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Exploring Lipid Nanoparticles for Cancer Therapeutics

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Abstract

Investigators are continuously developing novel nanotechnologies to meet the unlimited needs in the administration of therapeutic agents and imaging tools for cancer treatment and diagnostics. Lipid nanoparticles (LPNs), approximately 100 nm in size, are composed of various lipids and biochemical compounds designed to overcome biological barriers, enabling selective targeting of disease-affected cells for responsive therapies. Many pharmaceutically important compounds face challenges such as poor water solubility, chemical instability, and toxicity. Lipid-based nanoparticles (LPNs) have emerged as promising drug carriers for bioactive compounds, significantly enhancing the efficacy of chemotherapy by improving the antitumor effects of various chemotherapeutic agents.

LPNs offer advantages including excellent thermal and temporal stability, high loading capacity, ease of preparation, cost-effectiveness, and large-scale production potential. By encapsulating chemotherapeutic drugs within LNPs, it is possible to reduce the required therapeutic dosage and associated toxicities, decrease the likelihood of treatment resistance, and increase drug concentrations in tumor cells while minimizing exposure in healthy tissues. LPNs have been extensively studied in cancer treatment, yielding positive results in both in vitro and in vivo studies, as well as promising outcomes in clinical trials. This review provides an overview of the various types of LNPs developed in recent years, highlighting their applications and contributions to the treatment of different cancer types.

Keywords: Cancer, nanolipids, treatment, innovation

INTRODUCTION

A tumor is a type of disease characterized by abnormal cell growth that has the potential to spread to other cells or areas of the body [1]. It represents one of the leading causes of death worldwide, encompassing over 100 distinct types of cancer. In developing countries, infections such as Helicobacter pylori, hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), Epstein-Barr virus, and HIV are responsible for approximately 15% of cancer cases. These infectious agents contribute to cancer development, in part, by altering the genetic makeup of cells. Typically, multiple genetic changes are required before cancer can develop, with hereditary genetic abnormalities accounting for 5–10% of all cancer cases. Various signs and symptoms, along with medical tests, are crucial for identifying malignancies [2-3]. Once a potential cancer is suspected, further investigation is usually conducted through diagnostic imaging, followed by confirmation via biopsy. In 2015, approximately 90.5 million people were diagnosed with cancer globally, and in 2019, nearly 18 million new cases were reported annually [4-6]. The disease is responsible for about 8.8 million

deaths each year. Among men, the most common types of cancer include lung cancer, prostate cancer, colorectal cancer, and stomach cancer. In women, the most prevalent types are breast cancer, colorectal cancer, lung cancer, and cervical cancer [7-9]. Skin cancers also represent a significant health concern across both genders. Melanoma represents roughly 40% of all newly diagnosed cancer cases each year when taking into account the total incidence of cancer across all types. This significant proportion underscores the growing prevalence of skin cancers, particularly in populations exposed to high levels of ultraviolet radiation. Among pediatric cancers, acute lymphoblastic leukemia (ALL) and brain tumors are the most frequently occurring types, highlighting the vulnerability of children to these aggressive malignancies [10, 11]. In contrast, in Africa, non-Hodgkin lymphoma (NHL) emerges as the predominant cancer diagnosed in children, reflecting regional variations in cancer types due to factors such as genetic predisposition, environmental influences, and access to healthcare. These differences in cancer incidence among children worldwide emphasize the need for tailored approaches to diagnosis, treatment, and prevention strategies that consider the specific types of cancers prevalent in different geographic areas [12]. The application of nanoparticles in cancer treatment has emerged as a revolutionary approach in oncology, offering enhanced efficacy and reduced side effects compared to conventional therapies. Nanoparticles, typically ranging from 1 to 100 nanometers in size, can be engineered to improve drug delivery, enable targeted therapy, and overcome biological barriers that hinder the effectiveness of traditional treatments[11, 13]. One prominent example of nanoparticles used in cancer therapy is lipid-based nanoparticles (LPNs). These structures are composed of lipids and can encapsulate hydrophobic drugs, improving their solubility and bioavailability. LPNs are particularly advantageous for delivering RNA-based therapeutics, such as mRNA vaccines, which have gained attention for their role in treating various cancers and infectious diseases. Their natural composition allows for better biocompatibility and reduced toxicity [14]. Other types of nanoparticles include gold nanoparticles, which can be utilized for photothermal therapy. These particles absorb light and convert it into heat, selectively destroying cancer cells while sparing surrounding healthy tissue. Silica nanoparticles are also notable for their ability to carry drugs and imaging agents, enabling simultaneous therapeutic and diagnostic applications, known as theragnostic [15-17]. Polymeric nanoparticles serve as another versatile platform for cancer treatment. These nanoparticles can be engineered to release drugs in a controlled manner, enhancing therapeutic efficacy and minimizing side effects. They can also be functionalized with targeting ligands that bind specifically to cancer cell markers, allowing for precise delivery of chemotherapeutics [18]. The use of nanoparticles in cancer treatment not only enhances the delivery of therapeutic agents but also offers opportunities for combination therapies, which can address tumor heterogeneity and resistance mechanisms. As research continues to expand the understanding of nanoparticle interactions within biological systems, their integration into clinical practice holds great promise for improving patient outcomes in cancer care [19-21]. Nanolipids have emerged as a transformative technology in drug delivery, offering innovative solutions to the challenges associated with conventional drug formulations. These lipid-based nanocarriers, which include solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes, are characterized by their nanoscale dimensions and unique physicochemical properties [21-23]. Their design allows for the encapsulation of a wide array of therapeutic agents, including both hydrophilic and hydrophobic molecules, thereby addressing one of the major challenges in drug formulation: the poor solubility of many active pharmaceutical ingredients (APIs). The development of

