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Review Article

A Review on Preparation Methods of Drug Loading Solid Lipid Nanoparticles with the Application in various Cancer Treatment

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ABSTRACT

The pharmaceutical and cosmetics industries, as well as the domains of research and clinical medicine, have all benefited from the advent of Solid Lipid Nanoparticles (SLN) as a promising new drug delivery technique. These SLN are receiving more and more interest as colloidal drug carriers for integrating hydrophilic or lipophilic medicines recently. Technology is the newest development in cancer therapy and numerous compounds are currently being studied for use in medication delivery. It aids the pharmacist in creating a product with the greatest therapeutic benefit and the fewest possible negative effects. Lack of selectivity for tumor tissue is a major problem with anticancer drugs, resulting in significant side effects and low cure rates. Cancer is a group of diseases characterized by the unchecked growth and division of aberrant cells. Significant advantages of SLNs include low toxicity, high drug bioavailability, flexible drug integration and the possibility of industrial-scale production. The molecular structure of SLN preparations is crucial to their quality and this structure is in turn determined by the composition and the method of production. Furthermore, SLNs allow for the circumvention of a number of physiological barriers that obstruct the transport of drugs to tumours and are also capable of evading the multidrug resistance mechanisms that are inherent to cancer cells. This review article discusses the various SLN preparation techniques, various aspects to enhance drug loading in SLNs, as well as potential applications in cancer targeted medication therapy followed by their stability aspects.

Keywords: Solid lipid nanoparticles, Cancer, Microfluedics, Drug loading.

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INTRODUCTION

Over the course of the last five decades, significant progress has been made in the field of biomedicine, particularly in areas such as biochemistry, molecular biology, biophysics and cell biology. These scientific disciplines have contributed to enormous breakthroughs in our understanding of various diseases at the molecular level. This advancement has facilitated the synthesis of therapeutic molecules that have high efficacy in selectively targeting the pathological molecular and cellular mechanisms underlying the disease. This is particularly crucial within the domain of cancer research, where continuous progress is being achieved. Regrettably, the development of novel pharmaceuticals alone does not adequately augment their therapeutic efficacy. Certain drugs require encapsulation in drug carriers due to their lack of water solubility, rendering them unable to be administered directly. In certain instances, pharmaceutical compounds may encounter difficulties traversing cell membranes, leading to suboptimal accumulation at the intended site. In order to address this issue, it is necessary to administer pharmacological doses at elevated levels, leading to increased toxicity and a range of undesirable side effects. Consequently, the implementation of a focused drug delivery system has the potential to facilitate the transfer of optimal drug concentrations to the intended tissue or cell, thereby improving the bioavailability of the treatment and mitigating the adverse consequences associated with high dosages. The field of nanotechnology has expanded the range of therapeutic options for chemicals that are currently successful by developing efficient Drug Delivery Systems (DDS). The utilization of nanotechnology in the transportation and delivery of drugs has resulted in significant advancements in the field of medicine, giving rise to a novel discipline known as nanomedicine.[1] The development of various Drug Delivery Systems (DDS) has been achieved by integrating different characteristics such as surface charge, functional groups, PEGylation or other coating methods, attachment of targeted moieties, size (small or large), morphologies (spherical, rod-shaped, or cuboidal) and

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composition (organic, inorganic, or hybrid).[2] The aforementioned factors, including solubility, pharmacokinetic profile, cellular absorption, biodistribution pattern, circulation time and clearance mechanisms, can be improved by this approach.[1,2] The field of nanotechnology has experienced significant progress, resulting in the development of a diverse array of nanocarriers. These nanocarriers offer a multitude of opportunities to effectively tackle various therapeutic challenges by employing tailored strategies. The most extensively investigated organic Drug Delivery Systems (DDS) encompass liposomes, dendrimers, polymeric nanoparticles or micelles, polymer-drug/protein conjugates and lipid nanoparticles. In addition to the, inorganic nanocarriers such as carbon nanotubes and mesoporous silica nanoparticles have also been developed.[1-3]

Solid lipid nanoparticles, also referred to as "zero dimensional" nanomaterials, are a distinct class of nanomaterials. The definition is derived from the characteristic that all of their dimensions fall within the nanoscale range, specifically below 100 nm. In contrast, two-dimensional nanomaterials possess two dimensions exceeding the nanoscale, while one-dimensional nanomaterials have one dimension surpassing the nanoscale (e.g., self-assembled monolayer films). Solid Lipid Nanoparticles (SLN) is considered as colloidal drug carrier systems.[4-6] The fundamental components consist of water, an emulsifier and solid lipid. The term "lipid" encompasses a wide range of substances, such as triglycerides, partial glycerides, PEGylated lipids, fatty acids, steroids and waxes. Various emulsifiers from different classes, such as poloxamer, polysorbates, lecithin and bile acids, have been employed to achieve stability in the lipid dispersion. Although they exhibit variations in lipid composition, they have a striking resemblance to nanoemulsions. In the context of Self-Lipidization Nanoparticles (SLN), it is observed that a lipid substance with a solid state at normal room temperature, such as glycerides with a high melting point or waxes, is employed as a substitute for the liquid lipid typically used in emulsions.[7,8] Upon their inception in approximately 1970, nanoparticles were initially conceived as potential vehicles for vaccines and anti-cancer drugs. Within the realm of scholarly literature, there exists a plethora of innovative research articles pertaining to the field of solid lipid nanotechnology for the purpose of drug delivery. These articles delve into comprehensive discussions regarding the various techniques employed in the preparation of Solid Lipid Nanoparticles (SLN), as well as the characterization and classification of these nanoparticles. Additionally, these studies explore the structural properties of SLN, examine the factors that influence their formation and storage stability, elucidate the principles underlying drug loading onto SLN and investigate the characteristics of drug release from these Nanoparticles.[9-12]

