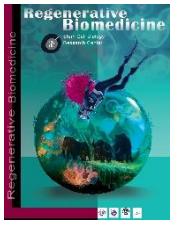

Regenerative Biomedicine

Production and Hosting: Shahid Sadoughi University of Medical Sciences

Journal homepage: jrb.ssu.ac.ir

Review Article

The Role of Phospholipid-Based Nanoparticles in Modern Cancer Treatment: Production, Applications, and Future Directions

Babak Arjmand[1*], Arian Emamifar[1], Mobin Mohammadi[2], Yekta Sadat Mirabedini[3], Ali Reza Mojavezi[1], Shayesteh Kokabi Hamidpour[3], Hamid Reza Aghayan[1]

1. Cell Therapy and Regenerative Medicine Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
2. Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran.
3. Iranian Cancer Control Center (MACSA), Tehran, Iran.

***Corresponding Author:**
Arjmand, Babak
Email:
barjmand@sina.tums.ac.ir

Received:
2025-02-24
Revised:
2025-04-13
Accepted:
2025-06-21

Volume:1
Issue no.3

Editor-in-Chief:

Behrouz Aflatoonian Ph.D.

Abstract

Cancer is regarded as the second leading cause of death globally. Over the past years, the growing prevalence of cancer has highlighted the need for innovative strategies to improve patient survival and enhance therapeutic effectiveness. In recent years, several novel approaches have emerged to improve cancer treatment with techniques including immunotherapy, targeted therapies, gene therapy, and nanotechnology. In this regard, nanotechnology has demonstrated potential in the field of medicine, especially in drug delivery, by allowing for the design and alteration of materials at the atomic and molecular levels. Nanoparticle-based therapies enhance the therapeutic efficacy of the drugs and reduce adverse effects by improving their distribution and bioavailability. Nanoparticles enhance drug retention in neoplasms, penetrate biological barriers, and enable more sophisticated targeted drug delivery. Among different types of nanoparticles, phospholipid–based nanoparticles are considered with the highest promise for biomedical uses. Phospholipid molecules are amphiphilic, which leads to possess both hydrophobic and hydrophilic regions. They are also a prominent part of cell membranes. Thus, the utilization of phospholipid nanoparticles enhances drug stability, prolongs circulation time, and enables controlled drug release. Phospholipid–based nanoparticles can be produced through variable methods that lead to various properties. However, challenges such as toxicity, changing features in the biological environment, and corona formation can disrupt the function of phospholipid–coated nanoparticles. Therefore, further research and exploration of phospholipid–coated nanoparticles can help access more precise, efficient, and patient-friendly cancer therapies.

Keywords: Cancer, Drug delivery, Nanotechnology, Phospholipid-Based Nanoparticles, PLNPs

How to cite this article:
Arjmand, B., Emamifar, A., Mohammadi, M., Miabedini, YS., Mojavezi, AR., Kokabi Hamidpour, SH., Aghayan, HR. The Role of Phospholipid-Based Nanoparticles in Modern Cancer Treatment: Production, Applications, and Future Directions. Regenerative Biomedicine, 2025; 1(3): 194-215.

Introduction

Cancer is a group of diseases that are characterized by uncontrolled cell proliferation (1). By 2050, it is predicted that there will be over 35 million new cancer cases which highlights a 77% increase compared to the statistics in 2022(2). The increasing prevalence of cancer globally necessitates the development of new therapeutic approaches to enhance treatment efficacy as well as improvement of patient survival rates (3). In cancer therapy, several innovations including immunotherapy, targeted therapies, personalized medicine, gene editing, and nanotechnology have been applied (4). Among these novel approaches, nanotechnology draws a great deal of attention, which involves using the atoms, molecules, or compounds at the nanometer level and giving special properties to them. As a result of their distinct size, nanoparticles exhibit new properties such as electrical conductance, chemical reactivity, magnetism, optical effects, and physical strength compared to their bulk counterparts (5).

The advancement of nanotechnology has penetrated several applications, such as tissue engineering, diagnosis, and drug delivery (6). Nanoparticle-based treatment can lead to improvements in patient survival, reduction of side effects of the treatment, maintenance of patient compliance, as well as better disease management and outcomes, particularly in cancer (1). Also, nanoparticles can enhance the distribution of drugs throughout the body, enhance permeability and retention (EPR) effects, and target specific cells using ligands or antibodies. Nanoparticles with high surface-to-volume ratios can overcome biological barriers, leading to improved bioavailability and therapeutic efficacy. Furthermore, nanoparticles can prolong the circulation half-life of drugs, and protect them from rapid degradation and elimination, while maintaining their therapeutic properties (7-12). Therefore, based on their unique properties, nanoparticles show promising applications in cancer diagnosis, treatment, and monitoring (13, 14). In biomedical applications, nanoparticles have to be hydrophilic and maintain superior stability in biological media (15). Therefore, the application of hydrophobic nanoparticles, such as inorganic nanoparticles, in biomedical sciences and engineering (e.g., gene and drug delivery and imaging) is limited due to their instability in aqueous environments and their capability to result in cytotoxicity (16, 17). Among nanoparticles, phospholipid-based nanoparticles (PLNPs) by improving bioavailability and targeting anticancer drugs play a crucial role in cancer treatment (18). Phospholipids as a natural component of cellular membranes have hydrophilic phosphatidylcholine (PC) head groups and hydrophobic hydrocarbon backbones. This characteristic facilitates the formation of various structures (19-21). The amphiphilic nature of phospholipids allows for the encapsulation of different kinds of molecules, whether hydrophilic in the inner aqueous compartment or hydrophobic in the lipid acyl chain region (22). The unique characteristics of phospholipids can improve permeability, controlled release, targeting efficiency, drug stability, versatility, prolonged circulation, and reduced toxicity (23). Considering the potential of phospholipids and the global impact of cancer, the application of PLNPs as a novel

approach to cancer management will be discussed.

