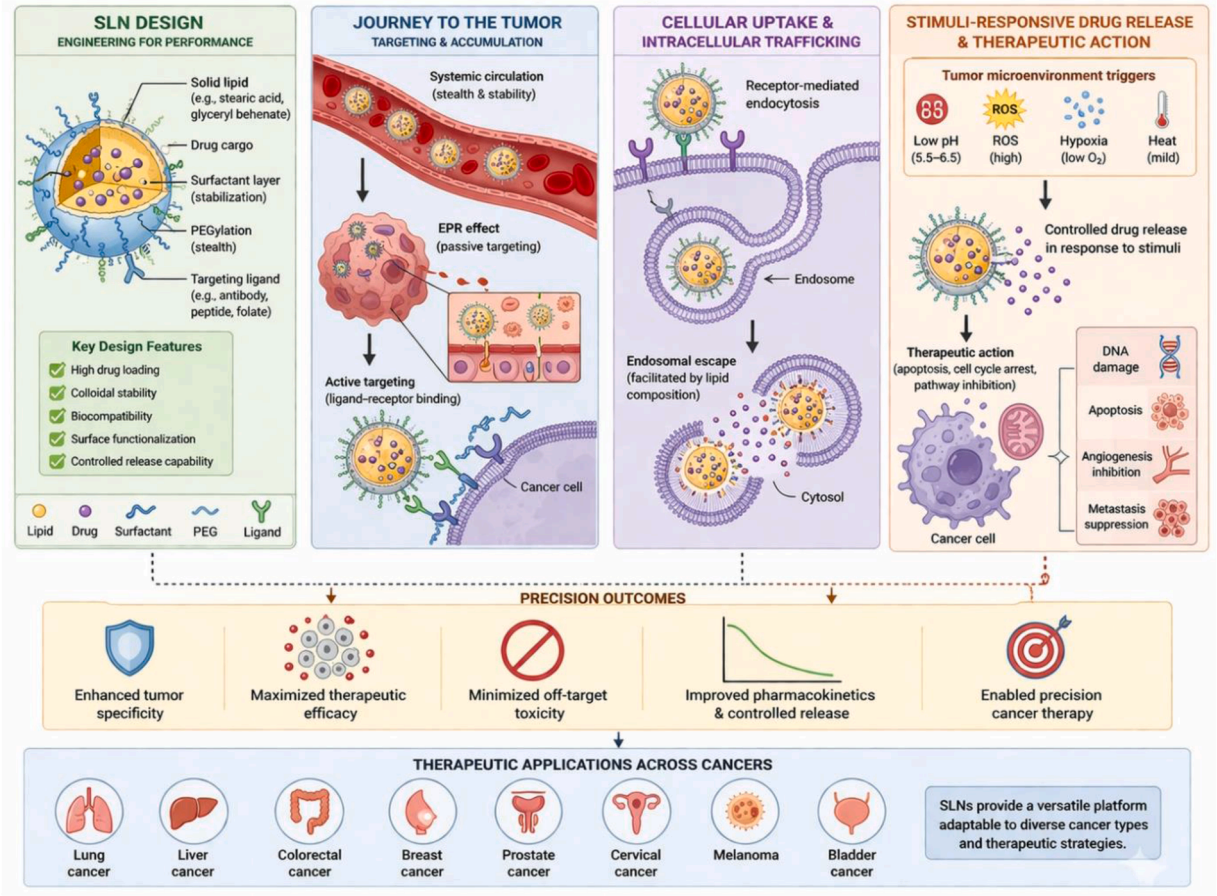

Fig. 2. Mechanistic framework of SLN-mediated precision drug delivery in cancer therapy. The schematic illustrates SLN design, systemic circulation and tumor targeting, cellular uptake and intracellular trafficking, and stimuli-responsive drug release (e.g., pH, ROS, hypoxia), leading to enhanced tumor specificity, controlled release, improved efficacy, and reduced toxicity.

cancer (NSCLC), the most common form of lung malignancy. The distinct anticancer mechanisms of PAC and CUR are shown in (Fig. 3A) and (B), respectively. Using high-pressure homogenization, both drugs were simultaneously incorporated into a stable lipid matrix to enhance their local concentration at tumor sites. This dual-delivery approach harnesses the strong chemotherapeutic activity of PAC together with the anti-inflammatory and chemosensitizing effects of CUR, thereby improving therapeutic response and reducing drug resistance. In vitro and in vivo evaluations demonstrated that PAC–CUR–SLNs exhibited superior anticancer efficacy compared with single-drug formulations. However, the extent of synergy is often inferred from tumor inhibition data without comprehensive mechanistic validation, such as pathway-specific or combination index analyses under standardized conditions [48].

When delivered via SLNs, these mechanisms are further enhanced through improved drug stability, targeted delivery, and controlled intracellular release, highlighting the role of SLNs in precision cancer therapy. Further investigations have focused on improving the bioavailability of curcumin using SLNs with different lipid matrices. Nanoparticles were prepared via sonication employing stearic acid, palmitic acid, or lauric acid as lipid components. Particle sizes varied significantly depending on lipid composition: stearic acid-based SLNs produced particles in the nanoscale range (14.70–149.30 nm), whereas lauric- and palmitic-acid systems generated larger particles (~469.53 nm and 502.83 nm), approaching the submicron range. These differences were attributed to variations in intermolecular interactions within the lipid matrix. Cytotoxicity studies in HeLa, A549, and CT-26 cells demonstrated consistently greater anticancer activity for curcumin-loaded SLNs than for free curcumin, with smaller particles showing enhanced cellular uptake and interaction. These findings highlight the critical role of lipid selection in governing physicochemical properties and therapeutic performance. Nevertheless, direct comparison across studies remains challenging due to differences in formulation methods, cell models, and experimental conditions [49].

Collectively, these studies indicate that SLNs can significantly improve drug solubilization, intracellular delivery, and anticancer efficacy in lung cancer models. However, most available data are limited to in vitro or short-term in vivo studies, with insufficient evaluation of long-term safety, pharmacokinetics, and clinically relevant models. In addition, important translational considerations such as inhalation-based delivery parameters (e.g., aerodynamic diameter, aerosolization stability, and lung deposition behavior), sterility, and pulmonary toxicity are rarely addressed. Therefore, future studies should focus on standardized evaluation frameworks, mechanistic validation, and clinically relevant delivery strategies to enable successful translation of SLN-based systems for lung cancer therapy.

4.2. Solid lipid nanoparticle–enabled therapeutic approaches for hepatocellular carcinoma

Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality due to late-stage diagnosis, poor drug bioavailability, and frequent recurrence. SLNs are increasingly utilized to enhance hepatic drug accumulation, control release kinetics, and enable receptor-targeted localization, thereby improving therapeutic efficacy while reducing systemic toxicity.

Long-circulating SLNs loaded with a curcumin derivative (CU1) were developed using HSPC and DSPE-PEG2000 lipids to overcome the poor