nanolipid systems is motivated by the need for more efficient drug delivery methods that can overcome biological barriers, improve bioavailability, and provide targeted therapy [24]. Traditional drug delivery systems often fall short in these areas, leading to suboptimal therapeutic outcomes and increased side effects. In contrast, nanolipids facilitate the controlled release of drugs and enhance their stability, making them particularly suitable for applications in oncology, vaccine delivery, and chronic disease management. One of the key advantages of nanolipid carriers is their ability to protect sensitive therapeutic agents from degradation, thereby preserving their bioactivity. For instance, SLNs are composed of solid lipids that maintain their structural integrity at physiological temperatures, which can significantly enhance the stability of encapsulated drugs [25-27]. In comparison, NLCs incorporate both solid and liquid lipids, allowing for improved loading capacity and a more flexible release profile. These properties make nanolipids particularly appealing for the formulation of poorly soluble drugs, as they can increase the dissolution rate and improve the pharmacokinetic profile of the drug [28]. The versatility of nanolipids extends to their surface engineering capabilities, which allow for the modification of their physicochemical properties to enhance targeting and reduce off-target effects. By attaching specific ligands or antibodies to the surface of nanolipids, researchers can achieve selective delivery to specific tissues or cells, such as tumor cells or immune cells. This targeted approach is crucial in minimizing adverse effects and maximizing therapeutic efficacy, particularly in cancer therapy where conventional treatments often affect healthy tissues. Recent advancements in nanotechnology have facilitated the development of innovative fabrication techniques for nanolipids, including microfluidics, high-pressure homogenization, and solvent evaporation methods. These techniques allow for precise control over particle size, morphology, and drug loading, which are critical parameters influencing the performance of nanolipid systems [29]. Furthermore, the advent of advanced characterization methods, such as dynamic light scattering (DLS) and transmission electron microscopy (TEM), has enabled researchers to better understand the behavior and interactions of nanolipids at the nanoscale. Despite the promising potential of nanolipids, several challenges remain in their clinical translation. Issues related to scalability, batch-to-batch reproducibility, and regulatory hurdles can impede the development of nanolipid-based formulations. Additionally, the long-term safety and biocompatibility of these systems must be thoroughly evaluated to ensure patient safety [29-31]. Ongoing research is focused on addressing these challenges, with an emphasis on optimizing formulation strategies and establishing standardized protocols for characterization and testing. Tumor nanotechnology has emerged as a promising therapeutic approach for delivering antitumor drugs effectively. Nanoparticles, which range in size from 1 to 100 nanometers, significantly enhance the bioavailability of therapeutic agents and improve the specificity of anticancer drugs. Recently, a variety of nanoparticles (NPs) and nanotechnology methods have been developed for cancer treatment. One particularly innovative type of nanoparticle is semiconductor quantum dots (QDs) [32-34]. These materials possess unique optical properties, including a wide excitation spectrum and a highly controlled intensity distribution. QDs represent a new class of fluorescent components that hold great potential for various biological applications, such as bioimaging, biolabeling, and biosensing [35]. Compared to traditional fluorophores, quantum dots offer several advantages. They are notably brighter, exhibit greater controllability over fluorescence intensity, and are less susceptible to photobleaching, which prolongs their usability in experimental settings. Additionally, multiple colors of QDs can be excited using a single light source, thanks to their broad absorption and narrow emission spectra [36]. This characteristic makes

QDs particularly suitable for applications involving the screening of cell receptors. To optimize their performance as effective fluorescence probes, the surfaces of quantum dots must be modified with various biological substances. Such modifications enhance their compatibility and functionality in biological environments, further expanding their potential for use in cancer diagnostics and treatment. Among the various nanoparticle formulations used in cancer treatment, we particularly focus on those based on lipid formulations [21]. Significant advancements in their preparation and alternative compositions have been achieved in recent years. Modifications to lipid nanosystems can facilitate evasion of the immune system, enhancing drug availability and efficacy. Additionally, these formulations can be engineered to be pH-sensitive, allowing for increased drug release in acidic environments typical of tumor tissues. They can also be conjugated with antibodies that target specific tumor cell receptors, such as folic acid (FoA), improving selectivity and effectiveness [37].

