RESEARCH PAPER

Multifunctional Lipid Polymer Hybrid Nanocarriers in Cancer Therapy: Recent Developments and Challenges

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ABSTRACT

Background: Compositions of various Nanoparticles (NPs) based on nanotechnology have potential as cancer treatments. Lipid Polymer Hybrid Nanoparticles (LPHNPs) helps to transport hydrophilic and lipophilic compounds simultaneously. The useful physical properties of polymers and lipids allow for improved drug encapsulation and provide a controlled release profile. LPHNPs have been developed to co-deliver plant-based compounds and anticancer drugs to enhance cytotoxicity against cancer cells. LPHNPs are used to transport medications to the cancer site with controlled manner.

Structure and Synthesis: The review examines the formulation, characteristics, and importance of LPHNPs in cancer treatment. In LPHNPs, the structural advantages of polymers and the biomimetic properties of lipids are combined, creating an advanced delivery system that improves medication stability and enhances therapeutic effectiveness. LPHNPs particles usually contain a polymer core, a lipid shell, and a PEG coating, which enables longer circulation times. The review discusses various synthesis methods, including one-step and two-step approaches, and explores both passive and active targeting methods for chemotherapy.

Clinical Potential: LPHNPs demonstrate particular promise in delivering poorly soluble drugs and addressing multidrug resistance in cancer treatment. The authors also address current challenges in clinical translation, including scale-up manufacturing issues and the need for further safety assessments. Despite these challenges, LPHNPs are considered a next-generation system in cancer therapeutics, providing improved performance compared to traditional nanocarrier systems.

Key words: LPHNPs, PLGA, PCL, Lipid-PEG

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1. Background

Nanotechnology plays an important role in modern medical applications. Applied for treating several medical conditions, including cardiovascular disorders and carcinoma. By engineering nanoparticles and nanodevices to target specific cells or tissues, drugs or therapeutic substances can be delivered with previously unheard-of precision. The effectiveness of treatment is enhanced by this focused approach, which also mitigates the negative side effects of conventional therapies. Nanotechnology also enables the creation of new diagnostic instruments that can identify illnesses early on, potentially leading to improved patient outcomes and higher survival rates. Therefore, the fact that nanoscale structures. [1]

Highly selective and effective nanoparticles innovated for drug delivery have created new possibilities for the treatment of several diseases, such as cancer, cardiovascular disorders, diabetes, and bacterial infections. Therapeutic nanoparticles can improve the solubility of poorly water-soluble drugs, reduce immunogenicity, and increase the drug half-life in systemic circulation. Drugs are released in a sustained manner, so frequent administration is reduced. Drugs are delivered to specific tissues or organs in a targeted manner, so systemic adverse effects are minimised. For combination therapy, more than two medications can be delivered at once to produce a better therapeutic effect. The majority of nanoparticles usually range in size from 10 to 1000 nm. Nanotechnology was developed during the last two decades in the medical field to treat diseases more effectively. Its features include site-specificity, receptor targeting at the right periods and doses, and the

elimination of hazardous medication effects. Various types of polymers are used to create nanoparticles, which can be natural, synthetic, or semisynthetic in nature.

Nanoparticles are commonly employed to transport therapeutic agents, such as medicines, biological molecules, and imaging substances, either encapsulated within or attached to the nanoparticles. Advanced nanocarrier technologies have been developed, but they face some limitations, such as the breakdown of incorporated active compounds and formulation instability.[2]

Frequently utilized nanocarriers include synthetic and natural materials designed to efficiently deliver therapeutic agents.[2] Liposomes and biodegradable polymeric nanoparticles are the most successful drug-delivery nanocarriers in clinical and preclinical products. Liposomes are round vesicles made of lipid layers. Liposomes have been extensively studied and employed to transport diverse bioactive compounds, including proteins, water-soluble and fat-soluble molecules, as well as ligands attached via physical interactions or covalent bonds.7,14 In 1995, Doxil became the first FDA-approved liposome-based drug for treating Kaposi's sarcoma associated with AIDS. Frequently employed lipids include amphoteric, electropositive, electronegative, and electrically neutral lipids. These may consist of various phospholipids, sterols such as cholesterol, long-chain fatty acids, and PEG-modified compounds. Several polymers frequently employed for this quest are poly(lactide-co-glycolide) (PLGA) and polycaprolactone (PCL).

Some remarkable positive outcomes have been reported compared to conventional delivery systems. Over time, the emphasis in nanoparticle design has shifted to nanoscale core-shell structures of greater complexity that use a unified delivery approach to incorporate numerous capabilities encapsulated in nanoparticles. Polymer–lipid hybrid nanoparticles serve as an effective and promising drug delivery system, merging the structural strength of bioresorbable polymers with the cell-mimicking features of liposomes.

CSLPHNs have a polymeric core made of degradable material, enclosed by a lipid layer composed of phospholipids. The hybrid architecture has several advantages, including customizable particle diameter, surface properties, enhanced drug encapsulation, loading of multiple medications, controlled release behaviour, and high stability in blood serum. This CSLPHNs system is composed of three functional components, all with unique properties, influencing the overall combined delivery system. This primary component is a bioresorbable, water-repellent polymer that acts as a vehicle for medications with low aqueous solubility.

The polymeric core provides sustained drug delivery via the delivery platform. The shell of the hybrid particles consists of water-attracting substances, typically PEGylated lipids. The membrane protects the elements from the immune system's absorption and promotes their long-term circulation. Manipulating the shell can help attach targeted ligands more easily. The tertiary unit consists of a single lipid layer lying in the region between the central core and the outer layer. The outer layer enhances medication encapsulation and release rates by minimising water penetration and diffusion from the core. [3] Lipid–polymer hybrid nanostructures are defined as a polymeric inner unit wrapped with multiple lipid layers forming the outer shell. Various types of methods are used for this preparation. Mixed with the initially produced lipids, they provide unique features to these nanoparticles. .[4] Because of their remarkable effectiveness, LPHNPs are presently being researched as a viable nanocarrier for drug delivery (5), (6), (7). These nanoparticles are composed of a hydrophobic inner polymer structure and an outer functional lipid coating. These nanoparticles exhibit a unique composition. The polymer core helped maintain stable drug encapsulation and controlled drug release (8), (9), (10). Drug-incorporated HNPs are designed as self-assembled combined nanoscale delivery systems (11), (12), (13). In recent decades, the creation of naturally degradable nanocarriers has sparked extraordinary interest, as seen by the rise in research articles and intellectual property rights (Gui et al., 2019; Rajana et al., 2022). LPHNPs have received great interest because they incorporate both lipid and polymeric nanoparticle characteristics. They show enhanced stability and improved medication carrying capacity (Kaviarasi et al., 2023). The structure of the LPHNPs incorporates biocompatible polymers and biomimetic lipids, which offer a great flexibility in delivering anti-cancer medications to the site of action (14). Breast carcinoma is a highly common invasive neoplasm and a major cause of neoplasm-associated mortality. In 2020, almost 2.3 million women had a BC diagnosis, and 6,85,000 people died worldwide(Tao et al., 2015). Nano-carriers bind to the surfaces of cellular membranes by adsorption or electrostatic interactions, which have the potential to harm cells (15), resulting in systemic side effects because of their potential

cytotoxicity in the human body and other biological systems. To reduce the adverse reactions of Palbociclib, enhance its targeting toward breast tumour cells, and mitigate the body-wide adverse effects associated with free Palbociclib, folic acid-conjugated Palbociclib-loaded lipid–polymer hybrid nanoparticles were created, formulated, and evaluated in the present study. The QbD technique was implemented to optimise FA-PLPHNPs, and the final formulation was thoroughly evaluated for a laboratory-based drug release study, particle dimension, surface charge, morphology, and entrapment efficiency. In folate receptor-positive BC cell lines (MCF-7 and MDA-MB-231 cells), the anti-cancer, apoptotic, and targeting efficacy of FA-PLPHNPs were thoroughly investigated.