Types of Phospholipid-based nanoparticles: A Brief Comparison

Phospholipid-based drug delivery methods have shown great promise in better and more successful delivery of drugs and ensuring more precise systemic drug delivery (24). The applications of phospholipids in drug delivery systems are versatile, as they serve as important components in a wide range of formulations, including liposomes, solid lipid nanoparticles (SLNs), micelles, vesicular gels, and etc. (25). As one of the types of PLNPs, Liposomes are vesicular structures primarily composed of phospholipids, resembling the structure of the cellular membrane (24). Liposomes were the first series of nanostructured drug delivery systems approved for cancer therapy (26). Research on the characteristics of liposomes has paved the way for the advancement of sophisticated drug delivery techniques utilizing liposomes structures. Also, numerous clinical trials have been conducted on liposomes, leading to the approval and commercialization of liposomal drugs such as DOXIL. Precisely, DOXIL delivers Doxorubicin and can be used as a therapeutic agent for breast and ovarian cancer (Supplementary table) (27-29). SLNs, the second group of PLNPs, have an uncomplicated design, their surface is easy to modify. They can encapsulate drugs and nucleic acid, making them suitable for specific drug and gene delivery. The third class is Lipid polymer hybrid nanoparticles (LPHNs). More precisely, LPHNs are a combination of liposomes and polymeric nanoparticles and can minimize the disadvantages of both. For example, liposome delivery can cause oxidation and peroxidation of lipids which the hybrid system can overcome (27). The major problem with LPHNs is their moderate plasma half-life. Nanostructured lipid carriers (NLCs) are the fourth type of phospholipid-based nanoparticles. As Liu et al. have stated, NLCs have some unique characteristics, like their ability to encapsulate multiple drugs and simply bind to specific ligands (30, 31). Finally, nano-emulsions are the last group mentioned, which are composed of oil, surfactant, and water-based phases. There is an amphiphilic emulsifier such as phospholipid that stabilizes the system formation. Nano-emulsions possess large surface area, enhanced circulation half-life, and superficial charge and are capable of passing through barriers due to their size and as a result, nano-emulsions can accumulate in cancer tissues (Fig. 1) (32).

Overall, phospholipid-based nanoparticles with the ability to enhance drug solubility, prolong circulation time, and target tumor cells can pave the way for more effective and patient-friendly cancer treatments.

Phospholipid-based Nanoparticles production

Phospholipids are used in drug delivery in mainly two ways: First, acting as the delivery substance themselves (e.g., liposomes) and second, acting as coatings for other nanoparticles (47, 48). Concerning the former, several methods are used to produce PLNPs. These nanoparticles include liposomes, SLNs, and NLCs (48). For liposomes, the methods commonly employed are the thin-film hydration method, ethanol injection, and microfluidic techniques in order to control their size and improve drug

loading (49). SLNs and NLCs are created using high-pressure homogenization, solvent evaporation, or ultrasonication, where phospholipids help stabilize the structure and control drug release (50).

As mentioned, due to the cellular membrane mimetic characteristic of phospholipids, they are used as coating components of other nanoparticles (51). Thus, besides forming the main structure of SLNs and NLCs (i.e., acting as the delivery substance themselves), phospholipids are also used to coat other types of nanoparticles (52, 53), which can be manufactured using multiple and various methods.

Phospholipid coated nanoparticles core Production Process

The production of PLNPs begins with the preparation of the core nanoparticles, then followed by the loading of the intended drug onto the core, and lastly the application of a phospholipid coating (54). The nanoparticle core can be constructed from various materials including lipids, polymers, or inorganic substances such as metal, ceramic, and semiconductor NPs (55). There are multiple production methods regarding the nanoparticle core. Lipid-based nanoparticle cores are manufactured using techniques that control lipid melting, emulsification, and particle size reduction (Table 1) (56). Concerning polymer nanoparticle cores, in general, two main strategies are employed, namely, the dispersion of preformed polymers and the polymerization of monomers (57). Once the nanoparticle core is synthesized, the next step involves encapsulating (i.e., loading) the nanoparticles with the therapeutic agent (drug, peptide, etc.) (Table 2) (58).

Capsulation Process

Encapsulation refers to the process of incorporating therapeutic agents into the nanoparticle structure. These nanoparticles can effectively encapsulate various types of drugs and exhibit enhanced stability and controlled release properties (48). Nanoencapsulation of therapeutic agents can be occurred through dissolving the therapeutic agent into the core material (e.g., lipid or polymer) before or during nanoparticle formation.

The encapsulation method can vary depending on the nature of the drug and the desired release profile (58). Techniques such as solvent evaporation, solvent diffusion, and salting-out are commonly used for drug encapsulation (Table 3) (70). During the process, the drug is either physically trapped within the nanoparticle matrix (as in nanoprecipitation or coacervation) or chemically bound to the lipid core, which influences the release kinetics and stability of the therapeutic agent. The engineered nanocarriers hold the potential to overcome significant limitations of traditional therapeutic products such as inadequate efficacy, susceptibility to enzymatic degradation, low bioavailability, and off-target side effects (71, 72).

