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Solid lipid nanoparticles in cervical cancer: a comprehensive review of a decade of progress and prospects

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Background: Cervical cancer is the second most commonly diagnosed cancer worldwide and the third leading cause of death among women, with approximately 604 127 new cases being reported in 2020. Conventional treatment methods, such as chemotherapy, radiation therapy, surgery, and hormonal therapy, often face significant challenges, including systemic toxicity and reduced efficacy, particularly in the advanced stages of the disease. The treatment of cervical cancer is further complicated by tumor heterogeneity, resistance mechanisms to chemotherapeutic drugs, and the persistent presence of HPV. However, in recent years, nanotechnological interventions, particularly solid lipid nanoparticles (SLNs), have gained increasing attention owing to their robust potential to effectively deliver chemotherapeutic agents while minimizing systemic toxicity. SLNs present a compelling solution for reducing side effects, enhancing drug solubility, improving stability and bioavailability, and overcoming the limitations and resistance associated with conventional treatment strategies. *Methods*: To provide the context and evidence, relevant publications were searched on Google Scholar, PubMed, ScienceDirect, Dimensions AI, and EBSCO host, using specific keywords such as "cervical cancer", "drug loading", "encapsulation efficiency", "HPV", "sustained drug release", and "solid lipid nanoparticles (SLNs)". We did not impose any restrictions on the publication date during the selection of papers. However, it is imperative to highlight that the initial reports containing specified keywords began publication in 2013. *Conclusion*: SLNs represent a promising frontier in drug delivery, particularly within cervical cancer therapeutics, because of their ability to facilitate the targeted delivery of chemotherapeutic agents and genetic materials. The potential of SLNs to encapsulate and protect vital therapeutic compounds presents significant opportunities for developing innovative treatment strategies including DNA and peptide vaccines. However, the lack of approved SLN-encapsulated vaccines for cervical cancer underscores the need for rigorous *in vivo* research and clinical trials to validate their safety and efficacy. Future studies should not only optimize SLNs for various agents but also explore diverse combination therapies to enhance therapeutic outcomes.

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1. Introduction

Cervical cancer (CC) develops from a malignant epithelial tumor that leads to the proliferation of cells in the cervix. The predominant cause is persistent infection of Human papillomavirus (HPV), particularly HPV 16 and 18.[1] Moreover, HIV-infected females have a 6-fold increased risk of developing CC compared to the general population.[2] Emerging evidence suggests that HIV and HPV co-infection significantly contributes to cervical carcinogenesis through multifactorial viral interactions, encompassing immunosuppression, chronic inflammation, and the induction of epithelial–mesenchymal transition (EMT)[3] (Table 1). The disease commonly presents as either less common adenocarcinoma (20–30%) or more common squamous cell carcinoma (70–80%).[4,5] Additionally, factors such as multiple sexual partners,[6,7] consistent use of oral contraceptives,[6] early initiation of sexual activity,[7] and a higher number of vaginal deliveries[8,9] are also associated with the development of CC. The risk factors associated with the development of cervical cancer are illustrated in Fig. 1.[10] Prognostic factors, including depth of cervical stromal invasion, tumor size, lymph node involvement, histological fea-

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Table 1 Key mechanisms linking HIV and HPV co-infection to cervical carcinogenesis. Reproduced from Pavone *et al.*[3] under the terms and conditions of the Creative Commons Attribution (CC BY) license

Aspect	Description	Impact on disease progression
Immune system dysfunction	HIV impairs the immune system primarily by depleting CD4+ T cells, leading to apoptosis and reduced functionality. This suppression extends to specific T lymphocytes against HPV oncoproteins E6 and E7, crucial for controlling tumor progression in HPV-infected cervical cells	Increased susceptibility to high-grade squamous intraepithelial lesions (HSILs) due to reduced immune surveillance and inability to control HPV infection, thus facilitating progression to CC
Dendritic cell (DC) dynamics	HIV infection results in an increased number of immature DCs in cervical tissues, characterized by low expression of maturation markers CD83 and CD86. These immature DCs are less effective in antigen presentation and initiating a robust T-cell-mediated response	Persistent HPV infection due to inadequate activation of immune responses against HPV, leading to sustained viral infection and increased risk of cervical lesion progression
Vaginal microbiome and inflammation	HIV-related changes in the vaginal microbiome lead to dysbiosis, characterized by an imbalance in microbial species that promotes a pro-inflammatory state. This inflammation can exacerbate HPV persistence and lesion progression	Chronic inflammation associated with microbial dysbiosis enhances HPV persistence and promotes the progression of precancerous lesions to CC due to a continuously inflamed environment
Epithelial–mesenchymal transition (EMT)	HIV proteins gp120 and Tat induce EMT in cervical epithelial cells. This process involves the loss of epithelial characteristics and gain of mesenchymal traits, facilitating tumor cell invasion, migration, and resistance to apoptosis	Accelerates the progression of cervical lesions, increases the invasiveness and metastatic potential of CC cells, and may lead to resistance to conventional treatments

tures, and International Federation of Gynecology and Obstetrics (FIGO) cancer stage, influence the prognosis of CC.[11–13] Higher FIGO stage, increased node involvement, larger tumors, and deeper invasion are associated with poorer prognosis, leading to worsened overall survival (OS) and disease-free survival (DFS).

CC ranks as the third leading cause of death in women globally and is the second most frequently diagnosed cancer in women, especially those under 25 years of age.[14] In 2020, there were 341 833 reported cases of CC worldwide, with a total of 604 127 new cases.[15] According to Global Cancer Statistics, it is projected that there will be approximately 13 820 new cases and 4360 deaths in 2024 due to CC in the US.[16] The incidence and mortality of CC vary based on the geographic and socioeconomic status of the country, with a heavy burden on low-middle-income countries (LMICs) and those with a lower Human Development Index (HDI).[17] Astonishingly, 88% of all deaths and 83% of new CC cases occur in LMICs, including India, Sub-Saharan Africa, and Latin America.[15,18]

The treatment of CC depends on the stage and extent of spread. This includes surgery, radiotherapy, and chemotherapy, with increasing research on immunotherapy and targeted therapy.[19] The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend specific surgical procedures, such as conization, loop electrosurgical excision procedure (LEEP), or radical trachelectomy, for fertility preservation in women diagnosed with early stage disease.[5] For women of childbearing age, radical hysterectomy or total hysterectomy with or without salpingo-oophorectomy is the treatment of choice.[20,21] Radical hysterectomy using the open technique is the preferred option for tumors greater than 2 cm and larger cervical lesions.[22] In the case of locally advanced stages (FIGO IIB/IIIB and FIGO IVA), concurrent chemotherapy with radiation therapy (RT) [external beam radiation therapy (EBRT), brachytherapy (internal RT), and intensity-modulated radiotherapy (IMRT)] followed by surgery is the most widely used method for managing CC.[23,24] RT alone is not used for treatment due to its association with numerous adverse effects such as abdominal cramps, diarrhea, pelvic pain, skin toxicity, and lymphedema, which reduce the quality of life (QoL).[25] Moreover, the treatment of locally advanced disease with chemoradiation has been associated with a high failure rate of 30–50%.[26] In treating metastatic CC (Stage FIGO IVB) and locally advanced cervical cancer, pelvic exenteration for localized recurrence and chemotherapy alone, or in combination with radiation therapy, followed by surgery are crucial treatment options.[27] Cisplatin is the most effective single agent, and the European Society for Medical Oncology (ESMO) recommends cisplatin over radiotherapy for local control and survival.[28] Research has shown that the efficacy of cisplatin increases when it is combined with other chemotherapeutic agents.[29,30] In a phase III study conducted by a gynecologic oncologic group, it was reported that combining cisplatin with topotecan and paclitaxel resulted in response rates of 39% and 29%, respectively.[31] However, the median progression-free survival (mPFS) and median overall survival (mOS) for metastatic and recurrent CC remain low despite advances in treatment.[28]

The combination of targeted therapies, such as Bevacizumab with Cisplatin, has significantly improved progression-free survival (PFS) and overall survival (OS) in metastatic diseases.[32,33] Additionally, immunotherapy targeting HPV oncogenes has been found to effectively target dysplastic precancerous lesions and malignant epithelial cervical cells.[34] This exploration has led to the development of various checkpoint blockades, vaccines, and adoptive T-cell therapies, each with varying rates of success and many currently under clinical trials.[35]

