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Role of LPHNPs a Next Generation with a Solid Structure, Distinctive Characteristics, and a Promising Future in the Medical Fields - An Updated Review

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LPHNPs are one of the most important applications in nanotechnology for many broad fields in pharmacy, medicine and diagnostics. In recent years, with the spread of the Covid-19 pandemic, they have been used in DNA vaccines. The reason behind this widespread use is their distinctive structure, which consists of a lipid monolayer surrounding the polymeric core. Moreover, their many types have contributed to the efficient delivery of active substances. Despite all this, there are challenges faced when dealing with LPHNPs, including the great need for tight control over the concentration of variables, the challenges of clinical transport of LPHNPs, and the challenges of instability due to storage. In this review, we discuss in a comprehensive analytical manner the general structure and types of LPHNPs, the most common methods of their preparation, the latest developments in these carriers, and provide examples of applications of using LPHNPs, potential challenges, and the most important features and additions that have improved them.

Keywords: DDS; Hybrid; LPHNPs; Lipid; LPNs; Nanoparticles; Nanotechnology; Next Generation; Polymer; Solid Structure.

The term "nanotechnology" is used in a variety of scientific, pharmaceutical, and medical domains. Materials, structures, devices, and systems are designed, characterized, manufactured, and applied using nanoscale dimensions. When physicist Richard Feynman demonstrated how to create things at the atomic and molecular levels in 1959, nanotechnology made its debut.[1] The name "Nano" in nanotechnology comes from the Greek word "Nanos," which meaning "dwarf".[2]Since the emergence of nanotechnology, the field of pharmacy, specifically drug delivery, has witnessed a tremendous boom, and it has overcome traditional methods of drug delivery in many characteristics and advantages .The possible advantages of nanocarriers are listed below: [3-5]

• improve a drug's overall pharmacokinetic and pharmacodynamic properties without modifying its molecular structure
• More effective tissue, cellular, and molecular focusing
• The ability to overcome various fundamental biological obstacles.
• Providing a variety of drugs with distinct chemical properties.

Numerous studies on Nano-systems for drug delivery and diagnosis have contributed to our understanding of the significance of each system. As a result, lipid-based nanocarriers have several benefits, including increased therapeutic agent trapping efficiency, economical manufacturing, but they also tend to exhibit reduced stability, rapid load release, and substantial polydispersity.

Furthermore, these nanostructures have limited potential for chemical alteration, which limits their use in active targeting strategies.[6]Conversely, the significant potential for chemical changes is a characteristic of polymeric nanosystems[7]

Other benefits of polymeric NPs include the potential to produce NPs with smaller sizes, lower polydispersity, and improved stability.[8]Lipid-polymer hybrid nanoparticles, which combine two systems into one, are a new breed of Nano-systems designed to take advantage of the benefits of both polymeric and lipid-based systems. These nanoparticles are composed of a polymeric core surrounded by a lipid shell (LPHNPs).[9] Due to its appealing qualities for drug administration, LPHNP forms of administration have been extensively studied and are receiving more and more attention.[10-12] By encasing the therapeutic drug of interest in a hydrophilic or hydrophobic polymer core and encasing it in a lipid layer, LPHNPs enhance the stability and biocompatibility of the nanomaterials when administered systemically.[13,14] Drugs that are both hydrophilic and lipophilic can be combined in LPHNPs.[15] LPHNPs nanocarrier for improving the solubility of drugs that are not very soluble in water.[16] One of the methods for creating LPHNPs.The two-step process, which is the conventional approach in which the lipid shell and polymer core are prepared independently and combined,Additionally, the unconventional Single Step Methods where LPHNPs self-assemble when lipid and polymer are simultaneously combined.[17] As for the applications in which it has been used in many fields, the most important of which are the medical fields, where it has been used as a carrier for antibiotics and has clearly increased their effectiveness.[18] It has proven a very effective role and has made a qualitative shift in the field of chemotherapy delivery due to its ability to follow different methodologies to be more selective for cancer cells than normal ones, thus ensuring an effective, selective, and safe treatment.[19] Its role was not limited to drug delivery and targeting, but it was also used in diagnosis, which increased biological safety,[20] It was utilized in gene therapy and vaccinations, and it demonstrated success in delivering the desired gene as well as high stability while storage for a year using specified procedures that did not lose effectiveness.[21]

Structure of hybrid formation

Lipid-polymer hybrid nanoparticles have a structure similar to polymeric nanoparticles and liposomes, as does their creation mechanism. LPHNPs have three primary components:

• A polymeric core encases the medication.
• A lipid monolayer surrounds the polymeric core.
• An exterior PEG layer that is sterically stabilized to increase the nanoparticles' circulation time in the bloodstream by preventing immune destruction.