Coating process

Coating refers to the addition of phospholipid layer(s) on the surface of the nanoparticle core. This step is crucial for improving the biocompatibility, stability, and targeted delivery of the nanoparticles (73). The coating of the nanoparticle surface by lipid layers (more specifically, phospholipid layers) emerged as a central step to guarantee nanoparticle colloidal stability in aqueous

solution and specific cell targeting functions (51). Phospholipids are the main components of cellular membranes and thus have excellent biocompatibility and are excellent candidates for the coating of medication-containing nanoparticles (51). The coating process typically involves hydrophilic and hydrophobic interactions between the lipid molecules and the nanoparticle surface. Once the core is prepared, phospholipids, often combined with surfactants or stabilizers like polyethylene glycol (PEG), are dissolved in organic solvents such as chloroform or ethanol (74). The coating process is generally initiated through self-assembly, where the phospholipids spontaneously form a lipid bilayer around the nanoparticle in an aqueous environment. Alternatively, the film hydration method can be employed wherein a thin phospholipid film is hydrated in the presence of the nanoparticle core that gives rise to the formation of a stable bilayer around the particle (9). The choice of phospholipids (such as phosphatidylserine or phosphatidylcholine) influences the particle's ability to interact with specific biological targets, such as diverse tumor cells (24). The coating may also be functionalized with additional molecules, such as PEG, to further enhance stability and extend the nanoparticles' residence time in circulation (75). In conclusion, the selection of specific phospholipids for nanoparticle coating plays an important role in deriving favorable therapeutic outcomes.

Isolation and Characteristics

The final step in the production process is the purification of the nanoparticles to remove unencapsulated drugs or excess phospholipids. On one hand, the formation of nanoparticles inherently results in higher heterogeneity due to the complex thermodynamics and kinetics involved. On the other hand, the size of nanoparticles affects their various features, such as bioavailability (76). Thus, isolation of the fabricated nanoparticles is necessary. Isolation can be conducted using multiple methods, which can be classified into two main categories: phase separation-based techniques and matter exchange-based techniques. Phase separation methods such as filtration and centrifugation rely on differences in size or density to separate nanoparticles. Matter exchange methods like dialysis and extraction work by transferring molecules or impurities through barriers using physicochemical phenomena like concentration gradients or partition coefficients (77). In addition, size exclusion chromatography could also be used to isolate nanoparticles by size (76).

After isolation, the nanoparticles are characterized for their size, shape, surface charge, encapsulation efficiency, and drug release profile. Size and morphology are usually determined using techniques such as dynamic light scattering (DLS), scanning electron microscopy (SEM), or transmission electron microscopy (TEM). The surface charge that is often measured as zeta potential is crucial for understanding the nanoparticles' stability and interactions with biological systems (78).

Accordingly, it can be deduced that the isolation and characterization of nanoparticles are vital steps in ensuring the purity, stability, and efficacy of the particles for targeted drug delivery applications.

