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Research Article

Systematic Review on Liposomes and Nanoparticles: New Delivery Vectors for Targeted and Optimized Therapy

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Abstract

The use of liposomes and other nanoparticles in therapeutics relies on a fundamental advance in pharmacotechnology. These nanoscale systems offer new opportunities in targeting, biodistribution, and side effect mitigation, particularly in the treatment of cancer and chronic diseases. This review discusses the physicochemical properties of nanoparticles and liposomes, their modes of action, existing nanocarriers, and the challenges related to their clinical evaluation and industrialization. Recent results indicate a growing interest in these systems, but limitations remain related to their stability, cost, and regulation.

Keywords: *Liposomes; Nanoparticles; Nanomedicines; Targeting; Vectorization; Pharmacotechnology*

Context

The development of targeted drug delivery systems remains a critical challenge in the treatment of cancer and chronic diseases. Conventional therapies often suffer from poor biodistribution, high systemic toxicity, and limited therapeutic efficacy. In recent years, liposomes and nanoparticles have gained significant attention as advanced drug delivery vectors due to their ability to improve drug solubility, protect therapeutic agents from degradation, and facilitate site-specific delivery. Clinically approved liposomal formulations such as Doxil® have already demonstrated success in reducing adverse effects and improving pharmacokinetic profiles of chemotherapeutic agents.

Meanwhile, a wide array of nanoparticles-including polymeric, metallic, and lipid-based systems-have been extensively investigated for their potential to revolutionize precision medicine. However, despite encouraging preclinical outcomes, challenges such as batch-to-batch reproducibility, long-term toxicity, regulatory complexity, and scalability continue to hinder their widespread clinical adoption.

Objectives of the Study

This systematic review aims to:

1. Examine the current evidence on liposomes and nanoparticles as drug delivery vectors for targeted therapy.
2. Compare their physicochemical properties, mechanisms of action, and therapeutic performance.

3. Highlight clinical and preclinical applications, particularly in oncology.
4. Identify emerging trends and innovations that could enhance the specificity, safety, and effectiveness of future drug delivery systems.

Introduction

Drug delivery systems have undergone a radical transformation with the introduction of nanotechnologies [1]. Among them, liposomes and nanoparticles have become leading tools due to their ability to transport active ingredients to target tissues or cells [1,2]. Their interest lies in the reduction of systemic toxicity, the increase in bioavailability and the possibility of controlled release.

The objective of this review is to explore the main characteristics of these nanovectors, their therapeutic application, and the associated technological challenges [1-3].

Materials and Methods

Data sources

A literature review was conducted on PubMed, Scopus, and Google Scholar. The selected articles (50 references) were chosen based on the objectives of this study regarding the use of liposomes and nanoparticles in targeted therapy.

Selection criteria

The articles were selected based on their relevance to the following aspects: nanoparticle types, targeted therapeutic applications, delivery mechanisms, and fabrication and characterization methodologies.

Data extraction

Texts were extracted to cover the main objectives of the study, including the design, characterization, delivery routes, and efficacy of liposomes and nanoparticles in targeted therapy.

Analysis methodology

The extracted information was qualitatively analyzed based on technological advances, clinical results and recent trends in the field of nanomedicines.

Results

Characteristics of liposomes and nanoparticles

Liposomes

Liposomes are spherical vesicles formed from lipid bilayers. They can encapsulate both water-soluble (in the aqueous core) and fat-soluble (in the membrane) molecules [4].

