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Review Paper

Therapeutic Potential of Solid Lipid Nanoparticles in Triple-Negative Breast Cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) is an aggressive and heterogeneous subtype of breast cancer characterized by the absence of estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2), resulting in limited treatment options and poor clinical outcomes. Conventional chemotherapy remains the primary therapeutic approach; however, it is often associated with systemic toxicity, low specificity, and the development of multidrug resistance. In recent years, nanotechnology-based drug delivery systems have gained significant attention for improving cancer therapy, among which solid lipid nanoparticles (SLNs) have emerged as a promising platformSLNs are biocompatible and biodegradable nanocarriers capable of enhancing the solubility, stability, and bioavailability of both hydrophilic and lipophilic drugs. Their ability to facilitate controlled and targeted drug delivery, along with improved cellular uptake and prolonged circulation time, makes them particularly suitable for TNBC management. Furthermore, surface modification strategies enable active targeting of tumorcells, thereby increasing therapeutic efficacy while minimizing adverse effects. SLNs also demonstrate potential in overcoming drug resistance through enhanced intracellular drug accumulation and co-delivery of therapeutic agents, including chemotherapeutics, phytoconstituents, and nucleic acids.This review highlights the design, mechanisms, and therapeutic applications of SLNs in TNBC, with a focus on their role in targeted drug delivery and resistance modulation. Additionally, current advances, safety considerations, and challenges associated with clinical translation are discussed. Overall, SLNs represent a promising nanotechnological approach for improving the efficacy and safety of TNBC treatment, although further clinical investigations are required to establish their full therapeutic potential.

INTRODUCTION

Breast cancer remains one of the leading causes of cancer-related morbidity and mortality among

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women worldwide. Among its subtypes, triple-negative breast cancer (TNBC) is particularly aggressive and clinically challenging due to the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). This lack of targetable receptors significantly limits the effectiveness of hormonal and HER2-targeted therapies, leaving chemotherapy as the primary systemic treatment option [1]. TNBC is associated with rapid tumor progression, high rates of metastasis, poor prognosis, and a higher likelihood of recurrence compared to other breast cancer subtypes [2].

Despite advances in conventional chemotherapy, the treatment of TNBC is hindered by several limitations, including non-specific drug distribution, systemic toxicity, low bioavailability, and the emergence of multidrug resistance (MDR) [3]. These challenges necessitate the development of novel therapeutic strategies that can improve drug delivery efficiency and enhance therapeutic outcomes while minimizing adverse effects. In this context, nanotechnology-based drug delivery systems have emerged as a promising approach for cancer therapy.

Solid lipid nanoparticles (SLNs) have gained considerable attention as an effective nanocarrier system due to their unique physicochemical and biological properties. SLNs are composed of physiological lipids that remain solid at body temperature, providing a stable matrix for drug encapsulation. They offer several advantages, including improved drug stability, controlled and sustained release, enhanced bioavailability, and excellent biocompatibility [4]. Furthermore, SLNs can be engineered for passive targeting via the enhanced permeability and retention (EPR) effect, as well as active targeting through surface modification with ligands such as antibodies, peptides, or polymers [5].

In the context of TNBC, SLNs have demonstrated significant potential in improving therapeutic efficacy by enhancing drug accumulation at tumor sites, facilitating intracellular drug delivery, and overcoming drug resistance mechanisms. Additionally, SLNs enable the co-delivery of multiple therapeutic agents, including chemotherapeutic drugs, phytochemicals, and nucleic acids, thereby supporting combination therapy strategies [6]. These features make SLNs a promising platform for addressing the current limitations of TNBC treatment.

This review aims to provide a comprehensive overview of the therapeutic potential of SLNs in TNBC, focusing on their design, mechanisms of action, and applications in targeted drug delivery. It also discusses recent advancements, challenges, and future perspectives in the development of SLN-based therapies for TNBC management.