Solid lipid nanoparticles (SLNs) have a uniform surface, with an average diameter ranging from 50 to 1,000 nm and possess a spherical morphology. The physiological and chemical characterization of solid lipid nanoparticles (SLNs) plays a crucial role in determining their behaviors, both *in vivo* and *in vitro*. The conventional Solid Lipid Nanoparticles (SLNs) consist of solid lipids in a temperature range of 25°C-28°C, emulsifiers for a brief duration and a suitable solvent for dissolving both lipid and non-lipid constituents (see Figure 1). Lipids, which are commonly considered to be safe chemicals, are commonly utilized in the production of Solid Lipid Nanoparticles (SLNs).[13] The compounds encompassed in this category consist of fatty acids and esters, cholesterol, triglycerides (such as caprylic and compritol® 888), as well as waxes (such as beeswax and carnauba wax). Poloxamers, sodium cholate and pluronic F68/F127 are considered as potential agents for emulsification. PEGylation, precise targeting and surface charge modifications are achieved by the utilization of organic salts, surface enhancers and ionic polymers. The categorization of SLNs is based on the specific location inside the SLN structure where the therapeutic molecule is inserted. These categories include: (a) drug-loaded shell, (b) drug-loaded core and (c) homogeneous matrix. Figure 2 presents a visual representation of the various applications and benefits. The production of a drug-loaded shell is achieved through the process of phase separation following the cooling of heated liquid droplets. The rapid decrease in temperature leads to the formation of liquid precipitation, which then solidifies as Super cooled Liquid Nitrogen (SLNs) upon further cooling. This category of SLNs demonstrates a strong alignment with topical circumstances. In contrast to the shell model, it is expected that the medication will undergo crystallization at an earlier stage compared to the formation of liquid precipitates. The drug-loaded core model, which adheres to Fick's law of diffusion, facilitates the gradual release of medicinal medications. Through the process of cold homogenization, lipophilic medications are evenly dispersed within the lipid matrix. Therefore, by the implementation of uncomplicated homogenization techniques, Solid Lipid Nanoparticles (SLNs) benefit from efficient production.[14,15] The subsequent section delves deeper into an extensive comprehension of diverse production methodologies.

A group of medical conditions referred to as cancer are distinguished by uncontrolled cellular proliferation, insensitivity to apoptosis and the ability of malignant cells to infiltrate adjacent tissues.[16] It is considered one of the leading causes of mortality worldwide.[17] Conventional administration of chemotherapy is often regarded as the most comprehensive approach for cancer treatment. However, this method is associated with several limitations, including inadequate drug solubility, limited specificity, elevated toxicity and a reduced therapeutic index.[18] One of the issues associated with chemotherapy is the development of resistance in cancer cells against the administered medicine. The phenomenon being discussed is often known as Multidrug Resistance (MDR), which pertains to the acquisition of resistance against a diverse array of pharmaceutical agents.[19] In addition, the administration of anticancer drugs elicits considerable discomfort

among patients due to the predominant use of intravenous or injectable routes, as opposed to oral administration.[20] Despite the various downsides, chemotherapy remains the predominant approach for cancer treatment in contemporary medicine.

Solid Lipid Nanoparticles (SLNs), have the potential to augment the efficacy of drugs by inhibiting resistance mechanisms. The nanoscale dimensions of these systems, coupled with their capacity for on-demand modifications, allow them to traverse diverse biological barriers and administer drugs to specific regions with few or no adverse effects.[21] In addition to the aforementioned advantages, the utilization of Solid Lipid Nanoparticles (SLNs) in the context of anticancer therapies has the potential to facilitate oral drug delivery and extend the duration of cancer cell exposure to therapeutic agents, surpassing the conventional modes of administration that are commonly employed.[20] This would involve employing less intricate and more pragmatic interventions for individuals under medical care.

The utilization of Solid Lipid Nanoparticles (SLNs) as a very encouraging approach for drug delivery systems in the field of cancer chemotherapy is predicated upon the recognition of cancer's profound impact on the worldwide populace and the imperative for enhanced pharmaceutical interventions. Consequently, the aims of this review are to collate relevant and up-to-date information regarding the utilization of SLNs as drug delivery platforms in the context of antitumor therapies, to ascertain the primary challenges in cancer treatment and the importance of the mechanisms employed by SLNs to enhance drug delivery and to discuss recent advancements in the application of SLNs as well as persistent issues in this field.

PREPARATION METHODS OF SOLID LIPID NANOPARTICLES

High Pressure Homogenization (HPH)

High Pressure Homogenization (HPH) is a reliable technique used in producing Solid Lipid Nanoparticles (SLNs). It expedites liquid flow by subjecting it to elevated pressures, resulting in a significant increase in velocity. The process fragments particles into submicron dimensions, with lipid content typically ranging from 5% to 10%. The standard production conditions involve 500 bar pressure and two or three homogenization cycles. Both hot and cold homogenization techniques are used in Hot Melt Extrusion (HME).