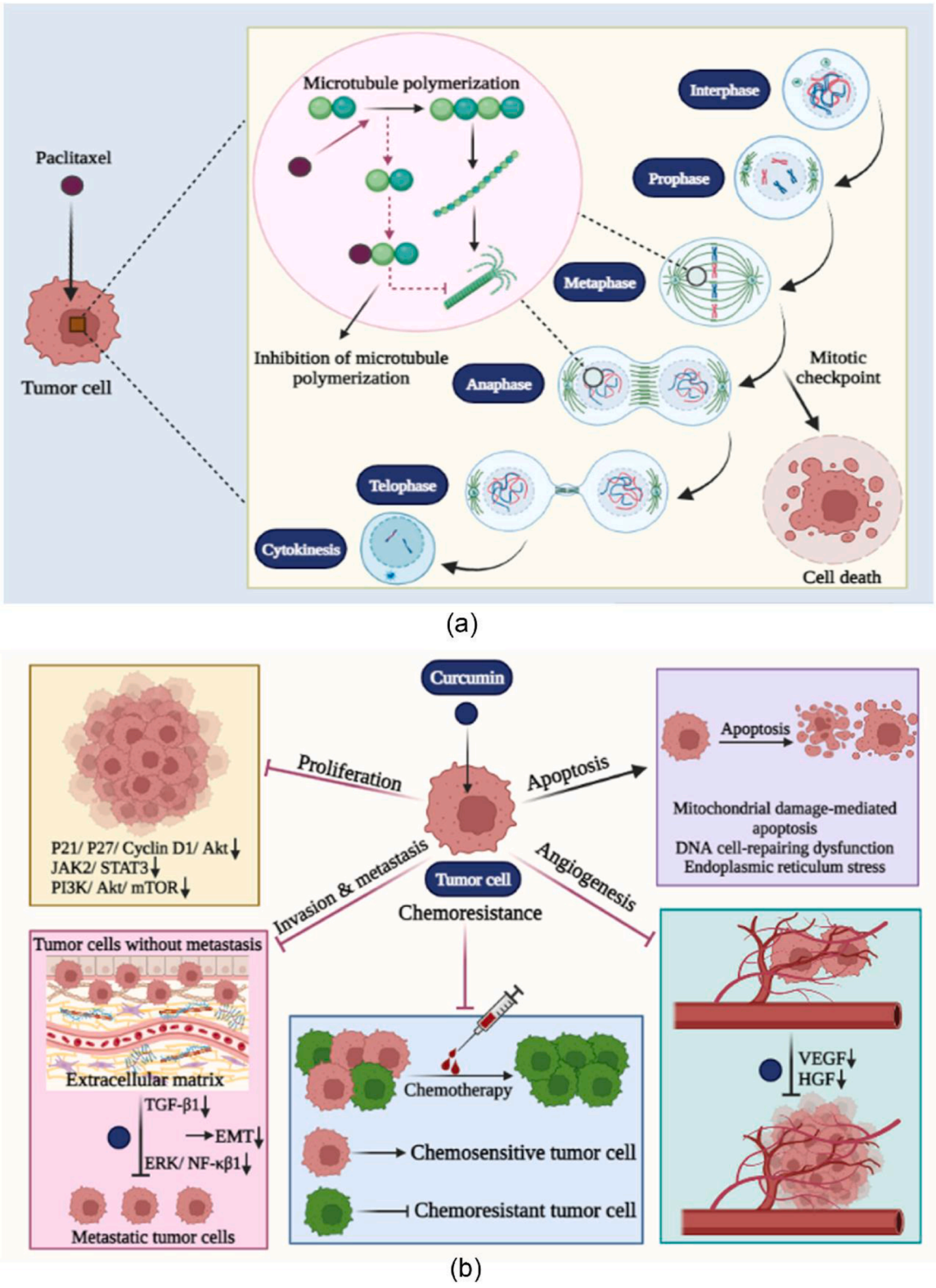

Fig. 3. Graphical presentation of the proposed action of Paclitaxel (a); and Curcumin (b). (reproduced with permission from Ref. [48]).

pharmacokinetics of native curcumin. The optimized CU1-LSLN formulation displayed a particle size of 122.10 ± 6.63 nm, a PDI of 0.19 ± 0.02, and a zeta potential of −36.30 ± 1.25 mV, while encapsulation efficiency and drug loading were 94.98 ± 0.90% and 4.53 ± 0.69%, respectively. Fluorescence imaging studies revealed markedly enhanced uptake in MHCC-97H cells, with internalization 3.24 times higher than curcumin and 2.98 times higher than CU1 alone after 3 h. These nanoparticles demonstrated inhibition of proliferation, migration, and invasion, along with apoptosis induction. Although mechanistic associations with pathways such as NF-κB, COX-2, MMP-2, MMP-9, and uPA were reported, further validation using pathway-specific assays is required to confirm causality. Pharmacokinetic evaluation indicated

substantially increased systemic exposure, with AUC values increased by 69.9-fold for curcumin and 85.9-fold for CU1 compared to free drugs. However, such large fold increases should be interpreted cautiously, as low baseline solubility of free curcumin may exaggerate relative improvements, and standardized dose normalization is essential for accurate comparison. Histological analysis indicated no evident liver toxicity, supporting preliminary safety [50].

To enhance receptor-mediated targeting toward HCC, cantharidin-loaded SLNs were engineered with glycyrrhetinic acid (GA) and folate (FA) ligands, individually or in combination, using ultrasonic emulsion dispersion. The formulations (CSLNs, GA-CSLNs, FA-CSLNs, and GA-FA-CSLNs) displayed particle sizes of 75–110 nm, zeta potentials near −10 mV, and entrapment efficiencies exceeding 95%. Hemolysis evaluation demonstrated negligible hemolytic activity (Fig. 4I), supporting compatibility with intravenous administration. Apoptosis induction in HepG2 cells (Fig. 4II and III) showed dose-dependent increases across all SLN formulations, with FA-CSLNs and GA-CSLNs demonstrating stronger apoptotic effects than GA-FA-CSLNs. While differences in efficacy were attributed to formulation-specific interactions, the proposed mechanism (e.g., GA-induced protective autophagy) requires further experimental validation. In vivo tumor suppression studies demonstrated high inhibition rates (96.46% for GA-FA-CSLNs and 89.92% for FA-CSLNs), confirming enhanced targeting efficiency and therapeutic potential [51].

Celecoxib-loaded SLNs were produced using an ultrasonic melt-emulsification method to improve the therapeutic utility of this selective COX-2 inhibitor. Formulations prepared with different lipid matrices yielded particle sizes spanning 238 to 757 nm, where particles at the higher end fall within the submicron range and may influence biodistribution behavior. Zeta potentials between −30 and −66.7 mV indicated stable colloidal systems, while entrapment efficiencies ranged from 86.76% to 96.6%. Release studies demonstrated controlled, burst-free drug delivery, with near-complete release within 24 h for optimized formulations. Cytotoxicity assays across HT29, Daoy, and HepG2 cells revealed sustained antiproliferative effects. Although initially developed for colon-targeted chemoprevention, the observed activity in HepG2 cells suggests potential applicability in liver cancer therapy; however, cancer-specific targeting and in vivo validation remain limited [52].

Collectively, these studies demonstrate that rational SLN design strategies including PEGylation, ligand functionalization, and lipid-matrix optimization can significantly enhance pharmacokinetic stability, tumor targeting, and anticancer efficacy in HCC models. However, most evidence is derived from in vitro or short-term in vivo studies, with limited use of clinically relevant models such as orthotopic or patient-derived systems. In addition, critical translational considerations, including sterility, endotoxin control, hemocompatibility, protein corona formation, and large-scale manufacturability, are rarely addressed. Variability in formulation design and experimental conditions further complicates cross-study comparison. Therefore, future investigations should emphasize standardized evaluation protocols, robust mechanistic validation, and translational feasibility to advance SLN-based therapies toward clinical application in hepatocellular carcinoma.

4.3. Solid lipid nanoparticle–mediated drug delivery systems for colorectal cancer treatment

Colorectal cancer remains a major clinical challenge due to limited drug permeability across the intestinal barrier and dose-dependent toxicity of conventional chemotherapeutics. SLNs have emerged as an effective strategy to enhance drug solubility, facilitate mucosal penetration, and improve intracellular drug retention, thereby increasing therapeutic efficiency in colorectal cancer treatment.

Quercetin-loaded SLNs (QuR-SLNs) were optimized using a Box–Behnken design to maximize encapsulation efficiency and minimize particle size. The optimized formulation exhibited high entrapment efficiency (97.8 ± 1.16%) and a mean particle size of 132.16 ± 4.1 nm. Structural characterization indicated partial crystallinity of quercetin within the lipid matrix. In vitro studies in Caco-2 cells demonstrated enhanced anticancer activity with an IC_{50} of 49 μM, along with morphological evidence of apoptosis. While these findings indicate improved efficacy, the mechanistic basis of apoptosis induction requires further validation through pathway-specific assays, and results derived from a single cell model may limit broader applicability [53].

To enhance colon-specific targeting, irinotecan (IRN) and daidzein (DZN) were co-encapsulated in SLNs with surface modification using hyaluronic acid (HA), bovine serum albumin (BSA), and an additional chitosan coating to improve epithelial interaction. The engineered nanoparticles exhibited nanoscale size, favorable zeta potential, and high entrapment efficiency. In vitro release studies showed biphasic drug release behavior. In HT-29 cells, HA-BSA-modified SLNs demonstrated significant cytotoxicity (75 μg/mL), inducing 67.8% G0/G1 arrest and increased apoptosis. Gene expression analysis indicated modulation of tumor-associated markers. Although these results suggest enhanced receptor-mediated targeting, the extent of specificity and in vivo targeting efficiency requires further validation, particularly in clinically relevant models [54].

Ethyl protocatechuate (PCAEE)-loaded SLNs were developed to improve bioavailability and anticancer activity. The optimized formulation showed a particle size of ~190 nm, PDI of 0.150 (indicating a narrow size distribution), and zeta potential of approximately −20 mV. Release studies demonstrated an initial burst followed by sustained release, and stability was maintained over three months. Cytotoxicity studies in CaCo-2 cells showed dose-dependent reduction in viability, while minimal toxicity was observed in healthy cells. Enhanced membrane penetration further supported improved delivery. However, translation of these findings requires evaluation in more complex biological systems and assessment of long-term safety [55].

A PEGylated SLN system was developed to improve the therapeutic performance of 5-fluorouracil (5-FU). The optimized formulation exhibited nanoscale particle size and improved colloidal stability, with enhanced drug encapsulation. In HCT-116 cells, PEGylated 5FU-SLN4 reduced the IC_{50} to 7.4 μM compared with 17.7 μM for free 5-FU, indicating improved cytotoxicity. Pharmacokinetic studies showed a 3.6-fold increase in AUC, and in vivo studies demonstrated enhanced tumor growth inhibition without significant toxicity. Western blot analysis (Fig. 5A–C) revealed suppression of EGFR and downstream signaling pathways (AKT and STAT3), suggesting inhibition of oncogenic signaling. However, while pathway modulation is evident, the direct causality between SLN delivery and specific molecular mechanisms requires further validation using controlled mechanistic studies [56].

Collectively, these studies demonstrate that SLN-based formulations can significantly enhance drug solubility, targeting efficiency, and anticancer efficacy in colorectal cancer models. However, most studies remain limited to in vitro or short-term in vivo evaluations, with insufficient use of clinically relevant models. Variability in formulation design, surface modification, and experimental conditions also complicates direct comparison across studies. In addition, key translational considerations including large-scale manufacturing, sterility, stability during gastrointestinal transit, and reproducibility are often not addressed. Therefore, future work should focus on standardized evaluation protocols, mechanistic validation, and translational feasibility to support clinical development of SLN-based colorectal cancer therapies.