Nanodrugs hold potential for use in combination with other therapeutic modalities, thereby enhancing patient responses to treatment. A variety of antitumor agents have been formulated into nanocarriers, including cisplatin, irinotecan (IRI), paclitaxel (PTX), doxorubicin (DOX), oxaliplatin, daunorubicin, cytarabine, and vincristine. Some of these formulations have been evaluated in clinical trials and are commercially available for clinical use. Notably, Doxil®, a liposomal formulation of DOX, was the first commercially utilized nanomedicine for cancer treatment [38-40].

This overview highlights the various types of lipid-based nanoparticles (LBNPs) that have been developed in recent years, along with their applications and contributions to the treatment of different cancer types [35].

COMPONENTS OF LIPID-BASED NANOPARTICLES

Lipid-based nanoparticles (NPs) exhibit a variety of structural types. Most lipid-based NPs are characterized by a near-spherical shape, featuring one or more lipid layers on their exterior. While liposomes, lipid nanoparticles (LNPs), and nanoemulsions (NEs) may have different internal structures, typical lipid-based NPs are primarily composed of cationic or ionizable lipids, which often contain tertiary or quaternary amines. These lipids are essential for encapsulating anionic drug payloads [21, 25].

To enhance stability, helper lipids are included to support the lipid layer and promote membrane fusion during formulation. Additionally, polyethylene glycol (PEG) lipids or surfactants are incorporated to improve colloidal stability, allowing for prolonged storage and preventing the rapid degradation of the encapsulated drugs upon introduction into systemic circulation [15].

Furthermore, nanoemulsions (NEs) contain an oil phase, which may consist of various types of glycerides such as tri-, di-, or mono-acylglycerols, as well as vegetable oils, mineral oils, and free fatty acids. This composition contributes to the overall functionality and effectiveness of lipid-based NPs in drug delivery applications (see figure 1) [41].

DIFFERENT LIPIDS USED IN THE PREPARATION OF NANO LIPIDS

Nonlipids are primarily composed of several types of lipids, each playing a crucial role in their structure and function. The most common are phospholipids, which form the fundamental lipid bilayer due to their amphiphilic nature; examples include lecithin and phosphatidylcholine. These lipids help create a stable membrane that encapsulates the core of the nanolipid [25]. Cholesterol is often added to enhance membrane fluidity

and stability, making the structure less permeable to unwanted substances. Glycolipids, such as galactosylceramide, can also be incorporated to facilitate cellular recognition and targeting, as their sugar chains interact with specific receptors on cell surfaces. Additionally, fatty acids, which can vary in saturation (like stearic acid for saturation or oleic acid for unsaturation), influence the physical properties of the nanolipid, affecting its flexibility and drug release profile [13]. Together, these lipids contribute to the overall efficacy of nanolipids in drug delivery applications. Cataionic and ionizable lipids are widely used in the recent development of nanolipids formulations encapsulate cancer drugs, drug encapsulation in lipid-based nanoparticles (NPs) relied on passive methods using zwitterionic lipids, which resulted in relatively low encapsulation efficiencies of less than 40% and limited transfection [34].

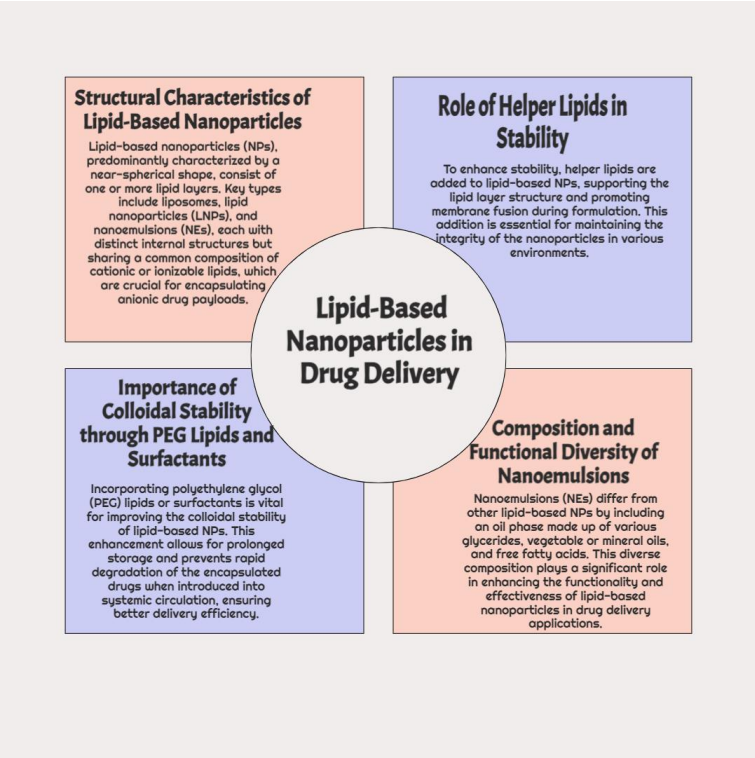

Figure 1: An overview of Lipid-Based Nanoparticles in Drug Delivery

The introduction of N-[1-(2,3-dioleyloxy) propyl]-N,N,N-trimethylammonium chloride (DOTMA) significantly improved anionic drug encapsulation through electrostatic interactions. However, the first generation of "lipoplexes" was highly unstable with broad size distributions, making them ineffective for in vivo delivery. To address this, 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), a biodegradable alternative to DOTMA, was developed for gene delivery applications. Dimethyldioctadecylammonium bromide (DDA), a quaternary ammonium lipid, emerged as another option due to its immunogenic properties, making it suitable for use as an immune adjuvant [41]. A notable trial involved the use of dioctadecyl-dimethyl-ammonium chloride (DODAC) to encapsulate plasmid DNA (pDNA), showing that lipid/pDNA particles had an extended