Hot homogenization

Emulsion homogenization, also known as hot homogenization, involves subjecting a drug-loaded lipid melt to temperatures over its melting point to create a pre-emulsion. This process is crucial for obtaining droplets within a few micrometers, as it significantly impacts the final product's quality. Hot homogenization is commonly used for temperature-sensitive compounds, but its efficacy is compromised when exposed to elevated temperatures. Cold homogenization is recommended for compounds with high temperature sensitivity and hydrophilicity.[22,23]

Cold homogenization

Cold homogenization is used to cool medication lipid melt, resulting in solidified lipidic mass. This solidified mass is crushed to create lipid microparticles, which are then transformed into solid lipid nanoparticles through high-pressure homogenization.[24]

Ultrasonication or high-speed homogenization

Ultrasonication, a cost-effective and rapid method for producing SLNs, offers a viable alternative to laboratory scale techniques. However, it's potential for yielding a wide variety of particle sizes and metal contamination is a concern. High-temperature ultrasonication and high-speed stirring techniques can enhance stability.[25-27]

Spray drying method

Spray drying is a viable alternative to lyophilization for converting solid lipid nanoparticles into pharmaceutical products. It induces particle aggregation through elevated temperature, shear pressures and partial melting. Optimal outcomes involve incorporating a 1% SLN component into a trehalose solution or mixtures.[28]

Supercritical Fluid technology

Supercriticality, a term used to describe fluids beyond critical pressure and temperature thresholds, is utilized in the production Of Solid Lipid Nanoparticles (SLNs). Techniques include Rapid Expansion of Supercritical Solution (RESS), Particles from Gas Saturated Solution (PGSS), Aerosol Solvent Extraction Solvent (ASES) and Supercritical Fluid Extraction of Emulsions (SFEE), with advantages like solvent elimination, dry powder particle use and moderate pressure and temperature settings.[29,30]

Solvent injection technique

The study utilized a water-miscible solvent for the injection of Solid Lipid Nanoparticles (SLNs). The lipid solvent mixture is introduced into an agitated aqueous phase, removing excess fat and facilitating lipid droplet generation at injection sites. The emulsion provided stability throughout solvent diffusion.[31,32]

Solvent emulsification/evaporation

The process involves dissolving a lipid in an organic solvent, emulsifying it and forming nanoparticles. High pressure homogenization is used for emulsification of the solution in aqueous phase, while low pressure evaporation removes the organic solvent.[33,34]

Microemulsion based SLN preparation

Gasco *et al*., (2009) utilized the microemulsion dilution technique to create Solid Lipid Nanoparticles (SLNs).[35] The process involves

agitating a blend of water, emulsifying agents, co-emulsifiers and low-melting fatty acids. The hot microemulsion is dispersed in cold water, stirring. The SLN can be converted into solid goods like tablets and pellets, but excessive water removal is crucial.[36]

Double Emulsion

In order to prevent the migration of drugs into the external water phase during the process of solvent evaporation in the external water phase of the water-in-oil-in-water (w/o/w) double emulsion, a stabilizer is employed to encapsulate the drug. The double emulsion technique was employed to create Solid Lipid Nanoparticles (SLNs) encapsulating Bovine Serum Albumin (BSA).[37]

Solvent emulsification-diffusion method

This technique involves using an oil phase with partial miscibility with water and an aqueous phase. The solvent and water are saturated, and the organic phase is emulsified. The medicine and lipid are dissolved in a solvent-saturated solvent and a specific amount of water is introduced to facilitate solvent diffusion. The solvent is removed using vacuum distillation or lyophilisation.[38]

APPROACHES TO ENHANCE DRUG LOADING IN SOLID LIPID NANOPARTICLES

Microfluidics-Based Drug Loading

Microfluidics is a cutting-edge approach for producing nanoparticles, particularly SLNs, with optimal control over their size, shape and drug-loading efficiency. This method includes manipulating fluids in microchannels under monitored conditions, allowing for the continuous and reproducible development of SLNs.

This technique has substantial advantages over traditional approaches, particularly in terms of precision, efficiency and the flexibility to customize drug delivery systems to meet individual demands. Microfluidics enables the production of drug carriers with superior pharmacokinetic and pharmacodynamic profiles, making it a disruptive force in pharmaceutical research and development.[39,40]

Key Features of Microfluidics in SLN Production

Precise Control and Reproducibility

Microfluidics allows the production of SLNs with narrow size distributions and high batch-to-batch reproducibility. It is particularly effective in controlling particle size and encapsulation efficiency.[41]

Scalability

Unlike traditional methods, microfluidics facilitates scale-independent production of SLNs, making it easier to transition from lab-scale to industrial-scale manufacturing.[42]

Enhanced Drug Loading

By optimizing flow parameters such as flow rate ratios and total flow rates, microfluidic systems can achieve higher drug loading and encapsulation efficiencies compared to bulk methods.[43]

Reduced Variability

Microfluidic methods ensure consistent nanoparticle properties, addressing the limitations of conventional techniques prone to operator-dependent variability.[44]

Co-Delivery Systems

Co-delivery based Solid Lipid Nanoparticle (SLN) are a novel way to drug delivery, especially for cancer treatment. By delivering