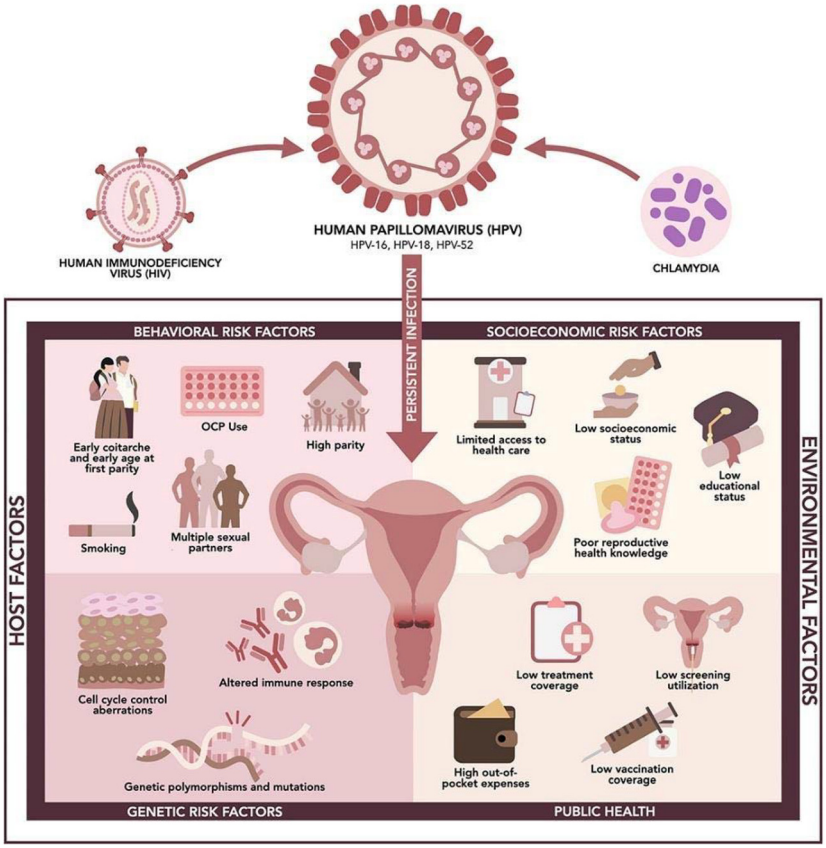


Fig. 1 Risk factors associated with CC. Reproduced from Lintao *et al.*[10] licensed under the terms of the Creative Commons Attribution License (CC BY).

Despite the wide range of treatment options, CC still faces numerous obstacles, particularly in the treatment of metastatic and locally advanced disease. There is a significant need to improve the survival outcomes of patients with stages IB3 to IVA undergoing chemoradiation.[36] Moreover, the long-term side effects of these therapies are a major concern due to the potential risks of bladder, bowel, and sexual dysfunction, severely impacting prognosis.[37] This highlights the urgent need for novel therapeutic approaches for the treatment of CC, particularly to achieve modest benefits for mOS and mPFS. Therefore, it is imperative to explore innovative delivery platforms, such as nanostructured lipid carriers (NLC), polymeric nanocarriers, and solid lipid nanoparticles (SLNs), which offer promising advantages in terms of drug bioavailability, tumor selectivity, and toxicity reduction.[38–40] The following section discusses the evolution and potential of nanotechnology, especially SLNs, as a transformative approach in CC therapy. This transformative approach can provide personalized therapy, minimize adverse effects, and optimize treatment efficacy. Current research is primarily focused on utilizing nanotechnological tools to enhance drug delivery, reduce side effects, ensure accurate diagnosis, and improve overall survival in the management of CC.[41,42] Extensive studies have been conducted on nanocarriers, such as lipid nanoparticles, dendrimers, and liposomes, because of their potential to cross the cell membrane and accumulate at the tumor site, thereby increasing the concentration of the drug at the target.[43,44] Furthermore, these nanocarriers can also play a crucial role in developing cost-effective HPV vaccines to enhance vaccine efficacy for the successful prevention of CC in women at higher risk.[45,46]

2. Nanotech as a transformative tool

Nanotech-based strategies have brought a substantial shift in therapeutic applications in various medical fields, including oncology.[47] The integration of nanomedicine, which employs nanoscale components to achieve therapeutic effects, has played a crucial role in driving this change. Their targeted drug delivery capabilities, stability, non-invasiveness, extended blood-circulation time, and lower toxicity profile have contributed to their appeal.[48]

The 21st century efforts have prioritized nanotechnology-based therapeutics as the leading approach to treat cancer.[48] This is largely attributed to the challenges of conventional treatments, which often struggle to cross biological membranes effectively and are prone to biological degradation.[49,50]

Moreover, nanotechnology holds great promise for the delivery of small molecules, genes, and biologics. For instance, it has been shown to effectively deliver antitumor drugs to various cancer cell lines, such as HeLa cells, human breast adenocarcinoma (MCF-7), human lung cancer cells, and human hepatocellular liver carcinoma cell line (HepG2).[51] Furthermore, Durán-Lobato *et al.* conducted a three-decade research to develop a nanotechnological formulation containing peptides, proteins, and monoclonal antibodies (mAbs) and reported significant advantages of this formulation, suggesting its potential shortly.[52] Nanotechnology is poised to revolutionize gene therapy by offering non-viral vector systems that can be tailored for specific functional transformations using peptides and protein ligands.[53] The emergence of multifunctional envelope-type nanodevices (MEND) has marked a significant leap forward, enabling precise control over intracellular trafficking. This capability is crucial for the advancement of next-generation therapies, particularly in the realm of gene therapy.

Nanotech presents a transformative approach to drug delivery in CC therapy, overcoming the limitations and challenges associated with conventional therapies. Their enhanced drug delivery mechanism improves the precision of targeted drug delivery reducing systemic toxicity.[54] Moreover, stimuli-responsive nanocarriers are designed to release their therapeutic payload according to the conditions of the tumor microenvironment.[55] The application of nano-delivery systems significantly enhances the pharmacokinetics and effectiveness of drug delivery compared to traditional dosage forms.[54,56] Among the different types of nanotechnologies, including liposomes, polymeric nanospheres, niosomes, and nano micelles, SLNs have become a leading and efficient nanotechnological option. They demonstrate excellent biocompatibility, a reduced toxicity profile, and increased stability. Their capability to incorporate both lipophilic and hydrophilic medications enhances their encapsulation efficiency and makes them efficient drug delivery systems. SLNs offer a promising avenue for advancing the treatment of CC through innovative drug delivery systems. This review provides an in-depth exploration of SLNs specifically tailored for CC therapy, with a focus on the development and optimization of these formulations. It addresses the various challenges encountered in the formulation process and highlights the potential opportunities for future research and applications. The primary objective is to assess how SLNs can serve as an effective method for delivering therapeutic agents in the management of CC, potentially improving treatment outcomes and minimizing side effects associated with conventional therapies.