1.1. Why is it necessary to create hybrid conjugates?

Combining two or more materials creates hybrid materials with novel properties. Stabilising and enhancing the therapeutic efficacy of specific medications is the main goal of conjugate polymer blending and hybrid material testing for drug administration. Chemical linking can prolong the bloodstream residence time and preserve biotic processes. In polymer studies, synthetic polymers are introduced in a stabilised form instead of conventional mixing to promote uniform interaction between lipids and polymers and to avoid the phase separation typically observed when biological or non- organic polymers are mixed. Despite the multiple benefits of the method, the primary objective involves reducing overall system toxicity by increasing conjugate solubility or stability (16), (17), (18). The administration of cytotoxic pharmaceuticals, including anticancer compounds, usually results in the creation of new therapeutic approaches because these medications lack specificity and selectivity and rely on traditional systemic biodistribution (19).

2. Lipid polymer hybrid nanoparticles (LPHNPs)

Lipid–polymer hybrid nanoparticles were designed to address the limitations associated with both lipid and polymer derived nanocarrier systems. Since the nanoparticles possess the combined properties of polymeric and lipid particles, they are referred to as “hybrid” (20). These nanoparticles demonstrate greater advantages compared with conventional polymeric nanoparticles and liposomal systems. such as increased durability and biocompatibility, Higher drug encapsulation, sustained drug release, longer systemic circulation, and better in vivo activity. (21). Lipid–polymer hybrid nanoparticles merge the robust Polymeric materials with lipid-mimicking properties. As a result, the drug can be released in a regulated manner without compromising entrapment capacity (22). By using combinations of many nanoparticles, nanotechnology has promise for oncological treatment. To examine the favourable and distinct features which provide LPHNPs the ideal choice for a nanocarrier system. This analysis will evaluate the widely used methods for employing them to target cancer cells. (Fig 1)

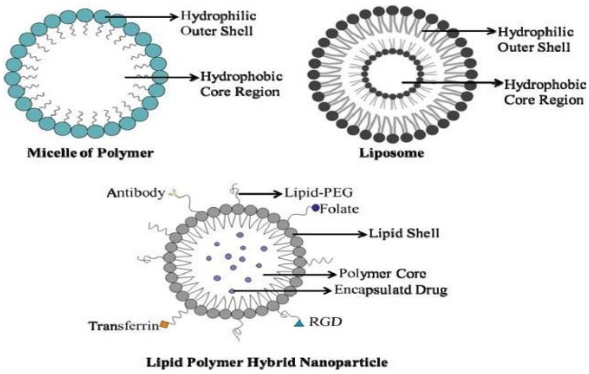


Fig.1. structural arrangement of the liposome, LPHNP, and polymer micelles with hydrophilic and hydrophobic cores. Arginylglycyl aspartic acid, or RGD.

2.1. LPHNPs' structural elements

Blending lipid components with polymeric nanoparticle technology to enhance performance, LPHNPs are formed by three structural components: a lipid–PEG coating on the surface serves as a steric stabilizer, preventing immune degradation and prolonging the circulation of LPHNPs in the bloodstream and a single layer of lipid that surrounds the polymer core. The middle lipid monolayer reduces the loss of entrapped medications during LPHNP formulation by blocking water penetration into the inner core (16), (23). For example, in one-step methods, the polymer precipitates when the organic solvent is added to an aqueous lipid-containing environment. Following this, the polymer self-assembles to produce a single-layer coating around the core. PEG-coated lipids spontaneously organise at this stage, positioning the PEG chains orient toward the surrounding water, securing the lipid moieties to the polymer core. Van der Waal, electrostatic, and hydrophobic interactions all gain thermodynamically from the hybrid formation (24), (25).

3. Choosing lipids and polymers logically to create LPHNPs

Polymeric nanoparticles are biodegradable delivery systems whose properties differ based on the type of material they contain (26). They can have a

variety of architectural configurations, such as Particulate nanocarrier, Central core structure, Micellar nanoparticles and Polymeric complexes. They may be constructed from Bio-based, partially modified, Man-made polymer (27), (28), (29), (30). LNs are widely prized because of their remarkable biocompatibility, which surpasses that of polymeric particles and enables the cells to absorb medicinal chemicals quickly. Pharmaceuticals' lipophilic solubility. The structural characteristics of the lipid matrix often lead to accelerated drug leakage, reducing the retention of therapeutic agents, their exclusion during storage, their tendency to mix, and their high instability in biological fluids are frequently the factors that restrict lipid particles' poor drug loading capabilities (31), (32).

4. Biodegradability of LPHNPs

For the treatment of tumours, biodegradable and biocompatible LPHNPs must be produced because non-biodegradable and bio-incompatible chemicals are hazardous. Generally, LPHNPs are made using substances approved by the U.S. Food and Drug Administration, Substances acknowledged as safe for use (GRAS status) (33). Numerous commercial formulations deemed safe for human use contain these polymers. Zhang and colleagues created a combination therapy of DOX and MMC that was delivered via LPHNPs to BALB/c mice, and their therapeutic outcomes in breast cancer were assessed (34). The conducted study demonstrated enhanced tumour site accumulation, prolonged systemic circulation, and controlled drug release for up to 24 hours. Within 72 hours, the body cleared the biocompatible LPHNPs after their hepatic degradation. Within 72 hours, the biologically compatible lipid–polymer hybrid nanoparticles were cleared from the body following their degradation in hepatic cells. High loading of doxorubicin and mitomycin C was achieved in the LPHNPs, which have also been examined. The outcomes reveal that, in contrast with the unmodified drugs, the combination with the drug regimen resulted in better apoptosis and less organ damage. The safety of LPHNPs was proven by this investigation.

5. Characterisation of LPHNPs

Important physical and chemical parameters that influence the in vivo characteristics of hybrid nanoparticles encompass their particle size, morphology, and surface charge. The distribution of particle diameters can be assessed using dynamic light scattering (DLS). The size and morphology of nanoparticles can be assessed using TEM or SEM. Several variables influencing LPHNP size and distribution were evaluated by Valencia and co-workers. Lipid and polymer solutions cannot be combined slowly enough. Rather, they must be forcefully combined to produce similar nanoparticles (35).

Through broadening of XRD peaks, the typical crystallite size of magnetite nanoparticles was found to be 9–53 nm by Upadhyay and colleagues. Other than instrumental broadening, the increase in X-ray powder diffraction peak width was specifically caused by particle/crystallite length and lattice stresses (36). The kind, amount, and crystal structure of the lipid all influence its capacity to be trapped. The efficiency with which medications are trapped by nanocarriers depends on how pharmaceuticals are distributed across aqueous and melting lipid environments (37). The incorporation of polar molecules is rare because they adhere poorly to the lipid network. On the other hand, lipid nanoparticles have successfully incorporated biotechnology-based APIs, enabling LPHNPs to perform the same tasks (38).

6. Categorization of LPHNPs

LPHNPs can be divided in to different types according to the arrangement of lipids and polymers.

(i) Nanoparticles with polymer core coated by a lipid shell.

(ii) Polymer-coated nanocarriers.

(iii) Hybrid nanoparticles composed of lipids and polymers.

(iv) Single-matrix Lipid-Polymeric Hybrid Nanoparticles.

(v)Erythrocyte membrane modified LPHNPs:

(i)Nanoparticles consisting of a polymeric core enclosed by a lipid shell.