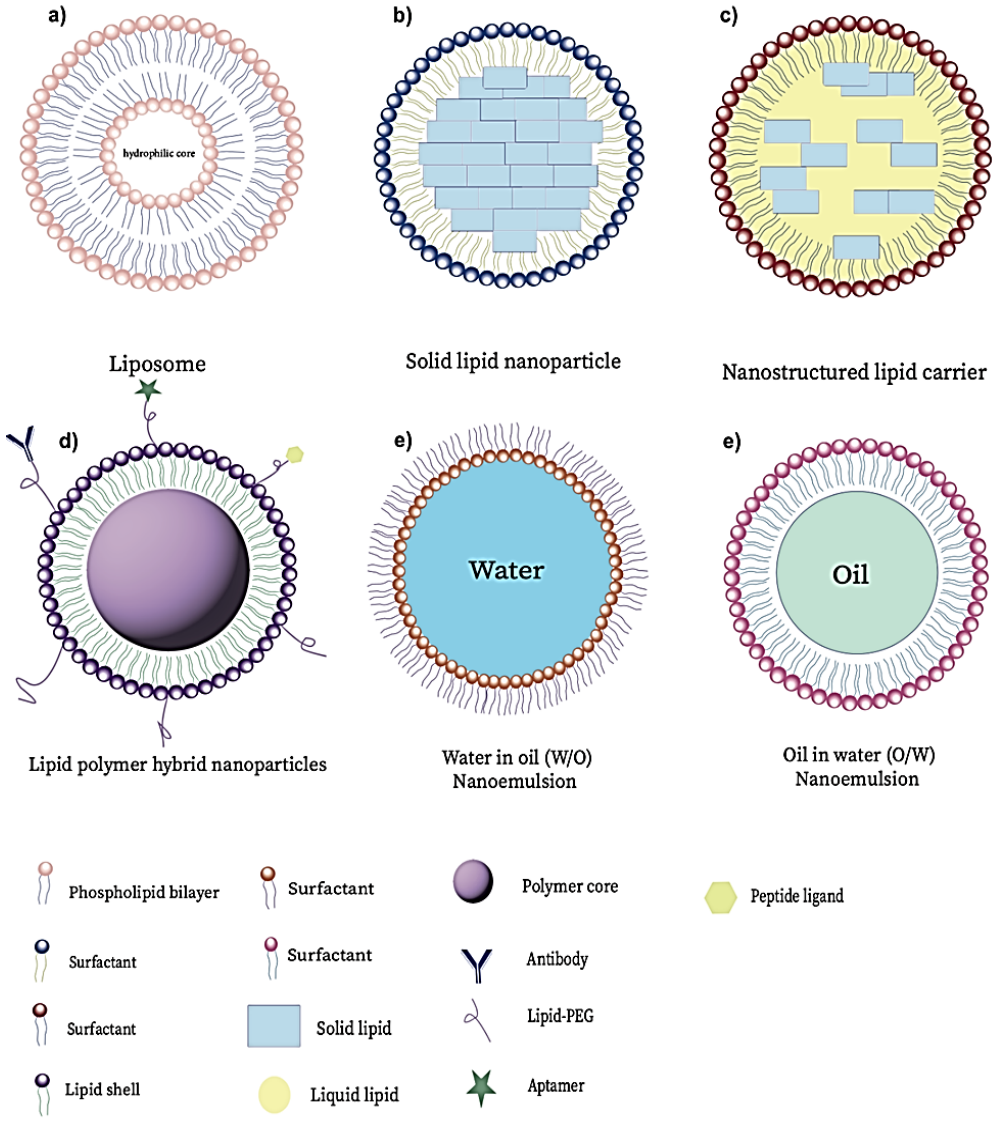

Figure 1. The general structure of the five types of phospholipid-based nanoparticles. (a) Liposomes consist of one or more lipid bilayers. They have a hydrophilic head and a hydrophobic tail, making them amphipathic. The phospholipid bilayer can be natural or engineered. (b) SLNs have a solid lipid core surrounded by a surfactant. The surfactant makes the core stable. The lipids maintain a solid form at both room and body temperature, and the drugs are embedded within the lipid layers. (c) NLCs comprise solid lipid and liquid lipid cores and surfactants as stabilizers. The solid lipid and liquid lipid ratio can vary from 70:30 to 99.9:0.1, and their combination generates an optimal system for drug incorporation. (d) LPHNs consist of a polymer core enclosed by a lipid monolayer and a lipid-PEG layer. Some targeting agents like antibodies and folate, can be attached to the lipid-PEG layer, and the drug is conjugated to the polymeric core. (e) Nanoemulsions are colloidal systems composed of oil, surfactant, and a water-based phase. In this system, one phase is distributed within another phase (known as the medium) using an emulsifying agent such as phospholipid. They are either water in oil or oil in water (32-38)(**Abbreviations:** Lipid-PEG, Lipid-Polyethylene glycol; LPHN, Lipid polymer hybrid nanoparticles; NLC, Nanostructured lipid carriers; SLN, Solid lipid nanoparticles;)

Table 1. Methods for preparation of lipid-based nanoparticles used by various researchers. (**Abbreviations:** High-Pressure Homogenization. HPH; Solid lipid nanoparticles, SLNs.)

Method	Brief Description	Ref.
HPH	A technique using high pressure (100–2000 bar) to break down particles by passing a liquid through a small gap. Hot-HPH uses elevated temperatures, while cold-HPH is performed below room temperature. Cold-HPH avoids the degradation of heat-sensitive drugs.	(59)
Oil/Water (o/w) Microemulsion Breaking	The method involves preparing a microemulsion by mixing lipid melt, drug, surfactant, and co-surfactant, then dispersing it in water at a low temperature (2–10 °C).	(60)
Solvent-Emulsification Diffusion	The lipid is dissolved in an organic solvent saturated with water and emulsified with water. Upon adding water, the organic phase diffuses into the continuous phase, forming lipid nanoparticles.	(5)
Solvent Injection Method	Lipids are dissolved in a water-miscible solvent and injected into a stirring aqueous solution. Key parameters include the nature of the solvent, lipid concentration, and diffusion of the solvent.	(61)
Water/Oil/Water (w/o/w) Double Emulsion	Used to prepare SLNs loaded with hydrophilic drugs. Hydrophilic drugs are dissolved in the inner phase, while lipids are in the organic phase, forming nanoparticles after diffusion of the organic solvent into the aqueous phase.	(62)
Ultrasonication	High-frequency sound waves are used for particle size reduction. Combined with homogenization, this technique produces SLNs with sizes ranging from 80 to 800 nm.	(62)
Supercritical Fluid Technique	Utilizes supercritical carbon dioxide to dissolve lipophilic drugs, combined with ultrasonication to prepare SLNs, typically for drug loading.	(63)

Membrane Contactor Technique	Lipid is pressed through a membrane at a temperature above its melting point, and water circulates beyond the pores, producing droplets that cool at room temperature to form SLNs.	(64)
Electrospray Technique	A novel method where electrodynamic atomization produces narrowly dispersed spherical SLNs of less than 1 µm, directly obtained in powder form.	(65)
Preparation of Semisolid Solid Lipid Nanoparticles	The lipid is melted and dispersed in a hot surfactant solution. After multiple cycles of dispersion and cooling, the formulation turns semi-solid as the lipid recrystallizes into SLNs.	(66)

Table 2. Methods for preparation of polymer nanoparticles conducted in studies.

Method	Brief Description	Ref.
Solvent Evaporation	Uses an oil-in-water (o/w) emulsion. A polymer is dissolved in an organic solvent with the drug and then emulsified in a surfactant-containing aqueous phase. The solvent evaporates, leaving solid nanoparticles.	(67)
Emulsification/Solvent Diffusion	A partially water-miscible solvent containing the polymer and drug is emulsified with an aqueous surfactant solution. Water is added to induce the solvent's diffusion, forming nanoparticles.	(57)
Emulsification/Reverse Salting-Out	It is similar to solvent diffusion but uses a salting-out agent (e.g., $MgCl_2$, $CaCl_2$) to separate the organic solvent from water, leading to polymer precipitation and nanoparticle formation.	(68)

Nanoprecipitation (Solvent Displacement)	A polymer dissolved in a water-miscible organic solvent is added dropwise into an aqueous phase under stirring, leading to instant nanoparticle formation due to polymer precipitation.	(69)

Table 3. Common methods regarding drug encapsulation

Method	Process	Ref.
Nanoprecipitation	Drug and polymer dissolved in a solvent, then added to a non-solvent, leading to nanoparticle formation	[35]
Emulsion-Solvent Evaporation	Drug and polymer dissolved in organic solvent, emulsified with aqueous phase, followed by solvent evaporation.	
Salting-Out	Uses a salting-out agent to precipitate the polymer, forming nanoparticles	
Supercritical Fluid Technology	Drugs and polymers are dissolved in a supercritical fluid (e.g., CO_2), then rapidly expanded to form nanoparticles.	
Coacervation	Phase separation of a polymer-rich phase encapsulates the drug.	