4.4. Solid lipid nanoparticles as targeted nanocarriers for breast cancer management

Breast cancer remains a leading cause of cancer mortality in women worldwide and often requires high-dose chemotherapy associated with systemic toxicity. SLNs provide a versatile platform to improve therapeutic precision through enhanced drug encapsulation, controlled

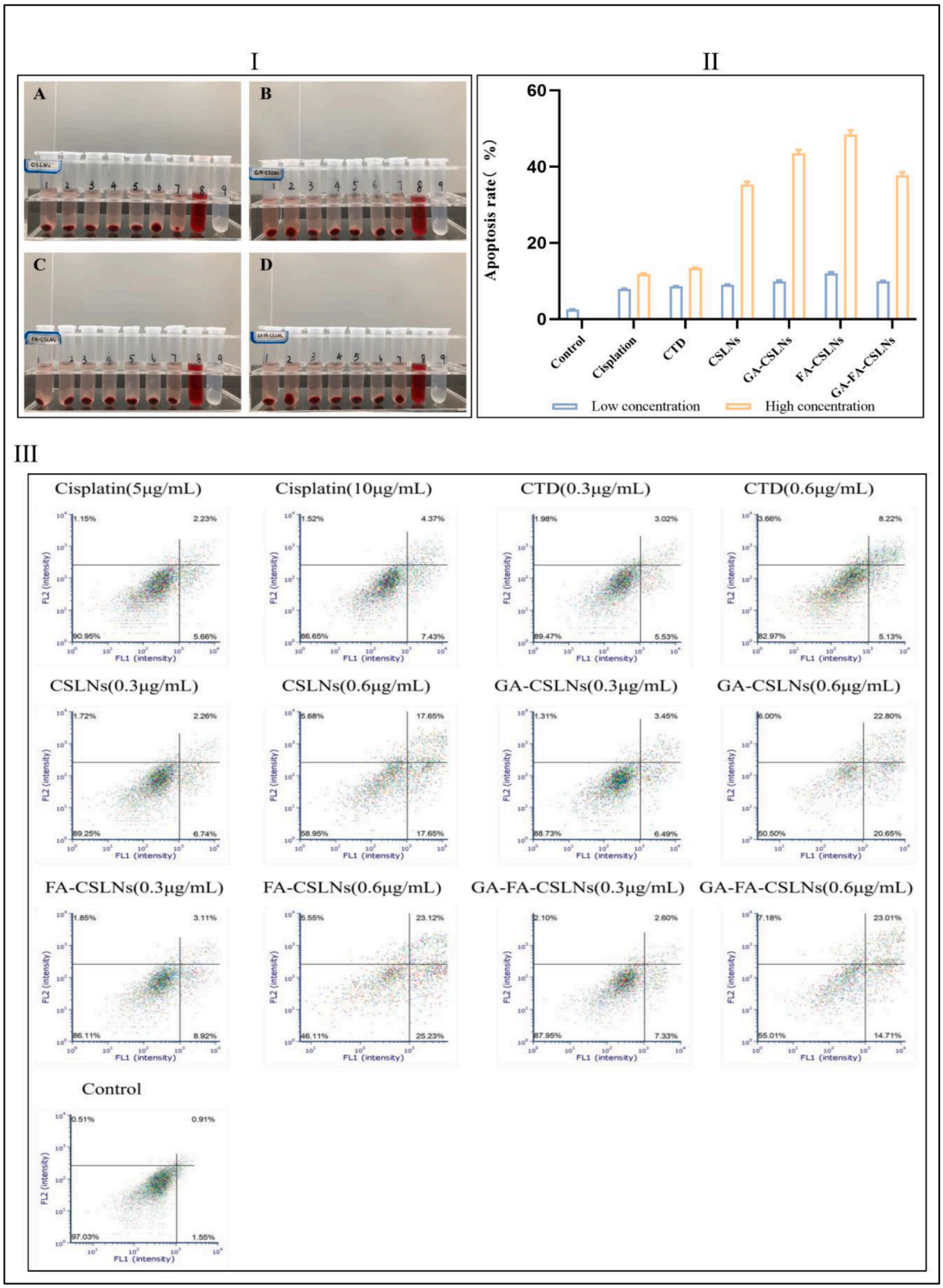

Fig. 4. I. Hemocompatibility evaluation of CTD-loaded SLNs. Visual observation of erythrocyte suspensions after incubation with (A) CSLNs, (B) GA-CSLNs, (C) FA-CSLNs, and (D) GA-FA-CSLNs confirms negligible hemolysis within the tested dose range.
II. Quantitative apoptotic response of HepG2 cells following treatment with CTD-loaded SLNs at varying concentrations. Data are expressed as mean ± SD (n = 3).
III. Flow-cytometry scatter plots demonstrating apoptosis levels in HepG2 cells after exposure to CSLNs and ligand-modified SLNs, indicating enhanced apoptotic induction with receptor-targeted formulations (reproduced with permission from Ref. [51]).

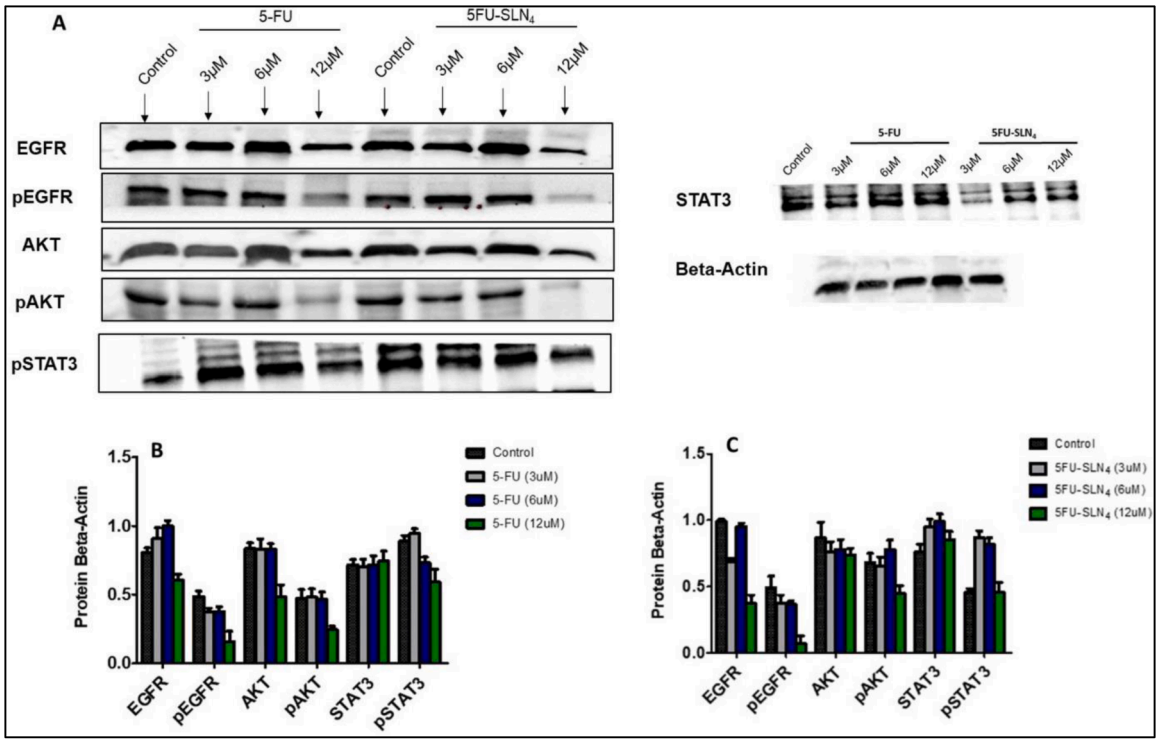

Fig. 5. Cellular apoptosis by 5FU-SLN4: Western blot analysis shows protein expression after 48 h treatment (A), with beta-actin as loading control. Quantitative expression changes for 5-FU (B) and 5FU-SLN4 (C) in HCT-116 cells are shown. Data presented as mean ± SD (reproduced with permission from Ref. [56]).

release, and surface functionalization for receptor-mediated targeting. These systems have demonstrated potential to improve pharmacokinetics, bioavailability, and intracellular accumulation of anticancer agents.

Lysine-modified epirubicin-loaded SLNs were developed to enhance cellular interaction through surface functionalization. The nanoparticles exhibited a mean size of ~148.5 nm with an entrapment efficiency of 86.1%. Structural characterization confirmed successful lysine conjugation, and controlled drug release was observed. Cytotoxicity studies in breast cancer cells showed reduced IC_{50} values compared to the free drug, indicating improved uptake and antiproliferative activity. However, the extent to which lysine modification alone contributes to enhanced efficacy requires further validation through comparative mechanistic studies [57].