The surface of lipids can be altered by adding (PEG) which increases their half-life in the These advantages make hybrid nanocarriers a viable option in several applications , as they enable the safe and effective administration of many drugs while also boosting the body's ability to respond to therapy with fewer side effects.The middle lipid monolayer functions as a molecular barrier, reducing medication loss and protecting the core from degradation by preventing water from migrating into the inner core. [11,22,23], Fig (1) [24]

Various Varieties of LPHNPs

Polymer core–lipid shell hybrid nanoparticles

Biodegradable nanocarriers called polymer core–lipid shell hybrid nanoparticles (PLHNPs) are employed in the delivery of therapeutic drugs and the treatment of various illnesses. They are made up of a stable lipoidal shell that envelops a polymer core, improving stability and encouraging the encapsulation of hydrophilic and lipophilic medications.[25,26,11]

Monolithic PLHNPs

The most basic type of PLHNPs are monolithic ones, which are merely combined Nano-systems of lipids and polymers or copolymers with the aid of surfactants. Lipids are dispersed across a polymeric/copolymeric matrix in this system.[27]

Like colloidal polymeric nanocarriers, monolithic PLHNP systems use phospholipids to create a carrier-like structure. PEG chain modification offers flexibility and simple alterations for physicochemical properties and toxicity.[28]

Core–shell type hollow PLHNPs

The hollow core-shell type PLHNPs are made up of an outside PEG lipoidal layer, a polymeric layer in the center, and an inner hollow positively charged lipidic core.[15]

While the outside lipoidal PEG layer inhibits macrophage absorption and improves fluid stability, the system's inner hollow core, which is filled with water or buffer, effectively encapsulates medications.[29]

Polymer-caged liposomes

Hybrid nanocarriers with biodegradable polymer or copolymer coatings improve therapeutic efficacy through controlled medication release and site-specific targeting. With their superior colloidal stability, stimuli-responsive release, and maximum stability in biological fluids, these hybrid nanocarriers offer long-lasting drug release and a large loading capacity.[30-32] Fig (2) [33]

Additions and Adjustments that helped improve the characteristics of LPHNPs

Surface-coated immuno-inert nanoparticles can bypass the reticuloendothelial system, enhancing the bioavailability of packaged medications.[34]

LPHNPs have attributes that enable them to efficiently increase drug administration by integrating the physical advantages of polymers with lipid properties. This integration enhances the ability to contain medications and provide controlled release.[35]

The surface of lipids can be altered by the addition of molecules such as PEG, which increases their half-life in circulation and decreases immune detection. These advantages make hybrid nanocarriers a potential option in oncology and gene therapy, as they enable the safe and effective administration of many drugs while also boosting the body's ability to reply to therapy with fewer side effects.[23]

LPHNP surface charge and its impact on intracellular internalization.Based on the types of cells of interest into which the nanocarriers will be delivered to deliver the intended medicine, anionic particles could seem to be more received than cationic particles.Negative charge interacts with the environment, leading to the formation of precursor lipid nanoparticles through repulsive electrostatic interaction in aqueous media.This emphasizes the importance of the charge in drug delivery to specific cells.[36]

Because of their biocompatibility, degradability, and prior use in US Food and Drug Administration (FDA)-approved items, biodegradable polymers like polylactic-co-glycolic acid (PLGA) typically make up the polymeric cores of LPHNPs.[37,12]

Approaches to fabricate LPHNPs

Preparation processes are critical in establishing the qualities of the final product, such as size, shape, and stability, which have a direct impact on its efficiency in a variety of applications. As a result, selecting the suitable method is determined by the nature of the substance to be loaded, the intended delivery purpose, the target site, and the carrier's design in relation to the desired goal and function.Numerous preparation methods have been devised to suit a wide range of materials and applications. These methods differ in terms of mechanics, efficiency, and cost, making selecting the best way an important decision.This section will go over the most important ways for preparing LPHNPs :