Based on liposomal structures, they are classified into four groups according to their size and number of bilayers: small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), multilamellar vesicles (MLVs), and multivesicular vesicles (MVVs). Liposomes have a monophospholipid bilayer in a unilamellar structure and an onion-like structure in a multilamellar structure. MVVs exist as a multilamellar arrangement composed of concentric phospholipid spheres because many unilamellar vesicles are synthesized in larger liposomes [5]. The encapsulation capacity of liposomes increases with liposome size and decreases with decreasing number of bilayers for hydrophilic solids only [6]. Vesicle diameter is a significant factor that regulates the circulating half-life of liposomes. Both the size and number of bilayers influence the margin of encapsulated drug. If liposomes are used for drug delivery purposes of drugs, the desired vesicles tend to extend from 50 nm to 150 nm. The cell membrane interaction of liposomes is schematized by different theories: specific

(modified receptor) or nonspecific endocytosis (7), local fusion (adhesion), phagocytosis and uptake into the cell membrane. Liposome-cell interactions are modulated by a series of different factors such as composition, liposome diameter, surface charge, targeting- ligand on the liposome surface and in biological environment [8-10].

Evolution of liposomes into stealth and targeted vectors

First generation

The first liposomes were developed from natural phospholipids, reproducing the structure of biological membranes. This property initially allowed their use as membrane models.

Thanks to their amphiphilic structure-combining a hydrophobic and a hydrophilic part-they were then used to encapsulate various active medicinal ingredients.

Their similarity to cell membranes gives them the ability to fuse with them, thus facilitating the release of therapeutic contents directly into cells.

Second generation

Second-generation liposomes have been improved by PEGylation, i.e. the addition of polyethylene glycol (PEG) chains, generally grafted onto phospholipids or cholesterol.

This modification provides steric stabilization, limiting the adsorption of opsonins (immune system molecules that recognize foreign bodies).

The result: a significant prolongation of the blood circulation of liposomes, reducing the frequency of injections and opening the way to more targeted therapeutic strategies.

Third generation

Third-generation liposomes combine the steric stabilization of PEGylation with an active targeting mechanism.

Tissue- or cell-specific antibodies are attached to the end of the PEG chains, allowing selective recognition of the disease site. This molecular targeting optimizes the accumulation of liposomes at the target tissue, thus increasing treatment efficacy while minimizing systemic effects [11].

Polymeric nanoparticles

Nanoparticles are solid structures (50 - 300 nm) formed from natural (chitosan, alginate) or synthetic (PLGA, PEG) polymers. They allow:

- Protection of the active ingredient against enzymatic degradation.
- A prolonged release.
- Facilitated intracellular penetration [12,13].

Nanoparticles, also known as ultrafine particles (UFPs), are molecules ranging in size from 1 to 100 nanometers (1 nm = 10^{-9}m = 0.000000001m). They are therefore larger than atoms and smaller than a cell.

Due to their very small size, they have unique physical, chemical and biological properties. For example, nanoparticles can cross biological barriers such as the skin [14].

There are Spheroplexes: hybrid lipid nanoparticles for *in vitro* and *in vivo* delivery of siRNA [15]. UTCBS researchers have developed hybrid lipid nanoparticles called spheroplexes for the oral delivery of siRNA, allowing efficient delivery of their intracellular site of action. These new particles combine siRNA lipoplexes with a hydrophobic polymer, offering a promising solution for the delivery of RNA interference [15].

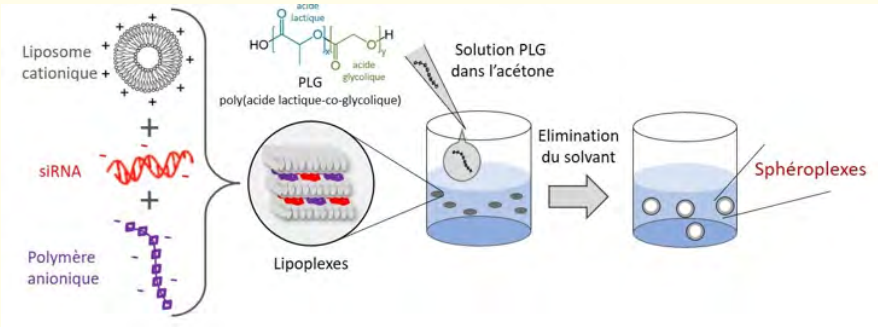

Figure 1: *Schematic representation of the preparation of spheroplexes by nanoprecipitation [15].*