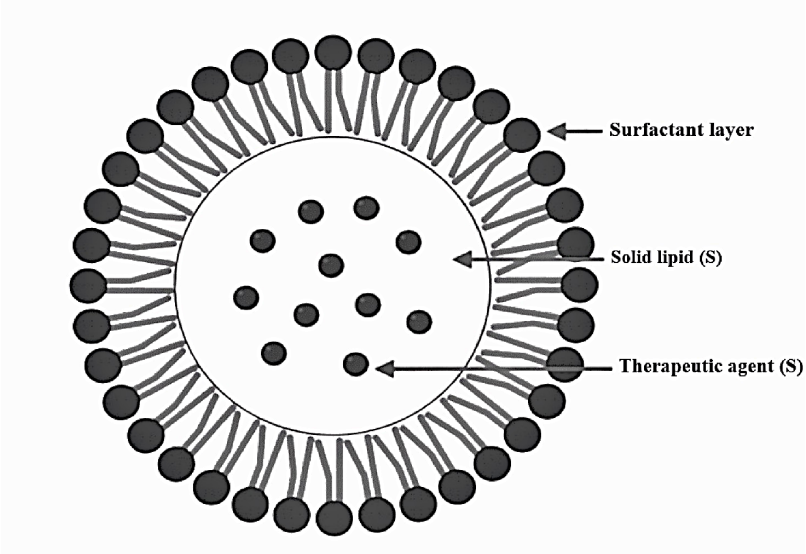

Figure 1: Structure of SLNs.

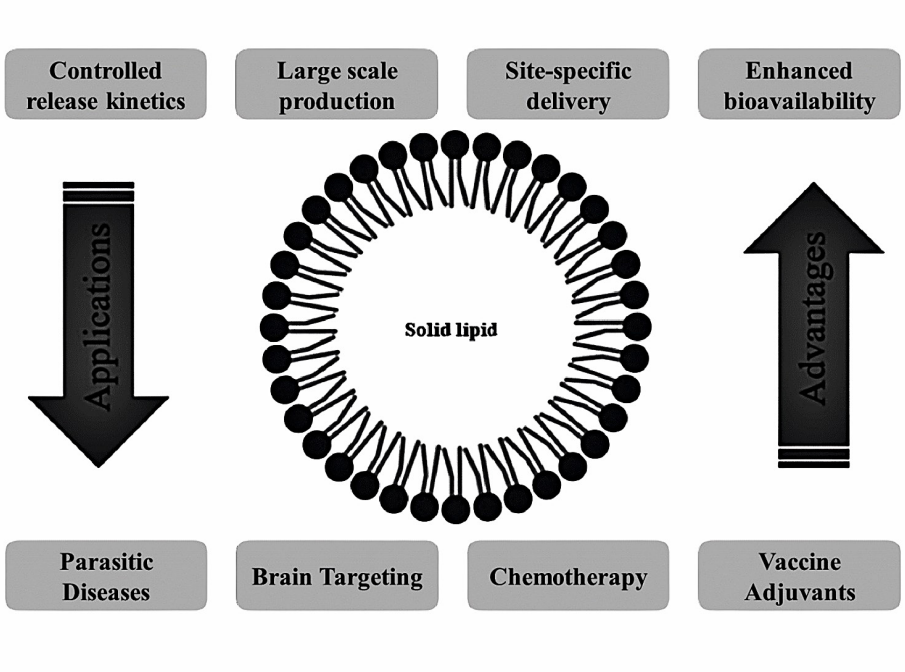

Figure 2: Representation of advantages and applications SLNs formulations.

several therapeutic compounds at once, these systems increase effectiveness and reduce side effects. Singh *et al.* demonstrated that when rifampicin was co-administered with isoniazid, encapsulation dramatically raised its plasma levels.[45]

Quality by Design (QbD) optimization

By methodically incorporating quality into the development process, Solid Lipid Nanoparticles (SLNs) optimized for Quality by Design (QbD) improve drug delivery systems. This method places a strong emphasis on comprehending process parameters and Critical Quality Attributes (CQAs), which improve product consistency and regulatory compliance. Particle size, entrapment efficiency and drug release patterns are among the factors that are detected and tracked in QbD.[46] Formulation variables are optimized using statistical techniques such as factorial designs and Box-Behnken.[47] During the formulation phase, methods such as Failure Mode Effects and Criticality Analysis (FMECA) are employed to detect possible hazards.[48]

Incorporation of Polyunsaturated Fatty Acids (PUFAs)

An innovative strategy to improve the bioavailability and therapeutic efficiency of Solid Lipid Nanoparticles (SLNs) is the addition of Polyunsaturated Fatty Acids (PUFAs). This technique makes use of the special qualities of SLNs, which are made of biodegradable lipids, to enhance PUFA delivery in a range of applications. Through structural lipid engineering, which involves modifying Triacylglycerols (TAGs) to place long-chain PUFAs at the sn-2 position for improved absorption, PUFAs may be incorporated into SLNs.[49] The stability and bioavailability of PUFAs are improved by techniques like nanoemulsions and nanoliposomes, which enable specific administration.[50]