Single Step Methods

The unconventional where LPHNPs self-assemble when lipid and polymer are simultaneously combined

Nanoprecipitation

The single-step nanoparticle deposition process consists of multiple major steps, as illustrated in the Fig (3)[38], which are as follows:

Prepare an aqueous solution.Then OP: A solution of soluble chemicals is created.To generate particles, gradually add the OP to the AP to create a mixture of necessary components.This mixing distributes organic molecules throughout the aqueous phase.Solvent Evaporation: After mixing, use a heating device or other methods to gradually extract the organic solvent.This concentrates organic molecules in the aqueous phase, causing them to cluster and form nuclei. Solvent Diffusion occurs when organic molecules diffuse into the aqueous phase during evaporation. This diffusion reduces surface tension, promoting the creation of a shell layer around the particles. Nanoparticles (LPHNPs) are formed by diffusing components and forming an outer shell.[39,40].The qualities of the resulting particles are determined

by the polymer ratio, the solvent concentration, the polymer's molecular weight, and mixing force. This approach is equally effective for integrating both hydrophobic and hydrophilic medicinal moiety.[41]

Two-step method

Which is the conventional approach in which the lipid shell and polymer core are prepared independently and combined, Additionally

Homogenization

(A)The aqueous PNPs suspension is applied directly to the dried lipid film. (B) An aqueous solvent is used to hydrate the thin lipid layer, allowing lipid vesicles to form more easily. The hydrated vesicles are then mixed with an aqueous premade nanoparticle suspension. For either process, the hybrids are then created via vortexing or ultrasonication of the mixture at a temperature greater than the lipids' phase transition temperature.[42] Fig (4).[24]

Thin Film Hydration

To prepare the thin film, dissolve a mixture of biomaterials (lipids and polymers) in appropriate solvents.

The mixture is subsequently dried, resulting in a thin layer on the container's walls.

To hydrate the thin film, use an aqueous solution at a temperature higher than the material's phase transition temperature (usually 65°C). Ensures materials remain liquid during the hydration process. Sonication: After hydration, the mixture is sonicated with ultrasound to minimize particle size and ensure uniform dispersion of hybrid structures. Two sonication cycles of 5 minutes each, with a rest period in between. Adjust the final concentration of hybrid systems (usually 5 mg/mL) once sonication is completed. These methods are used to build stable hybrid structures of lipids and polymers, ensuring that the resulting nanoparticles are uniformly distributed.[43-45]

Features and challenges

Lipid-polymeric nanocarriers, which mix lipids and polymers, provide up new possibilities for the development of smart drug delivery systems. Lipids promote the biological interface and bioavailability of drugs, whereas polymers improve the structural stability of nanocarriers. Furthermore, these devices provide regulated medicine release, allowing for precise and efficient delivery of dosages to the appropriate location[46].

Drug delivery, imaging, tissue engineering, and gene therapy are just a few of the clinical domains that urgently require their tiny size, biodegradable nature, and multitargeting capability.[10,47]

A recent study demonstrated that it is possible to accomplish site-specific targeting and increase tissue absorption of the medicine to be administered. The structural advantages of polymers and the analogous properties of lipids enable a more sustained release profile and greater drug encapsulation rates . [48]

Therapeutics can be encapsulated by them to increase their stability and stop fast leaking,