3. Fundamentals of SLNs

SLNs are unique colloidal drug delivery systems that are distinguished by their solid core and are capable of incorporating both hydrophobic and hydrophilic drugs.[57,58] Biodegradable and biocompatible solid lipids are used in their formulation with low toxicity, making them suitable for oral, parenteral, and topical administration.[57] They offer potential for improved drug stability, enhanced drug delivery, and biocompatibility.[59] Furthermore, they combine the advantages of emulsions and liposomes with those of polymeric nanoparticles.[60] SLNs provide numerous advantages over conventional drug delivery systems, such as biocompatibility and biodegradability, versatile route of administration, enhanced stability, low toxicity profile, straightforward production, and scalability.[59] The interaction of SLNs with biological barriers is determined by their physicochemical properties such as particle size, lipid composition, and surface charge. They provide the benefit of sustained drug release, thereby reducing the need for repeated administration.[61]

The major portion of SLNs is composed of solid lipids, typically including fatty acids, triglycerides, and waxes.[62] To maintain the stability of this core, it is surrounded by a layer of surfactants, which also reduce the surface tension and prevent aggregation. Commonly employed surfactants include polyoxyethylene (20) sorbitan monooleate, poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol), phosphatidylcholine, polyoxyethylene (10)-oleyl ether.[63,64] Emulsifiers play a crucial role in influencing various physicochemical parameters of SLNs, such as drug release kinetics and surface charge, and aid in the mixing of the aqueous and liquid phases.[65] Additionally, co-emulsifiers and co-surfactants, such as sodium cholate and sodium deoxycholate, are used to further stabilize the system and enhance the functionality and physicochemical properties of the nanoparticles.[66] Furthermore, other additives such as surface modification with polyethylene glycol (PEG) stearate were included to optimize the performance of drug encapsulation.[67]

The drug-loading mechanism of SLNs depends on the physicochemical properties of the lipid matrix and drug. There are three important types of mechanisms to consider: enriched core model, homogenous matrix model, and enriched shell model, as shown in Fig. 2.[65,68] In the enriched core model, a highly lipophilic drug is loaded onto the lipid core that is solubilized during the formation of the nanoparticle, making it suitable for drugs with a high affinity for the lipid core.[59] The homogeneous matrix model involves the distribution of drugs throughout the lipid matrix through cold homogenization, when both have the same solubility, allowing uniform dispersion of the drug in the matrix.[69] In the enriched shell model, the drug is affixed to the surfactant, which interacts with the lipid surface and localizes to the outer shell.[70]

SLNs can be produced through high-pressure homogenization (HPH) using either cold homogenization at room temperature or hot homogenization at elevated temperatures. Hot homogenization involves utilizing hot melt extrusion (HME) to uniformly pump the raw material.[72] The melted lipid is then combined with an aqueous solution of surfactant and subjected to HPH to reduce the size of SLNs. In cold homogenization, the solidified lipid–drug mixture is ground and subjected to HPH in a cold aqueous solution of surfactant.[73] Other methods for manufacturing SLNs are also employed,

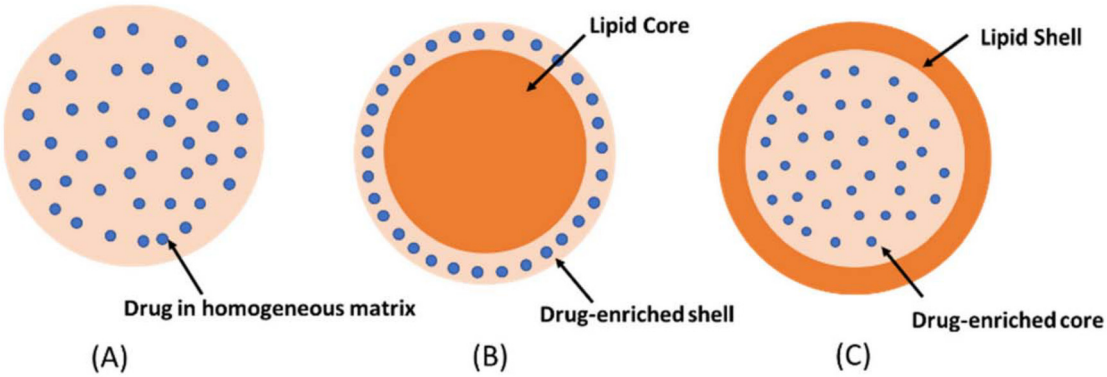


Fig. 2 The drug loading mechanism of SLNs (A) homogeneous matrix model (B) enriched shell model (C) enriched Core model. Reproduced from Chutoprapat *et al.*[71] under the terms and conditions of the Creative Commons Attribution (CC BY) license.

such as solvent emulsification–evaporation, the microemulsion technique, and the solvent injection method, which are beyond the scope of this review.

SLNs act by enhancing the drug delivery mechanisms and improving drug absorption and bioavailability. The reduced particle size and lipidic nature of SLNs enable their administration *via* various routes. Additionally, the solid lipid matrix facilitates controlled release of the drug, and the drug release mechanism can be modified by altering the composition of the lipid matrix and surfactant used.[74] Moreover, they prevent drug degradation, particularly for peptides and proteins, allowing for controlled release.[58] Orally administered SLNs are absorbed through M cell uptake, whereas intravenously administered SLNs are taken up by the liver and spleen.[62] Surface modification with PEG can redirect them to other tissues and organ references. When delivering biologics, active targeting is mainly employed.[75] The delivery of genetic material can occur through various mechanisms. Electrostatic binding involves the binding of cationic SLN to negatively charged nucleic acids, preventing enzymatic degradation and ensuring cellular uptake.[76] The clearance and elimination of SLNs depend on the route of administration. For example, elimination occurs *via* the hepatobiliary and fecal excretion of oral and parenterally administered drugs. SLNs administered *via* pulmonary delivery are cleared by the mucociliary escalator, and eventually through fecal elimination,[77] whereas ocular drugs are eliminated *via* lacrimal secretion.[78]

4. SLNs in cancer

The contemporary decade has seen a significant evolution in the development of cancer therapeutics.[79] Inventions such as small-molecule inhibitors,[79] immunotherapies,[80] chimeric antigen receptor [CAR]-T cell therapy,[81] and PROTACs[82] are transforming the field of oncology, providing significant therapeutic advantages for cancer patients. Despite these developments, substantial limitations persist, including treatment resistance,[83] high costs,[84,85] complex tumor microenvironment (TME),[86] and limited availability in low- and middle-income countries.[87] Moreover, owing to the heterogenic nature of the tumor, malignant cells are more likely to develop survival mechanisms.[88] This underscores the necessity for enhancing the currently used cancer therapies through the adoption of nanotechnological tools.

SLNs have emerged as a versatile nanoplatform for the delivery of anticancer agents across multiple malignancies, establishing foundational design strategies that are increasingly being adapted to CC therapy. For instance, Rahman *et al.*[89] developed SLNs containing curcumin (Cur-SLNs) to study their effective delivery and anticancer potential in lung cancer. Cur-SLNs displayed optimal properties (particle size of 114.9 ± 1.36 nm, zeta potential of −32.3 ± 0.30 mV, encapsulation efficiency of 69.74 ± 2.03%, and drug loading of DL, 0.81 ± 0.04%). *In vitro* studies on the A549 cell line demonstrated a significantly higher cellular uptake with substantial cytotoxicity (IC_{50} = 26.12 ± 1.24 μM) when compared to the control (Cur) group (IC_{50} = 35.12 ± 2.33 μM). In another study, Wang *et al.*[90] formulated resveratrol (Res)-embedded D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)-Res-SLNs to combat multi-drug resistance in breast cancer (BC). TPGS-Res-SLNs showed greater cytotoxicity than Res-SLNs and free resveratrol in SKBR3/PR cells. In addition, a potent apoptotic profile (57.40%), reduced cellular migration and invasion, and strong antitumor efficacy were found. The nanoformulation displayed a substantial reduction in drug efflux transporters, such as P-gp and BCRP expression. *In vivo* analysis of SKBR3/PR tumor-bearing mice showed stronger tumor growth inhibition and apoptotic profiles. Hatami *et al.*[91] developed Quercetin-loaded SLNs (QC-SLN) to investigate their anti-cancer effects on the triple-negative breast cancer (TNBC) cell line MDA-MB231. The QC-SLN modulated the expression of Bax and Bcl-2 at both the gene and protein levels, resulting in a considerable increase in the apoptotic rate with a significant reduction in cell viability, colony formation, and angiogenesis. Furthermore, PEGylated 5-FU-loaded SLNs reported profound effectiveness against HCT-116 cancer cells. Among the six batches assessed, PEGylated 5FU-SLN_4 displayed the most

effective results. These include a particle size of 263 ± 3 nm, zeta potential of 0.1 ± 0.02, EE of 81 ± 10%, enhanced suppression of tumor growth, downregulation of HER2 receptor expression, high cytotoxicity, and no reported hepatic and renal tissue toxicity.[92]