2. Triple-Negative Breast Cancer: Pathophysiology and Challenges

Triple-negative breast cancer (TNBC) is a highly heterogeneous and aggressive subtype of breast cancer defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This molecular profile not only distinguishes TNBC from other breast cancer subtypes but also contributes significantly to its complex pathophysiology and limited therapeutic options.

From a pathophysiological perspective, TNBC is characterized by substantial genetic, molecular, and phenotypic heterogeneity. Advanced genomic studies have revealed that TNBC comprises multiple subtypes with distinct gene expression patterns, including basal-like, mesenchymal, and immunomodulatory variants. These subtypes exhibit alterations in key signaling pathways such as PI3K/AKT/mTOR, MAPK, and DNA damage repair mechanisms, particularly involving BRCA1 mutations, which play a crucial role in tumor initiation and progression. Furthermore, dysregulation of epithelial–mesenchymal

transition (EMT) and increased expression of oncogenic transcription factors contribute to enhanced invasiveness and metastatic potential.

The tumor microenvironment (TME) also plays a pivotal role in TNBC progression. It consists of various cellular components, including cancer-associated fibroblasts, immune cells, and extracellular matrix elements, which collectively influence tumor growth, immune evasion, and therapeutic response. Interactions between tumor cells and the TME promote angiogenesis, inflammation, and immune suppression, thereby facilitating tumor progression and metastasis Additionally, TNBC often exhibits high levels of tumor-infiltrating lymphocytes (TILs), reflecting its immunogenic nature, which presents both challenges and opportunities for immunotherapy.One of the major challenges in TNBC management is its aggressive clinical behavior. TNBC is associated with rapid tumor growth, early recurrence, and a higher likelihood of distant metastasis to organs such as the lungs, brain, and liver. The absence of specific molecular targets limits the use of endocrine and HER2-targeted therapies, leaving chemotherapy as the mainstay of treatment. However, the effectiveness of chemotherapy is often compromised by systemic toxicity and variable patient response.Another critical challenge is the development of multidrug resistance (MDR), which significantly reduces therapeutic efficacy. Mechanisms contributing to MDR in TNBC include overexpression of efflux transporters, alterations in apoptotic pathways, enhanced DNA repair capacity, and tumor heterogeneity. These factors collectively lead to treatment failure and disease progression.Moreover, the lack of reliable biomarkers for early diagnosis and targeted therapy further complicates TNBC management. Although recent advances in molecular profiling and immunotherapy have shown promise, their clinical application remains limited due to variability in patient response and high treatment costs.

3. Solid Lipid Nanoparticles (SLNs): An Overview

3.1 Definition and Structure

Solid lipid nanoparticles (SLNs) are submicron colloidal carriers typically ranging from 10 to 1000 nm, composed of physiologically compatible lipids that remain solid at both room and body temperature. Structurally, SLNs consist of a solid lipid core matrix in which the drug is dispersed or dissolved, surrounded by a stabilizing surfactant layer. This solid matrix provides protection to encapsulated drugs and enables controlled drug release [1], [2]. The spherical morphology and lipid-based architecture contribute to enhanced stability, improved drug loading, and targeted delivery capabilities.

3.2 Composition of SLNs

SLNs are primarily composed of three key components: solid lipids, surfactants (emulsifiers), and active pharmaceutical ingredients (APIs). The lipid phase typically includes triglycerides, fatty acids, waxes, or steroids, which form the solid core of the nanoparticle. Surfactants such as phospholipids, polysorbates, or poloxamers are used to stabilize the dispersion and prevent aggregation. The selection of lipid and surfactant plays a crucial role in determining particle size, drug loading efficiency, and release behavior [2], [3]. Additionally, SLNs can encapsulate both hydrophilic and lipophilic drugs, enhancing their stability and bioavailability.

3.3 Methods of Preparation

Various techniques have been developed for the preparation of SLNs, each with specific advantages and limitations. Commonly used

methods include high-pressure homogenization (hot and cold homogenization), solvent emulsification–evaporation, microemulsion-based techniques, ultrasonication, and solvent diffusion methods. Among these, high-pressure homogenization is widely preferred due to its scalability and ability to produce nanoparticles with uniform size distribution [4], [5]. The choice of preparation method significantly influences the physicochemical properties, stability, and drug release characteristics of SLNs.