Surface functionalization

A crucial step in improving the efficacy of Solid Lipid Nanoparticles (SLNs) in biological applications is surface functionalization. This method optimizes transport and therapeutic efficacy by altering the surface characteristics of SLNs to enhance their interaction with biological systems. To improve stability and drug loading capability, SLNs are coated with a variety of biocompatible polymers and surfactants. Targeting capabilities and cellular absorption can be enhanced by the addition of functional groups. SLNs' biodistribution and cellular interactions can be influenced by modifying their size and shape.[51,52]

Combination of Lipophilic Additives

Solid Lipid Nanoparticles' (SLNs') stability, bioavailability and therapeutic effectiveness are all greatly improved by the addition of lipophilic additives. Emulsifying agents, solid lipids and active medicinal ingredients-which may be lipophilic or hydrophilic-make up SLNs. To maximize the effectiveness of SLNs in drug delivery systems, these elements must be carefully chosen and combined. Emulsifying agents, which can be hydrophilic or lipophilic, stabilize the SLNs and affect the active ingredients' release profiles and encapsulation effectiveness.[53] Lipophilic additives like tocopherol and ferulic acid were effectively encapsulated in SLNs by Oehlke *et al.* in 2017, exhibiting notable antioxidant activity and stability over time.[54]

Dual-Drug Loading

Co-delivery of multiple drugs is a novel way to improve therapeutic effectiveness and can be achieved by dual-drug loading in Solid Lipid Nanoparticles (SLNs). This technique enhances medication bioavailability and targeting by utilizing the special qualities of SLNs, such as controlled release and biocompatibility. SLNs made of solid lipids, such Compritol or Imwitor, acting as the drug carrier, offer stability and regulated release, according to research conducted by Elkateb *et al*., 2023 and Moinuddin *et al*., 2023. The stability and encapsulation efficiency are greatly influenced by surfactants like Brij 78 or Poloxamer 188. Drug combinations like dasatinib and hesperidin or darunavir and ritonavir are essential for obtaining synergistic benefits when treating SLNs.[55,56]

APPLICATIONS OF SLNS IN DIFFERENT CANCER

Breast Cancer

Breast cancer, being the second leading cause of cancer-related mortality among women, is a prevalent form of cancer in the female population. Nevertheless, due to the progress made in the field of breast cancer therapy and prevention, there has been a consistent yearly decline of 1.8% in the death rate of this disease since 1989.[57] The emergence of resistance to various chemotherapeutic agents, commonly referred to as Multidrug Resistance (MDR), is a substantial clinical challenge in the field of cancer treatment. Chemoresistance is commonly attributed to one of two mechanisms: either the physical transportation of drugs to the tumor is hindered (such as through inadequate absorption, heightened metabolism/excretion and/or limited diffusion of drugs into the tumor mass); or intracellular mechanisms that elevate the threshold for cell death are operative.[58-62] The efficacy of nanoparticles as agents for targeting tumors is widely recognized because to their passive targeting capabilities, which are facilitated by the increased Permeability and Retention (EPR) effect. In addition, the particles have the potential to evade detection by the reticuloendothelial system through the application of a polyethylene glycol/oxide (PEG/PEO) coating, hence extending their duration in circulation.[63]

Breast cancer, the most common cancer in women, has shown a consistent upward trend. Sentinel Lymph Node (SLN) procedures have shown efficacy in treating certain types of malignancies, such as breast cancer. Solid Lipid Nanoparticles (SLNs) have been used to overcome resistance in breast cancer cells by enhancing the therapeutic efficacy of paclitaxel, a medication administered via Nanostructured Lipid Carriers (NLC). The study involved the generation of mammospheres using MCF-7 breast cancer cells and found that SLNs showed superior transfection efficiency compared to Lipofectamine or free miRNA-200c. The therapy improved the half maximum Inhibitory Concentrations (IC_{50}) value of paclitaxel-loaded NLCs against cancer cells, suggesting its potential as a viable method for administering miRNA in breast cancer treatment.[64,65]

This study evaluates the efficacy of paclitaxel-SLN formulation compared to other formulations on drug-resistant and drug-sensitive MCF-7 cells. Results show that paclitaxel-SLN formulations showed a significant increase in IC_{50} concentration in drug-resistant cells and enhanced cellular internalization compared to other formulations. This suggests that solid lipid nanoparticles can effectively mitigate multidrug resistance pathways in breast cancer cells.[66] The study demonstrates the effectiveness of Solid Lipid Nanoparticles (SLNs) as carriers for curcumin against the MDA-MB-231 breast cancer cell line. Curcumin administration in SLNs enhances cellular drug absorption capacity, while diluted curcumin-SLN decreases cell viability and increases apoptotic cell count. This supports the use of SLNs as a potential treatment.[67]

A study on the efficacy of Sentinel Lymph Node (SLN) targeting breast tumors in an *in vivo* setting has shown that methotrexate can be effectively incorporated into Solid Lipid Nanoparticles (SLNs) and functionalized with fucose. This approach significantly enhances its cytotoxic impact on MCF-7 cells and enhances efficacy against induced breast cancer in rats. The modified SLNs also show greater drug accumulation within tumor tissues, indicating that the use of SLNs enhances breast cancer treatment efficacy.[68]