Hybrid polymer core–lipid shell nanoparticles have attracted considerable attention because of their effectiveness in drug delivery. Studies have shown that the structural properties of these hybrid nanoparticles are influenced by PLGA, which is a biodegradable hydrophobic polymer. They also consist of an external lipid-PEG conjugated layer capable of carrying hydrophilic therapeutic agents, along with an additional lipid layer that functions as a protective barrier on both sides. With enhanced drug encapsulation efficiency, the water-soluble anticancer compound salidroside (Sal) can be successfully loaded into a polymeric core–lipid shell system (PLGA-PEG-PLGA), which improves cellular uptake in cancer cells and also helps in decreasing the particle size. Figure 2A

(ii) Polymer-enclosed nanocarriers:

Polymer-encapsulated nanoparticles are developed to enhance the efficiency of drug delivery systems. They provide sustained or CR release of medication, improve drug stability, and reduce the chances of drug leakage. In these systems, an extra polymer layer is coated on the outer surface of the particle. For instance, the outer layer formed by polyacrylic acid can provide additional surface functionality. Carboxylic groups present in this polymer can be used to attach different linkers, which may produce pH-sensitive responses. In polymer-based liposomal systems, the surface of liposomes is modified to enhance their efficiency. Initially, liposomes are prepared, and later their properties are improved by coating them with polymeric materials such as polyacrylic acid that may also be functionalized with cholesterol on the surface. Enhances the surface properties of liposomes to operate by adding carboxylate groups [Lee et al., 2017]. Figure 2B

(iii) Hybrid nanoparticles composed of lipids and polymers:

This technique produces nanoparticles with a concentric structure consisting of layers arranged in an A–B–A pattern. The top layer is composed of lipids containing PEG, whereas the layer beneath it is the polymer intermediate layer (41). For instance, siRNA and a little therapeutic component can be loaded into a hydrophobic kernel to accomplish a combined drug delivery approach for cancer therapy targeting multidrug resistance (MDR) (42). Figure 2C

(iv) Single-matrix LPHNPs:

The nanostructures integrate a lipid layer with a polymer-based matrix. This novel product works similarly to a colloidal drug delivery system (43). Phospholipids, their fundamental structural components, can form vesicles. However, because PEG-lipids may form micelles at higher PEG concentrations, Phospholipids possess enough flexibility to undergo structural modification through the process of PEGylation. Figure 2D

(v) Erythrocyte membrane modified LPHNPs:

Several approaches have been evaluated to determine if PEG can adequately stabilise the nanoparticles under in vivo conditions. Erythrocyte membranes are used to create nanoparticles using the membrane lipid layer. Heating RBC's is commonly used to produce these nanoparticles. The RBC membrane contains polymer-based nanoparticles. The drug-loaded polymeric nanoparticles exhibit improved biological stability due to their encapsulated core and optimised surface features (44). The medication diffuses gradually through the lipid bilayer structure. The high lipid barrier may also cause the RBCs to discharge more slowly. Because red blood cell antigens vary between different blood types, performing crossmatching for transfusion can be complicated (43). Figure 2E

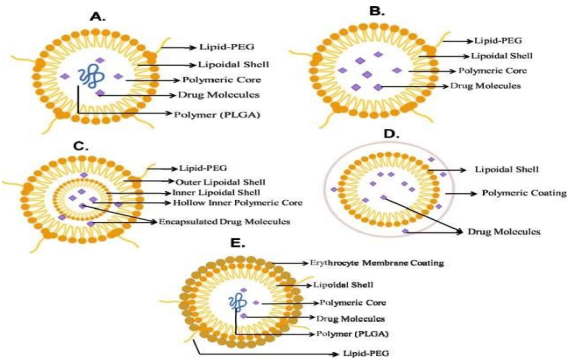
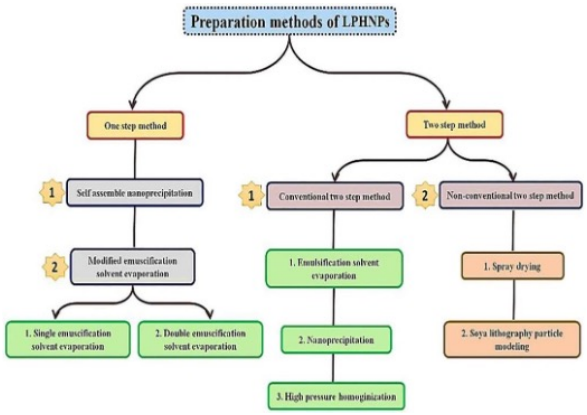


Figure 2 Classification of LPHNPs. (A)Nanoparticles consisting of a polymeric core enclosed by a lipid shell. (B)Polymer-enclosed nanocarriers (C)Hybrid nanoparticles composed of lipids and polymers (D) Single-matrix LPHNPs (E) Erythrocyte membrane modified LPHNPs

7. Various ways of synthesis of LPHNPs:

Although there are a variety of methods for creating LPHNPs, they may generally be divided as



2 groups: (1) two-step techniques and (2) one-step techniques. To support nanoparticles' claims as drug transporters, innovative and novel polymers have been tried (19)

7.1. Two-stage approach:

The two-step technique used in earlier research to prepare LPHNPs involved combining polymeric nanoparticles with previously formed liposomes. These structures were then connected through electrostatic interactions between the lipid shell and the polymer core (45). In another method, structured polymeric nanoparticles were incorporated into a dried lipid layer. In both approaches, energy supplied through vortex mixing, ultrasonication, or heating at a temperature above the lipid phase-transition point promotes the

assembly of the two components. Following this process, a purification step can be carried out to remove excess lipid or polymeric nanoparticles and to obtain isolated LPHNPs. [Fig. 3].

7.1.1. Conventional method

In laboratory-scale production, hybrid nanoparticles are typically synthesised through conventional preparation techniques. Several techniques such as emulsion formation, solvent elimination, High-pressure mixing process and precipitation method. Such nanocarriers are mixed with preformed lipid vesicles composed of electrostatically interactive lipids that associate with the polymeric nanoparticle surface. Before the addition of polymer-based nanoparticles, initially, the lipid was dissolved in a non-aqueous solvent, and the liquid phase was removed by evaporation, which produces a dry film. The solution was then processed by ultrasonic sonication or vortexing at thermal conditions exceeding the temperature at which the lipid transitions, which is essential for generating LPHNPs. The nanoparticles were recovered from the solution via centrifugation.

7.1.2. Non-conventional two-stage approach:

The primary application of this unconventional method is the mass production of LPHNPs. To create LPHNs, the current procedure employs several methods, including atomization drying, flexible lithography, and particle shaping. The atomization-drying process produces 400–500 nm-sized nanoparticles using a polymer of glutamic acid, lysine-based polymer, which are subsequently distributed in a

range of organic solvents that contain lipids (dichloromethane). The lipid polymer mixture was dried using atomization techniques to generate lipid-polymer hybrid nanoparticles. A related investigation, such as atomization drying, atomization freeze drying, was applied for the Preparation of Levofloxacin-encapsulated lipid-polymer hybrid nanoparticles as a dry powder for pulmonary drug delivery. Additionally, they created smaller LPHNs using a recently announced nano-spray drier.

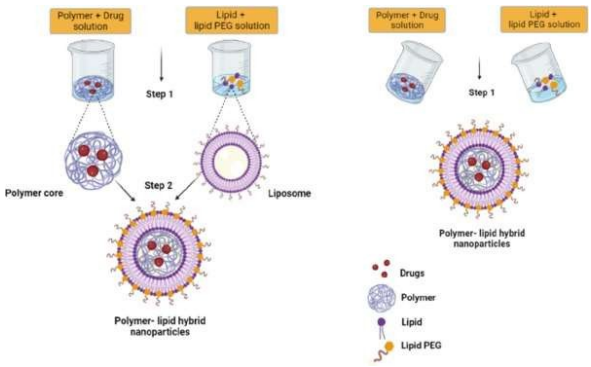


Figure 3: Different methods for the preparation of LPHNPs include the two-step method and the single-step method.

7.2. One-stage approach:

It has been demonstrated that two-step procedures are insufficient for scaling up and are time-consuming. In order to produce LPHNPs in a single step, considerable efforts have been undertaken to develop more effective synthesis procedures (48). This polymer is mixed with a lipid layer that contains PEG to form LPHNPs. Earlier techniques frequently employ emulsification–solvent evaporation/nanoprecipitation techniques (49). Using the nanoprecipitation method, the lipid/PEG-lipid aqueous solution is blended with a non-aqueous phase, including polymeric material and the hydrophobic drug is solubilised in hydrophilic organic solvent (acetone, ethanol, etc).

To produce an evenly distributed lipid solution during the premixing process, the aqueous phase is raised above the liquid transition temperature. (49). The non-aqueous phase is removed using ultrafiltration, membrane filtration, and evaporation. [Figure 3].