SLNs, through surface modification with specific targeting moieties, can be functionalized to selectively bind to overexpressed receptors in cancerous tissues. This approach facilitates the targeted delivery of encapsulated anticancer agents, resulting in enhanced local concentrations at the designated cancerous site.[75] For instance, Akanda and colleagues bioconjugated transferrin and curcumin in SLNs for effective delivery to prostate cancer cells. Their results indicated profound chemopreventive activity characterized by enhanced cellular uptake and an increased apoptotic profile.[93] In another study, transferrin-decorated tamoxifen citrate-loaded SLNs displayed a greater cellular uptake profile than tamoxifen citrate-loaded SLNs in MCF-7 BC cells, indicating the potential for targeted therapeutic approaches.[94] Additionally, folic acid-grafted oxaliplatin (OA) SLNs enhanced cellular uptake, resulting in substantial cytotoxicity, with a potent anticancer profile and significant sensitivity to HT-29 cells.[95] Furthermore, surface modification with folic acid actively delivers anticancer drugs in lung,[96] breast,[97,98] and colorectal cancers.[99,100] Although functionalization of SLNs with ligands such as transferrin and folic acid has demonstrated promising results in preclinical studies, their clinical translation remains challenging. Key obstacles include ensuring long-term stability of the ligand-modified SLNs, minimizing batch-to-batch variability in conjugation efficiency, and maintaining the integrity of active targeting formulations during storage and administration.[101,102] Despite these limitations, such surface modifications highlight the potential of SLNs to revolutionize cervical cancer therapy by enabling targeted drug delivery while minimizing systemic toxicity.

SLNs exhibit remarkable promise not only in therapeutic applications but also in the domain of tumor diagnostics. The incorporation of diagnostic agents such as superparamagnetic iron oxide and technetium-99 (^{99m}Tc) has proven to be highly effective and can be employed as a CNS MRI contrast and lymphoscintigraphic agent.[103] Furthermore, surface modification with specific compounds enhances the contrast and resolution, thereby enabling precise tumor mapping and characterization.[104]

The delivery of SLNs to the targeted cancer site is followed by their uptake and subsequent entry into the tumor, along with their interactions with the TME. Broadly, uptake mechanisms are classified into energy-dependent endocytosis (including clathrin-mediated, caveolae-mediated, clathrin- and caveolae-independent endocytosis, and micropinocytosis) and energy-independent non-endocytosis.[105,106] Endocytosis is a cellular internalization mechanism characterized by invagination of the plasma membrane in response to cellular receptor interactions. This inward budding process leads to the formation of endocytic vesicles, which undergo a cascade of biochemical processes that facilitate the release of the contents into the cellular environment.[107–110] While the current literature is limited to *in vitro* cell line studies that demonstrate clathrin-mediated endocytosis as the primary route, the lack of *in vivo* animal and human studies has prevented a strong conclusion. For instance, Martins *et al.* studied the uptake mechanism of four human glioma cell lines (U87, U251, A172, and U373) and one human monocytic cell line (THP1) and reported clathrin-mediated endocytosis as the primary pathway.[106] Similarly, Arana *et al.*[111] Cavaco and colleagues,[112] Granja and co-workers,[113] and Garanti *et al.*[114] also confirmed clathrin-mediated endocytosis in their experiments.

Notably, the uptake mechanisms are influenced by several factors, including their particle size, lipid composition, surface characteristics, and target cell type.[115–118] Following endocytosis, these nanoparticles navigate the intracellular environment through two main pathways: endosomal routing or endosomal escape. In the case of endosomal routing, the internalized SLNs undergo a series of maturation stages, starting with the formation of early endosomes that eventually mature into lysosomes.[119] The enzymatic and acidic conditions present within lysosomes promote the degradation of SLNs, leading to the release of the encapsulated molecules.[119] Conversely, during endosomal escape, some SLNs circumvent the endosomal pathway before reaching lysosomal degradation, allowing them to release their cargo directly into the cytosol.[120]

SLNs leverage the EPR effect within the TME, taking advantage of the abnormal vasculature and compromised lymphatic drainage to preferentially accumulate in tumor tissues. This passive targeting strategy enables prolonged drug release and minimizes systemic toxicity. Additionally, surface modifications like PEGylation can further improve tumor-specific interactions and circulation time.[117,121] However, the interaction of SLNs with TME lacks available data, posing a potential barrier to its clinical translation and demanding in-depth analyses.

These mechanistic insights and performance metrics derived from various cancer models provide an essential framework for applying SLNs to CC. In the following section, we shift focus to the specific application of SLNs in CC, examining current preclinical data, formulation strategies, and therapeutic outcomes.

5. SLNs in CC: targeting and drug delivery applications

SLNs are essential in the treatment of various cancers, and their benefits in cervical cancer are particularly notable. They have demonstrated impressive results in enhancing drug delivery to target cells, improving stability and biocompatibility, and achieving significant cytotoxic effects on cervical cells. Furthermore, their capability to incorporate both small molecules and genetic materials has led to remarkable outcomes.

5.1. SLNs for small molecule delivery

SLNs act as potential carriers, safeguarding drugs from the extracellular environment by facilitating passive or active drug

delivery. They play a pivotal role in targeted drug delivery by upregulating the receptor and enhancing drug specificity. SLNs can be tailored with chemotherapeutic agents to overcome challenges, such as low solubility, stability, and bioavailability. A study by Karamchedu and colleagues[122] demonstrated a three-fold increase in the cytotoxicity of morin hydrate, an anticancer bioflavonoid, when loaded into SLNs. The optimized SLNs exhibited a particle size of 92 nm, zeta potential of −23.5 ± 1.6 mV, 27.5% cell viability, and 87% encapsulation efficiency, improving intracellular delivery in HeLa CC cells. Additionally, Wang *et al.*[123] developed chitosan-coated cisplatin-loaded SLNs (as shown in Fig. 3A) to provide sustained drug release and increased stability in HeLa cervical carcinoma, minimizing side effects. The surface modification with chitosan improved the drug release profile of cisplatin (as shown in Fig. 3B), resulting in excellent dispersity and a significant reduction in cell viability with an IC_{50} value of 0.6125 μg ml^{-1}, leading to enhanced internalization and higher apoptosis.

Similarly, Chen *et al.* conducted a study on the development and evaluation of topotecan-loaded SLNs.[124] They prepared twenty SLN batches and optimized them using a face-centered 3^3-factorial experimental design. The optimized SLNs exhibited a mean particle size of 262.5 ± 8.32 nm, a PDI of 0.151, and a mean zeta potential of +20 mV. Cytotoxicity analyses performed on HeLa and SiHa cervical cancer cell lines showed significantly reduced cell viability ($P > 0.05$) compared to the control group. Additionally, the optimized SLNs demonstrated considerably higher IC_{50} values in cancer cells compared to normal cells. These optimized SLNs also showed an optimal stability profile when stored under refrigeration for up to six months. However, when exposed to room temperatures of 25 °C, the drug concentration within the SLNs decreased.

To achieve synergistic antitumor activity against CC, Liu *et al.*[125] developed *trans*-activating transcriptional activator (TAT)-functionalized SLNs for the co-delivery of paclitaxel (PTX) and α-tocopherol succinate-cisplatin prodrug (TOS-CDDP) (TAT PTX/TOS-CDDP SLNs). These SLNs were meticulously prepared using a solvent evaporation and emulsification method, which facilitated their successful internalization within HeLa cells. The formulation exhibited ideal physicochemical properties, featuring a particle size of 108.6 ±