Confocal microscopy analysis demonstrated enhanced intracellular retention of tamoxifen citrate (TC) delivered via SLNs. As shown in

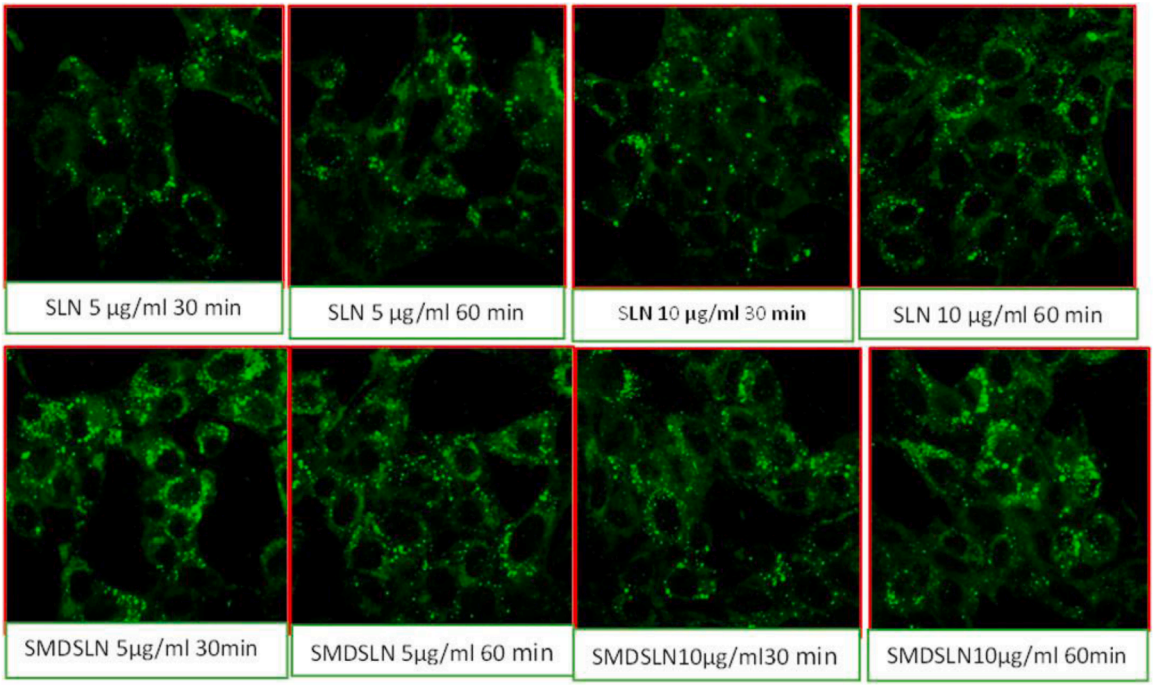

Fig. 6. Qualitative cell uptake of developed SLN formulations by confocal microscopy (reproduced with permission from Ref. [58]).

(Fig. 6), free TC exhibited rapid loss of fluorescence, whereas SLN formulations (D-SLNs and receptor-targeted SMD-SLNs) showed sustained intracellular retention up to 48 h. Enhanced uptake in SMD-SLNs was attributed to receptor-mediated endocytosis. In addition, transferrin-conjugated tamoxifen-loaded SLNs showed improved physicochemical characteristics (zeta potential: −7.0 ± 0.05 mV to −20.5 ± 0.05 mV; entrapment efficiency: 73 ± 2%) and superior cellular uptake in MCF-7 cells. Sustained release up to 120 h further supports their targeting potential. While these findings indicate improved intracellular delivery, quantitative validation of receptor specificity and in vivo targeting efficiency remains limited [58].

β-Carotene-loaded SLNs were formulated to overcome instability and low solubility issues. The optimized formulation showed good physical stability over six months and a zeta potential of −26.3 ± 1.3 mV, with diffusion-controlled release. Enhanced cytotoxicity in MCF-7 cells compared with free β-carotene suggests improved intracellular bioavailability. However, as β-carotene exhibits relatively modest intrinsic anticancer activity, the observed improvements should be interpreted in the context of formulation-enhanced delivery rather than strong inherent cytotoxicity [59].

For triple-negative breast cancer (TNBC), folic acid-functionalized SLNs co-encapsulating docetaxel and erlotinib demonstrated particle sizes <200 nm with PDI <0.35 (indicating moderate dispersity) and ~80% entrapment efficiency. These systems showed enhanced bioaccessibility and synergistic cytotoxicity, supported by combination index values. Mechanistic observations, including ROS elevation and mitochondrial disruption, suggest enhanced apoptotic signaling. However, confirmation of synergistic interactions under standardized conditions and validation in clinically relevant TNBC models are necessary [60].

Magnetite-containing SLNs were investigated for magnetically guided delivery of doxorubicin. Although drug entrapment was lower compared with conventional SLNs, controlled release and improved cytotoxicity in MCF-7 cells were observed. Enhanced therapeutic performance was attributed to increased cellular association under magnetic influence. However, the practical applicability of magnetic targeting in clinical settings requires further evaluation, including considerations of field strength, targeting precision, and safety [61].

Gefitinib-loaded SLNs prepared by emulsification–evaporation exhibited particle sizes of 472 ± 7.5 nm, which fall within the submicron range rather than the strict nanoscale domain. While these systems demonstrated sustained release and enhanced apoptotic signaling compared to free drug, the larger particle size may influence biodistribution and limit intravenous applicability. Increased expression of apoptosis-related markers (p53, caspase-3, and caspase-9) was observed; however, direct mechanistic linkage between SLN delivery and pathway modulation requires further validation [62].

Additionally, combination therapy using etoposide with quercetin-loaded SLNs demonstrated enhanced apoptotic activity in MDA-MB-231 cells. However, the absence of quantitative synergy metrics limits interpretation of the interaction between the two agents, and further studies are required to confirm additive or synergistic effects [63].

Collectively, these studies demonstrate that SLNs can enhance drug targeting, intracellular uptake, and therapeutic efficacy in breast cancer models through strategies such as ligand functionalization, co-delivery, and magnetic guidance. However, most findings are limited to in vitro or short-term in vivo studies, and variability in formulation design complicates cross-study comparison. In addition, key translational considerations including large-scale manufacturing, sterility, hemocompatibility, and long-term safety are often not addressed. Therefore, future research should focus on standardized evaluation models, mechanistic validation, and translational feasibility to support clinical development of SLN-based breast cancer therapies.

4.5. Solid lipid nanoparticle–driven targeted therapies for prostate cancer

Prostate cancer presents major treatment challenges due to poor drug permeability into tumor tissues, systemic toxicity of chemotherapeutics, and limited bioavailability of orally administered drugs. SLNs provide a versatile nanocarrier platform to enhance therapeutic selectivity, protect drug cargo, and improve pharmacokinetic behavior. Recent studies incorporate targeting ligands, surface engineering, and formulation optimization to improve intracellular drug delivery and anticancer effectiveness.

To improve receptor-mediated targeting, SLNs were engineered for delivery of doxorubicin to prostate cancer cells overexpressing luteinizing-hormone-releasing-hormone (LHRH) receptors. PEGylated lipids were conjugated with an LHRH-specific decapeptide and incorporated into nanoparticles prepared via solvent emulsification–evaporation. Physicochemical analyses confirmed suitable particle size, zeta potential, and stable drug loading. In LHRH-positive PC3 and SKBR3 cells, peptide-modified SLNs showed enhanced cytotoxicity and cellular uptake compared with free drug and non-modified SLNs. Flow cytometry demonstrated increased apoptosis, and sustained release supported prolonged drug availability. While these results suggest effective receptor-mediated targeting, quantitative validation of targeting specificity and in vivo biodistribution remains limited [64].

A quality-by-design (QbD) approach was employed to develop abiraterone acetate-loaded SLNs to address poor oral bioavailability. Optimization using Box–Behnken design yielded formulations with improved release and physicochemical characteristics. In PC-3 cells, SLNs demonstrated significantly higher cytotoxicity, with approximately 12.5-fold reduction in IC_{50} compared with free drug (Fig. 7IA). Confocal microscopy confirmed enhanced cellular uptake (Fig. 7IB and C), while ex vivo studies demonstrated a 3.75-fold increase in intestinal permeability and deeper tissue penetration up to 10 μm (Fig. 7II A–D). These findings indicate improved absorption and transport; however, translation of ex vivo permeability results to in vivo pharmacokinetics requires careful validation under physiological conditions [65].

Xanthohumol-loaded SLNs (XH-SLNs) were developed to enhance systemic exposure and anticancer activity. The optimized formulation exhibited a particle size of 108.60 nm, PDI 0.22 (indicating relatively narrow distribution), and zeta potential of −12.70 mV, with high entrapment efficiency. Sustained release and strong cytotoxicity in PC-3 cells were observed. Pharmacokinetic studies indicated improvements in Cmax, AUC, half-life, and mean residence time. Relative bioavailability increased substantially compared with the unformulated drug. However, extremely large percentage increases (e.g., >4000%) should be interpreted cautiously, as low baseline solubility and absorption of the free drug may exaggerate relative gains. Therefore, dose normalization and appropriate controls are essential for accurate comparison [66].

Collectively, these studies demonstrate that ligand-modified and QbD-optimized SLNs can enhance prostate cancer drug delivery through improved targeting, absorption, and pharmacokinetic performance. However, most studies remain limited to in vitro, ex vivo, or short-term in vivo models, with insufficient validation in clinically relevant systems. In addition, key translational considerations including large-scale manufacturability, sterility, long-term stability, and systemic safety are rarely addressed. Variability in formulation design further complicates direct comparison across studies. Therefore, future research should focus on standardized evaluation models, mechanistic validation, and translational feasibility to support clinical development of SLN-based prostate cancer therapies.