8. Drug release mechanism:

An important consideration in treating various diseases is the effective delivery of drugs. Traditional medications have poor selectivity, biodistribution, and effectiveness (50). LPHNPs act as a promising carrier for delivering water-insoluble compounds because they have a large capacity and release the drug gradually over time. Critical parameters affecting drug release from multi-component nanoparticles are drug dissolving capacity, medication polymer affinity, polymer breakdown rate and granule size. Compound diffusion and polymer disintegration allow medications that are physically enclosed to be released from hybrid nanoparticles. Besides drug diffusion, the hydrolysis of the linkage between the drug and polymer chains controls the release of chemically conjugated drugs (51). To assess the targeting ability and therapeutic efficiency of drug-loaded nanoparticles on specific cells, laboratory studies like cellular uptake and toxicity tests are often performed before animal

studies. Nanoparticles are labelled by scientists using fluorescence indicators such as FITC. After that, they placed the nanoparticles in a cell incubator to observe how efficiently the cells absorbed them. Following the removal of surplus particles, fluorescence microscopy, similar toLaser-based confocal microscopy, allows visualisation of nanoparticle internalisation and distribution. A fresh medium is applied once the cells have been cleaned. Cell health can be evaluated after 72 hours, and it can be determined through appropriate assays, including the ATP and MTT tests. Medicines covered with hybrid nanoparticles while maintaining their cytotoxicity. By delivering a bolus dose to sick cells, nanoparticles significantly increased the toxicity of opioids as compared to uncoated substances (52).

9. Studies of cytotoxicity and cellular uptake

LPHNPs that could be used to administer cisplatin were developed by Khan and his associates in 2019. The method is more biocompatible thanks to chitosan, a naturally derived polymer, and phospholipid S75, a soybean-derived phospholipid mixture containing about 74% phosphatidylcholine (53). Through lipid layer–cell surface interactions, fluorescence imaging and flow-cytometric analysis demonstrated cellular uptake of LPHNPs carrying the fluorscent dyes such as rhodamine and Hoechst (54). During in-vitro studies, cisplatin exhibited sustained and regulated release, primarily attributed to the lipid bilayer and, to a smaller degree, the polymer matrix that controls diffusion-based drug release. Cisplatin-encapsulated chitosan hybrid nanoparticles showed minimal initial cisplatin release because the drug remains confined within the inner polymer core, which is shielded from the external environment by the lipid layer (55). Polymer-lipid nanoparticles significantly improved the ADME profile and clinical effectiveness of gemcitabine, extending its half-life to about 4.2-fold compared with the commercial Gemko® formulation. The extended circulation time of the composite nanoparticle platform plays an important role in significantly decreasing tumour mass in mice compared with the Gemko®-administered group. Using the MTT test, the bio-compatibility and viability of MCF-7 and MDA-MB-231 cells loaded with LPHNPs or treated with free Gemcitabine (hydrochloride solution and Gemko®) were evaluated (56).

Strategies of targeting LPHNPs

LPHNPs frequently use both passive and active targeting techniques to distribute chemotherapeutic drugs to target cells or tumour tissue:(57)

9.1. Passive targeting

Nanoparticle technologies passively target a tumour by taking advantage of its blood artery pathophysiology. When a tumour is greater than 2 mm3, it becomes difficult to absorb oxygen, remove waste, and eat. Neovascularisation refers to the formation of new vascular networks by tumour tissue to supply nutrition and oxygenation. The absence of perivascular cells, a highly irregular basal lumina, and other reasons cause the gaps in blood vessels in cancer to range from 100 nm to 2 m. In addition Increased pressure within the tissue prevents lymph fluids from exiting the cancerous areas. The accumulation of leaked macromolecules occurs because of highly permeable cancer vessels and poor lymph flow. The process is known as "enhanced permeability and retention" (EPR) impacts. Due to their small size ,nanoparticles can move through the gaps of endothelial cells of blood vessels in cancerous tissues and accumulate in tumour tissues. Passive targeting of nanoparticles is expected to be based on this technology [Figure 4].

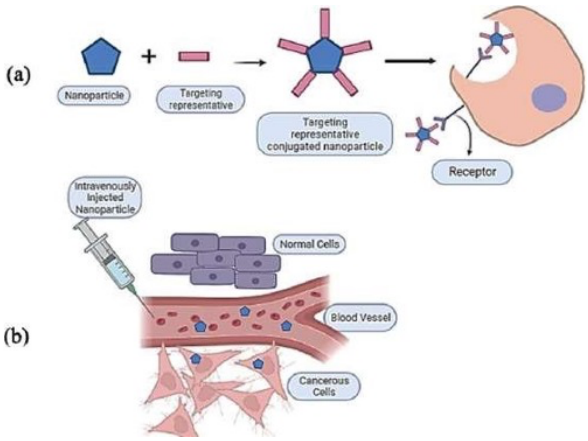


Figure 4. Targeting Approaches of LPHNPs (A) Active targeting (B) Passive targeting

9.2. Active targeting

To enable them to attach to highly expressed receptors present on cancer and endothelial cells, ligand molecules are attached to the surface of nanoparticles in ligand-based or active targeting techniques (58). By means of a mechanism known as receptor-mediated endocytosis, ligand conjugation facilitates their uptake by cancer cells (59), (60). Ligand-functionalized nanoparticles can use the excess of one or more receptor types found in many cancer cells as active targets. Consequently, it has been found that both cancer cells and endothelial cells are important cellular locations for a targeted delivery approach [Figure 4].

10. LPHNPs for the delivery of poorly soluble medication:

Most medications are classified as system II biopharmaceuticals, which have low water solubility and variable bioavailability. Many medications have a limited bioavailability because they are mildly basic (pKa = 3.7), largely ionised under low pH conditions, and have very poor aqueous solubility at neutral and acidic pH (1.0) (61). Its limited usefulness in clinical practice results from this. In recent years extensive research focused on drug-delivery approaches for low aqueous solubility and high lipophilicity, including molecular dispersion in solid matrix, colloidal emulsion system and nanoparticle formulations. With its many clinical benefits and large-scale manufacturing capabilities, nanotechnology has emerged as a highly promising approach for developing new drug-carrier systems in recent years (62).

11. Role of LPHNPs

Dehaini et al. (2016) reported a method to increase the effectiveness of docetaxel's tumour-penetrating properties through the combination of folate-Targeted LPHNPs (63). The formulation was developed using DSPE-mPEG2000 phospholipid and PLGA-COOH polymer. DID-tagged nanoparticles were injected into mice, and their presence in the bloodstream over time was observed. According to the findings, NPs were eliminated from the body using a biphasic pharmacokinetic model showing a half-life duration of 11.5 hrs.

Additionally, 24 hours later, the mice's blood still contained about 10% of the amount administered. After 24 hours, researchers discovered that the animals' livers and spleens had absorbed a significant portion of the NPs that had been administered to them. This was probably brought on by phagocytic mechanisms in the animal's immune system. Mice with docetaxel-loaded liposomal polyethene were used as a control (64). Huang and his colleagues conducted research to develop a nanosystem that might be utilised to combat multi-drug resistance (MDR), which is widely believed to be the primary cause of chemotherapy treatment failure. Psoralen, is a naturally derived compound that exhibits several biological activity including anti-cancer, anti-psoriasis, and anti-vitiligo effects, was loaded onto PLGA nanoparticles as part of the system (65). The results indicate that the hybrid nanosystem could be useful for treating breast cancer with drug resistance. Xiong et al. (2017) developed a new hybrid nanoparticle technology using cyclodextrin coupled with poly-L-lysine and hyaluronic acid (66). The nano-sized particles showed efficient cytoplasmic delivery of siRNA in prostate cancer cells while escaping from endosome. After the discovery of plasmid DNA, small interfering RNA or microRNA in the control, development, and multiplication of different types of tumour cells, gene therapy has made it feasible to use cancer treatment methods (67). Gene therapy techniques have also been used to increase the susceptibility of cancer cells to anticancer drugs. Suicide genes' ability to cause cancer cells to undergo apoptosis has been the subject of additional research (68).