3.4 Physicochemical Properties

The performance of SLNs is largely governed by their physicochemical characteristics, including particle size, zeta potential, crystallinity, drug loading capacity, and release profile. Particle size affects cellular uptake and biodistribution, while zeta potential determines colloidal stability. The crystalline structure of the lipid matrix influences drug incorporation and release kinetics. SLNs exhibit controlled and sustained drug release due to the solid lipid core, which reduces drug leakage and degradation [1], [5]. These properties can be tailored by modifying formulation parameters such as lipid type, surfactant concentration, and preparation technique.

3.5 Advantages and Limitations of SLNs

SLNs offer several advantages as drug delivery systems, including excellent biocompatibility, biodegradability, protection of labile drugs, controlled drug release, and improved bioavailability. They also enable targeted drug delivery and reduced systemic toxicity, making them suitable for cancer therapy applications such as TNBC [1], [4]. Additionally, SLNs can be produced without the use of organic solvents and are scalable for industrial production.

However, SLNs also have certain limitations, including limited drug loading capacity, potential drug expulsion during storage due to lipid crystallization, and challenges in maintaining long-term stability. Furthermore, polymorphic transitions of lipids may affect drug release behavior and formulation reproducibility [2], [5]. These limitations have led to the development of second-generation systems such as nanostructured lipid carriers (NLCs) to overcome these drawbacks.

4. Mechanisms of SLNs in Cancer Therapy

Solid lipid nanoparticles (SLNs) enhance anticancer efficacy through multiple mechanisms, including passive and active targeting, improved cellular uptake, and controlled drug release. These mechanisms enable efficient drug delivery to tumor tissues while minimizing systemic toxicity.

4.1 Enhanced Permeability and Retention (EPR) Effect

The enhanced permeability and retention (EPR) effect is a fundamental mechanism underlying passive targeting of SLNs in cancer therapy. Tumor vasculature is highly irregular and leaky, with endothelial gaps that allow nanoparticles (typically 100–800 nm) to extravasate and accumulate within tumor tissues. Additionally, the impaired lymphatic drainage in tumors leads to prolonged retention of nanoparticles at the tumor site.SLNs exploit this phenomenon to achieve higher local drug concentrations in tumors compared to normal tissues. This passive targeting enhances therapeutic efficacy while reducing off-target toxicity, making SLNs particularly suitable for treating aggressive cancers such as TNBC.

4.2 Cellular Uptake Mechanisms

SLNs enter cancer cells primarily through endocytosis pathways, including clathrin-mediated, caveolae-mediated, and macropinocytosis mechanisms. Due to their nanoscale size and lipid composition, SLNs exhibit enhanced interaction with cellular membranes, facilitating efficient internalization.Once internalized, SLNs can escape endosomal compartments and release the encapsulated drug into the cytoplasm, thereby increasing intracellular drug concentration. Additionally, SLNs may utilize lymphatic uptake pathways and chylomicron formation to enhance systemic absorption and targeted delivery.

4.3 Controlled and Sustained Drug Release

SLNs provide controlled and sustained drug release due to their solid lipid matrix. Drugs incorporated within the lipid core are released through diffusion, matrix erosion, or lipid degradation mechanisms. Initial burst release may occur from drug molecules located on the nanoparticle surface, followed by prolonged release from the inner core.This controlled release profile maintains therapeutic drug concentrations over an extended period, reduces dosing frequency, and minimizes systemic toxicity. It also protects labile drugs from degradation, thereby enhancing their stability and bioavailability.

4.4 Surface Functionalization and Targeting Strategies

Surface modification of SLNs enables active targeting of cancer cells by attaching ligands such as antibodies, peptides, folic acid, or polymers (e.g., PEG). These ligands specifically bind to overexpressed receptors on tumor cells, facilitating receptor-mediated endocytosis and improving targeting efficiency.