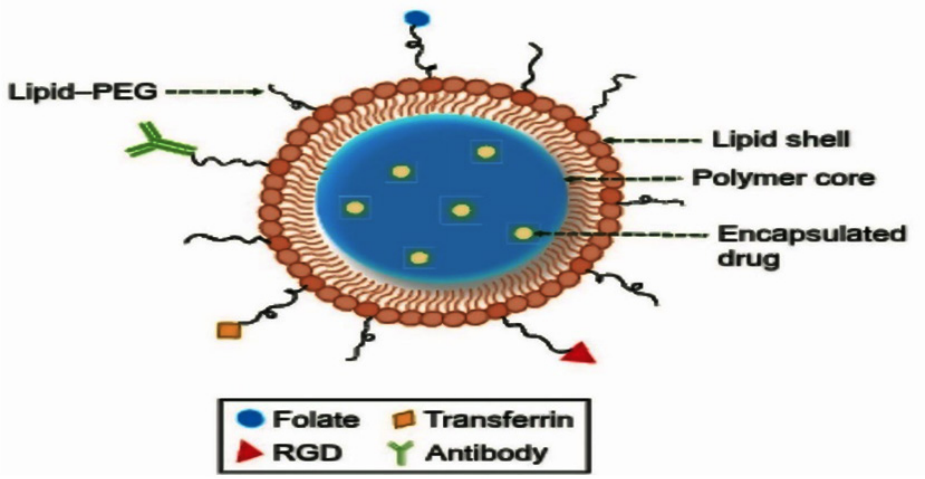

Fig. 1. (LPHNPs): 1) a polymer core encapsulating the drug, 2) a lipid mono-layer surrounding the polymer core, and 3) an outer lipid–PEG layer

extending their therapeutic effect as well as their toxicity.

There are numerous obstacles associated with the usage of LPHNs, as their formation necessitates intense control over the concentration of various variables, including the polymer to lipid ratio, particle size, and surface properties. Generating consistent and replicated production on a wide scale remains a major challenge.

This intricacy can cause batch-to-batch variability, which affects the overall quality and the effectiveness of the nanoparticles.[35]

Furthermore, since they often raise manufacturing costs, many synthesis stages are undesirable from a commercial standpoint. [49]

However, creating formulations that are ideal for a given application while having all the qualities that are desired is a difficulty that could impede clinical interpretation[50]

Significant technological obstacles must be overcome for LPHNPs to be clinically implemented successfully and completely. These obstacles include enhancing therapeutic loading efficacy, guaranteeing regulated drug release, avoiding immune cells, and optimizing NP accumulation at target areas .[51]

One of the most difficult challenges researchers face is the change in (L/P) mix after extended storage, which leads to drug leakage.[52]These nanoparticles must remain stable under a variety of environmental circumstances, including temperature and humidity changes.[53]

Areas of use

The use of LPHNPs in many applications due to its properties and features has been used in:

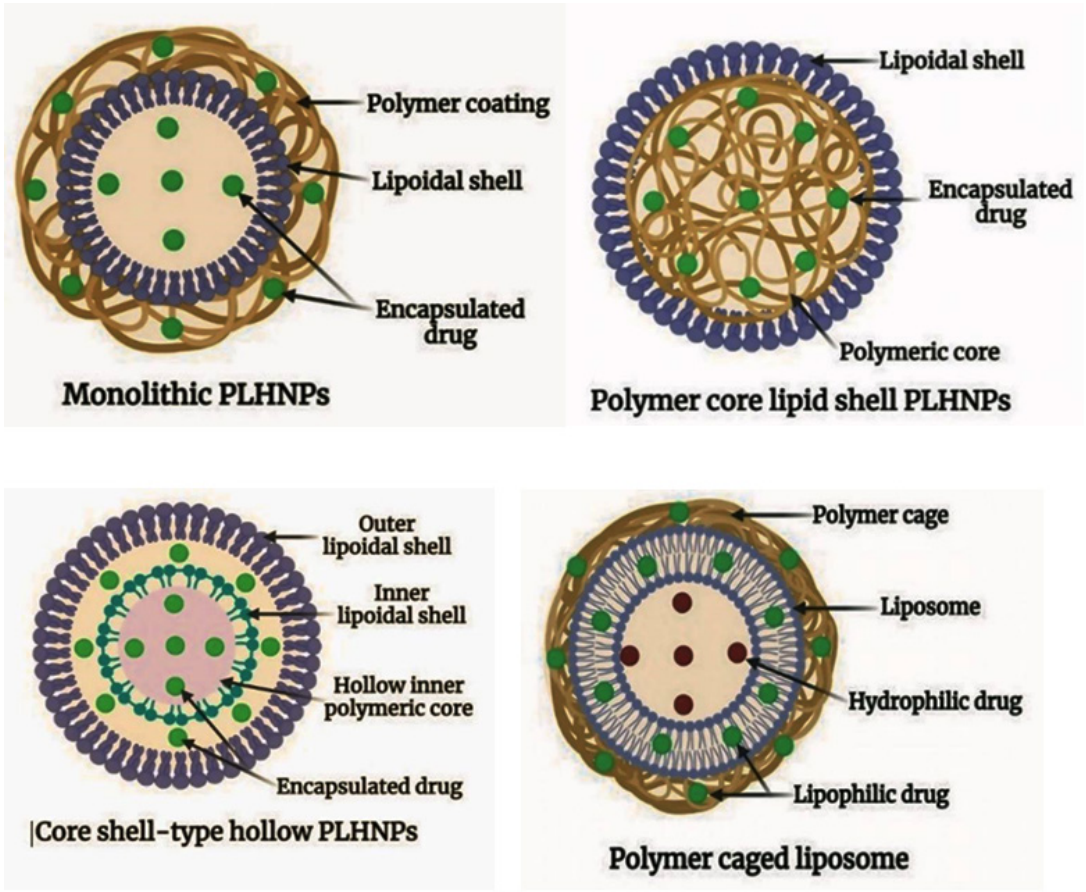

Fig. 2. Different types of PLHNPs. Figure 2 was Created with BioRender. Rizwanullah, M. (2024). Polymer lipid hybrid nanoparticles for phytochemical delivery: challenges, progress, and future prospects. Beilstein J. Nanotechnol. https://doi.org/10.3762/bjnano.15.118.

LPHNPs in Antibacterials

Clinicians frequently find it difficult to treat intracellular bacterial infections, and new techniques are required.[54]Although drugs reduced deaths and disease rates, antimicrobial resistance has created a severe concern in treating diseases that are infectious.[55] Most commonly used antibiotics have low intracellular penetration and long-term holding capabilities, which results in illness recurrence and antibiotic resistance .[56] Inside cells infections can be repeated and difficult to cure, because of the insufficient supply of medications in affected cells and weak immunity in the host.[57] Hence the inspiration for the need to use modern technologies in the delivery of antibiotics to ensure their appropriate delivery and increase their effectiveness. Studies have led to the selection of LPHNPs for their various features, and many previous studies have demonstrated their many advantages with outstanding their physical abilities, biocompatibility, and monitored release, as well as enhanced drug loading .In the past few years, uses related to antibiotic delivery have been reported.[58] The use of polymers in constructing hybrid systems has been shown to produce a more sustained medication release. whereas, the lipid enhances medication loading proficiency and membrane permeability.[59] It was used to solve

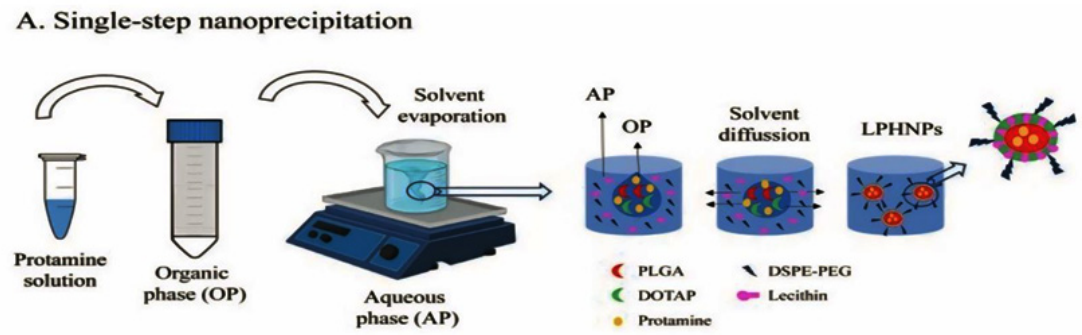

Fig. 3. Single Step Methods, Nanoprecipitation |Non-essential components (protamine, DOTAP, DSPE-PEG, lecithin) are added only to achieve specific goals, such as charge modification, improved stability, or interaction with biological targets