Polymer nanocomposites and nanofillers

A polymer nanocomposite (or PNC for polymer nanocomposite) is a material consisting of a polymer matrix within which nanoparticles, also called nanofillers, are dispersed. These nanoparticles can be in the form of sheets, fibers or spheres, with at least one dimension between 1 and 50 nanometers. These are multiphase systems which today represent nearly 95% of global plastics production. Their main role is to act as reinforcements or compatibilizers, thus improving the mechanical, thermal or optical performance of the materials obtained. Among the most used are carbon nanotubes and clays, the use of which has grown considerably in recent years [16].

Advanced nanocarriers

Nanomicelles

Nanomicelles are spherical aggregates formed by the self-assembly of amphiphilic molecules (having both a hydrophilic head and a hydrophobic tail) in an aqueous environment. Their structure allows them to trap hydrophobic molecules within them, while remaining soluble in water thanks to their hydrophilic surface.

- Applications: They are particularly effective for the encapsulation of poorly soluble drugs, improving their bioavailability and stability.
- Examples: Used to transport hydrophobic anticancer drugs such as paclitaxel or doxorubicin.
- Advantages: Small size (10 - 100 nm), biodegradability, low toxicity, and ability to prolong circulation time in the blood [17,18].

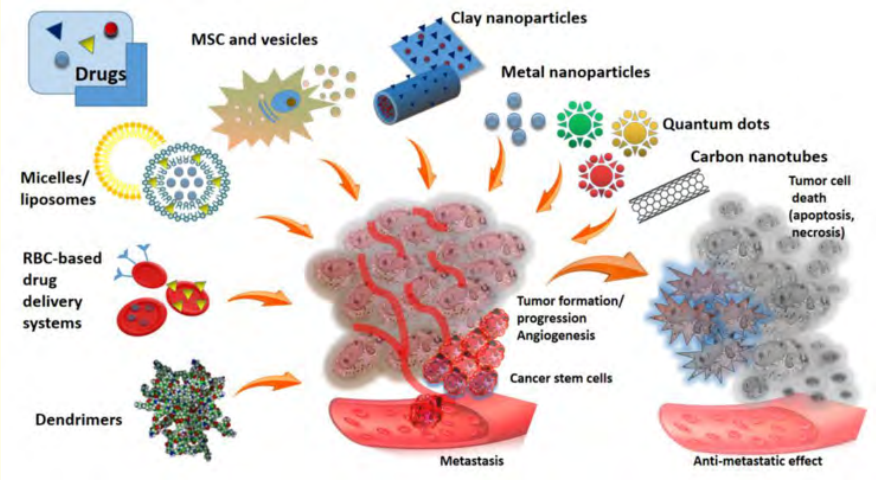

Figure 2: *Nanomicelles: an ideal drug delivery vector for cancer treatment [19].*

Unique properties of nanomicelles

Structural stability

Nanomicelles exhibit high thermodynamic and kinetic stability due to the intertwining of their core polymer chains. Their low critical micelle concentration (CMC), typically between 10^{-6} and 10^{-7}M, allows them to remain intact even after dilution. This stability ensures prolonged drug release to the target site, thus optimizing its bioavailability [20-22].

