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Review Article

Lipid-Polymer Hybrid Nanoparticles in Cancer Therapy: A Promising Nanotechnology-Based Drug Delivery System

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ABSTRACT

Cancer is one of the leading causes of mortality worldwide, with an increasing global burden and significant disparities in its incidence and treatment. Lipid-polymer hybrid nanoparticles (LPHNPs) represent a cutting-edge advancement in nanotechnology-based drug delivery for cancer therapy. These nanoparticles combine lipid carriers' biocompatibility with polymeric nanoparticles' structural stability, resulting in improved drug solubility, controlled release, and enhanced tumour targeting. LPHNPs enhance drug delivery to cancer sites through both passive and active targeting strategies, leveraging the enhanced permeability and retention (EPR) effect along with ligand-based targeting to increase drug concentration at tumor locations. The formulation of LPHNPs involves various preparation techniques, including high-pressure homogenisation, solvent evaporation, and nanoprecipitation, ensuring stability and optimal drug loading efficiency. Their structural composition consists of a lipid matrix encapsulating a hydrophilic or hydrophobic drug core, allowing versatile drug delivery applications. Characterisation techniques such as dynamic light scattering (DLS), zeta potential analysis, and transmission electron microscopy (TEM) assess particle size, surface charge, and morphology, which are crucial for therapeutic efficacy. Despite their advantages, challenges such as large-scale manufacturing, long-term stability, and potential cytotoxicity require further research. The integration of LPHNPs into cancer therapy offers a promising approach to overcoming conventional treatment limitations, enhancing patient outcomes with reduced systemic toxicity.

INTRODUCTION

Cancer is a class of disease conditions distinguished by uncontrolled proliferation of cells and a capacity for invasion or spread to other body regions (metastasis). [1] Cancer arises from genetic alterations that interfere with the normal regulation of the cell cycle, resulting in uncontrolled cell growth and evasion of programmed cell death. Key contributing factors include inherited genetic traits, environmental exposures (such as smoking, radiation, and toxic substances), and certain infections.[2,3] Cancer classification depends on the tissue involved, including carcinoma (originating in epithelial cells), sarcoma (in connective tissues), leukemia (in blood-forming tissues), and lymphoma (in the immune system). Treatment options typically involve surgery, chemotherapy, radiation therapy, and immunotherapy.[4]

The World Health Organization's International Agency for Research on Cancer (IARC) reports a growing global cancer burden, with considerable variation between regions and cancer types, as shown in Fig. 1.

These disparities highlight the urgent need for worldwide equitable access to cancer prevention, early detection, and treatment services.[5,6]

Anticancer drugs, also known as antineoplastic agents, inhibit the growth and spread of cancer cells by interfering with specific cellular processes, such as deoxyribonucleic acid (DNA) replication, mitosis, or signalling pathways. [7] These drugs are classified into several categories, including alkylating agents (e.g., Cyclophosphamide), antimetabolites (e.g., Methotrexate), topoisomerase

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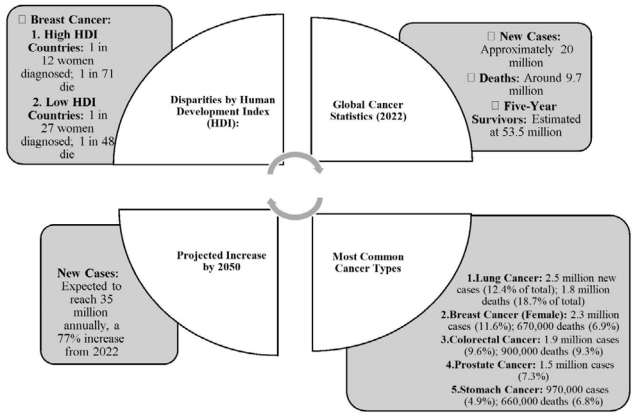

Fig. 1: Global cancer burden rising with regional and type-based disparities

inhibitors (e.g., doxorubicin), mitotic inhibitors (e.g., paclitaxel), and targeted therapies (e.g., imatinib).[8] Immunotherapy, including checkpoint inhibitors (e.g., Pembrolizumab), has emerged as an important therapeutic option. Therapeutic outcomes require individual drug use or specific drug combinations.[9] Hybrid nanoparticles (LPHNPs) represent a cutting-edge advancement in nanotechnology-based drug delivery for cancer therapy.

Drug Selection In Cancer

Multiple aspects determine the selection of medications for cancer therapy since tumours vary alongside essential markers, while overall patient health and treatment aim to play important roles. Selecting the proper drug helps maximise efficacy, minimise toxicity, and improve patient outcomes.[10]

Factors Influencing Drug Selection

Tumor type and stage

Cancer treatment decisions are shaped by both tumor type and stage. Different cancers respond to distinct therapies—lung cancer may benefit from immunotherapy, while leukemia often requires targeted therapy. The stage of cancer, from early (localized) to advanced (metastatic), determines treatment intensity. Early-stage cancers are often treated with surgery and adjuvant therapies, while advanced-stage cancers typically need systemic treatments like chemotherapy, immunotherapy, or targeted agents. Multimodal approaches are common in locally advanced cases. Personalized treatment considers tumor biology, spread, and patient factors, ensuring the most effective and tailored approach for improving survival and quality of life. [11-12]

Molecular and genetic markers

Molecular and genetic markers are crucial in selecting targeted cancer therapies. These biomarkers—such as gene mutations or protein overexpression—guide oncologists in choosing drugs that specifically act on tumor-driving alterations. For instance, epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer respond well to osimertinib, a targeted tyrosine kinase inhibitor, while human epidermal growth factor receptor 2 gene (HER2) amplification in breast cancer is effectively treated with trastuzumab, a monoclonal antibody. By identifying these markers before treatment, clinicians can tailor therapy to each patient, improving outcomes, minimizing side effects, and avoiding ineffective treatments. This personalized, precision medicine approach represents a major advancement in modern oncology care.[13-14]

Patient-specific factors

Patient-specific factors significantly influence cancer drug selection, ensuring safe and effective treatment. Age affects drug tolerance, with older adults often requiring adjusted doses due to decreased organ function. Liver and kidney function impact drug metabolism and excretion, necessitating dose modifications to avoid toxicity. Comorbidities such as heart disease or diabetes can complicate therapy, requiring tailored approaches. Functional ability is evaluated using the Eastern Cooperative Oncology Group (ECOG) performance scale, which helps determine a patient's ability to withstand treatment; those with better scores (0–1) may receive aggressive therapy, while those with poor scores (≥3) may benefit more from supportive or palliative care strategies.[15-16].