However, a limitation of such techniques involves the considerable cost and the requirement for advanced laboratory equipment to perform them. In various ways, LPHNPs aid in the therapy of cancer. They can place one or more medicinal medications in a capsule and deliver them to the injured area using various loading techniques. When it comes to drug trapping, drug entry into cells, and drug release speed, LPHNPs have demonstrated greater potential than conventional NPs. LPHNPs come in three varieties: Drug delivery approaches include systems with ligand-based active targeting, systems capable of carrying multiple drugs, and systems designed for a single drug. The effectiveness of the DDS is affected by the nano-sized particles and shape. We examined the surface charge and particle size of chitosan LPHNPs loaded with varying concentrations of cisplatin. Both fat-loving and water-loving DOX are consistently sent to tumour locations by the 173 nm LPHNPs (69). Stimuli-responsive LPHNPs were useful in cancer therapy because they were more adept at entering cells, dispersing evenly, releasing medications in response to stimuli, and travelling to the appropriate location. Unlike the free DOX group, the hybrid nano system successfully targeted the cancer cells and managed drug delivery at a pH of 6.55 (70). To increase the accuracy of clinical diagnosis, lipid-polymer hybrid nanoparticles improve the performance of drugs used for treatment as well as diagnosis. Imaging methods show the condition of the specific tissue. They can also assist in early cancer diagnosis and determine appropriate therapeutic strategies. Imaging materials, including fluorescent dyes, quantum dots, iron oxide, and inorganic nanocrystals, are widely used in molecular imaging methods such as magnetic resonance imaging (MRI), computed tomography (CT), and photoacoustic imaging. (PA) (71), (72). Under certain conditions, the polymer matrix core was loaded with a large quantity of imiquimod (a TLR7/8 agonist), while the lipid envelope mainly contained the

TLR4 agonist MPLA. The ovalbumen antigen was incorporated onto the surface of the cationic lipid through charge-based attraction and the mannose moiety of the PEG-conjugated lipid. 90% of DCs were targeted by this hybrid formulation after 48 hours, improving cell absorption of the medicinal therapy and demonstrating the particles' biocompatibility.

12. Challenges in clinical translation of LPHNPs

A range of medications could be distributed by LPHNPs (73). Their small size, naturally degradable materials, and ability to target multiple sites support their use in drug delivery, medical imaging, tissue regeneration, and genetic treatment. However, suggesting optimal formulations with all the necessary characteristics for specific implications could be a barrier to clinical translation (74). For the effective and widespread use of LPHNPs in clinical settings, several major technical challenges need to be overcome. Enhancing NP accumulation at target areas, avoiding immune cells, ensuring regulated drug release, and improving therapeutic loading efficiency are some of the goals of these experiments (75). The procedures involved in LPHNPs' clinical translation are illustrated in Figure 5.

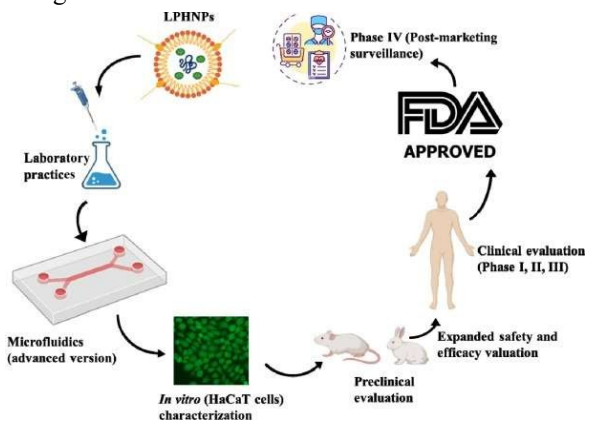


Figure 5. Schematic illustration of the clinical translation of LPHNPs

Currently, LPHNPs are mainly produced in laboratories, while manufacturing particles with similar characteristics for large-scale industrial production remains challenging. (76),(77),(78). From a financial perspective, several fabrication procedures are likewise undesirable because they usually result in higher manufacturing costs (79). An additional significant aspect is the potentially harmful impact of LPHNPs on living systems. The adoption of emerging technologies may potentially constitute a marketing hurdle for hybrid nanoparticle (HNP) systems because end users may be hesitant to try this new technology (80). Lipid nanoparticles frequently contain cholesterol, phospholipids, ionisable lipids, and PEGylated lipids.

Examples of LPHNPs Formation with Applications (81)

Muhammad Shafique et al. have effectively designed a technique to synthesise nanoparticles composed of both lipids and polymers, DOX-LPHNs, using the combination of magnetic agitation and ultrasonic treatment. which shows reduced particle size, improved stability, and excellent encapsulation efficiency, making them a good carrier for targeted drug delivery. Characterisation studies revealed that the prepared DOX-LPHNs had an enhanced amorphous nature, favouring improved solubility and oral bioavailability, as well as distribution of the drug throughout the lipid and polymer matrices. And also, they showed long-term physical stability at various temperatures, with minimal modifications in nanoparticle dimensions and distribution uniformity. Characterisation of the improved Lipid-Polymer Hybrid Nanoparticles and Doxorubicin-loaded Lipid-Polymer Hybrid Nanoparticles revealed particle diameter 150.82 nm and 185.43 nm, with favourable polydispersity indices (PDI) and zeta potentials. These characteristics show that the fabricated LPHNs are stable and suitable for oral administration. The incorporation efficiency and drug loading of DOX-LPHNs improved significantly following fine-tuning of oleic acid and ethyl cellulose concentrations. The optimised version, Doxorubicin-loaded Lipid-Polymer Hybrid Nanoparticles-4, demonstrated high entrapment efficiency (95.26%) and drug loading capacity (0.227%). FTIR analysis verified that DOX was compatible with the other formulation ingredients, indicating no significant chemical interactions. The results suggest that the prepared LPHNs and DOX-LPHNs have potential for improved oral bioavailability and stability. DOX-LPHNs exhibited a rapid initial drug release, which was subsequently followed by a slower, sustained release in vitro. A higher drug loading led to an extended-release duration. Analysis of the release kinetics showed that the semi-empirical release model provided the best fit, suggesting anomalous transport behaviour. Pharmacokinetic studies in rabbits demonstrated that Doxorubicin-loaded Lipid-Polymer Hybrid Nanoparticles achieved a higher maximum plasma concentration (Cmax) (3.333 µg/mL), shorter Tmax (0.31 h), and longer t1/2 (26.07 h) compared to marketed DOX, indicating improved bioavailability and sustained release.

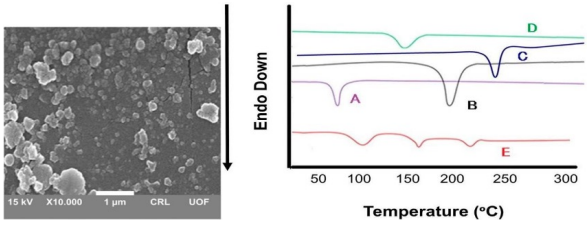
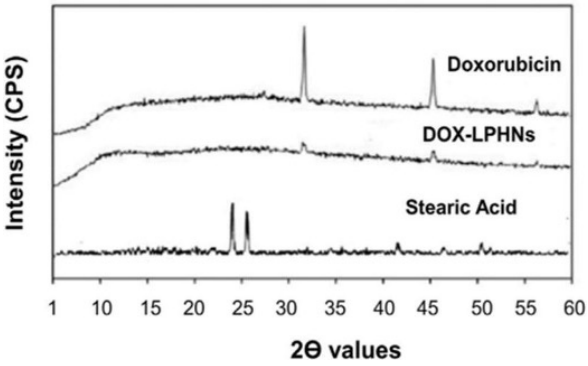


Figure 6

1. Sem Picture

2. Differential scanning calorimetry (DSC) thermogram of (A) Stearic Acid, (B) Doxorubicin, (C) Ethyl Cellulose, (D) Oleic Acid, (E) DOX-LPHNS-4.