Lung Cancer

Lung cancer is widely recognized as a prominent contributor to global mortality rates.[69] The term "non-small cell lung cancers" encompasses adenocarcinoma, squamous cell carcinoma and large-cell carcinoma, collectively representing the predominant types of lung malignancies (NSCLCs). Surgical intervention is commonly employed as a therapeutic approach for individuals diagnosed with early-stage Non-Small Cell Lung Cancer (NSCLC). The prognosis in terms of 5-year survival rates is contingent upon the specific stage of the disease.[70] The existing therapies for lung cancer have demonstrated limited efficacy due to their inability to effectively eliminate disseminated tumors while minimizing associated adverse effects. The occurrence of mutations in the p53 gene is commonly associated with several detrimental effects such as the reduction of tumor-suppressor activity, heightened drug resistance, impaired mutational repair, increased tumour angiogenesis, enhanced cell proliferation and suppression of apoptosis. These mutations have been identified as the primary factors responsible for the development of lung cancer.[71-74] Gene therapy has shown promise as a supplementary strategy for the treatment of lung cancer. Viral and non-viral vectors are the two predominant categories of vectors employed in the context of gene delivery. The issue of immunogenicity and toxicity associated with viral vectors has prompted scientific investigation into other methods of gene delivery that do not include the use of viruses.[75] Biodegradable nanoparticles have exhibited their superiority over alternative carriers within the realm of non-viral vectors due to their higher stability and ability to facilitate

controlled release.[76,77] Cationic and anionic nanoparticles are the two primary types of nanoparticles frequently employed in gene delivery techniques. Cationic nanoparticle methods utilize the ionic interaction between cationic polymers and anionic plasmid DNA to form stable polymer/lipids-DNA complexes.[78,79] There has been an increased interest in the potential use of Solid Lipid Nanoparticles (SLNs) and cationic lipid formulations as colloidal carrier systems.[80] The study revealed that the utilization of p53 gene/cationic lipid complexes could potentially serve as an alternative to viral delivery systems for the treatment of early endobronchial cancer.[81] Although cationic lipids exhibit lower potency compared to viral vectors, they may offer certain advantages when administered over a prolonged duration to several tumor sites dispersed across the bronchial epithelium. Furthermore, a significant proportion of nonviral gene delivery techniques now being investigated demonstrate no immunogenic response, as evidenced by previous studies.[82-85]

Lung tumors are a common cancer and the primary cause of cancer-related mortality in the United States.[86] The use of Solid Lipid Nanoparticles (SLNs) as a delivery system for naringenin in anticancer medication delivery has been investigated. Although naringenin-SLN showed a favorable cellular uptake pattern, the use of naringenin, which has not been proven effective against A549 cells, may have contributed to this outcome. The administration of naringenin with SCNs enhanced pharmacokinetic characteristics, including mean residence time and maximum plasma concentration. [87]

Lung malignancies can be treated with inhaled solid lipid nanoparticles (SLNs), but they have limitations like short residency periods and reduced tolerance. To overcome these, paclitaxel is injected into SLNs coated with folate-poly (ethylene glycol) and chitosan. Studies show that SLNs reduce IC_{50} values of M109HiFR lung cancer cells *in vitro* and enhance medication concentration *in vivo* in healthy and diseased mice.[88] Research suggests that incorporating erlotinib into Solid Lipid Nanoparticles (SLNs) could be a potential inhalation therapy for treating A549 cells. *In vitro* studies show less toxicity compared to unbound drug and erlotinib-loaded SCNs can disperse as an aerosol, making this approach suitable for delivering the drug to the lungs.[89]

Liver Cancer

The prevalence of hepatic malignancies as a cause of cancer-related deaths necessitates the development of novel therapeutic approaches.[90] The use of Solid Lipid Nanoparticles (SLNs) can be regulated by incorporating Superparamagnetic Iron Oxide Nanoparticles (SPIONs) in the presence of an external magnetic field. Sorafenib was encapsulated within SLNs and incorporated into HepG2 human hepatocarcinoma cells. Despite exhibiting cytotoxic effects, this method did not achieve the same potency as unbound drugs. Magnetic targeting and cellular uptake from SLNs have shown potential to enhance hepatocarcinoma treatment efficacy. The antiproliferative activity of SLNs containing linalool was found to be potent against HepG2 cells, depending on the dosage and duration of exposure.[91]

Hepatocellular Carcinoma (HCC) is a primary tumor of the liver that is widely recognized as one of the most prevalent cancers globally. Since the 1990s, Hepatocellular Carcinoma (HCC) has exhibited the second-highest mortality rate in China specifically attributed to cancer. Furthermore, on a global scale, HCC ranks third in terms of mortality rates for all cancer-related illnesses.[92] The liver is commonly affected by metastatic tumors, in addition to primary malignancies. Bartsch *et al*. (2004) suggested the use of stabilized lipid-coated lipoplexes for delivering antisense oligonucleotide (AS-ODN) to liver endothelial cells, both *in vitro* and *in vivo*.[93]

Colorectal Cancer

Colorectal cancer, causing an estimated 60,000 deaths annually, ranks as the second leading cause of cancer-related mortality in the United States and represents the most prevalent form of cancer in Western countries.[94] In order to enhance the targeted distribution of Oxaliplatin (L-OHP) to colon tumors, researchers developed chitosan nanoparticles that were conjugated with hyaluronic acid and encapsulated within pellets coated with Eudragit S100.[95] The utilization of Solid Lipid Nanoparticles (SLN) has been suggested as an innovative approach for drug transporters.[96] A prior formulation had been developed, consisting of a solution comprising doxorubicin, paclitaxel and cholesteryl butyrate (chol but). Doxorubicin exhibits a lower efficacy than anticipated in the treatment of colorectal cancer, as indicated by reference.[97] Silver Nanoparticles (SLN) are typically found in the colloidal size range. The ability to load SLN with hydrophilic and lipophilic medicines depends on the specific manufacturing method employed.[98,99] The composition of heated microemulsions used in the production of Solid Lipid Nanoparticles (SLN) can be adjusted to accommodate different types of medicine and methods of administration.[100]