Previous treatment and drug resistance

Previous cancer treatments—like chemotherapy, radiation, or targeted therapy—can lead to drug resistance, where cancer cells adapt and no longer respond to previously effective treatments. Resistance may be intrinsic or acquired after repeated exposure, limiting future treatment options. For instance, platinum-based chemotherapy can cause platinum resistance in ovarian cancer, requiring alternatives like poly(ADP-ribose) polymerase inhibitors (PARP), (e.g., Olaparib, Niraparib), especially in patients with breast cancer gene (BRCA) mutations. Similarly, resistance mutations such as T790M in EGFR-positive lung cancer may necessitate switching to next-generation drugs like osimertinib. Tailoring therapy based on resistance patterns is essential to improve outcomes and control disease.[17]

Major Types of Cancer Drugs

Cytotoxic chemotherapy

Cytotoxic chemotherapy is a cornerstone of cancer treatment that targets and kills rapidly dividing cells, a defining characteristic of cancer. However, it also impacts normal fast-dividing cells in the bone marrow, gastrointestinal tract, and hair follicles, leading to side

effects. Drugs like paclitaxel, used for breast and ovarian cancers, work by disrupting mitosis and preventing cell division. Common side effects include bone marrow suppression, nausea, vomiting, hair loss, and peripheral neuropathy. Despite its toxicity, cytotoxic chemotherapy remains essential in many treatment regimens, offering significant survival benefits, especially when tumors are sensitive to these agents. Therapy is typically administered in cycles.[18]

Targeted therapy

Targeted therapy in cancer treatment uses drugs that specifically target molecular changes in cancer cells, aiming to block pathways essential for tumor growth. Compared to standard chemotherapy, which affects both malignant and healthy cells, targeted treatments are more specific and have fewer adverse effects. Examples include imatinib for chronic myeloid leukemia, which blocks the breakpoint cluster region-Abelson Murine Leukemia Viral Oncogene Homolog 1(BCR-ABL) fusion protein, erlotinib for lung cancer, which inhibits the EGFR pathway, and bevacizumab for colorectal cancer, which targets vascular endothelial growth factor (VEGF) to prevent angiogenesis. Targeted therapy has shown higher efficacy and fewer side effects in cancers driven by specific genetic mutations.[19]

Immunotherapy

Immunotherapy enhances the body's immune system to fight cancer by boosting overall immune activity or targeting immune checkpoints that cancer cells exploit to avoid detection. Drugs like Pembrolizumab (Keytruda), a checkpoint inhibitor, blocked the programmed cell death protein 1 (PD-1 receptor) on T-cells, allowing them to recognize and attack cancer cells. Immunotherapy may result in long-term remission, has fewer adverse effects than chemotherapy, and has demonstrated effectiveness against melanoma as well as non-small cell lung cancer. However, it may cause immune-related side effects, and not all patients respond to it, limiting its universal effectiveness.[20]

Hormonal therapy

Hormonal therapy treats hormone-driven cancers by blocking hormone receptors or reducing hormone production. It is commonly used for estrogen receptor-positive breast cancer (e.g., tamoxifen) and prostate cancer. Inhibiting hormones like estrogen or testosterone slows or stops cancer growth. This therapy is highly targeted, causing fewer side effects than chemotherapy, and can prevent cancer recurrence or prolong remission. However, side effects may include hot flashes, joint pain, blood clots, or decreased bone density. Hormonal therapy plays a crucial role in managing hormone-sensitive cancers, offering both effectiveness and relatively manageable side effects compared to other treatments.[21]

Combination therapy

Combination therapy in cancer treatment involves using multiple drugs together to attack cancer cells through different mechanisms. This strategy increases effectiveness, reduces the risk of resistance, and can improve survival rates. Each drug targets cancer in a unique way, allowing a more comprehensive approach. A well-known example is the Folinic acid (leucovorin), 5-Fluorouracil (5-FU), and Oxaliplatin (FOLFOX)regimen for colorectal cancer, which includes folinic acid (enhances 5-FU), fluorouracil (blocks DNA synthesis), and oxaliplatin (damages DNA). Though combination therapy can lead to increased side effects and requires careful management, it remains a powerful and widely used method to treat various cancers with improved outcomes.[22]

Precision and personalized medicine

Precision and personalized medicine in cancer treatment involves tailoring therapies based on the genetic and molecular profile of a patient's tumor. This approach uses tools like genomic profiling and biomarkers to identify cancer-driving mutations, enabling the use of targeted drugs or immunotherapies. As an example, those suffering from non-small cell lung cancer (NSCLC) and EGFR mutations may receive erlotinib for better outcomes. Benefits include higher treatment success, fewer side effects, and avoidance of ineffective therapies. However, challenges include high costs, limited access to advanced diagnostics, and the possibility of drug resistance as tumors evolve. It represents a major advance in modern oncology.[23-24]

Drug selection in cancer treatment depends on a customized methodology that considers both tumor biological aspects, genetic profiles, and the patient's overall condition and past medication history. Advances in molecular diagnostics and targeted therapies continue to improve treatment outcomes and reduce adverse effects.

Formulation in Cancer Treatment

Drug formulation is crucial in enhancing the effectiveness of cancer treatments by enabling targeted delivery and sustained release of therapeutic agents. It helps extend the drug's stability and shelf life, ensuring prolonged activity within the body. Advanced formulations, such as nanoparticles and lipid-based carriers, allow for precise circulation to tumor sites, minimizing harm to healthy tissues and reducing side effects. Additionally, they can bypass biological barriers and overcome drug resistance mechanisms in cancer cells, such as efflux pumps. Innovative drug formulations significantly contribute to safer and more effective cancer therapy by improving bioavailability and reducing systemic toxicity.[25]

Table 1 delivers detailed information about the various cancer drug formulation methods.

Table 1: Formulation in cancer treatment

Aspect	*Description*	*Examples*
Solubility & Stability Enhancement	Many anticancer drugs have poor solubility, limiting absorption and effectiveness. Formulation techniques improve drug stability.	Liposomal Doxorubicin (Doxil): Enhances stability and reduces cardiotoxicity. Prodrug Capecitabine: Converts to 5-FU in the body for improved bioavailability.[26]
Drug Delivery Systems	Cancer drug administration affects their absorption, metabolism, and therapeutic impact.	Oral (Imatinib - Gleevec): Convenient for chronic myeloid leukaemia. Intravenous (IV) (Paclitaxel): Used for breast and ovarian cancer.[27]
Nanoparticle-Based Delivery	Nanocarriers improve drug targeting and circulation time and reduce systemic toxicity.	Albumin-bound Paclitaxel (Abraxane): Enhances solubility. Polymeric Micelles (Genexol-PM): Improves targeted drug release.[28]
Targeted & Localized Drug Delivery	Enhances precision by directly targeting cancer cells while sparing normal tissue.	Antibody-Drug Conjugates (ADCs) (Brentuximab vedotin): Used for Hodgkin's lymphoma. BCNU Wafers: Implant for localised brain tumour treatment.[29]
Controlled Release & Sustained Drug Action	Allows slow, steady drug release, reducing toxicity and increasing efficacy.	Injectable Hydrogels:Provide localised chemotherapy. Biodegradable Implants: Sustained release for weeks to months.[30]

The formulation challenges include toxicities, drug resistance mechanisms, and drug metabolism issues. High toxicity, which requires precise dosing. The drug resistance phenomenon can benefit from nanocarriers that serve to counteract multi-drug resistance (MDR).