4.6. Solid lipid nanoparticles for enhanced therapeutic efficacy in cervical cancer

Cervical cancer remains a major health challenge, particularly in low-resource settings where late diagnosis and limited therapeutic

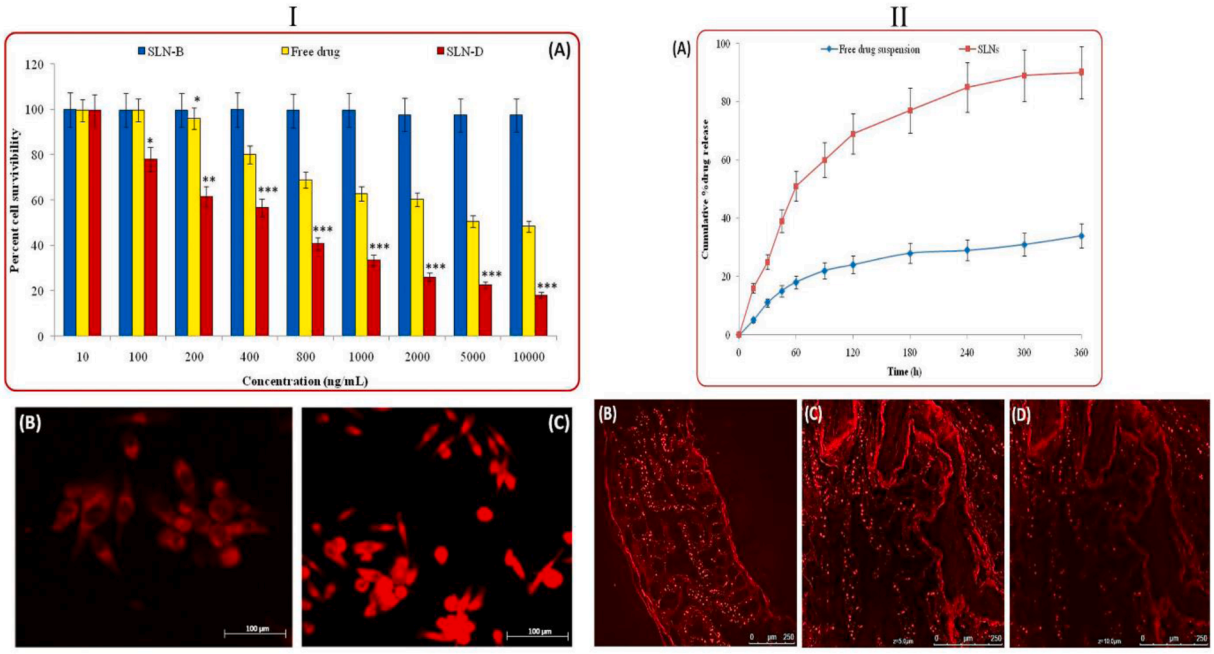

Fig. 7. I(A) Cell cytotoxicity of abiraterone acetate–loaded SLNs compared with free drug suspension on PC-3 cells determined by MTT assay. Data are presented as mean ± SD (n = 3); $p < 0.05$, p < 0.01, $p < 0.001$ vs. free drug. I(B–C) Confocal laser scanning microscopy images demonstrating enhanced cellular uptake of Rhodamine B–loaded SLNs in PC-3 cells compared with plain Rhodamine B dye after 4 h incubation. Fig. 7 II(A) Ex vivo intestinal permeation profile of abiraterone acetate from optimized SLNs and pure drug suspension using rat duodenum and jejunum; data presented as mean ± SD (n = 3); $p < 0.05$ vs. free drug. II (B) Confocal image of intestinal tissue showing localization of Rhodamine-loaded SLNs. II (C–D) z-stacking images at 5 μm and 10 μm depth indicating penetration of intact SLNs into intestinal tissue. (reproduced with permission from Ref. [65]).

accessibility contribute to poor clinical outcomes. Conventional chemotherapy is often limited by low tumor selectivity, systemic toxicity, and rapid drug clearance. SLNs have therefore emerged as promising delivery systems capable of improving drug stability, bioavailability, and intratumoral accumulation.

Polyoxometalate-loaded SLNs (P_5W_{30}-SLNs) were developed using biocompatible lipids to enhance the therapeutic potential of P_5W_{30}. The optimized formulation exhibited a particle size of 160.5 ± 8.61 nm, zeta potential of −32.57 ± 6.44 mV, and a PDI of 0.3814 ± 0.096, indicating moderate dispersity. Structural characterization (SEM, TEM, FT-IR, and DSC) confirmed compatibility between the drug and lipid matrix. In vitro evaluation in HeLa cells demonstrated enhanced cytotoxicity, with IC_{50} reduced to 3.02 ± 2.14 μg/mL compared with 7.93 ± 5.08 μg/mL for free P_5W_{30}. Comet assay results indicated DNA damage, and flow cytometry suggested cell-cycle arrest. However, while these findings indicate enhanced genotoxic and antiproliferative effects, detailed mechanistic validation of apoptotic pathways and molecular targets remains limited [67].

Further validation in an in vivo murine model demonstrated improved therapeutic performance. As shown in (Fig. 8A), treatment

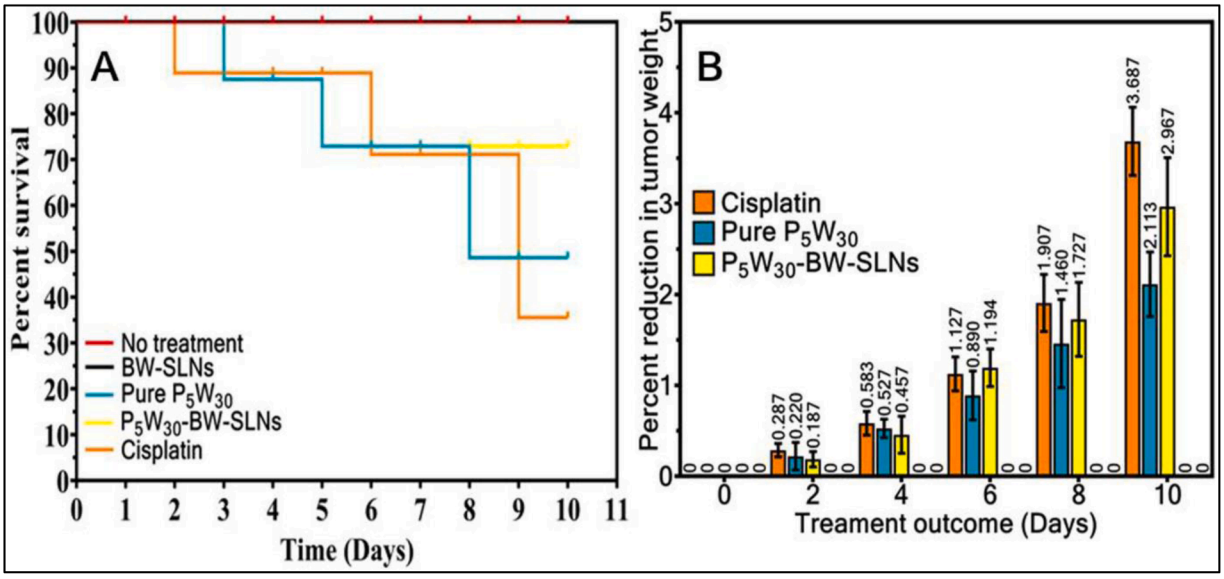

Fig. 8. (A) Survival rates and (B) tumor weight reduction in HeLa-bearing mice treated with P_5W_{30}, P_5W_{30}-BW-SLNs, or cisplatin over 10 days (reproduced with permission from Ref. [67]).

with P_5W_{30}-BW-SLNs resulted in improved survival compared with free drug and cisplatin over a 10-day period. Tumor weight reduction (Fig. 8B) was also more pronounced in the SLN-treated group (2.967 ± 0.543%) compared with free P_5W_{30} (2.113 ± 0.402%), indicating enhanced antitumor efficacy ($p < 0.05$). While these results support improved intratumoral retention and therapeutic activity, the relatively short study duration and lack of long-term survival or toxicity evaluation limit the assessment of sustained therapeutic benefit and safety.

Collectively, these findings demonstrate that SLN-based formulations can enhance drug delivery, intracellular activity, and antitumor efficacy in cervical cancer models. However, current evidence is largely limited to short-term in vitro and in vivo studies, with insufficient evaluation of long-term safety, pharmacokinetics, and clinically relevant models. In addition, key translational considerations such as large-scale production, sterility, and systemic toxicity remain underexplored. Therefore, future studies should focus on standardized evaluation protocols, detailed mechanistic validation, and long-term therapeutic assessment to support clinical translation of SLN-based cervical cancer therapies.

4.7. Solid lipid nanoparticle–integrated strategies for melanoma intervention

Melanoma is one of the most aggressive skin malignancies, characterized by rapid metastasis and resistance to conventional therapies. SLNs offer a promising platform to enhance drug stability, improve cellular uptake, and enable targeted delivery for melanoma treatment.

Hydroquinone–stearic acid–based SLNs were developed using a microemulsification method, where esterified hydroquinone was combined with surfactants and co-surfactants, followed by rapid dispersion to yield nanoscale particles. Spectroscopic analyses confirmed compatibility of formulation components, while dynamic light scattering indicated suitable particle size distribution and colloidal stability. In vitro studies in COLO-38 melanoma cells demonstrated dose-dependent inhibition of proliferation at SLN concentrations of 1.25–7.5 μL/mL. At 5 μL/mL, increased apoptotic activity was observed, accompanied by enhanced cleavage of PARP-1 (Fig. 9A), suggesting activation of apoptotic pathways.