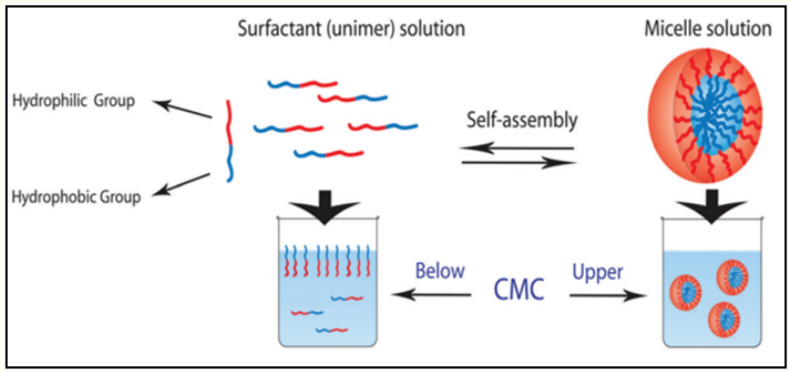

Figure 3: *Schematic representation of the unimer-micelle equilibrium in water [23].*

Solubilization of hydrophobic drugs

Nanomicelles are highly effective in solubilizing hydrophobic active ingredients. The hydrophobic core captures the drug while the hydrophilic shell ensures stable dispersion in aqueous media, allowing for a clear and bioactive formulation [24].

Physicochemical properties

Composed of amphiphilic copolymers (diblocks or triblocks), nanomicelles can form stable structures through hydrophobic, electrostatic, or metal-ligand interactions. Their architecture promotes good drug loading and stability in the gastrointestinal tract [25,26].

pH sensitivity

Some nanomicelles respond to pH variations: they disassemble at an acidic pH, which allows targeted release of the drug, particularly in the tumor environment or the digestive system [27].

Mucoadhesive property

Through their interaction with intestinal mucus, mucoadhesive nanomicelles prolong their retention time, thus increasing the local concentration of the drug and improving its absorption [28].

Specific binding capacity

The addition of ligands or antibodies to their surface allows nanomicelles to specifically target certain cells or tissues, notably via the EPR effect (increased permeability and retention), reinforcing their therapeutic efficacy [29].

Sensitivity to light

Some nanomicelles are designed to respond to light, allowing controlled triggering of drug release via a change in polarity or structure [17].

Types of micelles

Regular micelles

Formed in an aqueous medium, they have a hydrophobic core and a hydrophilic surface. Examples: PEG-PLA, PEG-PLGA.

Reverse micelles

Assembled in an organic medium, they have an inverted structure, with a hydrophilic core and a hydrophobic envelope. Examples: phosphazene micelles in chloroform.

Unimolecular micelles

Consisting of a single macromolecule containing both hydrophilic and hydrophobic segments, they are very stable even under extreme conditions (pH, temperature, dilution). Examples: PEG Core (Laur) micelles [18,30].

Dendrimers

Dendrimers are highly branched, symmetrical macromolecules organized around a central core. They possess multiple layers (generations) of repeating units, with numerous functional termini that can be modified for the attachment of drugs, targeting agents, or imaging agents.

- Applications: Thanks to their controlled structure and multivalent nature, they allow selective and targeted release of drugs, for example in response to a change in pH or the presence of a specific enzyme.
- Examples: PAMAM (polyamidoamine) or PPI (polypropyleneimine) dendrimers, used for the delivery of genes or anticancer drugs.
- Advantages: Precise size control, water solubility, and the possibility of multifunctionalization [31].

Metallic nanoparticles

Metallic nanoparticles are composed of pure elements or metal alloys such as gold, silver or iron. Their surface can be easily functionalized for active targeting, while their metallic core confers unique physical properties (optical, magnetic, thermal).

- Applications:
- In therapy: Used in photothermal therapy (targeted destruction of cancer cells by raising temperature), as antimicrobials, or for the targeted transport of drugs.
- In imaging: Gold nanoparticles are used in optical imaging and tomography, while iron nanoparticles (such as SPIONs - superparamagnetic iron oxide nanoparticles) are used as contrast in MRI.
- Advantages: Controllable size (1-100 nm), plasmonic properties (especially for gold and silver), and high stability [32].