Innovations include gene therapy, artificial intelligence (AI)-driven formulation design, and messenger ribonucleic acid (mRNA)-based cancer vaccines. AI for predictive drug design. The evolution of nanotechnology, targeted delivery, and controlled-release systems is revolutionising cancer drug formulation. These advancements improve treatment precision and patient outcomes and reduce side effects.[31,32]

Different Drug Delivery Systems in Cancer Treatment

Drug delivery in cancer therapy is pivotal in maximizing therapeutic efficacy while diminishing toxicity to healthy tissues. As briefly outlined in Table 2, advanced drug delivery systems are designed to improve the targeting of tumor cells, allowing for higher drug concentrations at the cancer site with fewer side effects. These systems enhance drug bioavailability, stability, and circulation time, ultimately improving patient outcomes. Techniques such as nanoparticles, liposomes, and polymer-based carriers offer controlled and sustained release, improve drug solubility, and overcome multi-drug resistance, making cancer treatment more precise, effective, and patient-friendly.

Advancements in drug delivery systems, notably nanotechnology, liposomes, lipid hybrid nanoparticles, hydrogels, and antibody-drug conjugates, have revolutionised cancer treatments. These innovations enhance precision, efficacy, and safety, reducing systemic toxicity and improving patient outcomes.

The Advantages Of The Nano Drug Delivery System

- Enhancements the stability of volatile pharmaceutical agents.
- They appear safer and more effective than conventional drug delivery systems.
- Medication delivery at specific sites.
- Drug resistance is eliminated.
- Reduces particle size, increasing drug solubility.
- Improves a formulation's dissolution rate.
- Increases the drug's bioavailability.
- A wide range of drug release rates must have been reached.
- Markdown for inter-patient variation.
- Improve the stability of currently unstable medications.
- The action begins fast.
- A little dose of medicine must be given. As a result, the medication concentration in the target tissue will be greater.
- If the administered dose is less, the toxic profile of the drug will be compromised.[46-48]

Nanoparticles (NPs) are particulate dispersions or solid particle drug carriers that are incapable of being biodegradable. The drug dissolves before being trapped, enclosed, or attached using a nanoparticle to matrix-based. Both nanospheres and nanocapsules are referred to collectively as nanoparticles. Nanocapsules mean the drug is confined to a cavity, surrounded by a unique polymer membrane. Nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Whereas traditional medication delivery methods have several limitations, nanotechnology provides prospects for use in medicine.[49] The capacity of nanoparticles to improve therapeutic index, specificity, and tolerance. The efficacy of many medications has garnered much interest.[50]

Table 2: Different drug delivery systems in cancer treatment

Drug delivery system	*Description*	*Examples*	*Advantages*	*Challenges*
Oral drug delivery	Oral chemotherapy is convenient but must overcome poor absorption and first-pass metabolism.	Imatinib (Gleevec) for chronic myeloid leukaemia. Capecitabine, a prodrug of 5-FU for colorectal cancer.	Non-invasive. Easy for long-term treatment.	Variable absorption. Requires high patient compliance.[33-34]
IV Infusion	Direct drug administration into the bloodstream for rapid effect.	Paclitaxel (breast cancer). Cisplatin (lung cancer, ovarian cancer).	Rapid action. Bypasses metabolism.	Systemic toxicity. Requires hospital visits.[34-35]
Nanoparticles--based drug delivery	Uses nanocarriers (liposomes, micelles, polymeric nanoparticles) to improve drug targeting.	Liposomal Doxil for breast cancer. Albumin-bound Paclitaxel (Abraxane) for pancreatic cancer.	Enhances bioavailability. Reduces side effects.	Complex formulation. High production cost. [36-37]
Lipid-polymer hybrid nanoparticles (LPHNPs)	Combines lipid carriers and polymeric nanoparticles to improve drug solubility, bioavailability, and targeting.	Paclitaxel-loaded LPHNPs for breast cancer. Curcumin-loaded LPHNPs for pancreatic cancer.	High stability and controlled drug release. Enhanced drug penetration into tumours.	Manufacturing complexity. Need for extensive biocompatibility studies. [37-38]
Liposome-based drug delivery	Encapsulation of drugs in lipid bilayers to improve solubility and reduce toxicity.	Doxil (Liposomal Doxorubicin). DaunoXome (Daunorubicin liposome).	Improves circulation time. Reduces cardiotoxicity.	Stability issues. Limited targeting ability. [39-40]
Antibody-drug conjugates (ADCs)	Monoclonal antibodies conjugated to cytotoxic drugs for targeted delivery.	Brentuximab Vedotin (Hodgkin's lymphoma). Trastuzumab Emtansine (T-DM1) for HER2+ breast cancer.	Highly specific targeting. Reduces systemic toxicity.	Expensive. Risk of drug resistance.[33,41]
Hydrogel-based drug delivery	Injectable hydrogels provide controlled, localised drug release.	BCNU wafers for brain cancer. PEG-based hydrogels for targeted therapy.	Sustained drug release. Minimises systemic toxicity.	Limited drug loading capacity. Requires surgical placement. [36,42]
Polymeric micelles	Self-assembled nanoscale carriers enhance solubility and targeting.	Genexol-PM (Paclitaxel micelle formulation). NK105 (polymeric micelle for doxorubicin delivery).	Increases water solubility. Passive tumor targeting (EPR effect).	Stability challenges. Rapid clearance in circulation.[39,43]
Implantable drug delivery systems	Biodegradable implants release drugs over an extended period.	Gliadel wafers (BCNU) for brain tumors. Leuprolide implants for prostate cancer.	Long-term drug release. Reduces systemic side effects.	Invasive procedure. Limited to localised cancers.[39,44]
Transdermal patches	Patches allow drug absorption through the skin for sustained systemic circulation.	Fentanyl patches for cancer pain management. 5-FU patches for skin cancer.	Non-invasive. Reduces gastrointestinal side effects.	Limited drug penetration. Not suitable for high-dose drugs.[33,45]

LHNPS in Cancer Therapy

Drug nanocarriers include liposomes as well as polymeric nanoparticles. Whenever they combine, they can be used as a powerful hybrid nanoparticle for many different therapeutic and diagnostic purposes, thus the term "lipid-polymer hybrid nanoparticle" (LPHNPs).[51]

LPHNPs are advanced nanocarriers integrating lipid-based and polymeric nanoparticles to optimise the delivery of drugs in oncology therapy. These hybrid nanoparticles combine biocompatibility, high drug-loading capacity, and controlled release properties, making them superior to traditional nanocarriers.[38,52]

Structural Composition of LPHNPs

LHNPs consist of the following components, shown in Fig. 2

Lipid core

The lipid core of LPHNPs significantly contributes to improved biocompatibility and facilitates effective drug loading. This core typically consists of biocompatible lipids such as phospholipids, cholesterol, and triglycerides, which

mimic natural cellular membranes, reducing toxicity and improving stability. Phospholipids provide structural integrity and aid in forming bilayer or micellar structures. Cholesterol enhances membrane rigidity and permeability control, while triglycerides contribute to the hydrophobic environment necessary for encapsulating lipophilic drugs. Together, these components create a stable core that not only protects the encapsulated drug but also allows for controlled release and targeted delivery within the body.[53]