3. PXRD analysis of DOX, DOX-LPHNs and stearic acid:

DFT simulations demonstrated significant interactions between DOX and the polymeric components, which support the successful formation of DOX-LPHNs. Toxicity evaluation indicated that DOX-loaded LPHNs were safe up to a dose of 400 mg/kg, while mortality increased at higher concentrations. The median lethal dose (LD_{50}) was found to exceed 1600 mg/kg, indicating low acute toxicity. (82)

Yajna Jaglal and colleagues reported the synthesis of lipid–polymer hybrid nanoparticles (LPHNPs) containing VCM as well as 18β-glycyrrhizin acid using a micro-emulsion method. In this method, the oil phase components (oleic acid and 18β-glycyrrhizin acid) were dissolved in ethanol, while the aqueous phase materials (polyallylamine hydrochloride, VCM, and Tween 80) were dispersed in distilled water. The oil phase was then gradually introduced into the aqueous phase with continuous stirring. Blank LPHNPs were produced using the same procedure without adding VCM and 18β-glycyrrhizin acid. Molecular dynamics simulations were conducted to examine the stability of the nano system composed of oil and water phases. The findings demonstrated that the constituents present in each phase remained closely associated, resulting in the formation of a stable complex. Moreover, the combined oil–water phase system containing a greater number of hydrogen bonds exhibited improved stability compared with the aqueous phase alone. The development of VCM-GAPAH-LPHNPs required optimisation of the lipid-to-polymer proportion to achieve a formulation with appropriate particle diameter, polydispersity index (PDI), and zeta potential (ZP). The optimised formulation had a mean particle diameter of 198.4 nm, a PDI of 0.255, an zeta potential of −3.808 mV. The drug encapsulation capacity and drug loading percentage were determined to be 69.464% and 13.453%, respectively. Molecular dynamics simulations additionally verified the structural integrity of the nano-system. The integrated oil–water phase system appeared more condensed and stable. The prepared VCM-GAPAH-LPHNPs demonstrated desirable particle size, PDI, and zeta potential characteristics. Drug encapsulation efficiency and loading capacity were measured as 69.464% and 13.453%, respectively. The antibacterial activity of various treatments against MRSA biofilms was also evaluated. Biofilms exposed to 18β-glycyrrhizin acid exhibited a higher biomass percentage compared with those treated with VCM. Furthermore, the VCM-GAPAH-LPHNP formulation markedly decreased biofilm formation ($p = 0.036$) and showed superior biofilm eradication efficiency relative to the other treatments. (83)

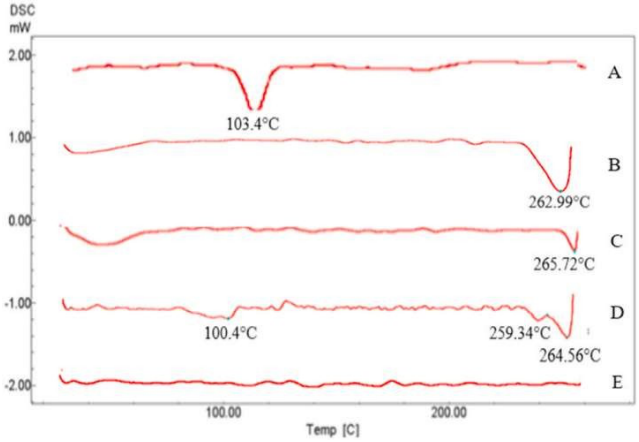
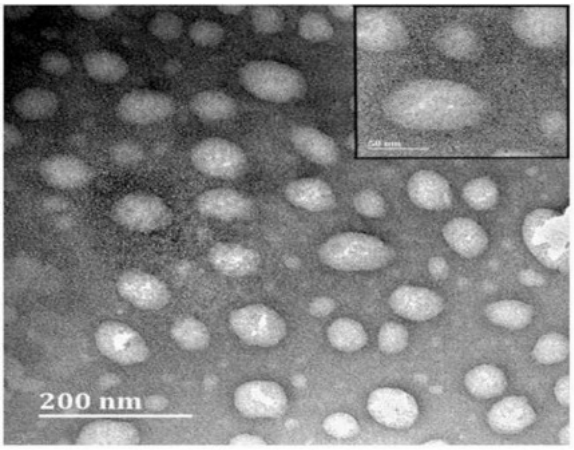
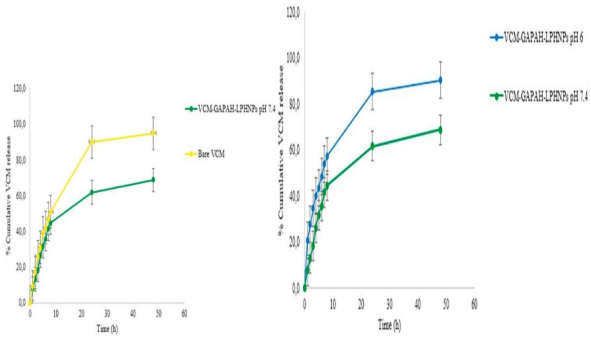


Figure 7

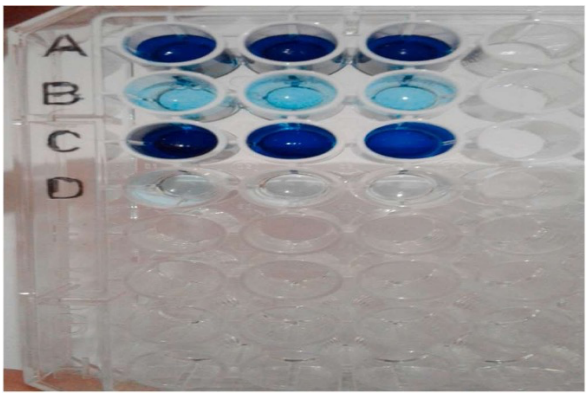
1. DSC Thermal Profile of VCM, PAH, GA, Physical Blend of VCM-PAH-GA, and Freeze-Dried VCM-GAPAH-LPHNPs



2. Transmission Electron Microscopy (TEM) Analysis of LPHNPs containing VCM and GAPAH



3. Assessment of the Release Profile of Free VCM and VCM–GAPAH encapsulated lipid–polymer hybrid nanoparticles at pH 7.4



4. Crystal Violet Biofilm Assay of MRSA Under Different Treatment Conditions (A) MRSA biofilms without any treatment (control) (B) MRSA biofilms exposed to free vancomycin (VCM) (C) MRSA biofilms subjected to treatment with glycyrrhetinic acid (GA) (D) MRSA biofilms exposed to VCM-GAPAH-LPHNP formulation.

VCM-GAPAH-LPHNPs, possessing a uniform spherical morphology and defined particle size, exhibited pH-responsive drug release, with a more rapid release observed under acidic conditions. The VCM-GAPAH-LPHNP formulation showed improved antibacterial activity against MRSA, particularly at lower pH levels. VCM acts by interfering with bacterial cell wall formation, whereas 18β-glycyrrhetinic acid affects bacterial cell membrane integrity and DNA replication processes. The simultaneous presence of VCM and 18β-glycyrrhetinic acid produced a synergistic antibacterial response, which improved therapeutic performance while lowering toxicity. Encapsulation of both VCM and 18β-glycyrrhetinic acid within LPHNPs enhanced their pharmacokinetic behaviour and therapeutic efficiency. Moreover, the formulation decreased cytotoxic effects and helped limit the emergence of antimicrobial resistance. Consequently, VCM-GAPAH-LPHNPs exhibited superior antibacterial performance with synergistic action and reduced toxicity, indicating their usefulness as an effective treatment strategy for MRSA infections.