Functionalized SLNs can selectively deliver drugs to tumor tissues while sparing normal cells, thereby enhancing therapeutic efficacy and reducing adverse effects. This approach is particularly beneficial in TNBC, where specific molecular targets are limited.

4.5 Stimuli-Responsive Drug Delivery

Stimuli-responsive SLNs are designed to release drugs in response to specific internal or external triggers such as pH, temperature, enzymes, or redox conditions. Tumor microenvironments typically exhibit acidic pH and elevated enzyme activity, which can be exploited for site-specific drug release.For example, pH-sensitive SLNs release drugs preferentially in acidic tumor environments, while temperature-sensitive systems respond to hyperthermia conditions. These smart delivery systems further enhance targeting precision and therapeutic outcomes while minimizing systemic exposure.

5. Therapeutic Applications of SLNs in TNBC

Solid lipid nanoparticles (SLNs) have emerged as versatile nanocarriers in the treatment of triple-negative breast cancer (TNBC), enabling improved drug delivery, enhanced therapeutic efficacy, and reduced systemic toxicity. Their ability to encapsulate diverse therapeutic agents and provide targeted delivery makes them highly suitable for managing this aggressive cancer subtype.

5.1 Delivery of Chemotherapeutic Agents

SLNs are widely utilized for the delivery of conventional chemotherapeutic drugs such as doxorubicin, paclitaxel, and docetaxel. These drugs often suffer from poor solubility, systemic toxicity, and non-specific distribution. Encapsulation into SLNs enhances drug stability,

prolongs circulation time, and facilitates targeted accumulation at tumor sites via passive and active targeting mechanisms.Studies have demonstrated that SLN-loaded chemotherapeutics significantly improve cytotoxicity against cancer cells while reducing adverse effects on healthy tissues. Additionally, SLNs enhance intracellular drug concentration and improve therapeutic index, thereby increasing treatment efficacy in TNBC [1], [2].

5.2 Delivery of Phytochemicals and Natural Compounds

Phytochemicals such as curcumin, quercetin, resveratrol, and silymarin possess potent anticancer properties but are limited by poor solubility, low bioavailability, and rapid degradation. SLNs serve as effective carriers for these bioactive compounds, improving their pharmacokinetic profile and therapeutic potential.Encapsulation of phytochemicals into SLNs enhances their stability, cellular uptake, and controlled release. Moreover, SLN-based delivery systems have demonstrated improved anticancer activity and reduced systemic toxicity compared to free phytochemicals, making them promising candidates for TNBC therapy [3], [4].

5.3 Gene Therapy and Nucleic Acid Delivery

SLNs have gained attention as carriers for gene therapy applications, including the delivery of small interfering RNA (siRNA), plasmid DNA, and microRNA. These nucleic acids can regulate gene expression, silence oncogenes, and restore tumor suppressor functions in cancer cells.Cationic SLNs, in particular, facilitate efficient binding and protection of nucleic acids from enzymatic degradation, enabling effective intracellular delivery. This approach has shown potential in modulating molecular pathways involved in TNBC progression and drug resistance.

5.4 Combination Therapy Approaches

Combination therapy using SLNs involves the co-delivery of multiple therapeutic agents, such as chemotherapeutic drugs and phytochemicals or drug–gene combinations. This strategy enhances therapeutic efficacy through synergistic effects, reduces required drug doses, and minimizes toxicity.SLNs enable simultaneous delivery of multiple agents with different mechanisms of action, improving treatment outcomes and overcoming multidrug resistance. Such combinatorial approaches are particularly beneficial in TNBC, where monotherapy often fails due to tumor heterogeneity.

5.5 Theranostic Applications

SLNs also hold promise in theranostics, which integrates therapy and diagnosis into a single platform. By incorporating imaging agents along with therapeutic drugs, SLNs enable real-time monitoring of drug distribution and treatment response.Theranostic SLNs can be used for targeted imaging of tumors and simultaneous drug delivery, allowing personalized treatment strategies. This approach enhances treatment precision and facilitates early detection of therapeutic outcomes in TNBC [1].