Polymeric core

The polymeric core of LPHNPs enhances drug stability and controls release kinetics, ensuring prolonged therapeutic effects. Polymers such as Poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), as well as chitosan, are commonly used for this purpose. PLGA, a biodegradable polymer, allows for controlled and sustained drug release, reducing the need for frequent dosing. PEG provides a hydrophilic coating that improves biocompatibility and reduces immune system recognition, enhancing circulation time. Chitosan, a natural polymer, offers antimicrobial properties and can further aid in drug encapsulation and controlled release. The polymeric core thus supports both the stability and targeted release of therapeutic agents.[54]

Surfactants and stabilizers

Enhance nanoparticle stability and drug dispersion. Tween-80, Poloxamers, and lecithin are frequently utilized. The molecular mechanics of lipid-polymer fusion are being studied at the moment. Different methods of manufacturing LPHNP possess distinct mechanisms for their development. When the polymer is introduced to a water-based solution with lipids, the lipids precipitate from the organic solution and quickly self-assemble into a single layer around the shell in a single-step procedure.[55] PEGylated lipid substances self-assemble during this stage as well, with the PEG chain extending outward into aqueous surroundings and the lipid component attached to the outer layer of the polymer shell. Developing a bilayer framework and adhering to the core first, then by the bilayer disintegrating and resulting in hydrophobic contact between the polymer and lipid chains, is one hypothesized mechanism of LPHNP synthesis during the two-step process. The hybrid creation is thermodynamically advantageous regarding water-hating, Van der Waals, and interactions between electrostatic charges.[53,56]

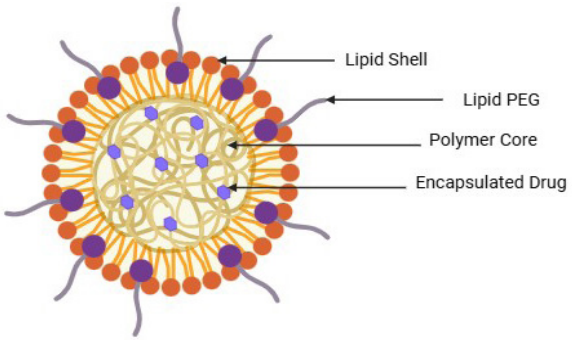

Fig. 2: Structure of LPHNPs

Mechanism of Action in Cancer Therapy

Lipid–polymer hybrid nanoparticles (LPHNPs) enhance the therapeutic index of anticancer drugs by leveraging multiple mechanisms that improve drug delivery and efficacy. Through passive targeting, LPHNPs exploit the enhanced permeability and retention (EPR) effect, allowing them to selectively accumulate in tumor tissues due to the leaky vasculature of cancer cells.[57] Active targeting is further enhanced by modifying LHNPs with ligands like monoclonal antibodies, peptides, or folic acid, thereby increasing their specificity and uptake by cancer cells.[58] Their polymeric shell enables controlled and sustained drug release, protecting the drug from premature degradation and minimizing systemic toxicity.[53] Furthermore, LPHNPs can overcome multi-drug resistance (MDR) by inhibiting P-glycoprotein (P-gp) efflux pumps, thereby increasing intracellular drug concentration in resistant cancer cells and enhancing therapeutic outcomes.[59]

Advantages of LPHNPS in Cancer Therapy

LHNPs deliver numerous advantages as drug delivery systems for cancer therapy compared to traditional treatment approaches. They combine lipid-based carriers' biocompatibility with polymeric nanoparticles' structural stability, resulting in an enhanced drug delivery process, controlled release, and decreased toxicities. Below are ten key advantages of LPHNPs, along with relevant examples.

Enhanced Drug Stability

LHNPs protect encapsulating pharmaceuticals from chemical instability and enzyme-mediated breakdown of bodily fluids. Example: Doxorubicin-LPHNPs improve the stability of doxorubicin in the bloodstream, preventing rapid degradation and prolonging its therapeutic effect.

High Drug Loading Capacity

The hybrid structure efficiently incorporates hydrophilic and hydrophobic drugs, leading to higher drug payloads. The therapy of Paclitaxel-LPHNPs enhances drug content while improving solubility, which mitigates the poor water solubility characteristic of paclitaxel.

Controlled and Sustained Drug Release

The polymeric shell regulates drug release, providing sustained therapeutic levels over time and reducing frequent dosing requirements. Example: 5-FU, LPHNPs allow controlled drug release in colorectal cancer, minimising systemic toxicity.[60]

Tumor-Selective Accumulation via Passive Targeting

LPHNPs exploit the EPR effect, allowing selective tumour accumulation due to leaky vasculature. Example: Liposomal irinotecan (Onivyde) uses passive targeting to increase drug concentration in pancreatic cancer cells.

Active Targeting for Improved Efficacy

Ligands, antibodies, or peptides can be attached to LHNPs to enhance their binding specificity toward cancer cells. Example: Folic acid-conjugated LHNPs for ovarian cancer actively target folate receptors overexpressed on tumour cells, improving treatment effectiveness.

Overcoming MDR

LHNPs help bypass P-gp efflux pumps, preventing drug expulsion from cancer cells and enhancing therapeutic outcomes. Example: Curcumin-LHNPs inhibit drug resistance mechanisms in pancreatic cancer, improving curcumin retention inside cancer cells.[61]

Reduced Systemic Toxicity and Side Effects

Targeted drug delivery minimises off-target effects, reducing damage to healthy tissues and lowering side effects. Example: Doxil (Liposomal Doxorubicin) reduces cardiotoxicity in breast cancer treatment by selectively delivering doxorubicin to tumour sites.

Improved Circulation Time and Bioavailability

The lipid-polymer hybrid structure prevents rapid clearance by the immune system, leading to prolonged blood circulation and enhanced drug absorption. Example: PEGylated LHNPs for lung cancer improve drug half-life by evading immune system detection.[61,62]

Capability for Combination Therapy

LHNPs allow multiple drugs to be co-delivered, enabling synergistic treatment strategies and improved therapeutic efficacy. Example: Paclitaxel and Curcumin-LHNPs provide a dual approach for breast cancer by combining chemotherapy with anti-inflammatory effects.

Potential for Personalized and Stimulus-Responsive Therapy

LHNPs responded to certain stimuli comprising pH, temperature, along enzymes, ensuring medication is released solely at the tumor site. Example: pH-sensitive LHNPs for prostate cancer release drugs within acidic tumor environments, reducing drug exposure to normal tissues.[63]

The new cancer treatment approach built around LHNPs provides better drug delivery precision alongside controlled substance release and lowered harmful side effects. The multivalent functions of nanocarriers demonstrate exceptional capability for customized combination cancer medicine, resulting in superior therapeutic results and enhanced treatment effectiveness. [52]

Properties of LPHNPS in Cancer Therapy

LHNPs offer enhanced stability, controlled drug release, improved bioavailability, biocompatibility, and targeted delivery, making them highly effective for cancer therapy with reduced side effects are briefly discussed in Table 3.