half-life of 7 hours in mice, compared to less than 10 minutes for naked pDNA. This prolonged circulation led to increased accumulation of the lipid/pDNA particles in distal tumors over 24 hours, with minimal accumulation in the liver and spleen. With advancements in lipid-based NPs, both DOTMA and DOTAP have been successfully utilized for mRNA delivery in cancer vaccines. Ionizable lipids, characterized by their native pKa values below 7, were developed to enhance anionic drug encapsulation while minimizing the systemic toxicity often associated with permanently charged cationic lipids. These ionizable lipids can load anionic payloads at pH values below their pKa, becoming positively charged, and then achieve a neutral exterior at physiological pH. Once inside the cell, where the pH is lower, these lipids are protonated, facilitating membrane destabilization and the release of their payloads into the cytoplasm [42]. Research indicates that an optimal pKa of around 6.5 is ideal for nucleic acid delivery in murine models. 1,2-dioleoyl-3-dimethylammonium propane (DODAP) and 1,2-dioleyloxy-N,N-dimethyl-3-aminopropane (DODMA) were among the first ionizable lipids developed for the delivery of antisense oligonucleotides (ASOs), significantly increasing their circulation half-lives in vivo after intravenous administration. Subsequently, Dilinoleyl-DMA (DLinDMA), a dilinoleoyl analogue of DODMA, was introduced for silencing apolipoprotein B (ApoB) in the liver. In a study using a murine factor VII (FVII) model for hepatic gene delivery, a new compound, 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-(1,3)-dioxolane (DLin-KC2-DMA or KC2), demonstrated superior efficacy in delivering FVII siRNA compared to DLinDMA. Recent lipid screening has identified a promising candidate, heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate (DLin-MC3-DMA or MC3), which showed exceptional siRNA delivery targeting TTR mRNA with an effective dose (ED50) of 0.005 mg/kg [41-43].

THE ROLE OF NANOLIPIDS IN CANCER THERAPY: ADVANTAGES AND DISADVANTAGES

Nanolipids, specifically solid lipid nanoparticles (SLNs), have emerged as a transformative approach in cancer therapy, leveraging their unique properties for enhanced drug delivery and targeted treatment. These nanocarriers provide significant advantages over traditional methods, but they also present certain challenges. This discussion will explore the benefits and problems associated with using SLNs in cancer treatments, supported by detailed examples that illustrate their potential and limitations (Figure 2) [44].

ADVANTAGES ASSOCIATED WITH USING SLNS IN CANCER TREATMENTS

1. Biocompatibility

SLNs are composed of safe lipids, such as triglycerides and fatty acids, which significantly reduce toxicity. For example, formulations using glycerol monostearate have shown high biocompatibility in various studies, making them suitable for systemic administration in cancer therapy [45].

2. Controlled Release

SLNs facilitate sustained release of drugs at targeted sites, allowing for prolonged therapeutic effects. An example is the use of SLNs for delivering paclitaxel, where the nanoparticles can be designed to release the drug gradually, maintaining effective concentrations at the tumor site over time [46].

3. Targeted Delivery
SLNs can be engineered with surface modifications, such as ligands or antibodies, to specifically target cancer cells. For instance, folate-conjugated SLNs have been developed that selectively bind to folate receptors overexpressed in certain cancers, such as ovarian and breast cancer. This targeted approach minimizes the impact on healthy tissues and enhances treatment efficacy [47].

4. Enhanced Drug Absorption
These formulations improve drug bioavailability by enhancing the absorption of poorly soluble drugs. An example is the formulation of curcumin-loaded SLNs, which significantly increased the bioavailability of curcumin in preclinical models, allowing for lower doses and improved therapeutic effects against various cancer types [48].

5. Versatile Formulation
SLNs can incorporate a wide range of therapeutic agents, including chemotherapeutics, proteins, and nucleic acids. For example, SLNs have been utilized to deliver small interfering RNA (siRNA) for gene silencing in cancer cells, showcasing their versatility in combination therapies that can enhance overall treatment efficacy [49].

6. Reduced Side Effects
By lowering systemic exposure, SLNs can lead to fewer side effects compared to conventional therapies. For instance, studies have shown that patients receiving doxorubicin in SLN form experience significantly fewer cardiotoxic effects than those receiving the free drug, thereby improving their overall quality of life during treatment [50].