6. SLNs for Overcoming Drug Resistance in TNBC

Drug resistance, particularly multidrug resistance (MDR), is a major obstacle in the effective treatment of triple-negative breast cancer (TNBC). It significantly reduces the efficacy of chemotherapeutic agents and contributes to tumor recurrence and poor clinical outcomes. Solid lipid nanoparticles (SLNs) have emerged as a promising

strategy to overcome these resistance mechanisms by enhancing drug delivery, improving intracellular drug accumulation, and modulating molecular pathways associated with resistance.One of the primary mechanisms of MDR in TNBC involves the overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein (P-gp), which actively efflux anticancer drugs out of cancer cells, reducing intracellular drug concentration. SLNs can bypass these efflux pumps by facilitating endocytic uptake, thereby enhancing intracellular drug retention and therapeutic efficacy. Studies have shown that drug-loaded SLNs significantly increase intracellular accumulation of chemotherapeutic agents compared to free drugs.In addition to bypassing efflux transporters, SLNs can modulate key signaling pathways associated with drug resistance. For instance, curcumin-loaded SLNs have been reported to inhibit the Akt/NF-κB signaling pathway, which is involved in the regulation of cell survival and drug resistance. This inhibition leads to reduced expression of resistance-related proteins and restoration of chemosensitivity in TNBC cells. Such molecular modulation enhances the effectiveness of conventional chemotherapeutics like doxorubicin.SLNs also improve drug bioavailability and stability, which are critical factors in overcoming resistance. Encapsulation of drugs within a lipid matrix protects them from enzymatic degradation and premature elimination, ensuring sustained drug release and prolonged exposure to cancer cells. This sustained release helps maintain therapeutic drug concentrations, reducing the likelihood of resistance development.Another important strategy involves the co-delivery of multiple therapeutic agents using SLNs. By simultaneously delivering chemotherapeutic drugs and resistance modulators (such as phytochemicals or gene-silencing agents), SLNs enable synergistic effects that enhance treatment efficacy. This combinatorial approach can effectively target multiple resistance pathways and improve therapeutic outcomes in TNBC.Furthermore, surface-modified SLNs, such as PEGylated or ligand-targeted systems, enhance tumor-specific delivery and reduce off-target drug distribution. This targeted delivery minimizes systemic toxicity and ensures higher drug concentration at the tumor site, thereby overcoming resistance associated with poor drug penetration.Despite these advantages, challenges such as variability in nanoparticle uptake, potential toxicity, and limited clinical validation remain. However, ongoing research continues to optimize SLN formulations to improve their efficacy in overcoming drug resistance in TNBC.

7. Preclinical and Clinical Studies

The therapeutic potential of solid lipid nanoparticles (SLNs) in triple-negative breast cancer (TNBC) has been extensively evaluated through preclinical investigations, including in vitro and in vivo studies, with emerging translational insights. These studies demonstrate the capability of SLNs to enhance drug delivery, improve therapeutic efficacy, and reduce systemic toxicity.

7.1 In Vitro Studies

In vitro studies play a crucial role in evaluating the cytotoxicity, cellular uptake, and therapeutic efficacy of SLN formulations against TNBC cell lines such as MDA-MB-231 and MCF-7. Numerous studies have demonstrated that SLN-encapsulated drugs exhibit significantly higher cytotoxic effects compared to free drugs due to enhanced cellular internalization and sustained drug release.For example, SLN-based formulations of chemotherapeutic agents and bioactive compounds have shown improved inhibition of cancer cell proliferation and

induction of apoptosis. Additionally, targeted SLNs, such as ligand-functionalized systems, have demonstrated enhanced receptor-mediated uptake and increased intracellular drug concentration in TNBC cells.Furthermore, combination-loaded SLNs (e.g., doxorubicin with curcumin) have shown synergistic anticancer effects, improving drug uptake and overcoming resistance mechanisms in vitro. These findings highlight the potential of SLNs to enhance therapeutic efficiency at the cellular level.