Types of LHNP in Cancer Therapy

LHNPs function as advanced drug delivery carriers that unite liposomal and solid lipid nanoparticle benefits with polymeric nanostructures, including PLGA and chitosan. Combining different structures within the system creates improved drug protection and precise drug delivery to specific tumours. LHNPs have multiple classification types depending on their composition and functionality, briefly discussed in Table 4.

The various LHNPs serve individual benefits for cancer therapy applications. Drug stability, targeted delivery properties, and controlled release functionality result from their lipid and polymeric material composition. The combination of features in LHNPs demonstrates the potential for serving as novel cancer treatments in upcoming medical developments.

Methods of Preparation of LPHNPS

LPHNPs are made through different preparation techniques that merge lipid-based formulation methods with polymeric nanoparticle production approaches. The production methods control how particles measure and maintain stability and drug incorporation while shaping a controlled drug release effect. Multiple methods serve as the basis for LPHNPs production, briefly discussed in Table 5.

The method of LPHNPs preparation requires consideration of both drug properties and desired nanoparticle dimensions and intended applications. Techniques like solvent evaporation, high-pressure homogenisation, and microfluidics offer different advantages and challenges. An appropriate method is crucial for optimising drug delivery in cancer therapy.

Limitations of LHNPS in Cancer Therapy

Despite their potential, LHNPs face challenges such as complex manufacturing, scalability issues, stability concerns, limited targeting efficiency, and regulatory hurdles, which hinder their widespread clinical application in cancer therapy. Discussed briefly as follows:

Complex and Costly Manufacturing Process

Specialized equipment and precise formulation parameter regulation are needed to produce LHNP through the ordered emulsification, solvent evaporation, and high-pressure homogenization sequence. Any slight modification in processing parameters causes the final product to develop inconsistent particle sizes and changes in drug loading and stability performance. High-pressure

Table 3: Properties of LPHNPs in cancer therapy

Property	*Description*	*Significance*	*Example*
Dual-component structure	LHNPs have a lipid shell and polymeric core, combining the advantages of liposomes and polymeric nanoparticles.	Enhances biocompatibility, drug encapsulation, and protection from degradation.	Paclitaxel-LHNPs use a lipid shell for stability and a polymeric core for controlled release in breast cancer therapy.[37]
High drug loading efficiency	LHNPs encapsulate both hydrophilic and hydrophobic drugs, allowing versatile drug delivery.	Enables co-delivery of multiple drugs, improving treatment effectiveness.	Doxorubicin and curcumin-LHNPs enhance the treatment of drug-resistant breast cancer.[64]
Enhanced stability in biological fluids	The polymeric core prevents mechanical breakdown, while the lipid layer prevents aggregation and drug leakage.	Ensures longer circulation time in the bloodstream, improving drug bioavailability.	PEGylated LHNPs improve plasma retention in lung cancer therapy.[65]
Biodegradability and biocompatibility	Made of natural lipids and biodegradable polymers, reducing toxicity.	Ensures safe breakdown in the body, reducing adverse effects.	Chitosan-based LHNPs for colorectal cancer allow prolonged drug release.[66]
Controlled & sustained drug release	LHNPs regulate drug release via diffusion and polymer degradation mechanisms.	Maintains therapeutic levels, reducing dose frequency and side effects.	5-FU LHNPs provide sustained drug release, improving colorectal cancer therapy.[67]
Passive & active tumor targeting	Tumor-specific delivery is achieved through passive targeting using the EPR effect and active targeting with ligands or antibodies. LHNPs also overcome drug resistance by evading efflux pumps like P-glycoprotein (P-gp), allowing drugs to remain inside cancer cells.	Improves drug accumulation at tumour sites, enhancing effectiveness.	Folic acid-conjugated LHNPs selectively target ovarian cancer cells.[68]
Overcoming MDR	Tumor-specific delivery is achieved through passive targeting using the EPR effect and active targeting with ligands or antibodies. LHNPs also overcome drug resistance by evading efflux pumps like P-glycoprotein (P-gp), allowing drugs to remain inside cancer cells	Increases chemotherapy success in resistant tumors.	Curcumin-LHNPs block MDR pathways in pancreatic cancer.[69]
Ability to deliver combination therapy	LHNPs allow the simultaneous delivery of chemotherapy, gene therapy, or immunotherapy drugs.	Provides synergistic effects, improving treatment outcomes.	Paclitaxel and Doxorubicin-LHNPs offer dual-action treatment for breast cancer.[70]
Stimuli-responsive drug release	Engineered to trigger drug release in reaction to variations in pH, temperature, or enzyme activity.	Enhances drug activation in tumors, reducing side effects.	pH-sensitive LHNPs release drugs only in acidic tumor conditions, improving prostate cancer therapy.[71]
Extended circulation & reduced clearance	PEGylation (PEG coating) prevents rapid reticuloendothelial system (RES) clearance.	Prolongs half-life, increasing tumor accumulation.	PEGylated Liposomal Doxorubicin (Doxil) improves drug delivery to ovarian cancer.[72-73]

homogenisation (HPH) represents a popular technique that requires high energy consumption, thus raising production expenses and creating hurdles for industrial-scale production.

Stability Issues and Short Shelf Life

The storage period of LHNPs presents challenges to stability because they naturally experience aggregation, drug leakage effects, and material breakdown that damages their structural integrity. Drugs might become lost from LHNPs before reaching their target area because their lipid shell faces problems with oxidation and hydrolysis. According to research analysis, store-dependent aggregation of LHNPs occurs at room temperature without stabilisers within weeks before their effectiveness is substantially reduced.

Potential for Rapid Clearance by the Immune System

Adding PEGylation (polyethylene glycol coating) prevents immune recognition, yet LHNPs experience quick removal by the reticuloendothelial system (RES), which restricts their circulation time. Drug effectiveness decreases when PEGylated LHNPs receive fast clearance because