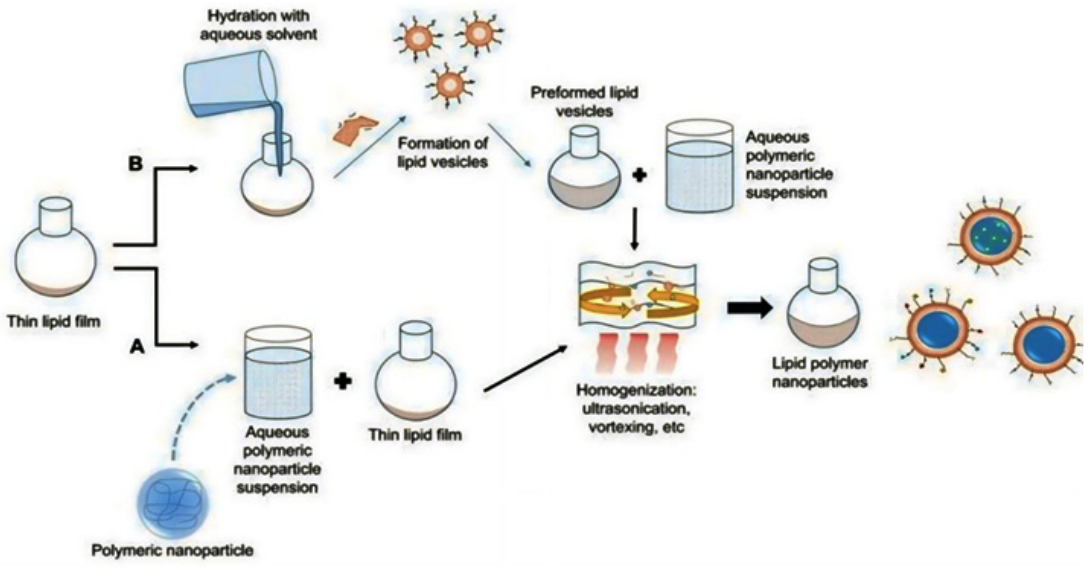

Fig. 4. Two-step method , Homogenization

the problems of oral antibiotics and convert them to effective topical ones. Hence, it has proven its ability to be flexible for use, raise the effectiveness of antibiotics, and increase their delivery capacity.[60]

LPHNPs in Cancer

In the medical field of today, cancer continues to be a problem that affects people from all socioeconomic backgrounds worldwide. Stimulus-responsive PLHNPs were successful in treating cancer due to their improved cellular internalization, superior dispersion, and precisely targeted, well-regulated stimuli-responsive release.PTX prodrug and RGD peptide are used to adorn the core-shell PLHNP surface. Associated with a redox-sensitive bridge (RGD-ss-PTX) led to enhanced antitumor efficacy in lung cancer through active targeting through integrin receptors and GSH-responsive drug release.[61]In order to maximize the therapeutic index and achieve success in cancer therapy, NPDS enhance biodistribution, a critical component. One practical strategy to get over MDR is to co-deliver P-gp inhibitors and anticancer medications in nanoparticle systems.[62]In breast cancer ,The tiny particle sizes (less than 200 nm), low polydispersity indices (H"0.1), high EE% (H"80%), and excellent stability of ANS(Anastrazole) loaded PLNPs were all effectively achieved .Moreover, PLNPs had an apoptotic effect on the estrogen-positive breast cancer cell line in contrast to the drug's free form. In conclusion, the produced PLNPs are valuable for additional in vivo testing because of their high potential to improve the therapeutic efficacy of ANS.[63]The 5-year survival rate for patients with (CRC) is around 65% and 12.5%, respectively, making it the second most lethal malignancy globally.[64-66] Additionally, LPHNPs were synthesized using a dual drug delivery strategy to co-deliver chemotherapeutic medications (doxorubicin) and epigenetic (20-deoxy-5-azacytidine, DAC).[67] By blocking the DNA methyltransferases that result in the epigenetic silencing of the protective genes, DAC increases the expression of tumor suppressor genes.[68]Following encapsulation in a PLGA core, DAC and doxorubicin were coated with a layer of lecithin and DSPE-PEG using a nanoprecipitation method. NPs showed synergistic