Imran Kazmi and co-workers designed and improved innovative mucoadhesive lipid–polymer hybrid nanoparticles (LPHNPs) designed for oral delivery of PPN using a three-factor Box–Behnken experimental design. The optimised formulation demonstrated favourable properties for efficient oral administration, including an average particle diameter of 151.2 nm, a polydispersity index (PDI) of 0.213, and a positive zeta potential of +24.31 mV. These physicochemical properties contributed to excellent colloidal stability and improved adhesion to the intestinal mucosal surface. Furthermore, the optimised PPN-LPHNPs displayed a spherical morphology with uniform distribution, along with high entrapment efficiency (%EE) of 83.54% and a drug loading capacity (%LC) of 6.71%. Stability investigations conducted in simulated gastric and intestinal environments verified that the optimised nanoparticles remained stable, showing negligible variations in particle size, PDI, %EE, and zeta potential. The optimised PPN-LPHNP preparation demonstrated an initial rapid drug release of approximately 38.54% within the first two hours, followed by a sustained release pattern extending up to 24 hours.
[84]

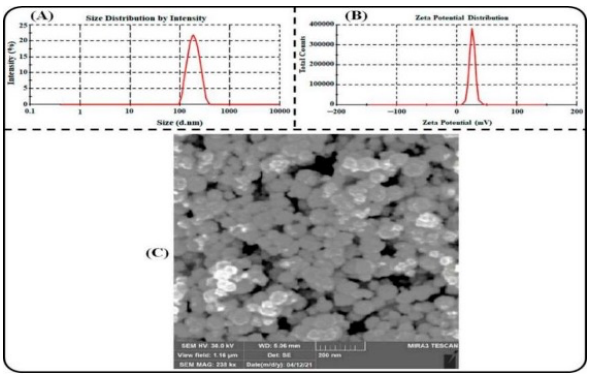
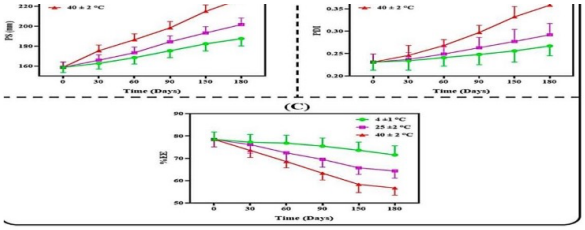
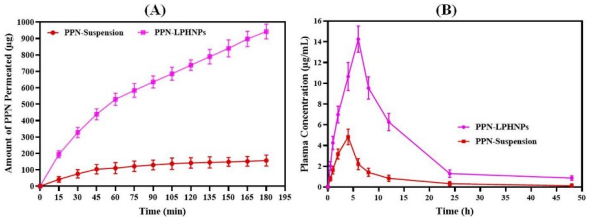


Figure 8

1. Figure presenting (A) average particle diameter along with particle size distribution, (B) zeta potential distribution pattern, and (C) SEM image of the optimised PPN-LPHNP nanoparticles.



2. Evaluation of the Colloidal Stability of PPN-LPHNPs under Different Environmental Conditions and Storage Durations Showing Variations in (A) Particle Size, (B) polydispersity index and (C) percentage of entrapment efficiency.

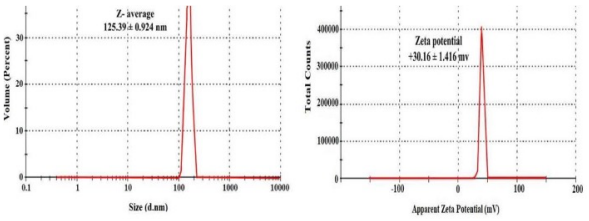


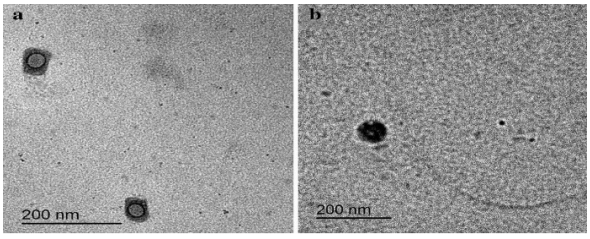
3. Illustration showing (A) Evaluation of Intestinal Permeation of PPN Suspension and PPN-LPHNPs and (B) Plasma Concentration–Time Profiles

Randa Hanie Awadeen and co-researchers formulated FST-incorporated LPHNPs applying a combined preparation approach that involved ultrasonication and a double emulsion (w/o/w) technique. The developed formulations (F1–F4) exhibited varied physicochemical characteristics. The drug entrapment efficiency (EE) ranged from 46.22% to 64.04%, whereas the drug loading capacity (LC) was recorded between 24.17% and 33.44%. The nanoparticle diameter varied within the range of 78.53 nm to 407.57 nm. The polydispersity index (PDI) values were reported between 0.334 and 0.429, indicating the distribution pattern of the particle sizes. Additionally, the zeta potential (ZP) values were measured between −17.13 mV and +33.53 mV. Moreover, the mucin adhesion efficiency of the nanoparticles was determined to lie between 31.52% and 39.08%.

Figure 9 1. Characterisation of the optimised FST-loaded LPHNPs showing

(a) particle size distribution and (b) zeta potential profile.





2. Transmission electron microscopy (TEM) micrographs illustrating (a) FST-loaded lipid–polymer hybrid nanoparticles (F3) and (b) uncoated FST nanoparticles (F1).

The developed FST-loaded LPHNPs (F3) were characterised using FTIR, DSC, and XRD techniques. No significant interaction was detected between FST and the other formulation components, confirming the effective incorporation of FST within the LPHNP matrix. The in vitro drug release analysis demonstrated a considerable enhancement in the release behaviour of FST from FST-loaded LPHNPs (F3) compared with the aqueous dispersion of the drug. The highest release rate was recorded in phosphate buffer solution at pH 7.4, showing sustained release for up to 48 hours. Kinetic evaluation indicated that the Higuchi diffusion model best described the release pattern, suggesting a diffusion-regulated mechanism. Additionally, the Korsmeyer–Peppas and Weibull models supported this release behaviour, indicating that FST-loaded LPHNPs (F3) could function as an efficient nanoscale carrier for prolonged oral drug administration. Animal experiments were conducted to investigate the therapeutic impact of oxidative stress in L-arginine-induced acute pancreatitis and FST-loaded LPHNPs (F3) on pancreatic tissue injury in rats. The findings demonstrated that the formulation significantly reduced pancreatic injury, inflammatory responses, and oxidative stress levels compared with the L-arginine group. Furthermore, the system exhibited improved antioxidant activity through the reduction of NF-κB expression and oxidative stress indicators. Overall, the results suggest that FST-loaded LPHNPs (F3) represent a promising formulation for the treatment of acute pancreatitis, offering enhanced stability, therapeutic efficiency, and antioxidant potential.[85]

Emanuela F. and collaborators prepared lipid–polymer hybrid nanoparticles (LPHFNPs) by combining preformed fluorescent polymer-based nanoparticles with liposomal vesicles through a two-step fabrication method. The therapeutic agent roflumilast, which is commonly used in the management of chronic obstructive pulmonary disease (COPD), was incorporated into these nanoparticles. The resulting LPHFNPs generally exhibited a particle size ranging from 70 to 110 nm, with a narrow size distribution and a core–shell structural arrangement consisting of a lipid outer layer and a polymeric core. The proportion of lipid content was approximately 44–51 wt%, and X-ray photoelectron spectroscopy confirmed the presence of phospholipids on the nanoparticle surface. Moreover, the nanoparticles displayed a relatively high surface PEG density with a brush-like structural organisation, which is beneficial for inhalation delivery. However, due to their small size, nanoparticle powders alone may not be suitable for direct pulmonary administration or optimal bronchial deposition. To address this limitation, a nano-in-micro (NiM) delivery strategy was applied, in which nanoparticles were encapsulated within water-soluble microparticles. This method enables the nanoparticles to be released once the microparticles dissolve in lung fluids, allowing them to efficiently disperse along the respiratory epithelium.