Table 4: Types of LHNPs

Type	*Description*	*Significance in cancer therapy*	*Example*
Liposome-Polymer Hybrid Nanoparticles (LPHNPs)	Liposome shell surrounds a polymeric core, offering high biocompatibility.	Enhances stability, drug loading, and tumour targeting.	Doxorubicin-LPHNPs for breast cancer therapy.[74]
Solid Lipid-Polymer Hybrid Nanoparticles (SLPHNPs)	A solid lipid shell stabilises a polymeric drug core, ensuring slow drug release.	It improves drug protection, reduces degradation, and enhances circulation time.	Curcumin-loaded SLPHNPs for colorectal cancer.[61]
Nanostructured Lipid-Polymer Hybrid Carriers (NLPHCs)	The liquid lipid phase enhances drug solubility, combined with polymeric stability.	Increases bioavailability and drug absorption.	Paclitaxel-loaded NLPHCs improve lung cancer treatment.[75]
Lipid-Polymer Hybrid Micelles (LPHMs)	Polymeric micelle core surrounded by a lipid layer, improving the solubility of hydrophobic drugs.	It enhances cellular uptake and prevents rapid drug elimination.	Docetaxel-LPHMs enhance tumour penetration.[76]
PEGylated Lipid Hybrid Nanoparticles (PEG-LHNPs)	Coated with polyethylene glycol (PEG) to reduce immune clearance.	It extends the circulation time and improves tumour accumulation.	PEGylated Doxorubicin-LHNPs for ovarian cancer.[77]
pH-Responsive Lipid Hybrid Nanoparticles	Designed to release drugs only in acidic tumour environments.	Reduces systemic toxicity and enhances tumor-specific drug release.	pH-sensitive LHNPs for prostate cancer.[78]
Enzyme-responsive lipid Hybrid Nanoparticles	Drug release occurs in response to tumor-associated enzymes (e.g., matrix metalloproteinases).	Improves targeted drug delivery to cancer cells.	Enzyme-activated LHNPs for pancreatic cancer.[79]
Multifunctional Lipid Hybrid Nanoparticles	Engineered for dual therapy (chemotherapy + gene therapy) or theranostics (therapy + imaging).	Allows real-time monitoring and enhanced treatment.	Paclitaxel+Small Interfering Ribonucleic Acid (siRNA)-LHNPs for multidrug-resistant breast cancer.[80]
Immuno-Lipid Hybrid Nanoparticles	Functionalised with antibodies or ligands to target specific cancer cells.	Enhances precision targeting for personalised cancer therapy.	HER2-targeting LHNPs for breast cancer.[81]
Magnetic Lipid Hybrid Nanoparticles (MLHNPs)	Integrated with magnetic nanoparticles for magnetic-guided drug delivery.	Enables localised drug release via an external magnetic field.	Iron oxide-LHNPs for targeted brain tumour therapy.[82]

target site drug accumulation remains minimal. The elimination of unmodified LHNPs from circulation occurs within a few hours during in vivo studies, which results in various difficulties related to drug delivery duration and forces scientists to develop stability and circulation time enhancement strategies.[37,53,86]

Limited Tumor Penetration

LHNPs encounter barriers when moving deeply into tumour tissues because solid tumours with thick extracellular matrices force them to remain at the edges of the tumours. The restricted drug penetration produces uneven delivery of medication, therefore diminishing treatment results and making untreated tumour regions less responsive to therapy. Such research into folic acid-conjugated LHNPs for ovarian cancer treatment revealed effective edge tumour uptake while demonstrating low penetration levels into hypoxic tumour cores, thus demanding improved methods to improve therapeutic impacts.

Regulatory and Clinical Translation Challenges

Few LHNP-based therapeutic products received regulatory approval because preclinical research raised ongoing questions about long-term safety and challenges in manufacturing feasibility and replication tests. The absence of standardised production methods and uncertainties about biodegradability and potential toxicity pose significant challenges for clinical translation. However, the liposomal formulation Doxil® achieved Food and Drug Administration (FDA) approval as well received clinical acceptance, even though LHNPs continue encountering regulatory difficulties because of ongoing difficulties with formulation development, safety assessments, and manufacturing scalability.[37,51] While LHNPs offer advanced drug delivery benefits, challenges such as manufacturing complexity, stability issues, immune clearance, tumour penetration limitations, and regulatory hurdles must be addressed before they become widely adopted in cancer therapy.

Applications of LPHNPs in Different Diseases

Lipid hybrid nanoparticles (LHNPs) have emerged as critical research entities because they enhance drug delivery and improve drug absorption while offering targeted therapeutic approaches to different medical

Table 5: Methods of LPHNPs preparation

Method	*Principle*	*Advantages*	*Limitations*	*Example*
Solvent evaporation method	The lipid and polymer are first dissolved in an organic solvent, after which the solvent is eliminated through vacuum drying or continuous stirring.	Simple, scalable, and suitable for hydrophobic drugs.	It requires toxic solvents, and residual solvents may affect safety.	Paclitaxel-loaded LHNPs for breast cancer.
Nanoprecipitation method	The organic phase containing the drug and polymer is added to an aqueous phase with lipids, leading to nanoparticle formation by precipitation.	Fast, reproducible, and avoids high temperatures.	Not ideal for highly water-soluble drugs.	Curcumin-loaded LHNPs for colorectal cancer.
High-pressure homogenization (HPH)	The lipid and polymer mixture are subjected to high pressure, breaking into uniform nanoparticles.	It produces stable, small-sized particles that are scalable for industrial production.	High energy input, possible thermal degradation of sensitive drugs.	Doxorubicin-loaded LHNPs for lung cancer.[60]
Emulsion-solvent evaporation method	Oil-in-water or water-in-oil emulsions are formed by solvent removal to create nanoparticles.	Suitable for encapsulating hydrophilic and hydrophobic drugs.	Multiple steps require stabilisers.	5-Fluorouracil (5-FU) LHNPs for pancreatic cancer.
Double emulsion method (W/O/W or O/W/O)	Two-step emulsification, first forming a primary emulsion (W/O or O/W), followed by secondary emulsification to create nanoparticles.	Encapsulates hydrophilic drugs efficiently.	Complex, requires precise control of surfactants and stabilisers.	Folic acid-targeted LHNPs for ovarian cancer.
Supercritical fluid technology	Supercritical carbon dioxide (CO_2) precipitates lipids and polymers into nanoparticles.	Solvent-free, environmentally friendly.	Expensive equipment and low drug loading.	PEGylated LHNPs for prostate cancer. [83]
Ultrasonication method	Lipid-polymer solution is subjected to ultrasonic waves, breaking it into nano-sized droplets.	Simple, it does not require high pressure.	Low yield, risk of drug degradation due to sonication.	HER2-targeting LHNPs for breast cancer.[14]
Microfluidic technology	Drug, polymer, and lipid solutions are mixed using microfluidic channels, allowing precise nanoparticle formation.	Highly controlled, scalable, and reproducible.	High initial investment in equipment.	RNA-loaded LHNPs for gene therapy in cancer.[84]
Layer-by-Layer (LbL) Assembly	Successive deposition of lipid and polymer layers creates a controlled structure.	Suitable for stimuli-responsive and controlled drug release.	It is time-consuming and requires multiple processing steps.	pH-sensitive LHNPs for tumor-specific drug release.
Spray Drying Method	Liquid lipid-polymer formulation is spray-dried, resulting in nanoparticle powder.	Suitable for long-term stability and solid formulations.	Requires optimisation for particle size and drug loading efficiency.	Spray-dried LHNPs for oral chemotherapy. [85]

conditions. These nanoparticles demonstrate effectiveness for different medical conditions because they possess three key characteristics: biocompatibility, controlled drug extrusion, and dual drug-holding properties for hydrophilic and hydrophobic medicines. Applications of LHNPs in different diseases are shown in Fig. 3 and briefly discussed below.