Application of phospholipid-based nanoparticles

Gene delivery

PLNPs like liposomes could be used to deliver genes specifically to cancer cells due to several factors (e.g., biocompatibility, stability, and tunable physicochemical properties). As nanocarriers for genetic tools, these nanoparticles have shown promise in addressing off-targeting and degradation problems common in traditional gene therapy methods, such as low transfection efficiency and poor stability in biological fluids. Moreover, the application of PLNPs has

greatly improved by incorporating various nucleic acid molecules, including short interfering RNA (siRNA), short hairpin RNA (shRNA), microRNA (miRNA), long noncoding RNA (lncRNA), and CRISPR/Cas9 (79). Also, new developments in nanotechnology have attracted more attention to how phospholipid vesicles can be used for gene therapy, drug delivery, biological detection, and cell mimics (80). As an example, using nude mice in a heterotopic tumor model showed that phospholipid-coated Ca(P-GDP)/pDNA/NLS hybrid nanoparticles were better at increasing the expression of the p53 gene. This, in turn, significantly slowed down the growth of tumors. Also, the results showed that phospholipid-coated Ca(P-GDP) nanoparticles, as a nonviral gene vector, have the potential to promote gene expression (81). Also, evidence has indicated that phospholipid chemistry can improve mRNA delivery by increasing membrane fusion and endosomal escape, which leads to more efficient gene delivery (82). Accordingly, it can be concluded that PLNPs can improve the efficacy of gene delivery and enhance the outcomes.

Imaging

Emerging as a promising tool in cancer imaging, PLNPs have shown the ability to enhance imaging contrast. Moreover, fluorescence imaging cystoscopy is a useful method for detecting cancer, but its application is limited due to its lack of specific tumor accumulation, vulnerability to photobleaching, and broad emission band. The resilience of fluorescence imaging cystoscopy for photobleaching, decreased background auto-fluorescence, and limited emission bands make upconversion nanoparticles (UCNPs) interesting. As an example, under 980 nm laser irradiation, the UCNPs boost up conversion luminescence from bladder cancer cells and show strong selective accumulation in cancer cells coated with a glycosylated phospholipid layer (83). Moreover, Indocyanine green (ICG) stands out as the only near infrared organic dye approved by the U.S. Food and Drug Administration (FDA) for human clinical imaging and diagnostic purposes. Although ICG exhibits the lowest toxicity to the human body compared to other approaches, its utilization has been limited by several challenges including temperature and light-dependent optical properties tendency to aggregate and degrade rapidly in an aqueous solution, and clearance rapidly from the body with a short half-life of 2 to 4 min. (84). To overcome these obstacles, nanoparticles and phospholipid coating can be applied. For instance, a nanoparticle consists of hydrophobic superparamagnetic iron oxide nanoparticles (SPIONs) as a core and lipid coating to facilitate the delivery of ICG. Also, the lipid-coated shell lets this nanoparticle carry Doxorubicin and enhances therapeutic efficacy alongside imaging capability. This structure leads to more accumulation of ICG and Doxorubicin within glioma cells (85). Furthermore, a new method has effectively developed folic acid ligand-conjugated lipid-coated polyaniline hybrid nanoparticles (FA-Lipid-PANI NPs), which show notable photothermal effects for tumor treatment and strong photoacoustic imaging signals. It has been revealed that the aforementioned nanoparticles can accurately position and eradicate tumors in vivo after intravenous injection. Accordingly, this multifunctional nanoparticle could play a crucial role in facilitating imaging and photothermal therapy, thereby improving therapeutic efficacy (86).

Hence, the use of phospholipid-based nanoparticles can be a promising approach to enhance the imaging techniques results and overcome some current limitations in this context (87).

Drug delivery

PLNPs can be used in cancer drug delivery due to their special characteristics (e.g., biocompatibility and biodegradability, improved drug solubility, and reduced systemic toxicity), which thereby can overcome the limitations of the traditional methods and enhance the drug delivery efficacy (88-92). Moreover, the mechanism of action in PLNPs (e.g., liposomes and micelles) is exploiting the Enhanced Permeation and Retention (EPR). to accumulate in tumor tissues due to their leaky vasculature and poor lymphatic drainage (89, 93). For instance, Abraxane® (albu LNPs min-bound PTX) is an example of a drug transport system that gathers in the tumor site via EPR. It must be considered that the EPR effect is affected by the nanoparticle's surface area and size. Conversely, in active targeting, the specific targets and molecules are identified, and as a result, the drug delivery will be enhanced. In active targeting, there are different kinds of ligands on the outermost surface of nanoparticles. Peptides, aptamers, antibodies, and small molecules are some examples of ligands coated on nanoparticles' surfaces (26, 43). Additionally, surface modification with ligands (e.g., antibodies, peptides) allows these nanoparticles to specifically bind to overexpressed receptors on cancer cells, enhancing targeted delivery and cellular uptake (94-96). Furthermore, different types of PLNPs can be used in drug delivery systems. For instance, liposomes (vesicles with a phospholipid bilayer that can encapsulate drugs in their aqueous core or lipid bilayer), micelles (formed by the self-assembly of phospholipids), and lipid-polymer hybrid nanoparticles (LPNs) (a hybrid class of nanoparticles aimed at combining the advantages of both polymeric nanoparticles and liposomes) each have their benefits that can further improve the drug delivery outcomes (93, 95-97).