DISADVANTAGES ASSOCIATED WITH USING SLNS IN CANCER TREATMENTS

1. Limited Drug Loading Capacity
While SLNs offer many advantages, they may have a limited drug loading capacity due to the solid lipid matrix. For example, in the case of paclitaxel-loaded SLNs, achieving high loading capacities can be challenging, necessitating additional formulation strategies such as the use of co-surfactants or lipid mixtures to enhance drug solubility [41].

2. Stability Issues over Time
Stability is a concern, as SLNs can be prone to drug degradation during storage. For instance, studies have indicated that certain SLN formulations may experience a reduction in drug content over time, impacting their efficacy. This requires careful management of storage conditions and formulation composition [39].

3. Potential Immune Response
In some cases, SLNs may provoke an immune response, which can complicate treatment. Research has shown that certain lipid-based formulations can activate the complement system, leading to hypersensitivity reactions in some patients. This necessitates a thorough understanding of the immunological interactions of SLNs [32].

4. Manufacturing Challenges
The production of SLNs involves complex processes, such as high-pressure homogenization or solvent evaporation, which may increase costs and complicate scalability. For example, the intricate techniques required for consistent production quality can hinder their integration into routine clinical practice [43].

5. Regulatory Hurdles
The introduction of SLNs into clinical practice faces stringent regulatory scrutiny. The lengthy approval processes require extensive preclinical and clinical data to

demonstrate safety and efficacy. For instance, the regulatory pathway for SLNs can be more complicated compared to traditional drug formulations, potentially delaying their availability to patients [42].

6. Limited Clinical Data

Although SLNs show promise, there is still limited clinical data establishing their efficacy and safety in diverse patient populations. More research is needed to solidify their role in cancer therapy. For example, while many preclinical studies demonstrate the advantages of SLNs, translating these findings into clinical practice remains a challenge [38].

Therefore, while nanolipids, particularly solid lipid nanoparticles, offer significant benefits in enhancing cancer therapy through targeted drug delivery and reduced side effects, several challenges must be addressed. Examples such as the use of paclitaxel, curcumin, and doxorubicin illustrate the potential of SLN formulations in improving treatment outcomes. However, concerns regarding drug loading capacity, stability, immune response, manufacturing challenges, regulatory hurdles, and limited clinical data must be carefully navigated to fully realize the benefits of nanolipid-based therapies in clinical settings. Understanding the balance between these advantages and disadvantages is crucial for advancing cancer treatment and improving patient outcomes [32].

PREPARATORY PROCESSES FOR SOLID LIPID NANOPARTICLES (SLNS)

The formulation of solid lipid nanoparticles (SLNs) involves several key ingredients, including lipids, emulsifiers, surfactants, stabilizers, co-surfactants, preservatives, cryoprotectants, and charge modifiers. SLNs primarily utilize solid lipids, often in the presence of water, and it is advisable to minimize the use of organic solvents [30].

Key Ingredients

Lipids: Common lipid types include triglycerides, fats, fatty acids, waxes, and steroids, all possessing sufficient lipophilic properties. Partial glycerides, such as Imwitor, are also utilized [30].

Emulsifiers: These are crucial for stabilizing the lipid dispersion during preparation and preventing nanoparticle agglomeration. The choice of emulsifiers depends on the desired delivery characteristics of the SLNs and their intended routes of administration [30].

Specific Compositions: Examples of lipid constituents include: Comprital (10%), Cetyl palmitate (10%), Ethyl oleate (30%), Glycerol (4%), Isopropyl myristate (3-4%), Lecithin (9%), Various triglycerides (e.g., trimyristin, tripalmitin), Polymers such as PEG (various forms) and phospholipids[31].

Preservatives and Cryoprotectants: Common preservatives include thiomersal, while cryoprotectants may involve gelatin, glucose, mannose, and others [36].

Charge Modifiers: These include compounds like dipalmitoyl phosphatidylcholine and stearoyl amine, which are utilized during the preparation and stabilization of SLNs [33].

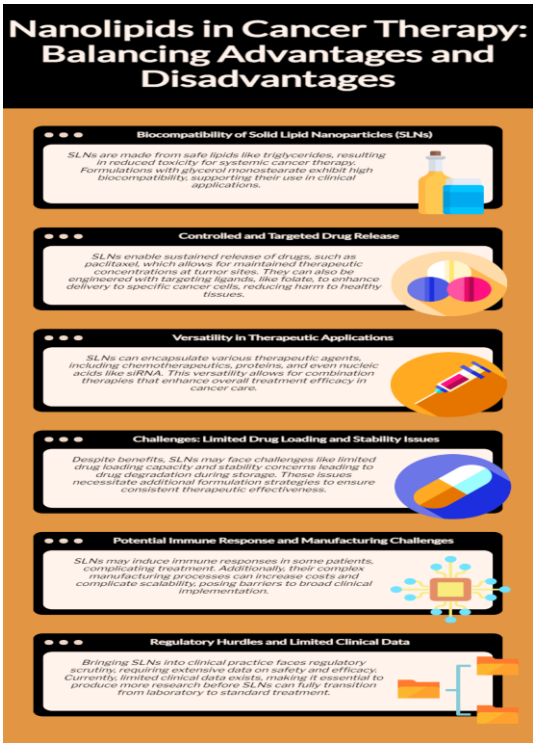

Figure 2: Nanolipid use in cancer therapy: Balancing Advantages and disadvantages

Manufacturing Techniques

Several techniques are employed in the production of SLNs, with high-pressure homogenization (HPH) and microemulsion methods being particularly popular for large-scale industrial applications. The influence of microemulsion parameters on the size and shape of SLNs, as well as the incorporation of crystalline structures of the drugs, has been explored, contrasting them with non-lipidic nanoparticles produced under hydrophilic conditions.