Further molecular evaluation showed upregulation of p53 and its downstream effector p21ˆWAF1/Cip1 (Fig. 9B), indicating involvement of cell-cycle regulatory mechanisms. In addition, SLN treatment reduced migration and invasion of melanoma cells, suggesting potential antimetastatic effects. While these findings support enhanced anticancer activity, the direct mechanistic linkage between SLN-mediated delivery and specific signaling pathways requires further validation using targeted molecular and pathway-specific assays.

Safety evaluations in fibroblast and immune cell models demonstrated acceptable cytocompatibility and minimal immunomodulatory effects. However, these assessments remain limited to in vitro conditions, and comprehensive in vivo toxicological and immunological evaluation is necessary to confirm systemic safety [68].

Overall, these findings demonstrate that SLN-based formulations can enhance intracellular delivery, induce apoptosis, and reduce metastatic potential in melanoma models. However, current evidence is largely restricted to in vitro studies, with limited validation in clinically relevant in vivo models. In addition, variability in formulation strategies and lack of standardized evaluation frameworks complicate cross-study comparison. Critical translational considerations, including large-scale production, long-term safety, and regulatory feasibility, remain insufficiently addressed. Therefore, future studies should focus on mechanistic validation, standardized testing protocols, and comprehensive in vivo evaluation to support clinical translation of SLN-based melanoma therapies.

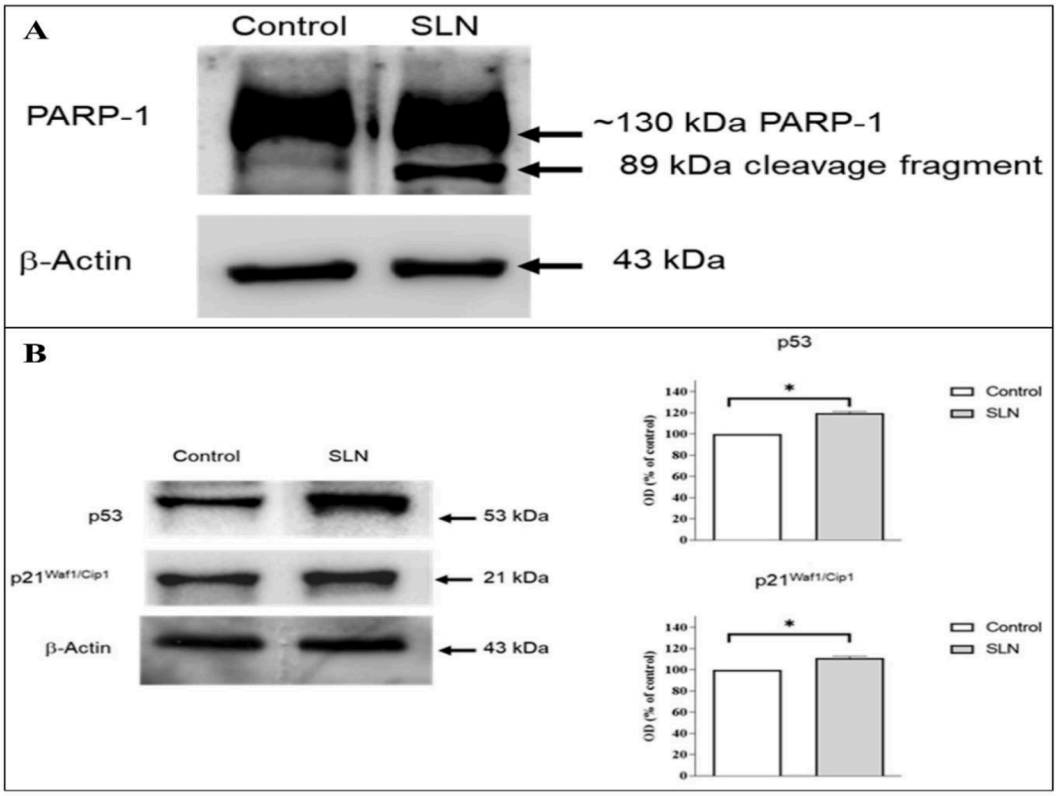

Fig. 9. (A) PARP-1 cleavage in COLO-38 melanoma cells following SLN treatment (5 μL/mL, 24 h). (B) Upregulation of p53 and p21ˆWAF1/Cip1 in COLO-38 cells after SLN treatment, quantified as optical density (% of control). β-Actin served as loading control (*$p < 0.01$ vs. control) (reproduced with permission from Ref. [68]).

4.8. Solid lipid nanoparticles for localized and mucoadhesive delivery in bladder cancer

Intravesical therapy for bladder cancer is often limited by rapid drug wash-out during urination and the low permeability of the urothelial barrier. To address these challenges, quercetin-loaded SLNs have been developed to enable localized and prolonged drug exposure. Stearic acid was used as the lipid core, while mucoadhesive polymers such as chitosan, HPMC, and Carbopol were incorporated into poloxamer-407 in situ gels to enhance tissue adhesion and residence time.

The formulations exhibited favorable physicochemical characteristics, including high colloidal stability, excellent encapsulation efficiency (>97%), and sustained drug release for up to 142 h. DSC analysis confirmed thermal stability of the systems. In vitro studies using T-24 bladder cancer cells demonstrated strong concentration-dependent cytotoxicity, with IC_{50} values ranging from 1.6 to 8.9 μg/mL, indicating effective antiproliferative activity. However, the translation of in vitro cytotoxicity to in vivo therapeutic performance requires further validation under physiologically relevant intravesical conditions. Ex vivo evaluations demonstrated strong mucoadhesive performance on bovine urinary bladder mucosa. As shown in (Fig. 10 IA), chitosan-coated SLNs exhibited enhanced tissue adherence compared to uncoated systems, while incorporation into mucoadhesive gels resulted in the highest fluorescence retention following repeated artificial urine washings. Quantitative analysis (Fig. 10 IB) confirmed that gel-based coated systems retained >50% of fluorescence after the final washing cycle, indicating prolonged residence.

Confocal microscopy further revealed improved mucosal penetration behavior. As illustrated in (Fig. 10 IIA), coated and gel-formulated SLNs showed increased fluorescence infiltration, while depth–intensity profiles (Fig. 10 IIB) indicated penetration up to ~350 μm for optimized formulations. These findings suggest that the combination of mucoadhesive coating and in situ gel systems enhances both retention and tissue penetration. Nevertheless, the extent to which these ex vivo observations translate to in vivo intravesical delivery remains to be established. Rheological analysis demonstrated gelation near physiological temperature (~25 °C) and erosion times of 24–27 h, supporting suitability for sustained intravesical application [69]. Collectively, these results indicate that quercetin-loaded SLNs integrated with mucoadhesive gels can improve drug residence, mucosal penetration, and local therapeutic efficacy in bladder cancer models.

A consolidated comparison of SLN formulations across different cancer types, including lipid composition, physicochemical characteristics, and therapeutic performance, is presented in Table 2, highlighting the critical influence of formulation design on biological outcomes.

Despite these promising findings, many studies remain limited to in vitro and ex vivo evaluations, with insufficient validation in clinically relevant in vivo models. The limited use of advanced models such as orthotopic and patient-derived xenograft (PDX) systems, along with inadequate survival and long-term toxicological analyses, further restricts the predictive value of current data. In addition, key translational considerations such as large-scale manufacturability, sterility, long-term stability, and reproducibility are not comprehensively addressed, and variability in formulation design complicates cross-study comparison.

To address these gaps, a comparative overview of representative in vivo studies, including formulation strategies, therapeutic outcomes,