Translating phospholipid based nanoparticles in cancer therapy

The limitations associated with traditional methods in cancer therapy such as drug resistance, recurrence, and side effects, lead to the development of more efficient approaches (98, 99). Among the new approaches, PLNPs as a practical approach can overcome many of the current obstacles. Due to their unique structural characteristics, they can transport both types of hydrophobic and hydrophilic drugs. Hydrophobic drugs can be loaded into the core, while hydrophilic biomolecules can be either loaded into the lipid layer or conjugated onto the surface. Furthermore, compared to polymeric nanoparticles, they can provide higher drug-loading capacities for hydrophobic drugs. They can provide stability to their cargo in the physiological environment and exhibit remarkably controlled drug release profiles due to the slow degradation rate of polymers in the core and the diffusional barrier of the lipid shell (97). To shed light on this, Letrozole an aromatase inhibitor is used in the treatment of estrogen-positive breast cancer. The poor solubility of Letrozole, its systematic adverse effect, and the development of resistance to aromatase inhibitors restrict its clinical application. Additionally, COX-2 inhibitors, especially celecoxib, interrupt the

cycle of PGE2 stimulating effect on estrogen production, and integrating them with letrozole demonstrates a synergistic effect on breast cancer therapy. In order to prevail over the limitations and develop multidrug treatment, a novel nanoparticle enveloping protamine nano capsules within the drug-phospholipid complex bilayer has been developed, which leads to the biphasic release of celecoxib. The initial release is induced by complexation with the phospholipid shell, followed by prolonged release from the oily core. Also, the phospholipid bilayer protects the core from red blood cells (RBC) and serum proteins, ensuring prolonged circulation and delayed clearance of both drugs after intravenous administration (100). Additionally, the simultaneous use of DOX and paclitaxel (PTX) is a first-line lung tumor treatment. The two drugs show different behaviors regarding their solubility in water and mechanism of action. DOX is a hydrophilic drug that binds to DNA or RNA to inhibit the synthesis of nucleic acids. In contrast, PTX is a hydrophobic drug targeting tubulin and inhibiting cell mitosis. To overcome this barrier, a lipid-coated hollow calcium phosphate (LCP) nanoparticle has been developed. In the LCP structure, the DOX was encapsulated in the hollow core while the lipid bilayer effectively houses hydrophobic PTX. This drug delivery approach demonstrates a better uptake of LCP by cancer cells with good biocompatibility of drugs despite their properties in the biological environment (101). Above their standard application, phospholipid nanoparticles can be combined with other methods to enhance their therapeutic performance. For instance, Camptothecin (CPT) is a type of quinoline that plays a crucial role in anticancer therapy by inhibiting nuclear topoisomerase I. Despite the significant efficacy of CPT in vitro, its clinical application is hindered by several problems such as enhanced binding to serum albumin and staying in its original lactone form in the acidic environment of the urinary tract, which can lead to renal damage. To overcome the challenges, a special nanocomposite was developed featuring a thin layer of 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and l-α-dipalmitoyl phosphatidyl glycerol (DPPG) in a 1:1 molar ratio on the surface of superparamagnetic Fe3O4 nanoparticles through high-affinity avidin-biotin interactions. Due to the incorporation of a mixture of DPPC and a negatively charged phospholipid (DPPG), the stability of the nanocomposite was enhanced. The lipid-coated structures maintain the active form of CPT inside cells. Additionally, when the coated nanoparticles are heated through a magnetic field, the release of CPT is increased, which enhances drug-induced apoptosis of cancer cells (102). Furthermore, Bevacizumab and Gefitinib are two medications that can be applied in the treatment process of non-small cell lung cancer (NSCLC). Bevacizumab is crucial in dampening angiogenesis, tumor growth, and metastasis by affecting vascular endothelial growth factor (VEGF). Also, Gefitinib, by inhibiting the epidermal growth factor receptor (EGFR), demonstrates its anticancer advantages. Based on the acidic properties of the NSCLC microenvironment and the disadvantages of traditional nano drug deliveries, such as the toxicity of Gefitinib to normal cells, a novel nanocomposite liposome has been developed. It is coated with PH (Potential of Hydrogen)/GSH(Glutathione)-responsive MnO_2 nanorods, along with Gefitinib and Bevacizumab. These particles

demonstrate enhanced biocompatibility and sustained release ability while also alleviating hypoxia characteristic of tumors by converting MnO_2 to Mn and reactive oxygen species (ROS) by H_2O_2 and GSH. Worthy to note that the release of the drug happens when the MnO_2 nonroad responds to the acidic microenvironment of the tumor, which helps in reducing side effects. Application of MnO2@Lipo-coated gefitinib and bevacizumab in patients can reduce drug dosage, prolong the time of drug action, lower side effects, and facilitate multiple drug therapy (103).

In conclusion, proper use of the unique structure of PLNPs can lead to the mitigation of the limitations associated with traditional therapeutic approaches and offer improved methods for drug delivery.

Advantages of Phospholipid-Based Nanoparticles

PLNPs represent a promising approach in cancer therapy, offering many advantages that overcome challenges faced by conventional therapeutic agents. They exhibit biocompatibility, high stability, the ability to combine both hydrophilic and hydrophobic materials in one system, and compatibility with different drug administration methods (104). Nanoparticle-encapsulated drugs provide a broader therapeutic range by shielding the cargo against changes. Also, nanoparticles morphological and surface characteristics can be tailored for different purposes. For example, PEG-modified nanoparticles can evade the mononuclear phagocytic system, and as a result, the drug concentration increases (105).