7.2 In Vivo Studies

In vivo studies using animal models provide critical insights into the pharmacokinetics, biodistribution, and antitumor efficacy of SLNs. Several studies using murine xenograft models of TNBC have demonstrated that SLN-based formulations significantly reduce tumor growth and improve survival rates compared to conventional therapies.For instance, lipid-based SLNs loaded with anticancer agents have shown enhanced tumor accumulation via the enhanced permeability and retention (EPR) effect, leading to improved therapeutic outcomes. In a study involving SLN-based delivery of anticancer compounds, tumor growth inhibition of up to approximately 70–80% was observed in TNBC-bearing mice, indicating strong antitumor activity.Additionally, SLNs have been shown to improve pharmacokinetic profiles by prolonging drug circulation time and reducing systemic toxicity. Targeted SLNs further enhance tumor-specific delivery, minimizing off-target effects and improving therapeutic index.

7.3 Clinical Trials and Translational Status

Despite promising preclinical results, the clinical translation of SLNs in TNBC therapy is still in the early stages. Currently, most SLN-based systems remain under preclinical investigation, with limited direct clinical trials specifically focused on SLNs for TNBC. However, lipid-based nanoparticle systems, including liposomes and related carriers, have successfully progressed into clinical applications, demonstrating the translational potential of lipid nanocarriers.Recent reviews indicate that SLNs offer advantages such as improved therapeutic efficacy, reduced toxicity, and enhanced drug targeting, making them strong candidates for future clinical development. Nevertheless, challenges such as large-scale manufacturing, formulation stability, regulatory approval, and long-term safety evaluation need to be addressed before widespread clinical application.Ongoing research is focused on optimizing SLN formulations, incorporating targeting ligands, and integrating multifunctional approaches such as theranostics to facilitate their clinical translation in TNBC treatment.

8. Safety, Toxicity, and Regulatory Considerations

The clinical translation of solid lipid nanoparticles (SLNs) for triple-negative breast cancer (TNBC) therapy depends significantly on their safety profile, toxicity behavior, and compliance with regulatory standards. Although SLNs are generally regarded as biocompatible and biodegradable, a comprehensive evaluation of their toxicological and regulatory aspects is essential for their successful clinical application.

8.1 Safety and Toxicity Profile of SLNs

SLNs are primarily composed of physiological lipids and surfactants that are generally recognized as safe (GRAS), contributing to their favorable biocompatibility. Their lipid-based nature allows for reduced cytotoxicity compared to polymeric or metallic nanoparticles. However, toxicity may arise depending on factors such as particle size, surface charge, lipid composition, and route of

administration.Preclinical studies have demonstrated that SLNs exhibit relatively low acute and chronic toxicity, with minimal immunogenicity and good tolerability in biological systems. Nevertheless, accumulation of nanoparticles in organs such as the liver, spleen, and lungs due to uptake by the mononuclear phagocyte system (MPS) may lead to potential long-term toxicity concerns.Additionally, high surfactant concentrations or inappropriate lipid selection may induce cytotoxic effects, oxidative stress, or membrane disruption. Therefore, careful optimization of formulation parameters is crucial to ensure safety and minimize adverse effects.

8.2 Pharmacokinetics and Biodistribution

The pharmacokinetic behavior and biodistribution of SLNs play a critical role in determining their therapeutic safety and efficacy. SLNs typically exhibit prolonged circulation time and enhanced accumulation in tumor tissues due to the enhanced permeability and retention (EPR) effect.Once administered, SLNs undergo opsonization and are primarily cleared by the reticuloendothelial system (RES), leading to accumulation in organs such as the liver and spleen. This biodistribution pattern may limit drug availability at the target site and raise concerns regarding off-target toxicity.Surface modification strategies, such as PEGylation, can reduce opsonization, prolong systemic circulation, and improve tumor-specific targeting. These modifications enhance therapeutic efficiency while minimizing unintended toxicity.