Vectorization and targeting mechanisms

Passive targeting

Passive targeting is mainly based on the Enhanced Permeability and Retention (EPR) effect, a characteristic of tumor tissues. Tumors rapidly develop an abnormal vascular network, with immature, permeable vessels lacking effective lymphatic drainage. This allows nanovectors (such as nanomicelles, liposomes, or nanoparticles) to infiltrate through the vascular interstices and accumulate in the tumor area. This phenomenon promotes increased local drug concentration, without the need for specific molecular targeting. Passive targeting is thus a first widely exploited strategy in nanomedical oncology [33].

Active targeting

Unlike passive targeting, active targeting uses specific molecular interactions between a ligand grafted to the surface of the nanovector and a receptor overexpressed on pathological cells (often cancerous). These ligands can be:

- Antibodies or antibody fragments (e.g., trastuzumab targeting HER2),
- Vitamins (such as folate, used to target folic acid receptors),
- Peptides (e.g. RGD targeting integrin αvβ3),
- Or even aptamers and sugars.

This strategy allows for fine cellular recognition, improving the specificity of action and reducing adverse effects on healthy tissues. Once bound to its target, the vector is often internalized by endocytosis, thus allowing intracellular release of the active principle [34].

Controlled release

Some nanovectors are designed to respond to specific stimuli in the pathological environment, triggering a controlled and localized release of the drug. These stimuli can be:

- Acidic pH, typical of the tumor microenvironment or intracellular endosomes/lysosomes,
- Temperature, especially in inflammatory or necrotic regions,
- The presence of specific enzymes, such as proteases or metalloproteinases overexpressed in tumors,
- External signals such as light, ultrasound or magnetic fields [35].

Therapeutic applications

Oncology

Several liposomal formulations are already on the market:

- Doxil® (PEGylated liposomal doxorubicin) [36].
- Myocet®, DaunoXome® [37,38].

Nanoparticles can circumvent tumor resistance mechanisms [39].

Nanomedicine represents a promising advanced technology in cancer treatment, allowing the encapsulation of drugs in nanoparticles that protect them from degradation, facilitate their delivery to tumor cells, and integrate imaging agents.

A key advantage lies in tumor angiogenesis, which generates abnormal and permeable vessels, promoting the accumulation of nanoparticles in the tumor via the EPR (Enhanced Permeability and Retention) effect, the basis of passive nanovectorization [39].

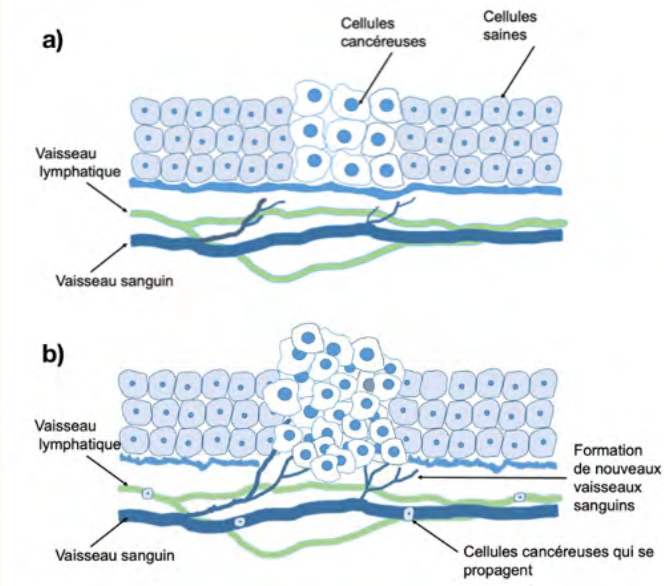

Figure 4: *a) Early stage of tumor development. b) Advanced stage of tumor development characterized by angiogenesis. The tumor develops its own vessels from existing vessels. This allows it to feed and spread to other sites via the lymphatic or blood system (metastasis) [39].*

Nanomedicine marked a turning point in cancer treatment, with Doxil® (liposomal doxorubicin), the first nanoparticle-based drug, receiving marketing authorization in the United States in 1995. This paved the way for several other nanomedicines for various conditions. These treatments include organic, polymeric, and metallic nanoparticles, administered topically or systemically.