Nanoparticles enable receptor binding, and by using them, the active targeting of tumors is possible (106). Another advantage of PLNPs is the reduction in systemic toxicity by being extremely selective and allowing a gradual release of therapeutic agents (107). Additionally, the customized PLNPs can include responsiveness to specific stimuli and enable regulated drug release. For example, the recently created ionizable cationic lipids, used in liposomes and lipid nanoparticles (LNPs), respond to pH changes (105). As for the specific advantages of different types of PCNPs, liposomes are easily created, and their size, composition, and layered structure can be customized for different applications. Also, they can be loaded with various types of nanoparticles, so their range of possible applications increases (27).

SLNs can enter the biological membranes and increase the drug concentration in targeted sites by improving their penetration. NLCs can improve the drug loading capacity and enhance stability by blocking drug leakage from the nanocarriers during storage. By that, they can overcome the limitations of SLN (108). Their unique characteristics make PLNPs a potential platform for future drug delivery research and development, enabling more effective and safer treatments.

Challenges and limitations

PLNPS, such as liposomes and LNPs, have shown promise in cancer therapy due to their biocompatibility, ability to encapsulate both hydrophilic and lipophilic drugs, and potential for targeted delivery (109). However, several challenges and limitations hinder their clinical application (Table 4)(110).

Table 4. Phospholipid-based nanoparticles challenges in cancer therapy

Challenge	Description	Ref.
Stability and Scalability	Issues with stability, degradation, and complex preparation processes	(111)
Targeted Delivery	Difficulty in achieving precise targeting and effective tumor penetration	(111-113)
Biological Barriers	Challenges in crossing the blood-brain barrier and understanding nano-bio interactions	(114, 115)
Pharmacokinetics	Poor pharmacokinetics and bioavailability, drug resistance	(116, 117)
Clinical Translation	Regulatory hurdles, manufacturing challenges, and limited clinical success	(111, 112, 117)

Conclusion and future projection

In order to enhance the efficacy and mitigate the side effects of conventional treatment in cancer, attention has been paid to developing novel approaches (118). The application of PLPNs has emerged as a promising approach, which has now become a flexible and effective platform that can influence various aspects of cancer management including diagnosis and treatment (51). In cancer diagnostics, imaging methods like fluorescence imaging utilize agents to enhance imaging quality (119). Nonetheless, the effectiveness of these methods is hindered by the lack of specific tumor accumulation and the vulnerability of agents to photobleaching. Therefore, PLNPs have been integrated into delivering imaging agents. The improved stability of PLPNs in physiological environments and reduced toxicity, by loading agents into PLNPs facilitated safer imaging. Furthermore, the modifiable surface of PLNPs can lead to target specific cells and accumulate in cancer cells, thereby enhancing imaging accuracy(119). In treatment, several chemotherapeutic agents, such as PTX, are hydrophobic, and suffer poor solubility and limited effectiveness (120, 121). Compared to conventional drug delivery approaches, PLNPs offer a superior alternative by enhancing the biocompatibility of the cargo, leading to high stability in the physiological environment, and enabling the combination of both hydrophilic and hydrophobic materials within a single delivery system (122, 123). Beyond drug delivery, PLNPs can enhance

cancer treatment by delivering genetic materials. For instance, Small interfering RNA (siRNA) is a promising agent in gene silencing cancer treatment. However, its low charge density and stiff backbone structure decrease the loading efficiency and subsequent clinical applications. To overcome this obstacle, siRNA and phospholipid conjugate together. Above the enhancement in siRNA loading efficiency, this conjugation leads to embedding hydrophobic anticancer drugs (124). In addition to siRNA, the Oncolytic adenovirus have been promising in cancer treatment. In recent years, it has been indicated that the coating of adenoviruses with lipids and calcium phosphate reduces liver sequestration, improves targeted delivery, and increases therapeutic efficacy in vivo (125).

Notably, the application of PLNPs is not only in delivering medications but also in food fortification. For instance, adding iron to food can prevent anemia, but the instability of iron (Fe^{2+} turns into a different form of Fe^{3+}) often changes the taste of food. To reduce the effect of aforementioned modification, a special molecule called 1,2-bis(10,12-tricosadiynoyl)-sn-glycero-3-phosphocholine (DC8,9PC) has been developed. Following exposure to UV light, the DC8,9PC link together and create a stable particle that can prevent iron from transformation. In animal studies, this approach exhibits a reliable and cost-effective way of delivering iron to cells without any toxicity (126). On the one hand, iron insufficiency impaired immunological functions, potentially hindering cancer immunosurveillance, and altering the tumor immune microenvironment. On the other hand, the prevalence of iron deficiency in cancer patients particularly in those with colorectal cancer is high (127-129) . Therefore, the utilization of food enriched with iron particles encapsulated with phospholipid plays an important role not only as a treatment approach but also in managing anemia in affected individuals.

Besides the advantages of PLNPs, several challenges remain including potential nonspecific uptake, aggregation in biological environments, and immunogenicity (130). Additionally, complexities in formulation, stability issues, and regulatory obstacles disrupt their clinical applications (131). Nevertheless, PLNPs can be applied in personalized medicine for cancer treatment. To experience less harmful and more effective therapies, the combination of PLNPs with patient genetics is useful (132, 133).