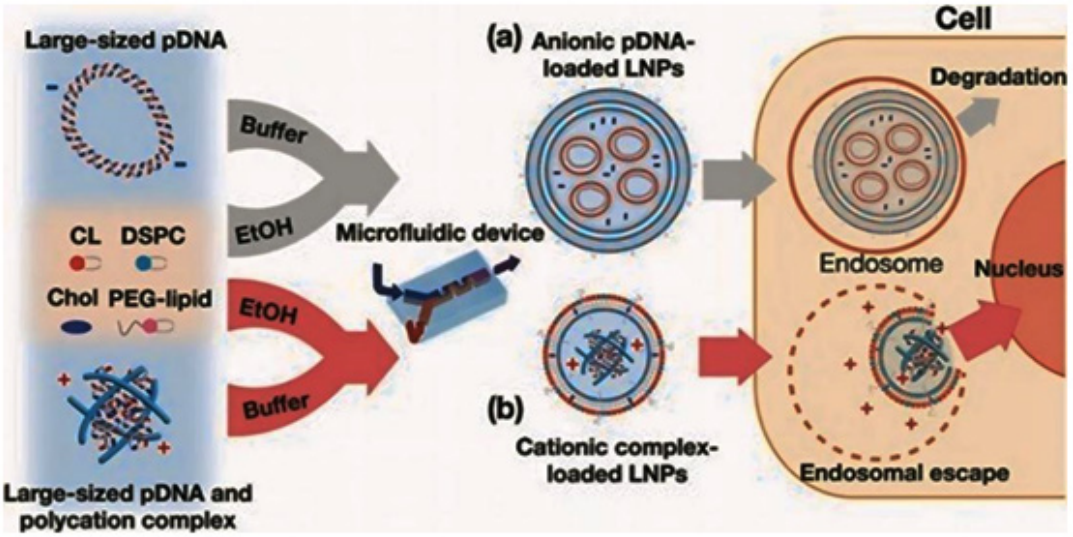

Fig. 5. Diagrammatic illustration of large-scale pDNA transfection techniques using (a) covenantal LNPs and (b) LNPs loaded with the polycation-pDNA combination. The components of both LNPs include 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol (Chol), ionizable (pH-sensitive cationic) or cationic lipid (CL), and 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG-lipid). (a) The LNPs contained negatively charged pDNA. The endosome was unable to efficiently release large pDNA into the cytoplasm. (b) Endosomal escape may be accelerated by LNPs loaded with positively charged pDNA-polycation core nanoparticles.[87]

growth suppression when tested on the human breast cancer cell line MDAMB-231.[69]Garg et al .presented an a single-step self-assembled nanoprecipitation technique for creating MTX-encapsulated LPHNPs for treatment of breast cancer. These LPHNPs were also successful in treating various types of cancer.[70-73]

LPHNPs in Diagnosis

LPNs have recently been exploited in the bioimaging area for medical diagnostics as delivery systems for contrast agents, such as inorganic nanocrystals and quantum dots (QD), which are frequently used in (MRI) and (CT). Applications of LPNs in bioimaging are driven by their great stability and excellent biocompatibility, much like medication and gene delivery.[74]

To find tumorigenic lung tissue, a variety of multimodal NPs have been utilized in conjunction with proteins, antibodies, and contrast agents.(MNPs) and (AuNps) are the most nanomaterials are utilized in the diagnosis of lung cancer. Because they can scatter light in the visible wavelength, hybrid AuNPs with strong stability and biocompatibility can be effective imaging agents. For both in vitro and in vivo targeted CT-scan imaging of SPCA1 cells (human lung cancer), folic acid-modified dendrimer-entrapped gold nanoprobes (Au DENPs-FA) are described as promising nanomaterials.[75]

These NPs' ultrasmall size allows them to pass through tumor stroma and tumor stem cells, and they are also being explored for use in the delivery of drugs to brain tumors.[76]

These hybrid NPs were created using nanoprecipitation techniques, in which a polymer, such as poly(lactic-co-glycolic acid), serves as the NP's core-shell, and a PEGylated lipid, such as 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-(methoxy[polyethylene glycol]-2000), is applied to the poly(lactic-co-glycolic acid) to coat its surface and stabilize drug, gene, and dye polymer-encapsulated.[77]