8.3 Regulatory Considerations for SLNs

The regulatory approval of SLN-based formulations remains a significant challenge due to the complexity of nanomedicines. Although SLNs are composed of excipients already approved for pharmaceutical use, their nanoscale properties introduce additional safety and quality considerations.Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require comprehensive evaluation of nanocarriers, including physicochemical characterization, toxicity studies, pharmacokinetics, and long-term safety data.

Key regulatory challenges include:

- Lack of standardized guidelines for nanoparticle characterization
- Variability in manufacturing processes and scalability issues
- Difficulty in predicting long-term toxicity and environmental impact
- Need for reproducibility and batch-to-batch consistency

Furthermore, any modification in formulation, route of administration, or excipient composition requires additional safety validation, even if the individual components are previously approved.

9. Challenges and Limitations

Despite the promising therapeutic potential of solid lipid nanoparticles (SLNs) in triple-negative breast cancer (TNBC), several challenges and limitations hinder their widespread clinical application. These limitations are primarily related to formulation constraints, stability issues, scalability, and translational barriers.One of the main challenges associated with SLNs is their limited drug loading capacity, which arises from the highly ordered crystalline structure of solid lipids. This rigid structure restricts the incorporation of drug molecules, particularly hydrophilic compounds, thereby reducing encapsulation efficiency and therapeutic effectiveness. Furthermore, during storage, lipid crystallization and polymorphic transitions may lead to drug expulsion from the lipid matrix,

resulting in reduced drug content and inconsistent release profiles.Another significant limitation is the stability of SLN formulations. Although SLNs are generally stable systems, they may undergo aggregation, particle growth, or gelation over time, especially under varying environmental conditions such as temperature and pH. Additionally, the presence of surfactants, while essential for stabilization, may induce cytotoxicity or irritation at higher concentrations, thereby affecting the safety profile of the formulation.The initial burst release phenomenon is another concern associated with SLNs, where a significant portion of the drug is rapidly released from the nanoparticle surface. This can lead to suboptimal therapeutic outcomes and increased risk of systemic toxicity. Moreover, controlling drug release kinetics remains a challenge due to variability in lipid composition and crystallinity.From a manufacturing perspective, scale-up and reproducibility remain critical hurdles. Although techniques such as high-pressure homogenization are scalable, maintaining uniform particle size distribution, drug loading, and batch-to-batch consistency is challenging. Variations in preparation methods can significantly influence the physicochemical properties and performance of SLNs.Another major limitation is the lack of comprehensive understanding of SLN behavior in biological systems, including interactions with proteins (protein corona formation), cellular uptake pathways, and long-term biodistribution. These uncertainties complicate the prediction of therapeutic outcomes and safety profiles.In addition, clinical translation of SLNs is still limited, as most studies remain at the preclinical stage. Challenges such as regulatory approval, long-term toxicity evaluation, and cost-effectiveness need to be addressed before SLNs can be widely adopted in clinical practice. The absence of standardized guidelines for nanoparticle characterization and evaluation further delays their regulatory acceptance.Finally, the encapsulation efficiency and formulation complexity pose additional challenges. Achieving high drug loading while maintaining stability and controlled release requires careful optimization of formulation parameters, including lipid type, surfactant concentration, and preparation method.

10. Emerging Trends and Future Perspectives

The field of solid lipid nanoparticles (SLNs) in triple-negative breast cancer (TNBC) therapy is rapidly evolving, with several innovative approaches being explored to overcome current limitations and enhance therapeutic outcomes. Emerging trends focus on advanced lipid systems, targeted delivery, precision medicine, immunotherapy integration, and computational design strategies.

10.1 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) represent the second generation of lipid nanoparticles developed to overcome the limitations of SLNs, particularly low drug loading and drug expulsion during storage. NLCs are composed of a mixture of solid and liquid lipids, resulting in a less ordered lipid matrix that enhances drug incorporation and stability.These systems provide improved encapsulation efficiency, controlled drug release, and reduced risk of drug leakage. NLCs have demonstrated superior performance compared to SLNs in delivering chemotherapeutic agents and bioactive compounds in TNBC models.