High-Pressure Processing (HPP)

HPP has been recognized for its feasibility and consistency in SLN production, yielding spherical nanoparticles with good stability. For instance, when comparing tetrandrine-loaded SLNs prepared via HPP and ultrasonication, HPP produced smaller and more stable nanoparticles with better drug incorporation. Various analysis techniques, including Transmission Electron Microscopy (TEM) and Zeta potential analysis, are used to assess the characteristics of the SLNs. HPP applies a combination of pressure gradients and mechanical forces to create reliable and stable SLNs. High-quality homogenizers can adjust parameters such as turbulence, shear, cavitation, and process intensity to optimize SLN characteristics based on drug loading and delivery needs. This method results in smaller particle sizes, increased surface area, enhanced drug loading, and improved bioavailability, making it widely used in bulk pharmaceutical preparations. Additionally, the HPP process can lead to a reduction in the molecular weights of polymeric materials and may generate free radicals due to high shear stress [44].

Hot High-Pressure Processing (HPP) Method

In the hot HPP method, lipids are heated above their melting points, transforming them into liquid state materials. This increase in temperature reduces the viscosity of the preparation-stage liquid materials, leading to a decrease in the resultant particle sizes. However, this process has several disadvantages. Elevated temperatures can significantly increase the decomposition rate of the embedded drug, and unpredictable changes in lipid composition may occur. Additionally, drug losses from the aqueous phase can be observed due to the high kinetic energy involved in the preparative steps (see figure 3) [45].

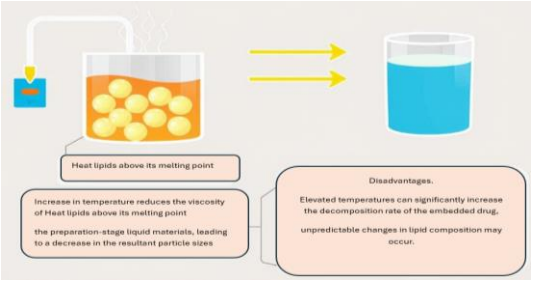

Figure 3: Hot High-Pressure Processing (HPP) Method for preparing Nanolipids

Cold High-Pressure Processing HPP Method

To address the limitations of the hot HPP method, the cold HPP approach was explored. In this method, a hydrophilic and thermo-labile drug was encapsulated within a solid lipid nanoparticles (SLNs) matrix. Larger particles were created by diffusing solid lipid into a chilled surfactant solution. This mixture formed a uniform preparation, both at and below room temperature (RT), which was subsequently broken down by gravitational forces [46].

Solvent Emulsification Method

In this technique, lipids were emulsified through high-pressure processing (HPP) in a liquid state by dissolving them in organic solvents, such as cyclohexane and chloroform. These solvents are immiscible with water and evaporate easily, leaving behind precipitated nanoparticles. This process was conducted at 25°C and was sensitive to temperature changes (See figure 4) [47].

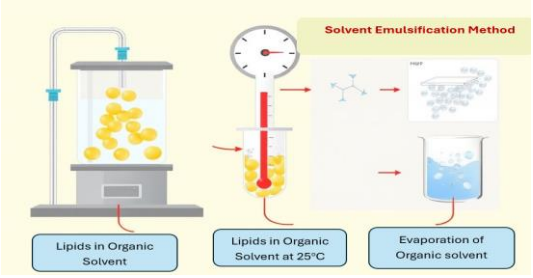

Figure 4: Solvent Emulsification Method for preparing Nano lipids

Emulsification-Sonication Method

In this method, drugs were added to liquefied lipids at temperatures of 5–10°C, along with a hot surfactant solution. The resulting emulsion was sonicated to decrease

particle size. The SLNs obtained were then cooled to room temperature. However, this process posed a risk of metal contamination due to the use of a metal probe during ultra-sonication [48].

Aqueous Needle Process

This process also employed organic solvents that are water-miscible and offered a faster production rate while being cost-effective. It closely resembles the solvent diffusion method. In this technique, lipids in organic solvents were rapidly injected under pressure through a needle into a liquid surfactant solution (See figure 5) [49].

Solvent Emulsion-Scattered Method

In this method, organic solvents that are partially water-miscible were utilized for the preparation of solid lipid nanoparticles (SLNs) through solvent diffusion. When saturated with water, these diluents became stable under heat and temperature changes. The organic liquids were fully saturated to achieve thermodynamic equilibrium. The resulting mixture was then transferred to water under constant stirring to solidify the dispersed phase, resulting in the formation of SLNs. An overview of this preparation method is illustrated in figure 6 [50] .