Brain Tumor

Brain cancer diagnosis is a significant challenge for healthcare systems. Studies show that Solid Lipid Nanoparticles (SLNs) can improve treatment. In a study, indirubin was administered to a U87MG glioblastoma-astrocytoma cell line, showing promising results in augmenting the drug's cytotoxic impact, especially in acidic conditions, using SLNs.[101,102]

The blood-brain barrier is a significant obstacle in brain cancer therapy. Chemicals can be used to modify the surface of Solid Lipid Nanoparticles (SLNs) to target highly expressed receptors in the blood-brain barrier. Apoprotein E (ApoE), a molecule that recognizes low- or very low-density lipoprotein receptors, can be used to coat LDL or VLDL-like SCNs. This approach could lead to increased accumulation of nanoparticles in the brain, potentially

improving the administration of medications in therapeutic interventions involving the central nervous system.[103]

The use of Solid Lipid Nanoparticles (SLNs) with ApoE surface alteration and methotrexate, a lipophilic ester form, has been shown to reduce glioblastoma tumors in F98/Fisher rat models. This method reduces drug extraction from the brain and plasma and has been shown to facilitate cellular transcytosis and integration through the blood-brain barrier. This approach has been demonstrated in a cellular monolayer mimicking the blood-brain barrier.[104]

The Solid Lipid Nanoparticle (SLN) is a lipid-based formulation with exceptional efficacy in targeting therapeutic agents for brain tumor treatment, produced using micro-emulsion or high-pressure homogenization techniques.[105] The mechanism by which SLNs cross the Blood-Brain Barrier (BBB) and Blood-Tumor Barrier (BTB) remains uncertain, although it is believed that the internalization of SLNs is facilitated through the endocytosis of SLNs by endothelial cells. It has been proposed that the adsorption of plasma proteins in circulation onto the surface of Solid Lipid Nanoparticles (SLNs) may promote the process of endocytosis.[106] Pharmaceutical substances have the capability to be encapsulated within the lipid matrix of Solid Lipid Nanoparticles (SLNs), so affording protection against degradation. The management of drug unloading within target tumor tissues might be influenced by the surface coating and lipid composition of the SLN.[107] The blood-brain barrier was successfully traversed by drugs, particularly when they were coated with polysorbate (Tween) surfactants on Nanoparticles.[108] SLN has the potential to revolutionize the preoperative and intraoperative detection of brain tumors. Estimates suggest that around 43,800 primary brain tumors are reported annually in the United States.[109-111]

The utilization of nanotechnology for the imaging of gliomas has been proposed, leading to a significant rise in the application of nanodevices for the identification and management of brain malignancies.[112] Numerous investigations have shown a diverse array of potential targeting strategies for nanoparticles, encompassing peptides, cytokines, pharmaceuticals, antibodies and ferromagnetic compounds. Nanoparticles administered systemically are rapidly cleared from the body through the reticuloendothelial system. The methodology encompasses the processes of opsonization of nanoparticles, macrophage phagocytosis and uptake by the liver and spleen.[113] The retention of hydrophilic molecules on the surface of nanoparticles can impede their complete elimination by the reticuloendothelial system.[114] Nevertheless, it is worth noting that commonly employed coating compounds such as polyethylene glycol or pluronic, which are utilized to create a hydrophilic coating, may exhibit immunogenic or pro-inflammatory properties.[115] The study suggests that nanoparticles with a diameter of 200 nm can cause toxicity in cerebral endothelial cells, potentially crossing the blood-brain barrier. However, a separate investigation found contradictory results for identical nanoparticles with a diameter of 300 nm. The study also found that supplementary substances like manganese oxide can enter the brain through the olfactory pathway.[116]

Gastro-intestinal Cancer

Solid Lipid Nanoparticles (SLN) has been introduced as a novel drug carrier method for oral administration in the treatment of gastrointestinal malignancies. These nanoparticles have enhanced bioavailability and reduced irregular absorption due to their sticky properties. Absorption occurs via the mucosa of the gut through Peyer's patches, intracellular uptake and the paracellular pathway. Eldem's study integrated SLN into spherical pellets and examined its release for oral administration. SLN granulates or powders can be incorporated into various pharmaceutical dosage forms like pellets, pills, or capsules.[23] The stability of colloidal carriers in gastrointestinal fluids is crucial for oral administration. Factors influencing their behavior include their composition, size and environmental conditions. The construction of innovative and efficient colloidal drug carrier systems for oral administration has often overlooked critical aspects.[114-116]