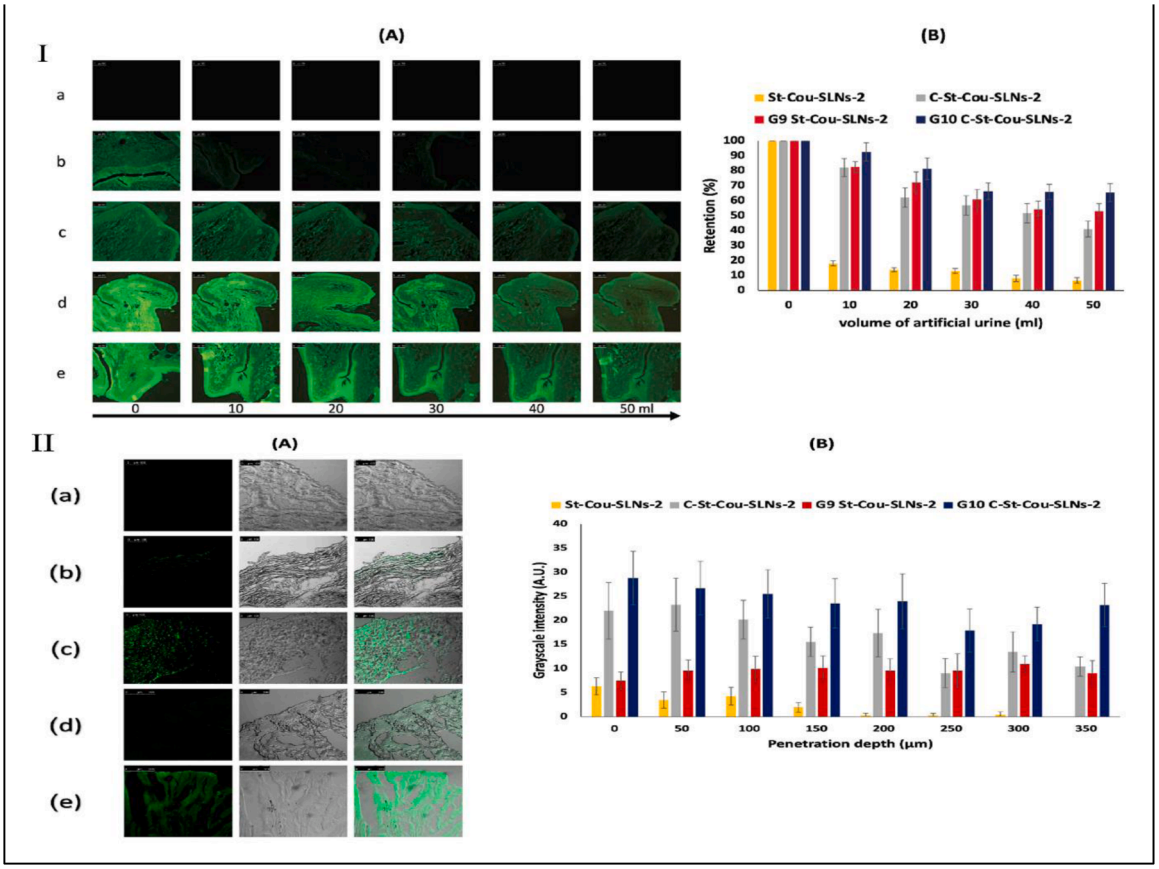

Fig. 10. **I(A)** Fluorescence images showing the retention of coumarin-6–labelled SLN formulations on bovine urinary bladder mucosa after washing with increasing volumes of artificial urine: (a) Control, (b) St-Cou-SLNs-2, (c) C-St-Cou-SLNs-2, (d) G9St-Cou-SLNs-2, (e) G10C-St-Cou-SLNs-2. **I(B)** Retention (%) after successive washing cycles. **II(A)** CLSM images illustrating the penetration of fluorescent SLN formulations into bovine urinary bladder tissue: (a) Control, (b) St-Cou-SLNs-2, (c) C-St-Cou-SLNs-2, (d) G9St-Cou-SLNs-2, (e) G10C-St-Cou-SLNs-2. **II(B)** Fluorescence intensity versus penetration depth. Abbreviations: G9 – carbopol/poloxamer-407 gel; G10 – chitosan/poloxamer-407 gel; Cou – coumarin-6; St – stearic acid; C – coated; SLNs – solid lipid nanoparticles. (reproduced with permission from Ref. [69]).

Table 2
Solid lipid nanoparticle-based drug delivery strategies in cancer therapy: formulation approaches, physicochemical features, and therapeutic outcomes.

Drug / Payload	Cancer Type	Lipid System / Surface Strategy	Particle Size (nm) / Zeta Potential	Key Biological Outcome	Ref.
4-Hexylresorcinol	Lung cancer (A549, HeLa, CT-26)	Hot-melt homogenization SLNs	169.4–644.8 nm / −19.8 to −40.3 mV	Stronger antiproliferative activity vs. free drug	[47]
Paclitaxel + Curcumin	NSCLC	Dual-drug HPH-SLN	n/a	Synergistic tumor inhibition in vitro & in vivo	[48]
Curcumin	Lung cancer	Sonication with stearic/palmitic/ lauric acids	14.7–502.8 nm / negative charge	Smallest SLNs showed highest cytotoxicity	[49]
CU1 (curcumin derivative)	Hepatocellular carcinoma	PEGylated long-circulating SLNs (HSPC/DSPE-PEG2000)	122 nm / −36.3 mV	69.9-fold ↑AUC; improved apoptosis & migration inhibition	[50]
Cantharidin	Hepatocellular carcinoma	GA/FA dual-ligand modified SLNs	75–110 nm / ~−10 mV	Dose-dependent apoptosis; up to 96% tumor inhibition	[51]
Celecoxib	HepG2, colon, brain cancers	Ultrasonic melt-emulsification SLNs	238–757 nm / −30 to −66.7 mV	Sustained release; strong cytotoxicity up to 72 h	[52]
Quercetin	Colorectal (Caco-2)	Box-Behnken optimized SLNs	132 nm	IC_{50} = 49 μM; apoptosis-mediated cell death	[53]
Irinotecan + Daidzein	Colorectal (HT-29)	HA-BSA-chitosan coated SLNs	Nanoscale / high EE%	67.8% G0/G1 arrest; enhanced mucosal penetration	[54]
Ethyl Protocatechuate	Colorectal cancer	Tween-80 stabilized SLNs	190 nm / −20 mV	Dose-dependent cytotoxicity; selective vs healthy cells	[55]
5-Fluorouracil	Colorectal (HCT-116)	PEGylated SLNs	n/a	2.3-fold higher cytotoxicity; EGFR/ AKT/STAT3 inhibition	[56]
Epirubicin	Breast cancer	Lysine-modified SLNs	~148.5 nm	Improved uptake; lower IC50 than free drug	[57]
Tamoxifen	Breast cancer (MCF-7)	Transferrin-decorated SLNs	−7 to −20 mV	Strong receptor-mediated uptake; 120 h retention	[58]
β-Carotene	Breast cancer (MCF-7)	Palmitic acid SLNs	–26.3 mV	Enhanced bioavailability & stability	[59]
Docetaxel + Erlotinib	TNBC	FA-functionalized dual-drug SLNs	<200 nm / PDI <0.35	Synergistic cytotoxicity; anti-migration	[60]
Doxorubicin	Breast cancer (MCF-7)	Magnetite-embedded SLNs	n/a	Higher apoptosis due to magnetic targeting	[61]
Gefitinib	Breast cancer (MCF-7)	Emulsion-evaporation SLNs	472 nm / −15.2 mV	↑p53, caspase-3/9 → apoptosis	[62]
P_5W_{30}	Cervical cancer (HeLa)	SLNs (biocompatible lipids)	160.5 nm / −32.6 mV	50% ↓IC_{50}; improved survival & tumor suppression	[67]
Hydroquinone–stearic acid	Melanoma (COLO-38)	Microemulsion-SLNs	n/a	PARP-1 cleavage; p53/p21↑; ↓ metastasis	[68]
Quercetin	Bladder cancer (T-24)	Mucoadhesive SLNs + in-situ gel	High retention in mucosa	IC_{50}: 1.6–8.9 μg/mL; deep tissue penetration	[69]

and translational relevance of SLN systems across different cancer models, is presented in Table 3. These findings collectively emphasize the need for standardized evaluation protocols and robust in vivo validation to facilitate the clinical translation of SLN-based therapies.

5. Regulatory and industrial translation of SLN technologies

The clinical translation of SLNs relies on their recognition as fully characterized, reproducible, and quality-controlled therapeutic products rather than simple formulation enhancements. Regulatory bodies such as the FDA and EMA acknowledge that nanocarriers exhibit size- and surface-dependent biological interactions and therefore require specific evaluation beyond conventional drug products [83]. Key quality attributes that govern SLN safety and performance include particle-size distribution, polydispersity, surface charge, lipid crystallinity, drug retention, sterility, endotoxin content, and residual solvent levels. Robust characterization must employ complementary analytical modalities such as DLS, NTA, TEM/SEM, DSC, XRD, FT-IR, HPLC, and ICP-MS to ensure accurate assessment of structural and functional properties.

Industrial translation necessitates scale-up strategies capable of maintaining critical material attributes while ensuring batch-to-batch uniformity. High-pressure homogenization with controlled thermal profiles, membrane-contactor systems, and continuous microfluidic emulsification represent practical manufacturing routes delivering high throughput and reduced variability. In-line process analytical technologies (PAT) such as real-time DLS, inline viscometry, and Raman mapping are increasingly adopted to control critical process parameters during continuous production. Moreover, the implementation of regulatory quality frameworks including ICH Q8–Q11 supports a systematic Quality Risk Management approach, where design spaces are established using statistical and predictive modelling such as DoE and Monte-Carlo simulations [84]. Despite technological progress, challenges remain due to the absence of harmonized global standards for nanomedicine assessment, which leads to uncertainty during regulatory review. Successful industrialization of SLNs therefore requires both technological optimization and generation of comprehensive regulatory documentation that clearly correlates nanoscale structural attributes with clinical performance [85]. Despite promising preclinical outcomes, translation of SLNs into clinical applications remains limited. Key challenges include large-scale reproducibility, long-term stability, regulatory standardization, and variability in biological responses due to protein corona formation and patient-specific factors. Addressing these issues requires integration of quality-by-design approaches, advanced analytical tools, and standardized regulatory frameworks to ensure consistency and safety of SLN-based therapeutics.

6. Clinical landscape of SLN-based therapeutics

Although SLNs have shown remarkable promise in preclinical oncology, their advancement into the clinic has been gradual due to translational complexities inherent to nanomedicine. Nevertheless, several SLN-based formulations have achieved market approval in non-oncology areas, reinforcing their industrial feasibility [86]. In cancer therapy, SLN-enabled drug products have progressed into early-phase trials by demonstrating improved pharmacokinetic profiles, reduced systemic toxicity, and enhanced tumor uptake. Their lipidic composition facilitates favorable biodistribution, membrane interaction, and protection of labile molecules from metabolic degradation, while PEGylation enables prolonged blood residence and reduced opsonization. Ligand-functionalized SLNs exploiting receptors such as EGFR, folate receptor, LHRH receptor, and CD44 have shown dose-sparing effects and

Table 3
Representative in vivo performance of solid lipid nanoparticle systems in cancer therapy.