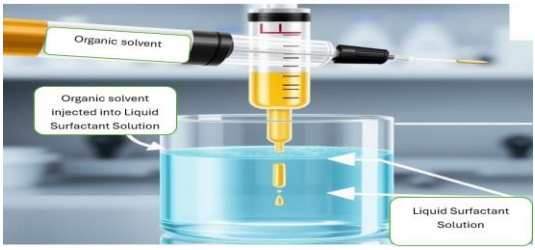

Figure 5: Aqueous Needle Process Method for preparing Nanolipids

Double Emulsion Method: Water-in-Oil-in-Water Emulsions

This method led to the formation of lipospheres, which are slightly larger than SLNs. A hydrophilic drug was embedded within the liquid lipid phase, and stabilizing agents were used to prevent the drug from escaping from the liquid core to the external layer of the double emulsion [51].

APPLICATIONS IN CANCER THERAPY

Lipid-Based Nanoparticles (LBNPs) encompass a broad and diverse range of nanoparticles, playing a crucial role in breast cancer (BreC) therapy. Among these, liposomes are particularly favored due to their excellent biocompatibility and capacity to encapsulate various therapeutic agents. Currently, LBNPs are being investigated in numerous studies, with some, such as Doxil and Abraxane, already approved for BreC treatment. This section highlights the latest significant advancements in the application of LBNPs for treating prevalent cancer types table 1 [52-55].

Glandular Carcinoma

Currently, the primary lipid-based nanoparticles (LBNPs) being explored as potential treatments for prostate cancer include nanoemulsions (NEs), liposomes, and solid lipid nanoparticles (SLNs). Ahmad et al. recently developed an oil-in-water NE containing a toxoid therapeutic agent attached to an omega-3 fatty acid, which effectively reduced the toxoid IC50 in PPT2 cell lines by 12-fold, leading to a more significant reduction in tumor size in tumor-bearing rats compared to AbraxaneTM. Similar antitumor effects

were observed in PC-3 cells when the NE was loaded with catechin extract, known for its anticancer properties. For liposomes, 22Rv1 prostate cancer cells were treated with PEG-folate-targeted oleuropein liposomes, which enhanced apoptosis, bioavailability of oleuropein, and overall survival in in vivo models. Hua et al. also created nanoparticles comprising diversified liposomes loaded with docetaxel and a gold nanorod, achieving complete suppression of prostate cancer cell growth through a combination of treatment modalities, including radiation. There are numerous applications of these technologies across various cancer types, including lung, nervous system, liver, and pancreatic cancers. Recent years have seen significant modifications and the synthesis of new nanoparticles [54-56].

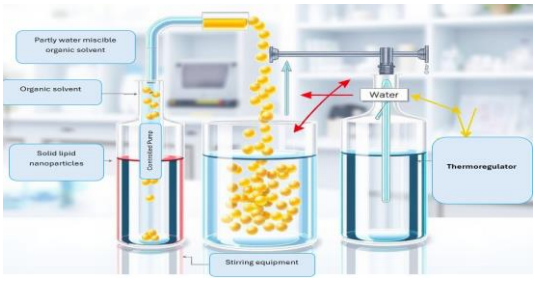

Figure 6: Solvent Emulsion-Scattered Method for preparing Nanolipids

Bowel Cancer

Bowel cancer is a significant health issue due to its high mortality rate, being the second leading cause of cancer deaths, coupled with a rising incidence. LBNPs present a promising strategy to enhance existing treatment options, especially for advanced colorectal cancer, where conventional chemotherapy (like 5-FU used alone or with other drugs) or monoclonal antibodies (such as bevacizumab, trastuzumab, and cetuximab) may not be effective [55]. Research indicates that a thermosensitive gel-mediated 5-FU microemulsion improves Caco-2 permeability and cellular uptake, as well as its accumulation in rectal tissue when compared to a standard 5-FU microemulsion. Low et al. developed an advanced system based on Pickering emulsions, utilizing a magnetic cellulose nanocrystal loaded with curcumin (CUR), which allows for controlled drug release in response to an external magnetic field. This method effectively inhibited HCT116 cell growth in both monolayer and multicellular spheroid models. Additionally, Ektate et al. activated macrophages within the tumor microenvironment using lipopolysaccharide (LPS) from attenuated Salmonella bacteria, paired with DOX-thermosensitive liposomes and high-intensity focused ultrasound [56]. This technique improved doxorubicin (DOX) internalization through alterations in membrane fluidity, leading to reduced tumor growth in vivo. Efforts in liposome characterization are also being applied to enhance colorectal cancer (CRC) therapies. For instance, Moghimipour et al. utilized fatty acid (FoA) modifications to improve 5-FU uptake in CT-26 cells, resulting in a lower IC50 and decreased tumor volume. Kaseem et al. developed niosomes containing imatinib mesylate (IM), which significantly reduced the IC50 of the free drug by 16-fold in HCT-116 cells [57-59].