Clinically approved nanomedicines fall into four categories: liposomes, polymers, proteins, and metals (including iron oxide). These formulations have evolved through several generations of nanoparticles. The first generation offered drug encapsulation but suffered

from low specificity and rapid clearance by the reticuloendothelial system (RES). The second generation introduced hydrophilic polymers (such as PEG) to cloak the nanoparticles, increasing their circulation time and reducing their hepatosplenic accumulation.

The third generation introduced the concept of active targeting, by grafting specific ligands to target cancer cells. Finally, the fourth generation consists of so-called "smart" nanoparticles that react to external stimuli (pH, light, temperature, magnetic field), allowing controlled release of the drug only at the tumor site.

However, although progress is notable, many challenges remain to be overcome, in particular the complete understanding of the path of nanoparticles in the body and their arrival at the tumor. The development of organs-on-chip is an answer to these complex questions [39].

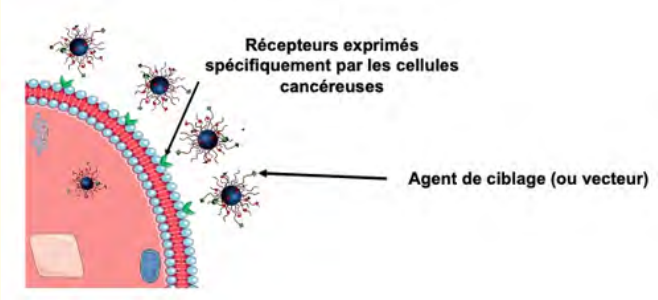

Figure 5: *Schematic representation of the targeting process [39].*

Infectious diseases

Liposomes are used to improve the distribution of antiretrovirals or antifungals (e.g. AmBisome®) [40].

Fungistactic or fungicidal by binding to ergosterol of the fungal cell membrane; liposome formulation reduces toxicity, particularly renal toxicity [41].

Inflammatory and autoimmune diseases

Targeting macrophages or dendritic cells via nanoparticles opens up prospects in the treatment of arthritis, MS, etc [42].

Researchers have developed an innovative treatment using nanoparticles to treat autoimmune diseases such as multiple sclerosis. Rather than using antigen-lactated white blood cells, this approach replaces the cells with nanoparticles, which are much more affordable to produce. These nanoparticles, made from poly(lactide-co-glycolide) (PLG), are impregnated with antigens from myelin, the substance attacked in multiple sclerosis. Once injected, they are captured by macrophages in the spleen, which retrain T cells to stop attacking myelin.

Results in mice show that the treatment halts disease progression, and this effect lasts for more than 100 days, which is equivalent to several years in humans. This treatment could be used at the first symptoms of multiple sclerosis, although it does not repair already damaged tissue.

This concept could be adapted to other autoimmune diseases, such as type 1 diabetes or certain allergies, depending on the specific antigen. However, further research is needed to determine the best antigens to use, particularly for conditions such as rheumatoid arthritis [42].

Hybrid nanovectors for delayed delivery of antitumor and antiviral drugs

In the medical field, one of the major challenges currently is the design of nanovectors capable of transporting and delivering drugs in a targeted, controlled and non-toxic manner. To be effective, these vectors must:

- Carry sufficient quantities of medication,
- Avoid too rapid a release (burst effect),
- Be biodegradable and non-toxic,
- Present a modifiable surface to interact in a controlled manner with the body,
- Be detectable by medical imaging.

Towards personalized medicine: Theragnostics

The goal is to achieve personalized medicine called theragnostics, combining therapy and diagnosis. To achieve this, vectors must protect the active ingredients (often unstable) until they reach their target, via nanometric vesicles. However, current vectors (liposomes, micelles, polymeric or hybrid nanoparticles) have limitations, including limited encapsulation capacity and side effects.