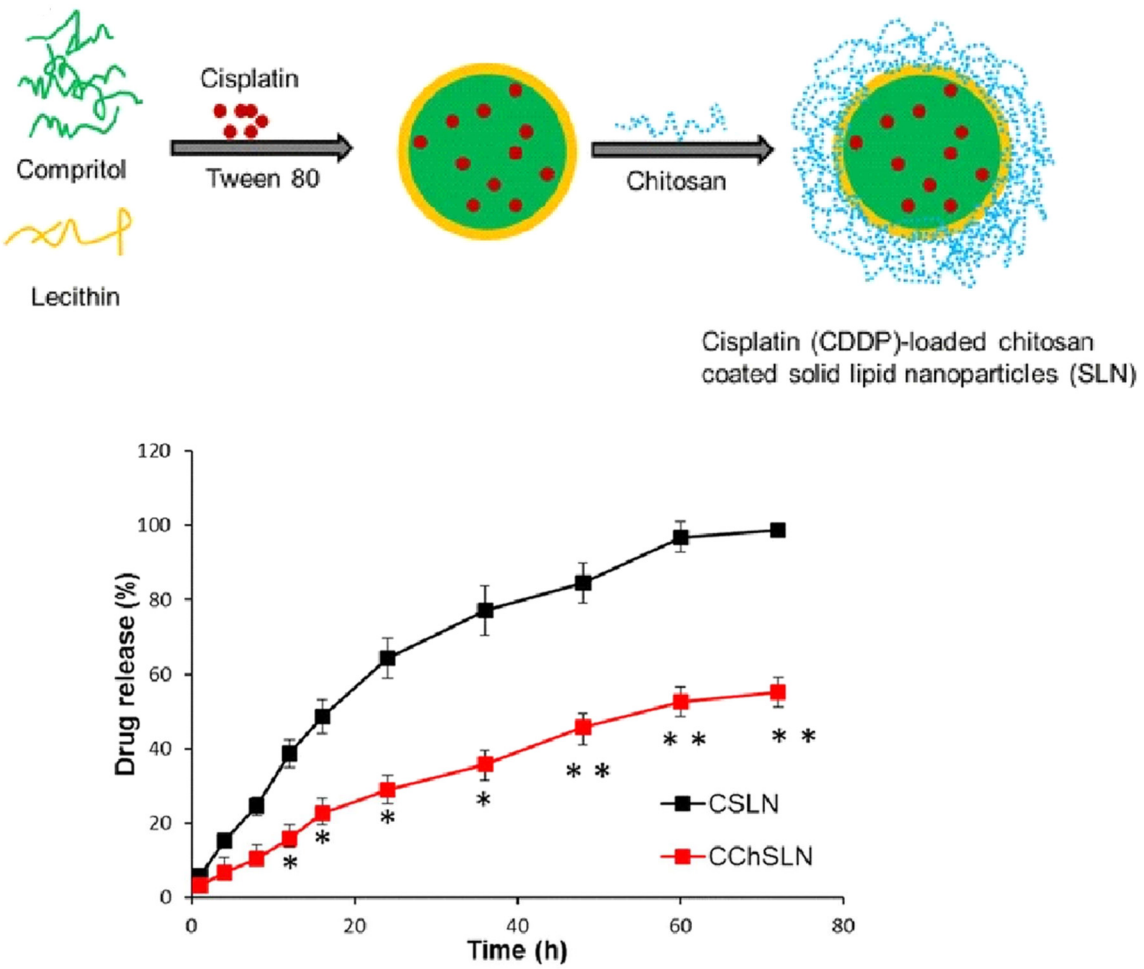


Fig. 3 Schematic representation of chitosan-loaded cisplatin-loaded SLN and the drug release profile of chitosan-loaded cisplatin-loaded SLNs. Reproduced from ref. 123, under the terms of the Creative Commons CC BY license.

3.1 nm, a zeta potential of −31.2 ± 2.7 mV, and an encapsulation efficiency (EE) of approximately 90% for both PTX and CDDP. *In vitro* release studies indicated a slower release from the TAT PTX/TOS-CDDP SLNs compared to the PTX/TOS-CDDP SLNs ($P < 0.05$). Additionally, a faster drug release was observed at pH 5.0 than at pH 7.4 ($P < 0.05$). The cellular uptake efficiency of the TAT-modified SLNs was significantly higher than other SLNs ($P < 0.05$). Furthermore, treatment with TAT PTX/TOS-CDDP SLNs resulted in significant reductions in tumor volume in cervical cancer-bearing mice compared to other SLNs ($P < 0.05$). These SLNs demonstrated an impressive tumor inhibition rate (TIR) of 72.2%, surpassing that of the PTX/TOS-CDDP SLNs, thereby emphasizing the importance of TAT modification (as shown in Fig. 4). Following *in vivo* administration of TAT PTX/TOS-CDDP SLNs, drug concentrations within the tumor remained relatively stable at all measured time points until 24 and 48 hours, while the concentrations in the PTX/TOS-CDDP group significantly decreased.

In a separate study, Wang *et al.* introduced hyaluronic acid-decorated Pluronic 85-coated SLNs loaded with paclitaxel (HA-PTX-P85-SLN) to combat multidrug resistance in CC.[126] Pluronic-85 is a potent inhibitor of P-glycoprotein (P-gp), that causes multiple drug resistance (MDR) in cancer cells. The surface modification with hyaluronic acid enabled active targeting of overexpressed receptors CD44 and CD168, facilitating enhanced delivery of paclitaxel to tumor cells, even those with multidrug resistance. HA-PTX-P85-SLN displayed desirable particle size, zeta potential, and EE. The cellular uptake efficiency of the formulation was found to be significantly greater compared to other SLNs ($P < 0.05$). Additionally, HA-PTX-P85-SLN demonstrated considerable cytotoxicity towards cervical cancer cell lines than other formulations. For HeLa/PTX cells, the formulation displayed IC_{50} of around 0.2 nmol mL^{-1}, which was exceptionally low compared to other formulations, such as PTX-P85-SLN (0.9 nmol mL^{-1}), PTX-SLN (2.7 nmol mL^{-1}) and free PTX (8.2 nmol mL^{-1}). The resistance index of HA-PTX-P85-SLN (*i.e.* 2.5) was nearly 5.5-fold lower than that of free PTX (*i.e.* 13.7). The *in vivo* antitumor efficacy of the formulation exhibited the highest tumor growth inhibition among other treatment groups. Furthermore, the mice within this group displayed no weight loss, whereas in those treated with free PTX or saline, the weight loss was observed.

The recent study conducted by Adeyemi and colleagues focused on the delivery of 5-Fluorouracil (5-FU) loaded SLNs using thermo-sonic-nano-organogel (TNO) variants to achieve a rate-modulated intracervical drug release.[127] The *in vitro* assessment revealed an initial burst of drug release on day 1 followed by consistent and sustained release for 14 days. Notably, TNO variant 1 demonstrated superior sustained release over 15 days compared to TNO-2 and TNO-3. It was observed that the SLN : TNO ratio influenced the biodegradation and release rate, with a higher ratio decreasing the swelling ability of TNO formulations. Additionally, essential oils (EOs) have been recognized as important anti-cancer agents in cervical cancer cell lines, specifically HeLa (HPV 18) and SiHa (HPV 16). Studies have highlighted their effectiveness in reducing tumor volume and angiogenesis.[128] Despite their potential to inhibit cell proliferation and induce apoptosis, the bioavailability of essential oils is limited due to their poor stability, high volatility, and susceptibility to degradation when exposed to oxygen, light, and heat.[129] Encapsulation of EOs offers a promising approach for successful delivery into cancer cells. For instance, encapsulation of *Eucalyptus globulus* EO has demonstrated an enhanced cytotoxic effect with an IC50 of 21.30 μg mL^{-1} against HeLa cell lines.[130] However, it is imperative to note that the FDA has only classified a few EOs as "Generally recognized as safe" (GRAS), and there is a dearth of animal studies, emphasizing the necessity for future research to establish their safety and efficacy in CC treatment. In another study, a temperature-sensitive gel-loaded SLN was prepared to enhance *in vivo* drug absorption and reduce local

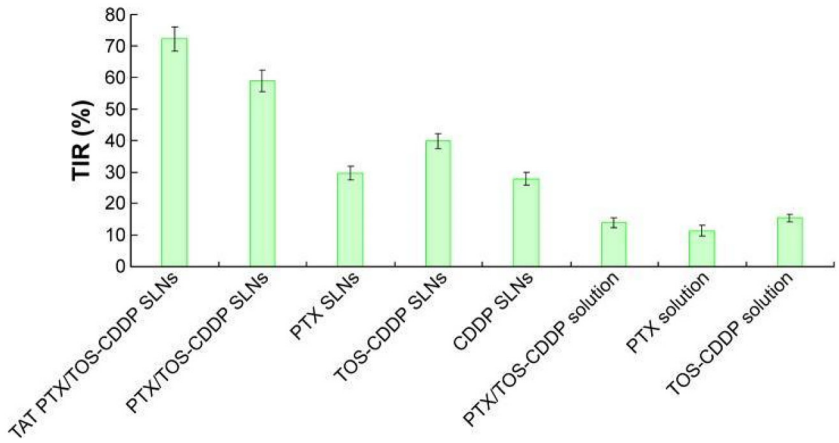


Fig. 4 Tumor inhibition rate of various formulations on cervical cancer-bearing mice. Reproduced from Liu *et al.*,[125] with permission from Dove Medical Press Limited under the terms of the Creative Commons Attribution-Non-commercial License (CC-BY-NC) (2017). (Figure legends: CDDP, cisplatin; PTX, paclitaxel; SD, standard deviation; SLNs, solid lipid nanoparticles; TAT, trans-activating transcriptional activator; TIR, tumor inhibition rate; TOS-CDDP, α-tocopherol succinate-cisplatin prodrug).

irritation after vaginal delivery.[131] It exhibited a superior antiproliferative action compared to conventional powder, along with S and G0/G1 phase arrest in HeLa cancer cells. Moreover, it proved to enhance biocompatibility and sustained drug release by adhering to the vaginal mucosa.