STABILITY ASPECT OF SOLID LIPID NANOPARTICLES

Lipid crystallinity, surfactant interactions, particle size and environmental variables like pH, light and temperature all affect how stable Solid Lipid Nanoparticles (SLNs) are. Drug ejection may result from polymorphic changes in lipids, whereas surfactants stabilize particles by stopping them from aggregating. Colloidal stability is guaranteed by a high zeta potential (>±30 mV) and an ideal particle size (<200 nm). Stability is improved by environmental factors including darkness and cold. Stability is further enhanced by stabilizing methods including lyophilization with cryoprotectants and surface modifications such amphiphilic inulin derivatives. These tactics guarantee SLNs' continued stability as efficient drug delivery vehicles.[117]

Lipid Crystallinity and Polymorphism

During manufacturing, lipids solidify to produce SLNs. The effectiveness of encapsulation and long-term stability are strongly impacted by the degree of crystallinity and polymorphic transitions. For example, recrystallization and polymorphic transitions caused by the usage of highly organized lipid lattices may result in drug ejection.[117]

Influence of Surfactants

By lowering surface tension and inhibiting aggregation, surfactant concentration and selection are crucial for stabilizing SLNs. For instance, it was discovered that Pluronic F68 and Tween 80 gave SLNs good stability. However, the lipid utilized and the storage conditions affect how effective they are.[118]

Environmental Factors

Temperature and Light

Particle aggregation and size growth can result from SLNs being destabilized by storage temperature and light exposure. These effects are reduced when stored in dark, siliconized vials at lower temperatures (e.g., 8ºC).[119]

pH and Ionic Strength

Destabilization of SLNs has been noted in gastrointestinal settings and they can be susceptible to variations in pH and ionic strength. Under these circumstances, stability can be increased by optimizing the surfactant composition.[118]

Particle Size and Zeta Potential

Good colloidal stability is indicated by stable SLNs, which often have tiny particle sizes (<200 nm) and high zeta potential values (>-30 mV). For example, Shah *et al*. (2014) showed that SLNs with ideal zeta potential and particle size stayed stable in a refrigerator for more than two months.[120]

Surface Modifications

Amphiphilic macromolecules, such as comb-shaped insulin derivatives, can be used to modify SLNs in order to decrease crystallinity, limit aggregation and improve stability over time. For instance: Using such changes, Peng *et al*. (2019) showed enhanced long-term stability.[121]

Stabilization Techniques

Cryoprotectants**:** During freeze-drying, lyophilisation using Cryoprotectants such as mannitol or trehalose helps avoid aggregation.

Optimization of Lipid and Surfactant Ratios**:** While preserving the intended drug release characteristics, stability is improved by a balanced lipid-to-surfactant ratio.[122]

CONCLUSION

Solid Lipid Nanoparticles (SLN) is a promising drug delivery method that has helped the pharmaceutical, cosmetics, research and clinical medical industries. Recently, SLN are gaining popularity as colloidal drug carriers for hydrophilic or lipophilic medications. Technology in cancer treatment is young, and several substances are being explored for medicine delivery. It helps the pharmacist create a medicine with maximum therapeutic efficacy and minimal side effects. Due to their lack of tumor tissue selectivity, anticancer medicines have high side effects and low cure rates. Low toxicity, high drug bioavailability, flexible drug integration and industrial-scale production are SLN benefits. The composition and production process determine the molecular structure of SLN preparations, which determines their quality. SLNs can also bypass physiological barriers that prevent medication delivery to tumors and avoid cancer cells' multidrug resistance processes. This review covers solid lipid nanoparticle manufacturing methods and cancer targeted drug therapy applications.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DDS: Drug Delivery System; **SLN:** Solid Lipid Nanoparticles; **MDR:** Multidrug resistance; **HPH:** High pressure homogenization; **HME:** Hot melt extrusion; **RESS:** Rapid expansion of supercritical solution; **PGSS:** Particles from gas saturated solution; **ASES:** Aerosol solvent extraction solvent; **SFEE:** Supercritical fluid extraction of emulsion; **W/O/W:** Water-in-oil-in-water; **BSA:** Bovine serum albumin; **EPR:** Permeability and repention; **PRG/O:** Poluethylene glycol/ oxide; **NLC:** Nanostructured lipid carriers; **miRNA:** microRNA; **IC_{50}:** Half maximum inhibitory concentration; **MDA-MB:** M. D. Anderson and Metastasis breast cancer; **MCF:** Michigan Cancer Foundation; **NSCLC:** Non-small cell lung cancer; **SPION:** Superparamagnetic iron oxide Nanoparticles; **HCC:** Hepatocellular carcinoma; **AS-ODN:** Antisense oligonucleotide; **L-OHP:** Oxaliplatin; **ApoE:** Apolopoprotein E; **BBB:** Blood brain barrier; **BTB:** Blood tumor barrier.

SUMMARY

Solid Lipid Nanoparticles (SLN) is gaining interest in the pharmaceutical, cosmetics, research and clinical medicine industries as a promising new drug delivery technique. These nanoparticles are increasingly used as colloidal drug carriers for integrating hydrophilic or lipophilic medicines. SLNs offer significant advantages such as low toxicity, high drug bioavailability, flexible drug integration and the possibility of industrial-scale production. They also circumvent physiological barriers that obstruct drug transport to tumors and can evade multidrug resistance mechanisms inherent to cancer cells. The molecular structure of SLN preparations is crucial to their quality, determined by the composition and production method. This review article discusses various SLN preparation techniques and potential applications for solid lipid nanoparticle technology in cancer targeted medication therapy.

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