LPHNPs In Gene therapy

Gene therapy has become a powerful treatment option for many illnesses, including cancer.[78]Thus, gene-delivery devices, genetic engineering, and gene therapy based on traditional Chinese medicine have all been extensively researched. But it's still unclear if gene therapy will be clinically successful.[79]In order to get beyond the drawbacks of traditional gene carriers, there is a growing need for a hybrid vector.[80]Lipid–polymer hybrid nanospheres (LPHNSs) were created recently to combine the advantages of polymeric NSs with liposomes.[81,82].Gene delivery via some non-viral vehicles, such as cationic polymers like PEI (also known as polyplex) and cationic lipid DOTAP (also known as lipoplex), is preferable to viral delivery.[83]

LPHNPs In DNA Vaccin

LNPs have numerous benefits for delivering nucleic acids, such as low cytotoxicity, specific organ targeting, and high transfection efficiency.

These considerations led to the approval of RNA interference medications (such as Onpattro) and mRNA vaccines (such Comirnaty and SpikeVax) for COVID-19.[84-86]

They found that positively charged complexes increase the transfection efficiency of big pDNA. By characterizing and structurally examining LNPs, we also found that a small LNP size and a unilamellar structure are necessary to allow the transfection of large-sized pDNA [88,89]

The LPHNP has delivered mRNA with encouraging early results. [90] Lecithin, DSPE, PEG-lipids, 1,2-dioleoyl-3-trimethylammonium propane, 1,2-dilauroyl-sn-glycero-3-phosphocholine, and 1,2-distearoyl-sn-glycero-3-phosphocholine are common lipids utilized in LPHNP. However, polymers including polylactic acid, polycaprolactone, and PLGA are frequently utilized in LPHNP. Furthermore, to create peptide-polymer hybrid nanoparticles for mRNA distribution, a peptide-based vector (RALA) and a polymer (PLA) have been mixed.[91]

Additionally, PEG-Lipid C14-2000-formulated modified LPNs with the biodegradable polymer PBAE demonstrated effective mRNA transport to the lungs. [92] LPNs are a new nucleic acid delivery method, as evidenced by this and the documented co-delivery of siRNA and mRNA with lipidoid polymer hybrid nanoparticles .[93,94] In terms of hydrophobic, van der Waal, and electrostatic interactions, the hybrid formulation is thermodynamically advantageous.[24]

It is yet unknown how stable an mRNA vaccine created using these intriguing hybrid systems will be.

CONCLUSION

In conclusion, LPHNPs are considered as promising nanocarriers in the medical field. They have unique properties because they combine two systems into one. Including increased therapeutic agent trapping efficiency, lower polydispersity, enhance the stability and biocompatibility of the nanomaterials when administered systemically. Able to improve the solubility of drugs that are not very soluble in water. Drugs that are both hydrophilic and lipophilic can be combined in LPHNPs. In the field of Antibacterial, they have greatly contributed to raising the delivery capacity of antibiotics and their availability for a long period in the circulation to give high effectiveness, as it is a flexible application as it contributed to delivering some antibiotics locally, which gave high hope for its application

In addition, it gives encouraging promises in the field of cancer, where scientists are still searching for the best ways to deliver a target and reduce the side effects of chemotherapy. We find that LPHNPs show a distinctive aspect due to their small size, absorption efficiency and high targeting ability. Moreover, in diagnosis, they showed a positive aspect when used with contrast agents to detect diseases and cancerous tissues.

As for gene therapy, which has become a powerful treatment for many diseases, it was dealt with as an alternative to viral vectors for delivery, which expands the applications of LPHNPs. In many studies, the ability to deliver mRNA has been demonstrated, which has increased its importance for use in vaccines. Despite these developments and applications, LPHNPs still need more clinical studies and further studies of their structure and structure to be more stable over time. Fortunately, in the near future, LPHNPs will be a strong and competitive option for drug delivery.

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This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Author Contributions

Conceptualization, Wael Abu Dayyih. And Shahed Amran Alsulman ; investigation, Wael Abu Dayyih and Shahed Qassim Albtoush; writing—original draft preparation, Wael Abu Dayyih ; Shahed Amran Alsulman ; Shahed Qassim Albtoush; Omar Alasasfeh, writing—review and editing, Wael Abu Dayyih ; Shahed Amran Alsulman. and Omar Alasasfeh. All authors have read and agreed to the published version of the manuscript.

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