Despite notable advancements, SLNs encounter substantial challenges in vaginal drug delivery, particularly concerning pH compatibility, mucoadhesion, and mucosal retention time.[116,132,133] The vaginal environment, with its acidic pH range of 3.8–4.5, necessitates the development of SLNs specifically tailored to maintain stability and therapeutic efficacy under such conditions.[132] For instance, chitosan-coated SLNs have emerged as promising candidates for vaginal application due to their pH-responsive mucoadhesive properties.[132] Chitosan exhibits enhanced adhesion in acidic environments, primarily through electrostatic interactions between its positively charged amino groups and the negatively charged mucin glycoproteins present in the vaginal mucus.[116,132] This enhances SLN retention at the site of action, potentially improving therapeutic outcomes. However, excessive mucoadhesion can be counterproductive, leading to entrapment of the SLNs within the superficial mucus layer, which is subject to continuous turnover and clearance.[116,134] To overcome this limitation, strategies involving the development of mucus-penetrating particles (MPPs) have been adopted. These include surface modifications such as PEGylation or the design of nanoparticles with diameters below 200 nm, facilitating their diffusion through the mucus barrier and promoting interaction with the underlying epithelial tissues.[116]

5.2. SLNs for gene drug delivery

SLNs are particularly well-suited for delivering therapeutic genes due to their capacity to encapsulate genetic material and protect it from degradation. They also provide sustained release profiles, which enhance therapeutic outcomes. Developed vaginal suppositories that combined small molecules with genetic material for the localized treatment of cervical cancer. They incorporated paclitaxel and Bcl-2 siRNA into the SLNs to target specific oncogenes.[135] The study evaluated the transfection efficiency and physicochemical properties of the formulations on cancer cells, demonstrating their potential for simultaneous drug delivery at reduced doses, even in cells resistant to paclitaxel.

Shah *et al.* demonstrated the uptake of stearic acid-based SLNs in human epithelial cells through the clathrin-mediated endocytic pathway.[120] This energy-dependent mechanism efficiently transports the nanoparticles *via* the formation of vesicles. Other pathways such as micropinocytosis and ligand–receptor interaction are poorly understood in CC. Furthermore, understanding the interaction of SLNs with the TME is crucial, considering its unique characteristics such as the acidic environment, hypoxia, and the presence of matrix metalloproteinase, which enhance their efficacy and delivery. Current literature primarily focuses on targeted drug delivery with chemotherapeutic agents and genetic material in CC. However, to optimize delivery and personalize treatment approaches, comprehending the interaction of SLN with TME is imperative. A profound understanding of TME can facilitate its modulation to make it less conducive for tumor growth. Based on TME characteristics, patients can be stratified for effective treatment regimens, thereby improving their overall survival.

6. Formulation development and optimization

The formulation of SLNs involves key aspects ranging from lipid selection and their optimization to toxicity and safety profiles. Lipids are selected based on their melting points, ability to form stable formulations, and compatibility with the drug because their selection directly affects drug solubility, polydispersity, and particle size.[136,137] Lipids with optimal solubilizing capacities, such as glyceryl monooleate and glyceryl monostearate,[138] are preferred because they provide optimum miscibility with multiple drugs, enhance stability, and result in smaller particle sizes.[139] Achieving low polydispersity, typically below 0.3, results in an excellent homologous particle size distribution in a reproducible SLN formulation.[73] Ultrasonication and high-shear homogenization are commonly employed to achieve low polydispersity.[140]

Additionally, maintaining a zeta potential of >+30 mV or < −30 mV prevents aggregation, thereby ensuring colloidal stability and playing a vital role in cellular uptake by tumor cells.[141] The surface charge in cancer cells is typically negative owing to increased glycolysis-associated lactate formation and substantial expression of sialic acid.[142,143] Therefore, formulating SLNs with cationic lipids will generate a magnetic effect towards the targeted tumor, boosting drug uptake and leading to an optimal formulation, as proven by Carbone *et al.*[144] and Luo *et al.*[145]

The size range of SLNs varies depending on the preparation method and formulation parameters. For instance, Charcosset and co-workers utilized the membrane contractor method for SLN preparation and obtained sizes ranging from 70 nm to 215 nm.[146] Another group of researchers used sonication methods[147] and reported a particle size range of 200–300 nm. Moreover, decreasing the lipid concentration and increasing the solvent-to-lipid ratio can result in smaller particle sizes.[148] Additionally, the choice and concentration of surfactants play a significant role in influencing the particle size and stability. For instance, increasing the concentration of cationic surfactants (dioctadecyldimethylammonium bromide and cetylpyridinium chloride) increases the zeta potential, resulting in smaller particles and enhanced stability.[149] The addition of emulsifiers, such as polyethylene glycol sorbitan monolaurate, has also been reported to decrease particle size owing to their increased surface activity.[150]

The potential of SLN as nanotechnological tools in clinical scenarios necessitates their successful *in vitro* and *in vivo* applications. *In vitro* analyses utilizing cell lines encompass crucial parameters, such as particle size, zeta

potential, EE, DL, drug release patterns, cellular uptake, cytotoxicity, and apoptosis.[151,152] On the other hand, *in vivo* studies involve essential assessment of pharmacokinetic parameters, biodistribution, and antitumor efficacy.[151,153,154] For instance, Rodenak-Kladniew and colleagues[153] determined the mean diameter, size distribution, and zeta potential using photon correlation spectroscopy and laser Doppler anemometry. Stability studies were carried out to investigate the mean particle size, PDI, zeta potential, and EE, while the release patterns were assessed using a dialysis membrane. The MTT assay was employed to determine cell viability, and uptake studies were performed using fluorescence microscopy in A549 (human alveolar adenocarcinoma basal epithelial cells) and HepG2 (human liver carcinoma cells) cell lines.[153] SLNs displayed a particle size of 90–130 nm, zeta potential of −4.0 mV, PDI lower than 0.2, and EE greater than 80%. Furthermore, Jang *et al.* conducted *in vivo* tissue distribution and antitumor efficacy studies in tumor-bearing mice, and *in vivo* pharmacokinetic studies of camptothecin (CPT)-SLNs in rats. CPT-SLNs displayed significant CPT concentrations within tumor thigh, considerable anti-tumor efficacy, and substantial CPT plasma concentrations compared to free CPT.[155]

SLNs are generally considered safe and biocompatible nanocarriers. However, their overall safety profile can be substantially influenced by factors such as the lipid matrix composition, the choice of surfactants, and the nature of excipients used.[136] Additionally, SLNs undergo rigorous regulatory assessment due to various toxicological concerns, including surfactant-related toxicity, the presence of degradation byproducts, and unresolved long-term safety risks. Collectively, these actors pose major barriers to their successful clinical translation.[156–161]

To illustrate, cationic surfactants can induce potential toxicities. The systemic administration of 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) has been shown to provoke inflammatory reactions.[156] Similarly, the use of Cetyltrimethylammonium bromide (CTAB) has been reported to activate neutrophils and induce oxidative stress, leading to profound inflammation and ultimately cell death.[157] Secondly, polymorph transformation of lipid matrices, particularly from α- to β-crystal forms, can result in premature drug expulsion and erratic drug release profiles.[117,162] Emerging evidence further indicates that degradation byproducts from SLN formulations may activate the immune system and trigger inflammatory signaling pathways.[163,164] Despite these findings, current formulation optimization strategies often lack comprehensive characterization of lipid–surfactant interaction byproducts, making regulatory approval more challenging.[117,158] Thirdly, the employment of PEGylated nanoformulation may lead to the production of anti-PEG antibodies.[159,160] These antibodies tend to accelerate the clearance of the formulation from the bloodstream, compromising therapeutic efficacy.[159,160] Furthermore, they alter the biodistribution of the encapsulated drug, potentially increasing the risk of off-target effects and adverse events.[159,160]

7. Studies

We have conducted a thorough analysis of all the research on the use of SLNs for drug delivery in CC and have summarized the findings in Tables 2 and 3. Furthermore, our search did not yield significant information on biologics and patents.