Cancer Therapy

LHNPs established their position in modern pharmaceutical research because they support enhancing drug delivery, increasing bioavailability, and delivering targeted treatment for diverse diseases. Laboratory studies confirm that LHNPs combine three significant benefits, including compatibility with living tissue, programmed drug release, and dual drug compatibility, leading to their powerful medical uses for treating several diseases. Cancer drug delivery substantially benefits from utilizing LHNPs because they use passive and active targeting approaches to enhance specific tumor drug accumulation. The drug retention level, bioavailability, and enhanced tumor penetration occur through these nanoparticles while their systemic toxicity decreases. Breast cancer therapy experiences better drug retention and reduced drug resistance by using doxorubicin-loaded LHNPs, according to Wang *et al.* Research has demonstrated that paclitaxel-loaded LHNPs modified with folic acid achieve efficient and specific delivery to cells affected by ovarian cancer. [37,38]

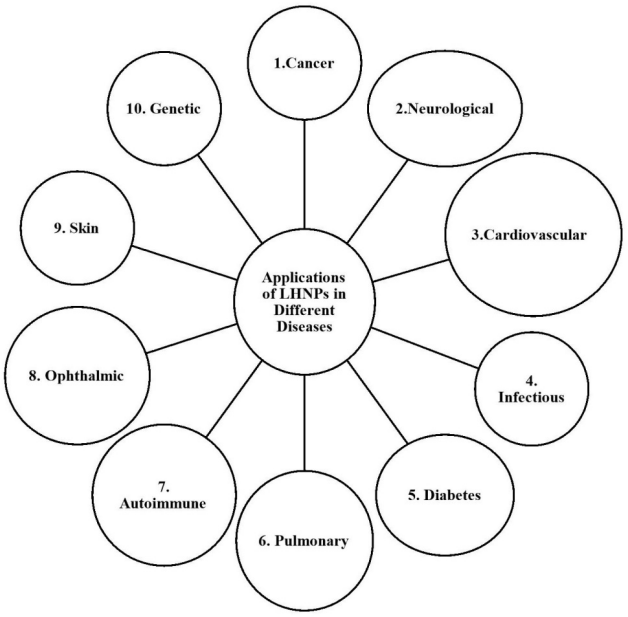

Fig. 3: Applications of LHNPs in different diseases

Neurological Disorders (Alzheimer's and Parkinson's Disease)

The delivery of neuroprotective agents to the brain depends heavily on LHNPs since these nanoparticles excel at crossing the blood-brain barrier (BBB) in neurological diseases, including Alzheimer's and Parkinson's. Drug delivery to the brain benefits from this feature because it exceeds what standard drug formulations can achieve. Research indicates that LHNPs, which contain curcumin, improve both brain penetration and lower the formation of amyloid plaques in Alzheimer's disease patients. The brain release of dopamine elevated through levodopa-loaded LHNPs resulted in Parkinson's patients experiencing better motor function.[14] The promising test outcomes demonstrate that LHNPs have potential value for treating different forms of neurological diseases. [54,87-89]

Cardiovascular Diseases

Through LHNPs, drugs can be effectively delivered to treat cardiovascular diseases by minimising atherosclerosis build-up while stopping thrombus formation and managing hypertension conditions. Because LHNPs can guide drug compounds to artery plaque accumulations, they decrease cardiovascular health risks. Research reveals that atorvastatin-loaded LHNPs successfully decrease artery plaque formation, improving heart disease therapy. Low-density lipoprotein nanoparticles containing nitric oxide show the ability to maintain stable blood pressure levels, which could be a new way to treat hypertension. Drinking cardiovascular medications through LHNPs provides enhanced therapeutic benefits and decreases adverse effects that spread throughout the body.[90,91]

Infectious Diseases (Bacterial and Viral Infections)

LHNPs are efficient therapeutic agents for infectious diseases because their design enables better antimicrobial agent performance and drug dosage control. This unique feature supports antibacterial resistance treatment and vaccine distribution processes. Research results show that LHNPs containing vancomycin enhance bacterial destruction of methicillin-resistant *Staphylococcus aureus* (MRSA). The delivery of antigens into vaccines as well as immune response initiation became possible through the utilisation of LHNPs in the creation of mRNA vaccines, including Pfizer-BioNTech and Moderna, according to Wang *et al*. The inclusion of LHNPs since their integration into vaccine technologies has led to better vaccine performance and has reshaped vaccination processes.[38,92]

Diabetes Management

Drug delivery through LHNPs provides diabetes patients with sustained insulin management, eliminating the need for multiple regular injections. Patient compliance thus improves, and so does long-term glucose regulation. Scientific research has shown that LHNPs containing oral insulin achieve protection from stomach deterioration, which enables the drug to reach the intestines effectively. Drug bioavailability is improved when diabetic patients use metformin-loaded LHNPs. LHNPs enable controlled drug release in diabetes therapy, providing better effectiveness and convenience than standard delivery techniques.[93,94]

Pulmonary Diseases (Asthma and Chronic Obstructive Pulmonary Disease - COPD)

Pulmonary diseases, which include asthma and COPD, are successfully treated through LHNP-based therapy delivery methods. Through inhalation therapy, LHNPs provide focused drug delivery to the lungs, minimising the symptoms that spread throughout the body. In asthma care, budesonide-loaded LHNPs extend therapeutic benefits for anti-inflammation and exhibit decreased adverse effects on treatment safety. The antibacterial action of ciprofloxacin-loaded LHNPs proves effective against respiratory tract infections, according to Wang *et al*. LHNPs are an attractive treatment choice for respiratory diseases since their structure enhances drug delivery to the lungs.[38,95,96]

Autoimmune Disorders (Rheumatoid Arthritis and Lupus)

Targeted drug delivery of anti-inflammatory pharmaceuticals to inflamed tissues becomes possible through LHNPs, reducing systemic toxicity for individuals with autoimmune rheumatoid arthritis and lupus. Methotrexate contained within LHNPs exhibits improved joint penetration along with better drug retention as a rheumatoid arthritis treatment, which boosts inflammation control. Research has shown that hydroxychloroquine-

loaded LHNPs enhance lupus treatment while decreasing treatment-related toxicity, according to Wang *et al.*[39] LHNPs combine controlled drug-release mechanisms with elevated drug accessibility to deliver substantial benefits for autoimmune condition care.

Ophthalmic Diseases (Glaucoma and Age-Related Macular Degeneration - AMD)

LHNPs represent a powerful method in ophthalmology for extending drug longevity in eyes, reducing the need for repeatedly using eye drops. The increased drug availability provided by LHNPs prevents vision deterioration when treating glaucoma patients and those with AMD. Scientific research indicates that LHNPs containing brimonidine increase drug performance for controlling intraocular pressure in patients with glaucoma. The retina benefits from extended drug retention provided by LHNPs containing bevacizumab, making them an optimal therapeutic solution for AMD. Lipid-core nanoparticles (LCNP)--based drug formulations maintain drugs within the eyes longer, enhancing treatment performance and patient medication adherence.[97-98]

Skin Disorders (Psoriasis and Skin Infections)

LHNPs serve effectively as treatment agents for two important skin disorders: psoriasis and bacterial skin infections. Drug penetration throughout multiple layers of the skin becomes enhanced through nanoparticles, according to Torchilin (2014). Research indicates that LHNPs loaded with Tacrolimus provide better skin penetration and decreased inflammatory responses in psoriasis patients. The antibacterial performance of silver nanoparticle-loaded LHNPs extends to treating different skin infections, which establishes them as a promising clinical solution in dermatology.[18] LHNPs provide controlled medication delivery, which results in sustained drug impact while reducing adverse effects.[36,99-100]