Drug / System	Cancer Model	Key Formulation Strategy	In Vivo Outcome	Translational Insight	Ref
Pterostilbene-loaded solid lipid nanoparticles	Lung cancer (mouse model)	Herbal compound encapsulation in lipid nanoparticles	Tumor inhibition: 64.55% vs 59.97% (free drug)	Improved efficacy with reduced systemic toxicity	[70]
Doxorubicin-loaded lipid nanoparticles	Breast cancer (murine model)	Lipid-based nanocarrier delivery	Tumor inhibition: 78.5% vs 56.8% (free drug)	Enhanced pharmacokinetics and reduced cardiotoxicity	[71]
Hispolon-loaded lipid nanocarriers	Hepatocellular carcinoma	Lipid nanocarrier system	Increased bioavailability (~2-fold) and tumor targeting	Improved oral delivery and liver accumulation	[72]
Irinotecan and Doxorubicin co-loaded lipid nanoparticles (hyaluronic acid-coated)	Colon cancer	Ligand-targeted co-delivery system	Reduced tumor marker levels and improved tissue recovery	Targeted delivery and enhanced therapeutic response	[73]
Paclitaxel-loaded peptide-targeted solid lipid nanoparticles	Triple-negative breast cancer (4T1 model)	Peptide-mediated targeting	~82% tumor reduction and reduced metastasis	Targeted therapy with anti-metastatic potential	[74]
Temozolomide-loaded solid lipid nanoparticles	Glioblastoma (orthotopic model)	Brain-targeted lipid nanoparticles	Reduced tumor size and increased brain drug levels	Improved blood–brain barrier penetration	[75]
Myricetin-loaded dual ligand-modified solid lipid nanoparticles (folic acid and chitosan)	Tumor-bearing mice	Dual ligand targeting strategy	Reduced tumor volume and angiogenesis	Enhanced targeting and anti-angiogenic activity	[76]
Transferrin-modified solid lipid nanoparticles	Lung cancer (xenograft model)	Receptor-mediated targeting	Significant tumor suppression	Improved cellular uptake and tumor targeting	[77]
Abiraterone-loaded solid lipid nanoparticles	Prostate cancer	Quality-by-design optimized formulation	Increased bioavailability and therapeutic efficacy	Improved oral delivery performance	[65]
Prodrug-loaded solid lipid nanoparticles (4NSG system)	Pancreatic cancer (patient-derived xenograft model)	Prodrug-based nanocarrier	~2-fold tumor reduction	Clinically relevant validation using PDX model	[78]
Paclitaxel and curcumin co-loaded solid lipid nanoparticles	Lung cancer (xenograft model)	Co-delivery system	78.42%vs 40.53% tumor inhibition	Synergistic therapy and resistance reduction	[79]
Transferrin-modified lipid nanoparticles (MGF system)	Lung cancer	Targeted nanoparticle delivery	Sustained drug release and tumor suppression	Improved pharmacokinetics and targeting	[80]
Paclitaxel and curcumin solid lipid nanoparticles	Lung cancer	Co-loaded nanoparticle system	Enhanced tumor targeting and efficacy	Improved therapeutic synergy	[81]
Glycyrrhetinic acid and folic acid dual-targeted solid lipid nanoparticles	Liver cancer	Dual ligand targeting	Strong tumor inhibition with low toxicity	Suitable for targeted intravenous delivery	[51]
Betulin-conjugated lipid nanoparticles	Breast cancer	Transporter-targeted nanoparticle system	Reduced tumor volume (765 vs 1450 mm^3)	Improved tumor localization and pharmacokinetics	[82]

improved intratumoral localization in animals [83].

However, several barriers must still be addressed for consistent clinical success. The tumor microenvironment often varies significantly between patients, limiting the predictive value of animal models and complicating EPR-based targeting. Protein corona formation in vivo may obscure targeting ligands and alter nanoparticle trafficking. Furthermore, regulatory expectations for chronic toxicity, immunogenicity, and nanoparticle accumulation require more extensive validation than conventional chemotherapeutics. As nanotoxicology standards mature and predictive preclinical models evolve, SLNs are expected to progress into late-stage trials, particularly for parenteral delivery of high-potency anticancer agents with narrow therapeutic indices [87].

7. Challenges, emerging innovations, and future opportunities

Despite substantial progress, SLN technology still faces mechanistic and translational challenges that restrict its widespread clinical adoption. Polymorphic transitions of lipids during storage can lead to drug expulsion and instability, while non-specific recognition by the reticuloendothelial system accelerates clearance and decreases therapeutic exposure. Heterogeneity of tumor vasculature can compromise passive targeting, and unpredictable protein corona formation may reduce specificity of actively targeted designs. In addition, reproducible large-scale manufacturing remains technically demanding, and long-term safety data are insufficient to fully predict chronic exposure risks in humans [88].

To address these limitations, next-generation SLNs are increasingly being engineered as stimuli-responsive or “smart” nanocarriers capable of responding to tumor-specific microenvironmental cues. These systems enable spatially controlled drug release, thereby enhancing tumor selectivity while minimizing systemic toxicity.

Among these, redox-responsive SLNs exploit the elevated intracellular glutathione (GSH) levels in cancer cells. For instance, a disulfide lipid-based SLN co-delivering Plk1 siRNA and 2-deoxyglucose (2-DG) demonstrated GSH-triggered cleavage of disulfide bonds, resulting in rapid intracellular payload release. This system effectively induced G2/M cell-cycle arrest and inhibited glycolysis, leading to enhanced antitumor activity in non-small cell lung cancer models [89]. pH-responsive SLNs represent another widely explored strategy, leveraging the acidic tumor microenvironment to trigger drug release or surface charge conversion. A lipid-coated nanoparticle system incorporating (2E)-4-(dioleostearin)-amino-4-carbonyl-2-butenonic acid exhibited pH-dependent charge switching, which significantly enhanced cellular uptake and achieved approximately 25-fold higher tumor accumulation compared to normal liver tissue in hepatocellular carcinoma models [90].

Hypoxia-responsive SLNs further enhance therapeutic precision by targeting oxygen-deficient tumor regions. For example, nitroimidazole-functionalized PEG-based lipid nanocarriers undergo enzymatic reduction under hypoxic conditions, leading to structural destabilization and accelerated drug release. Such systems have demonstrated improved apoptotic activity and tumor suppression in preclinical models [91]. Similarly, lipid-based nanocarriers co-delivering chemotherapeutics and hypoxia-targeting agents have shown the ability to reverse hypoxia-induced drug resistance, thereby enhancing treatment efficacy in aggressive cancers such as triple-negative breast cancer [92].

In addition, reactive oxygen species (ROS)-responsive and dual-stimuli systems offer further control over drug release. A lipid-like prodrug system incorporating boronic acid linkages enabled a cascade response in which acidic pH initiated structural changes, followed by H_2O_2-mediated drug activation, resulting in enhanced antitumor efficacy with reduced systemic toxicity [93]. Another dual-responsive SLN system combining pH-sensitive acetal bonds and ROS-triggered degradation demonstrated significant tumor growth inhibition through controlled docetaxel release in breast cancer models [94].

Collectively, these examples highlight that stimuli-responsive SLNs can overcome key limitations of conventional nanocarriers by enabling

precise spatiotemporal drug delivery. However, challenges such as formulation complexity, reproducibility, and regulatory approval remain to be addressed for successful clinical translation.

Beyond stimuli-responsiveness, additional innovations include stealth surface engineering using PEG and zwitterionic polymers to evade immune clearance, mitochondria-targeting ligands to enhance apoptotic signaling, and co-delivery of nucleic acids (siRNA/mRNA) to overcome multidrug resistance and modulate tumor biology. Furthermore, theranostic SLNs incorporating imaging agents enable simultaneous diagnosis and therapy, supporting real-time monitoring of treatment response. Advances in microfluidic manufacturing and artificial intelligence-driven formulation design are also expected to improve scalability and reproducibility. As these technologies continue to evolve, SLNs are poised to transition from passive delivery systems into adaptive nanoplatforms capable of precision-guided and personalized cancer therapy.

8. Conclusion

Solid lipid nanoparticles have emerged as a versatile and clinically relevant nanoplatform capable of overcoming fundamental delivery barriers in oncology. Their biocompatible composition, tunable architecture, and physicochemical stability enable improved solubilization, targeted biodistribution, and controlled drug release, while surface functionalization facilitates selective accumulation within the tumor microenvironment. Preclinical evidence consistently supports superior antitumor responses for SLN-enabled therapies through enhanced cellular uptake, prolonged systemic exposure, apoptosis induction, and suppression of metastatic behavior.

Future research should prioritize regulatory-aligned manufacturing, standardized nanotoxicology evaluation, and mechanistic investigations that link nanoparticle structure to biological performance. Advanced hybrid constructs integrating imaging agents, gene-therapy tools, and stimuli-responsive components offer new routes toward precision oncology. With continued optimization in design, safety, and scalability, SLNs hold strong potential to progress into clinically validated nanosystems capable of transforming cancer treatment through safer, more effective, and patient-specific therapeutic strategies.

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Kandanagolla Sumalatha: Writing – review & editing, Writing – original draft. **Rathinasamy Gandhimathi:** Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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