8. Clinical trials and translational studies

After conducting an extensive search using the keywords "Solid lipid nanoparticles" and "Cervical cancer" using the website clinicaltrial.gov, it is clear that no SLN-based therapies have progressed to clinical trials for managing cervical cancer. This gap in data highlights significant barriers across multiple domains, including technical, regulatory, and financial challenges.[165–169]

Notably, from a technical perspective, limitations in manufacturing and scalability are particularly pronounced. During the manufacturing process, SLN can undergo polymorphic transitions within lipid matrices, which may result in drug expulsion and consequent loss of therapeutic efficacy.[165,166] Furthermore, processes such as HPH require stringent temperature control; even slight deviations can contribute to batch-to-batch variability.[167] Moreover, lipids and thermally unstable molecules lose their functional integrity when subjected to steam-based sterilization or gamma irradiation techniques, highlighting sterilization as another crucial technical limitation.[166] At an industrial scale, producing SLNs presents significant challenges. Variability in equipment design, the absence of standardized process parameters, and difficulties in achieving reproducibility and uniformity across batches greatly impede scalability.[169] Additionally, the lack of standardized protocols for analyzing lipid polymorphism, assessing long-term stability, and thoroughly characterizing nanoparticles poses additional obstacles to gaining regulatory approval.[165,167,168] On the financial front, insufficient funding during the preclinical phase, combined with the substantial costs associated with compliance to Good Manufacturing Practice (GMP), has impeded the translational progression of SLN-based systems into clinical settings.[165,168] These various challenges highlight the urgent need for future translational studies that can address these gaps, facilitating the clinical adoption of SLNs in the treatment of cervical cancer.[165,168]

9. Challenges and future opportunities

Nano-drug delivery systems, particularly SLNs, have achieved considerable progress in developing effective anti-cancer formulations. The advantageous properties of SLNs compared to other delivery systems, along with their widespread application have revolutionized the field of oncology.[170] Despite their potential, the clinical translation of SLNs remains hindered by

Table 2 Overview of SLN formulation and evaluation parameter

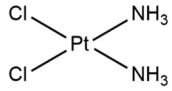
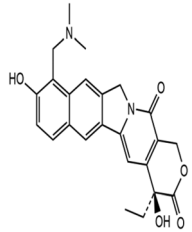
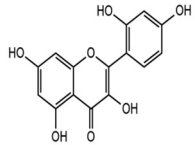
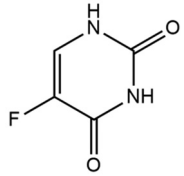
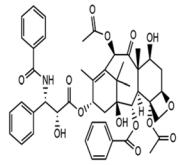
S. no.	Drug name	Structure	Utility	Excipients used	Advantages	Limitations	Result	Model	Cell culture model	Evaluation protocol	Intracellular uptake studies	Ref.
1.	Cisplatin		CC	Glyceryl dibehenate and monooleate of sorbitan ethoxylated	Decreased cell viability at low concentration, superior efficacy over CSLN, enhanced internalization and drug release	Lack of *in vivo* studies	↑ cytotoxicity and apoptosis rate (40%), ↓ IC_{50} (0.6125 mg ml^{-1}), ↓ particle size (80–300 nm)	*In vitro*	HeLa cell line	MTT assay for cytotoxicity. Cell viability, apoptosis rate and IC_{50}	Confocal laser scanning microscopy (CLSM)	123
2.	Topotecan		CC	Cetyl palmitate, Polysorbate 80, chloroform, methanol, water	Enhanced bioavailability, efficient encapsulation of hydrophilic, hydrophobic and amphiphilic drug	Lack of *in vivo* studies	↓ toxicity of drug, ↑ stability, mean drug loading (PDL) value was observed to be 92.03 ± 3.65%, indicating efficient loading of topotecan into the SLNs, ↓ PDI (0.151), and ↓ mean particle size (262.5 ± 8.32 nm)	*In vitro*	HeLa and SiHa cell line	Particle morphology, PDI, zeta potential and *in vitro* release	Not specified	124
3.	Morin hydrate		CC	Glyceryl monostearate, lecithin soy, polysorbate 80 and chloroform	High drug loading capacity, controlled drug release, improved biocompatibility	Lack of *in vivo* studies	↑ encapsulation efficiency (87.1%), ↓ zeta potential (−23.5 mV), and ↓ particle size (92 nm)	*In vitro*	HeLa cell line	Particle size, zeta potential, stearic stability, encapsulation efficiency, *in vitro* drug release	Not specified	122
4.	5-FU		CC	Poly-L-lactic acid, palmitic acid, PVA, dichloromethane, methanol, ethylene glycol, ethanol, dimethyl sulfoxide	Site-specific stimuli-responsive drug delivery, controlled drug release	Lack of *in vivo* studies, single drug model, lack of clinical validation	Rate modulated release (44.29% under single stimuli and 67.13% under combined stimuli after 15 days), ↓ zeta potential (−23.2 mV), indicating good stability of the SLNs, ↓ particle size (450.9 nm), PDI value (0.541), EE (33%) reflecting the amount of 5-FU successfully encapsulated in the SLNs	*In vitro*	Not specified	Particle size, PDI, biodegradation analysis, 5-FU release	Not specified	127
5.	Paclitaxel+α-tocopherol succinate-cisplatin prodrug		CC	Glyceryl monostearate, soybean lecithin, TAT peptide with terminal cysteine, 4-dimethyl aminopyridine, DSPE-PEG-Maleimide, *N*,*N*′-dicyclohexyl-carbodimide	High tumor accumulation, superior anti-tumor efficiency, enhanced internalization with HeLa cells, synergistic effect	—	↓ toxicity *in vivo*, ↑ tumor inhibition rate (72.2%) of TAT-modified SLNs, zeta potential of TAT PTXTOS-CDDP SLNs ↓ to −31 mV, indicating stability in the formulation, ↓ size of 109 nm, ↑ EE (90%), the drug loading (DL) of PTX ranged between 3.5% and 5.9%, while the DL of CDDP ranged from 2.3% to 4.4%	*In vitro* and *In vivo*	HeLa cell lines	Physicochemical properties (size, morphology, release profile), cytotoxicity evaluation, IC_{50} value	Cellular uptake efficiency was analyzed using fluorescent probe and coumarin-6	125

Table 3 Overview of genetic drug SLN formulation

S. no.	Genetic Sequence PLUS Drug	Use	Excipients used	Advantages	Limitations	Model	Cell culture model	Result	Evaluation parameter	Intracellular uptake studies	Ref.
1.	siRNA + Paclitaxel	CC	Gelucire® 50/13, Span® 85, Tween® 80, dichloromethane, DOTAP, dimethylsulfoxide, PEG 6000	Reduced dose in systemic circulation, less toxicity, possibility of self-administration, potential for local drug delivery	Lack of *in vivo* studies, lack of study on long-term stability and adverse effect	*In vitro*	HeLa cell lines	Simultaneous release of Bcl-2 siRNA and paclitaxel in vaginal suppository	Particle size, PDI, zeta potential, cytotoxicity, *in vitro* drug release, and transfection ability	Not specified	135

several critical limitations, including low drug-loading capacity, physical instability, potential toxicity, and manufacturing complexities. These challenges collectively impede regulatory approval and limit their commercial viability.[162,171] One of the primary barriers to SLN progression into late-stage clinical trials is their propensity for polymorphic transitions during storage.[162] For example, SLNs formulated with stearic acid often undergo a transition from the metastable α-form to the more stable β-form, leading to core destabilization and expulsion of encapsulated drugs, such as progesterone, into the external dispersion medium.[162]