10.2 Targeted and Ligand-Based SLNs

Targeted SLNs involve surface modification with ligands such as antibodies, peptides, folic acid, or aptamers to achieve active targeting of cancer cells. These ligands bind to overexpressed receptors on TNBC cells, such as folate receptors

or epidermal growth factor receptors (EGFR), facilitating receptor-mediated endocytosis.Ligand-based targeting enhances drug accumulation at tumor sites, improves therapeutic efficacy, and reduces systemic toxicity. Recent studies have shown that targeted SLNs significantly enhance cellular uptake and tumor specificity in TNBC, making them a promising strategy for precision drug delivery.

10.3 Personalized Nanomedicine

Personalized nanomedicine is an emerging approach that tailors nanoparticle-based therapies according to the genetic and molecular profile of individual patients. Given the heterogeneity of TNBC, personalized treatment strategies can significantly improve therapeutic outcomes.SLNs can be customized to deliver specific drugs or gene therapies based on tumor biomarkers, enabling precision targeting and minimizing adverse effects. Integration of molecular diagnostics with nanotechnology is expected to revolutionize TNBC management by providing patient-specific therapeutic solutions.

10.4 Integration with Immunotherapy

The combination of SLNs with immunotherapy represents a promising strategy for enhancing anticancer immune responses. SLNs can be used to deliver immunomodulatory agents such as checkpoint inhibitors, cytokines, or tumor antigens, thereby enhancing immune system activation against cancer cells.In TNBC, which is considered an immunogenic tumor subtype, SLN-based delivery systems can improve the efficacy of immune checkpoint blockade therapies by enhancing drug delivery to tumor-infiltrating immune cells. This combinational approach has shown significant potential in preclinical studies.

10.5 Artificial Intelligence in Nanoparticle Design

Artificial intelligence (AI) and machine learning are increasingly being utilized to optimize nanoparticle design and formulation. AI-based models can predict key parameters such as particle size, drug loading efficiency, release kinetics, and biological interactions, thereby accelerating the development process.In SLN research, AI can assist in selecting optimal lipid compositions, surfactants, and preparation methods to achieve desired therapeutic outcomes. This data-driven approach enhances reproducibility, reduces experimental costs, and improves the efficiency of nanoparticle development for TNBC therapy.

CONCLUSION

Triple-negative breast cancer (TNBC) remains a highly aggressive and therapeutically challenging malignancy due to its molecular heterogeneity, lack of hormone receptors, and limited targeted treatment options. Conventional therapies, although widely used, are often associated with systemic toxicity, poor selectivity, and the emergence of multidrug resistance, leading to suboptimal clinical outcomes.Solid lipid nanoparticles (SLNs) have emerged as a promising nanocarrier system capable of addressing many of these limitations. Their biocompatible and biodegradable lipid matrix enables efficient encapsulation of diverse therapeutic agents, including chemotherapeutics, phytochemicals, and nucleic acids. SLNs enhance drug solubility, stability, and bioavailability while providing controlled and sustained drug release. Furthermore, their ability to exploit passive targeting via the enhanced permeability and retention (EPR) effect, along with active targeting through surface functionalization, significantly improves drug accumulation at tumor sites.

Importantly, SLNs play a crucial role in overcoming drug resistance in TNBC by enhancing intracellular drug delivery, bypassing efflux transporters, and enabling combination therapy approaches. Preclinical studies have demonstrated improved therapeutic efficacy and reduced systemic toxicity, highlighting their potential as an advanced drug delivery platform.Despite these advantages, challenges such as limited drug loading capacity, stability issues, scale-up difficulties, and regulatory hurdles must be addressed to facilitate clinical translation. Emerging strategies, including nanostructured lipid carriers (NLCs), targeted delivery systems, personalized nanomedicine, and integration with immunotherapy and artificial intelligence, are expected to further enhance the effectiveness of SLN-based therapies.

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