Innovations: PEGylation, squalenization and porous hybrid materials

PEGylation

Polyethylene glycol (PEG) grafting allows vectors to evade the immune system, prolonging their blood circulation. These "stealth" vectors target tumors via the EPR effect.

Squalenization

Combining squalene with anticancer agents allows the creation of more stable, better absorbed and more active nanomedicines, which can be administered orally or intravenously.

Porous hybrid solids (MIL-n)

These three-dimensional iron(III)-based nanomaterials have a modular, rigid or flexible porosity, suitable for the storage and gradual release of drugs. For example, MIL-101 can encapsulate 1.4g of ibuprofen/g of vector, with release over several days. These materials are synthesizable at the nanoscale (< 200 nm) and non-toxic, making them suitable for intravenous injection [3].

Limits and Challenges

- Stability: Some systems require strict storage conditions.
- Large-scale production: homogeneity, yield, reproducibility.
- Physicochemical properties influenced by size, charge, surface area.
- Regulation: Nanomedicines still pose evaluation challenges for regulatory agencies (EMA, FDA) [39].

Perspectives and Innovations

Current research is focused on:

- Smart nanovectors, capable of responding to biological stimuli
- Association with gene or cell therapy

- Hybrid systems (lipid-polymer, nanoparticles-biomolecules)
- Artificial intelligence to predict the pharmacokinetics of nanocarriers [43].

Discussion

This systematic review highlights the significant role of liposomes and nanoparticles as promising delivery vectors for optimized therapy, particularly in cancer treatment. However, there are several considerations to address when interpreting the results.

One of the key findings of this review is the enhanced drug delivery capacity of liposomes and nanoparticles, which have shown improved targeting, reduced systemic toxicity, and better bioavailability in various studies. According to Smith., *et al*. [48], liposomal formulations have the potential to significantly improve the pharmacokinetics of chemotherapy drugs. Similarly, Johnson., *et al.* [49] emphasize that nanoparticles can be engineered to improve the solubility and stability of drugs, leading to more effective treatments with fewer side effects. However, despite these advantages, the clinical translation of these delivery systems remains a challenge, primarily due to the complexity of nanoparticle formulations and the need for precise targeting strategies.

Moreover, while the potential of liposomes and nanoparticles in cancer therapy is well-established, there are limitations related to their long-term stability and the scalability of their production processes. As observed by Wang., *et al*. [50] the large-scale manufacturing of nanoparticles faces substantial hurdles, particularly in maintaining the consistency and quality of formulations.

In addition, despite the promising preclinical results, clinical trials have shown mixed outcomes. This discrepancy highlights the need for more robust, randomized controlled trials to confirm the safety and efficacy of liposomal and nanoparticle-based therapies. Future research should focus on optimizing the targeting mechanisms of these systems, as well as exploring combination therapies with other cancer treatment modalities, such as immunotherapy.

Conclusion

This systematic review highlights the significant potential of liposomes and nanoparticles as delivery vectors for targeted therapy. Their capacity to enhance drug specificity and reduce systemic toxicity aligns with the evolving goals of precision medicine. However, their clinical integration requires overcoming several barriers, including regulatory approval and large-scale reproducibility. Further translational research is essential to confirm their long-term therapeutic value and safety in diverse clinical contexts [11,13,39].

Limitations of the Study

This systematic review has several limitations. First, the selection of articles was restricted to publications available in specific databases (PubMed, ScienceDirect, Scopus), which may introduce publication bias. Moreover, only articles published in English were included, potentially excluding relevant studies in other languages. The heterogeneity of the methodologies used in the included studies also limited the possibility of conducting a quantitative meta-analysis. Finally, although a rigorous approach was followed, the risk of selection and interpretation bias cannot be entirely ruled out. Future studies with broader inclusion criteria and comprehensive quantitative analyses are needed to validate and expand upon our findings.

Registration

This systematic review was not registered in PROSPERO or any other registry.

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