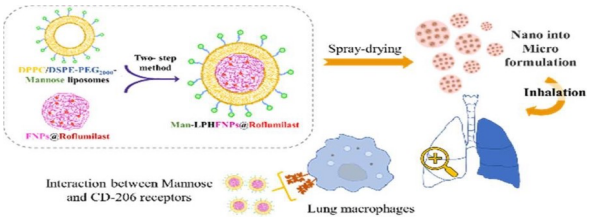
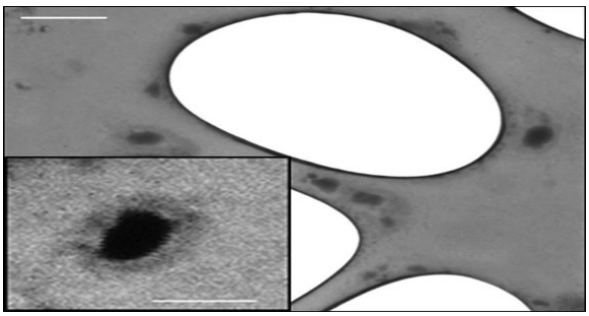
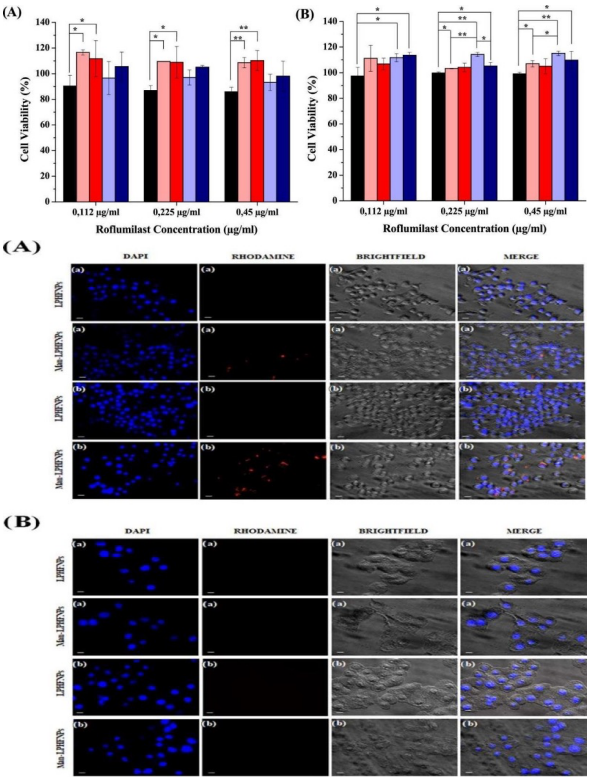


Figure 10

1. Two-Step Fabrication of Fluorescent Polymer Nanoparticles and Lipid Vesicles

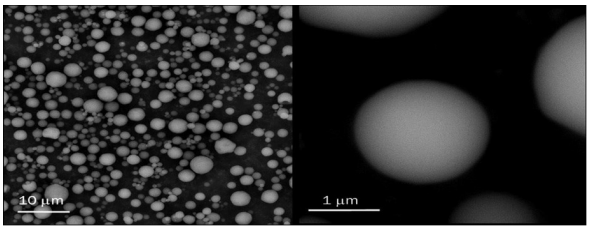


2. STEM micrograph of Man-LPHFNP formulation



3. Evaluation of cell viability after 24 hours in (A) RAW 264.7 and (B) 16-HBE cell lines exposed to free Roflumilast (black), LPHFNPs (pink), LPHFNPs loaded with Roflumilast (red), Man-LPHFNPs (light blue), and Man-LPHFNPs encapsulating Roflumilast (blue). Statistical significance was indicated as ($P < 0.05$; $P < 0.001$).

4. Fluorescent microscopy observation of (A) RAW 264.7 and (B) 16-HBE cells after incubation periods of (a) 4 h and (b) 24 h. Scale bar indicates 10 µm.



5. SEM micrographs presenting NiM particle structures. (sn 5000×, dx 66000×).

Furthermore, to overcome aerodynamic constraints of the nanocarrier during inhalation, a pulmonary drug delivery formulation composed of mucus-penetrating Man-LPHFNPs loaded with Roflumilast, along with poly(vinyl alcohol) (PVA) and L-leucine (Leu), was developed. The formulation was produced using the NiM technique followed by a spray-drying process. Spherical NiM particles with appropriate sizes suitable for efficient lung deposition were obtained [86].

According to Rania A. H. Ishak et al., innovative lipid–polymer hybrid nanoparticles (LPHNPs) were designed to efficiently deliver the RU drug. These nanoparticles consisted of a PLGA polymeric core surrounded by a lipid layer composed of soybean phosphatidylcholine and PEG-SAA. A 2^3 full factorial experimental design together with a single-step modified nanoprecipitation method was applied to optimise the nanoparticle formulation. The prepared LPHNPs exhibited high drug encapsulation efficiency, appropriate particle size, and low PDI (polydispersity index). The nanoparticles demonstrated a spherical morphology, multilayer lipid structures, and SAA protective layers.

The drug-release profiles were comparable among all nanoparticle formulations, extending up to 6 hours. The findings highlighted the significant role of Solutol and TPGS in brain-targeted delivery, showing performance comparable to the standard surfactant Tween 80, and providing support for further research in neuropharmaceutical applications. Plasma pharmacokinetic studies of RU following intravenous administration revealed notable differences between the drug solution and various LPHNP formulations. Likewise, the area under the curve (AUC_{0}–t) was highest for Solutol-LPH nanoparticles.

The investigation further indicated that lipid–polymer hybrid nanoparticles can substantially enhance the bioavailability and pharmacokinetic behaviour of RU. Time-dependent plasma concentrations of RU after intravenous administration of the drug solution (A) and RU-encapsulated LPH nanoparticles (B) in rats at 5 mg/kg were evaluated. The inset in panel (B) shows plasma RU levels between 4 and 48 hours, presented as mean ± SE (n = 6). The distribution of RU across different organs, including the brain (C), liver (D), spleen (E), and kidney (F), following intravenous injection of RU-loaded LPH nanoparticles in mice at 5 mg/kg, was also assessed. The highest AUC and Cmax in the brain. The bioavailability (Fr) of RU varied across tissues and formulations, with TPGS-LPH NPs showing a Fr of 1.13 in the liver, Solutol-LPH NPs showing a Fr of 0.94 in the liver, and Tween-LPH NPs showing a Fr of 2.26 in the liver. These findings suggest that the different LPH NPs formulations have distinct effects on the tissue distribution and bioavailability of RU [87].

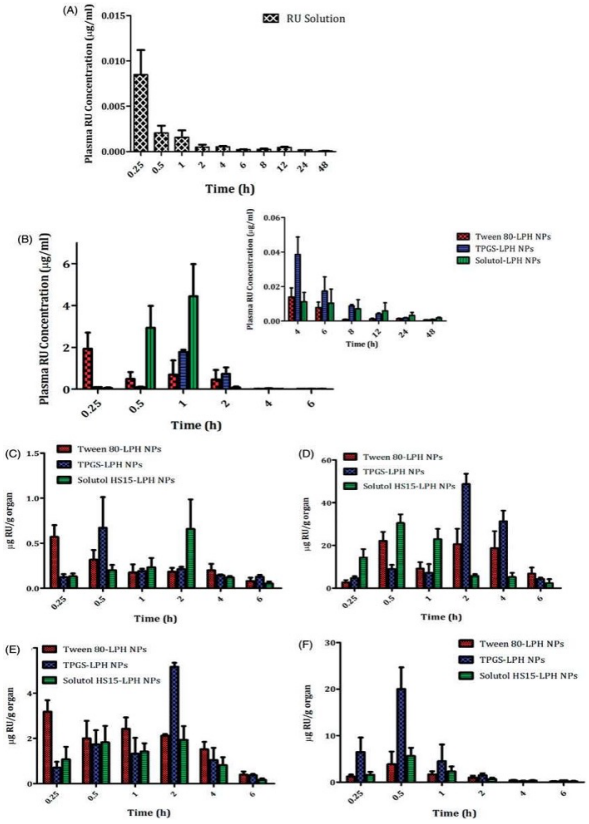


Figure 11. Time-dependent plasma levels of RU after intravenous delivery of the drug solution (A) and RU-encapsulated LPH nanoparticles (B) in rats at 5 mg/kg. The inset in panel (B) depicts plasma RU levels between 4 and 48 h. Values are reported as mean ± SE (n = 6). Distribution of RU in various tissues, including brain (C), liver (D), spleen (E), and kidney (F), following IV injection of different RU-loaded LPH nanoparticles in mice at 5 mg/kg. Data represent mean ± SE (n = 3). (87)

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