Genetic Disorders (Gene Therapy for Cystic Fibrosis and Hemophilia)

The final important role of LHNPs involves gene therapy because they serve as effective delivery vehicles for genetic disorder treatments, including cystic fibrosis and hemophilia. The nanoparticles function effectively as transporters by moving genes and DNA, ribonucleic acid (RNA), and clustered regularly interspaced short palindromic repeats (CRISPR) components to destination cells. Studies using Clustered Regularly Interspaced Short Palindromic Repeats – CRISPR-associated protein 9(CRISPR-Cas9) containing LHNPs successfully corrected genomic mutations for treating cystic fibrosis in lung cells. Laboratory results demonstrate that LHNPs carrying factor IX mRNA show an enhanced ability to enhance blood clotting during preclinical studies of hemophilia. The protection of genetic material by LHNPs and their capacity to direct cell intake propose these vesicles as an appealing platform for future gene therapy procedures. [101]

Characterisation of LPHNPs

The characterisation of LHNPs is shown in Fig. 4 and briefly discussed below.

Particle Size and Size Distribution

The dimensions of LHNPs determine medication transport ability, tissue access, and cell internalization. Research personnel typically use dynamic light scattering (DLS) to assess nanoparticle stability via examinations of particle size and the polydispersity index (PDI).[17] Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) directly visualize particle morphology and size. [102-104]

Zeta Potential (Surface Charge)

The surface charge of LHNPs can be determined through zeta potential measurements because this measurement influences stability, aggregation behaviour, and cellular interactions. Colloidal stability increases when measuring high absolute zeta potential values that exceed ±30 Millivolts (mV).

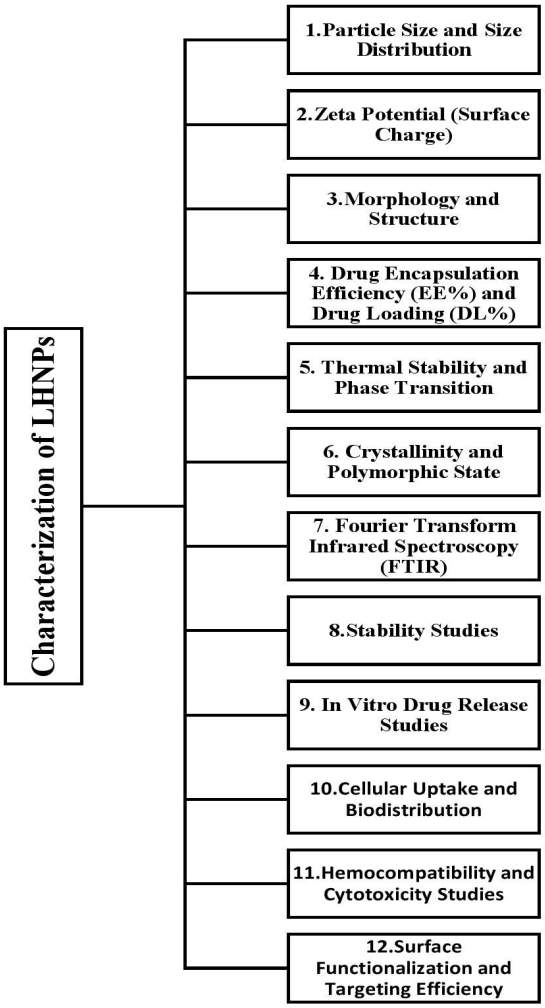

Fig. 4: Characterisation of LHNPs

Morphology and Structure

The assessment of LHNPs consists of two essential characterisation techniques, which include transmission electron microscopy (TEM) and atomic force microscopy (AFM). The lipid shell and polymeric core characteristics of hybrid nanoparticles are confirmed using these evaluation methods.

Percentage of Entrapment Efficiency (EE%) and Drug Release (DL%)

The drug-holding capacity evaluation of LHNPs relies on two essential parameters: EE% and DL%. High-performance liquid chromatography (HPLC) and ultraviolet-visible spectroscopy (UV-visible spectroscopy tools) determine these analytical parameters.[102,105-107]

Thermal Stability and Phase Transition

Lipid and polymer integration within LHNPs can be detected using the thermal analysis method formulated as differential scanning calorimetry (DSC). Thermogravimetric analysis (TGA) stability testing procedure uses controlled heating conditions to determine weight alterations.

Crystallinity and Polymorphic State

The X-ray diffraction (XRD) method helps ascertain the drug crystallinity or amorphous composition in LHNPs. Drug crystallinity reduction indicates better lipid-polymer matrix dispersion, which enhances solubility.

FTIR – Chemical Interaction Analysis

LHNP formulation analysis by FTIR reveals all chemical bonds between compounds like lipids, polymers, and drugs. The peak intensity and position modifications during FTIR analysis confirm drug incorporation success as well as possible drug-polymer interactions. [54,108]

Stability Studies

Stability assessments of LHNPs span different temperature and humidity values using periodic DLS and HPLC measurements of size, zeta potential, and drug content evaluation. [88]

In-vitro Drug Release Studies

Research on drug release from LHNPs typically employs dialysis membrane diffusion techniques. Analysis of the drug release profiles requires mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, which help understand the release mechanisms. [108]

Cellular Uptake and Biodistribution

Investigating LHNP cellular uptake and localisation uses two technological methods: Fluorescence microscopy and confocal laser scanning microscopy (CLSM). Flow cytometry helps determine the number of nanoparticles that enter cellular structures.[18] The biodistribution evaluation of LHNPs is performed through a combination of positron emission tomography (PET) and near-infrared fluorescence (NIRF) imaging procedures. [88]

Hemocompatibility and Cytotoxicity Studies

Biocompatibility, together with non-toxicity, needs to be present in LHNPs. Hemolysis assays determine the red blood cells' interaction with LPNPs, as described by Danhier *et al*. Laboratory experiments using MTT, XTT, and CCK-8 assays determine the safety of the materials for cell lines at various points before clinical use. [35,109]

Surface Functionalization and Targeting Efficiency

The pharmacological properties of LHNPs can be improved by attaching drug-specific ligands, including folic acid, peptides, and antibodies. The binding efficiency and ligand interactions are examined through surface plasmon resonance (SPR) and enzyme-linked immunosorbent assay (ELISA).[90,110]

Conclusion

LPHNPs offer a promising approach to cancer therapy by enhancing drug solubility, stability, and targeted delivery while minimizing systemic toxicity. Their unique structural composition and advanced drug delivery capabilities position them as a potential breakthrough in oncology. Challenges such as large-scale production, long-term stability, and biocompatibility need to be overcome for successful clinical application. Future studies should focus on refining formulations, advancing smart-targeting strategies, and conducting comprehensive preclinical and clinical trials. Integrating LHNPs with emerging technologies, such as personalised medicine and AI-driven drug design, could revolutionize cancer treatment, leading to safer and more effective therapies.

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