Furthermore, the highly ordered crystalline matrix of SLNs significantly restricts their drug-loading capacity, typically capping it at approximately 10%, especially for hydrophilic compounds.[57,162] This limitation has shifted the focus towards NLCs, which incorporate liquid lipids into the matrix to enhance drug entrapment efficiency.[57] For instance, NLCs containing oleic acid have demonstrated up to 30% higher encapsulation of antifungal agents compared to their SLN counterparts, thereby offering greater promise for systemic antifungal therapies.[57] As of 2025, no SLN-based systemic therapeutic has progressed beyond Phase II clinical trials, with the majority of approved SLN products restricted to topical applications, such as clotrimazole-loaded SLNs for localized fungal infections.[116,171] These ongoing challenges highlight the pressing need for innovative formulation approaches, including the development of hybrid SLN–NLC systems, to overcome current limitations and facilitate successful clinical translation.

SLNs have been reported to be thermodynamically unstable during storage. The lipid composition and the method of SLN preparation may cause microphase separation leading to lipid segregation and resulting in a variable drug release pattern.[172–175] Moreover, these formulations demonstrate unacceptable drug-loading efficiency. The ordered crystalline lattice of the formulation allows a smaller space for drug incorporation in between the fatty acid chains. Polymorphic transitions during the production and storage of SLNs often result in drug expulsion and particle growth which affects the release pattern and overall bioavailability of the formulations.[57,174,176–178]

The employment of different production techniques followed by significant discrepancies in the selection of lipid, surfactant concentration, and mixing methods often lead to substantial variations in the particle size, surface characteristics, and drug encapsulation efficiency. These differences produce batch-to-batch variabilities, which negatively affect the pharmacokinetics and pharmacodynamics of the formulations and ultimately clinical translation and industrial scale-up.[179,180] Another limitation which may delay the preclinical to clinical transition process is the utilization of mouse models for studying the effects of SLNs on cancer. These models often fail to accurately describe the morphology of intratumoral vasculature over time. Additionally, studies have highlighted significant structural and functional variations between orthotopic and ectopic mouse models, as well as human tumors,[181,182] which collectively affect the translation process. As a result, it

is advisable to incorporate a more representative model such as the "prime editor mouse". This innovative model allows for the precise engineering of various mutations in cell lines and organoids obtained from primary tissues. By doing so, it effectively mimics cellular heterogeneity and the TME, which could be particularly beneficial for studying lethal cancers, such as cervical cancer.[183] Furthermore, using novel techniques such as tumour-on-a-chip can forecast the behavior of SLNs in CC within a controlled environment that closely mimics human tissue responses.[184–187]

Moreover, understanding the interaction of SLNs with the TME is essential, given TMEs' unique characteristics such as the acidic environment, hypoxia, and the presence of matrix metalloproteinase, that may enhance the efficacy and delivery of SLNs.[188–192] Current literature primarily focuses on targeted drug delivery with chemotherapeutic agents and genetic material in CC. However, to optimize delivery and personalize treatment approaches, comprehending the interaction of SLN with TME is imperative. A profound understanding of TME can facilitate its modulation to make it less conducive for tumor growth. Based on TME characteristics, patients can be stratified for effective treatment regimens, thereby improving their overall survival. Additionally, future research should focus on optimizing vaginal SLNs. The local action *via* vaginal delivery followed by active targeting with suitable overexpressed receptors can provide a synergistic targeted action. Furthermore, recent advances in nanotechnology may allow the development of personalized SLN formulations tailored to meet individual patient needs by addressing specific tumor characteristics.[189]

10. Conclusion

SLNs represent a transformative drug delivery system with advanced mechanisms for targeted drug delivery. Their effectiveness in administering various chemotherapeutic agents, coupled with genetic strategies, has revolutionized cancer therapeutics. Moreover, significant theranostic opportunities are awaiting exploration following a thorough and prompt analysis of CC. Future research should focus on the optimization and characterization of SLNs for specific chemotherapeutic agents to bolster their controlled drug-release profiles. It is essential to investigate combination therapies beyond paclitaxel and cisplatin to achieve a synergistic effect on antitumor activity. A broader exploration of novel anti-cancer compounds, such as targeted kinase inhibitors, immune checkpoint inhibitors, and next-generation alkylating agents, will be crucial in diversifying SLN applications. In particular, SLN formulations can be designed to overcome drug resistance mechanisms by incorporating multidrug-resistant (MDR) inhibitors to improve intracellular drug retention and therapeutic efficacy. The development of MEND represents a major advancement, allowing precise control of intracellular trafficking, which is vital for next-generation therapies, especially gene therapy. Additionally, further research should focus on tuning the physicochemical properties of SLNs, such as particle size, lipid composition, and surface charge, to enhance cell uptake, tumor penetration, and bioavailability.

The development of synergistic combination therapies is a major frontier of SLN research. In addition to conventional chemotherapy, combining SLNs with immunotherapy, gene therapy, and radiotherapy can enhance anti-tumor effects. For example, SLNs that co-encapsulate immune checkpoint inhibitors (*e.g.*, PD-1/PD-L1 inhibitors) with chemotherapeutic drugs may boost immune system activity while reducing systemic toxicity. Moreover, SLNs can be tailored for personalized medicine by incorporating patient-specific genetic and molecular markers. Predictive models driven by AI can assist in designing individualized SLN formulations based on a patient's tumor genetic profile, optimizing treatment efficacy, while minimizing adverse effects.

Although SLN-based therapeutics and vaccines hold immense promise, their translation from bench to bedside requires overcoming key hurdles. Rigorous *in vivo* studies, along with extensive preclinical and clinical trials, are necessary to validate the safety, efficacy, and pharmacokinetics of SLN-based therapies. Furthermore, establishing a robust regulatory framework with stringent quality control measures is imperative for guaranteeing the safety and efficacy of SLN-based formulations. Addressing concerns regarding immunogenicity, off-target effects, and long-term stability of SLN formulations will be critical in ensuring regulatory approval and widespread clinical adoption. Regulatory agencies, including the U.S. FDA requires comprehensive characterization of physicochemical properties, safety profiles, and stability data for approval of drug delivery systems. SLNs, in particular, must meet stringent criteria, including controlled particle size distribution, optimal zeta potential, low PDI, and appropriate ligand density, to ensure consistency, efficacy, and safety. Despite meeting these criteria, SLNs may still face regulatory rejection owing to critical formulation-related challenges. These include suboptimal bioequivalence, physical instability, and unresolved toxicity concerns such as macrophage-induced apoptosis or cytokine storm induction observed in preclinical models. Addressing these issues through robust preclinical evaluations and strategic formulation optimization is essential for regulatory success.

Despite the potential to encapsulate DNA, mRNA, and peptides and protect them from degradation, there are currently no SLN-encapsulated vaccines specifically approved for CC. These SLNs can be tailored to deliver DNA vaccines encoding HPV oncogenes such as E6 and E7 oncoproteins. The encapsulated SLNs would be taken up by antigen-presenting cells (APCs), eliciting a robust immune response. Additionally, peptides can be encapsulated in molecular adjuvants to enhance their uptake by the innate immune response. While ongoing research on nanotherapeutics for vaccine delivery is promising, none of them have been approved for clinical use, highlighting the critical need for further studies. Future research must focus on overcoming the existing formulation and stability challenges to develop effective SLN-based vaccine.

Author contributions

Pooja Tiwary, Krishil Oswal, Ryan Varghese, Ravi Vamsi Peri: conceptualization, data curation, formal analysis; Ryan Varghese: project administration, supervision; Pooja Tiwary, Krishil Oswal: writing – original draft, writing – review and editing, Pardeep Gupta: supervision. All authors commented on subsequent revisions and provided references.

Conflicts of interest

The authors declare that there are no competing interests.

Data availability

The data in this *Review* article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

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