Breast Cancer

Breast cancer is the leading cause of cancer death among women, and significant advancements are being made through the development of nanoparticles, particularly

in treating metastatic disease. In studies involving the MCF-7/ADR cancer cell line, nanoemulsions preloaded with doxorubicin (DOX) and bromo tetra trandrine (W198, a P-glycoprotein inhibitor) have been examined, resulting in increased cellular uptake and accumulation of DOX in cancer cells while reducing stomach and cardiac toxicity. Conversely, DOX liposome formulations have been tested in clinical trials. Pegylated liposomal doxorubicin (PLD) combined with lapatinib has been utilized in HER2-positive breast cancer patients (stage Ib) to determine the optimal combination of both therapies at maximum tolerated doses. Additionally, Phase 3 trials involving Myocet in combination with cyclophosphamide (CM) or vinorelbine (MV) for breast cancer patients have been established. Solid lipid nanoparticles (SLNs) are also being explored in breast cancer research. Yu et al. proposed a method for delivering paclitaxel (PTX) and modified DNA using a pH-sensitive ligand, which effectively reduced tumor volume while minimizing PTX deposition in other organs. Furthermore, Garg et al. developed a fucose-methotrexate SLN that preferentially accumulated in tumor tissue within just 2 hours post-treatment, unlike free methotrexate, which spread throughout the kidneys, liver, and spleen [60-63].

Table 1: Lipid-based nanoparticles in treatment of different types of cancer

Composition	Chemotherapy	Type of Cancer	Mode of Operations	Delivery Mechanism	Pharmacokinetics	Reference
PEGylated liposomes	Paclitaxel	Melanoma	i.v.	Prolonged blood circulation with targeted release at tumor sites.	Increased half-life due to PEGylation; better tissue penetration.	[47]
Liposomes	Doxorubicin	Breast cancer	i.v.	Encapsulation within lipid bilayers for stable delivery.	Prolonged circulation time; reduced clearance rate.	[46]
pH-responsive liposomes	Mitoxantrone	Breast cancer and renal cancer	i.v.	Release triggered by acidic environment of tumors.	Variable release rates based on tissue pH; enhanced bioavailability.	[48]
Enzyme/pH dual-sensitive micelle-liposomes	Paclitaxel	Metastatic breast cancer	i.v.	Dual-responsive mechanism using enzymes and pH for release.	Altered pharmacokinetics due to dual-trigger release; improved targeting.	[49]
Hybrid lipid-based nanoparticles	Docetaxel	Metastatic peritoneal carcinoma	i.v.	Combination of lipid and polymeric components for enhanced delivery.	Enhanced drug retention and distribution in tumor sites.	[50]
Thermo-sensitive exosome-liposome hybrid nanoparticles	Zoledronate	Lung cancer	i.v.	Release activated by localized heat application.	Improved targeting and reduced systemic exposure due to localized action.	[51]
	Docetaxel	Cholesterol modified CpG carcinomas	Intra-tumoral	Direct tumor injection for localized drug action.	Rapid distribution in tumor tissue; minimal systemic effects.	[54]

Stomach Cancer

Stomach cancer is the fifth most common cancer globally and a leading cause of cancer-related deaths. Surgical removal is only an option for cases where the cancer has not spread to the lymph nodes. For advanced stomach cancer, combination chemotherapy is typically required, which often comes with severe side effects. New treatments utilizing nanotechnology are currently under investigation to improve patient outcomes. Liposomes have been extensively used in gastric cancer (GC) therapy, either alone or in

conjunction with agents like Arg-Gly-Asp peptides, SATB1 siRNA/CD44 antibodies, or in DNA complex formulations. Their application has enhanced drug deposition in cancer cells, particularly in animal models with SGC7901 cells that express high levels of integrin α5β1. Liposomes have also shown improved targeting precision and successfully reduced SATB1 gene expression by approximately 80% in CD44-positive GC stem cells. Additionally, liposomes have identified peritoneally dispersed MKN-45P GC cells, decreasing their accumulation in the liver. Early studies on solid lipid nanoparticles (SLNs) in GC indicated that etoposide (VP16) had enhanced efficacy in SGC-7901 cells, increasing growth inhibition and inducing cell cycle arrest at the G2/M phase while triggering mitochondria-mediated apoptosis. Li et al. developed an SLN that works in conjunction with ATRA, sorafenib, and miR-542-3p, which improved the absorption of both anticancer agents and exhibited synergistic effects on MGC-803 cells [64-66].

CONCLUSION

Lipid-Based Nanoparticles (LNPs) represent a diverse and extensive category of compounds used to treat various diseases, particularly cancers. Among these, liposomes are the most commonly employed due to their excellent biocompatibility and flexibility, although Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) have gained popularity recently. However, research on these nanoparticles is still limited, with many studies exploring innovative methods to utilize LNPs for treating different types of cancer. Some of these approaches have progressed to advanced stages and are entering clinical trials.

Conflict of interest

The author states that the research was carried out without any commercial or financial ties that might be seen as a potential conflict of interest.

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