Moreover, combining PLNPs with other therapeutic modalities, such as immunotherapy and radiotherapy, could improve treatment efficacy and overcome resistance mechanisms (134, 135). PLNPs are also quite helpful in cancer treatment since continual research is expected to generate innovative nanoparticle designs that improve drug loading, targeting, and release characteristics (136-138). Moreover, PLNPs present a fresh approach to cancer treatment with considerable potential for the next advancements. Realizing their complete potential in clinical cancer will need both overcoming current challenges and constant research and improvement.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Kumar N, Fazal S, Miyako E, Matsumura K, Rajan R. Avengers against cancer: A new era of nano-biomaterial-based therapeutics. Materials Today. 2021.

2. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. Ca. 2025 Jan 16;75(1):10. .

3. Falzone L, Salomone S, Libra M. Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. Frontiers in Pharmacology. 2018;9.

4. Gupta A. Advancements in Cancer Treatment: A Review of Emerging Therapies and Innovations. International Journal for Research in Applied Science and Engineering Technology. 2024.

5. Nikalje APG. Nanotechnology and its Applications in Medicine. Medicinal Chemistry. 2015;5:1-9.

6. Yatalaththov FG, Fadhlurrahman AG, Rahma AH, Fitri H. Current progress of nanotechnology in medicine: application in drug delivery, diagnostic, tissue engineering, and nanobots. Indonesian Journal of Pharmacology and Therapy. 2024.

7. Cho K, Wang X, Nie S, Chen ZG, Shin DM. Therapeutic Nanoparticles for Drug Delivery in Cancer. Clinical Cancer Research. 2008;14:1310 - 6.

8. Kadam RS, Bourne DWA, Kompella UB. Nano-Advantage in Enhanced Drug Delivery with Biodegradable Nanoparticles: Contribution of Reduced Clearance. Drug Metabolism and Disposition. 2012;40:1380 - 8.

9. Mishra D, Hubenak JR, Mathur AB. Nanoparticle systems as tools to improve drug delivery and therapeutic efficacy. Journal of biomedical materials research Part A. 2013;101 12:3646-60.

10. Pudlarz AM, Szemraj J. Nanoparticles as Carriers of Proteins, Peptides and Other Therapeutic Molecules. Open Life Sciences. 2018;13:285 - 98.

11. Sultana S, Khan MR, Kumar M, Kumar S, Ali MM. Nanoparticles-mediated drug delivery approaches for cancer targeting: a review. Journal of Drug Targeting. 2013;21:107 - 25.

12. Zade A, Shastri DA. Nanoparticle-Based Drug Delivery: Enhancing Bioavailability and Therapeutic Efficacy in Pharmaceutical Applications. Journal of Internal Medicine and Pharmacology (JIMP). 2024.

13. Alexiou A, Vairaktarakis C, Tsiamis V, Ashraf GM. Application of Efficient Nanoparticles for Early Diagnosis and Treatment of Cancer. Current drug metabolism. 2015;16 8:662-75.

14. Sell M, Lopes AR, Escudeiro M, Esteves B, Monteiro AR, Trindade T, Cruz-Lopes L. Application of nanoparticles in cancer treatment: a concise review. Nanomaterials. 2023;13(21):2887.

15. Fang C, Bhattarai N, Sun C, Zhang M. Functionalized nanoparticles with long-term stability in biological media. Small (Weinheim an der Bergstrasse, Germany). 2009;5(14):1637.

16. Pandey P, Dahiya M, editors. A BRIEF REVIEW ON INORGANIC NANOPARTICLES2016.

17. Luchini A, Vitiello G. Understanding the Nano-bio Interfaces: Lipid-Coatings for Inorganic Nanoparticles as Promising Strategy for Biomedical Applications. Frontiers in Chemistry. 2019;7.

18. Patil J, Pawde D, Bhattacharya S, Srivastava S. Phospholipid Complex Formulation Technology for Improved Drug Delivery in Oncological Settings: a Comprehensive Review. AAPS PharmSciTech. 2024;25 5:91.

19. Sun T, Sun Y, Zhang H. Phospholipid-coated mesoporous silica nanoparticles acting as lubricating drug nanocarriers. Polymers. 2018;10(5):513.

20. Simons K. Cell membranes: A subjective perspective. Biochim Biophys Acta. 2016;1858(10):2569-72.

21. Gillella S, Rishitha S, Divyanjali M, Amzad S, Anu B, Girish C, Apparao C. Lipid-Based Nanoparticles. Journal of Innovations in Applied Pharmaceutical Science (JIAPS). 2024:17-24.

22. Huang X, Li M, Bruni R, Messa P, Cellesi F. The effect of thermosensitive liposomal formulations on loading and release of high molecular weight biomolecules. Int J Pharm. 2017;524(1-2):279-89.

23. Sen O, Sarkar P, Das S, Giri NK, Sarkar S, Jana S, et al. Membrane Permeability and Drug Targeting Potential of Phospholipid-Based Nanocarriers in Lung Cancer Therapy. ChemistrySelect. 2024;9(40):e202403174.

24. Li J, Wang X, Zhang T, Wang C, Huang Z, Luo X, Deng Y. A review on phospholipids and their main applications in drug delivery systems. Asian Journal of Pharmaceutical Sciences. 2015;10(2):81-98.

25. Singh RP, Gangadharappa HV, Mruthunjaya K. Phospholipids: Unique carriers for drug delivery systems. Journal of Drug Delivery Science and Technology. 2017;39:166-79.

26. Alavi M, Hamidi M. Passive and active targeting in cancer therapy by liposomes and lipid nanoparticles. Drug Metabolism and Personalized Therapy. 2019;34(1).

27. Anwar DM, Hedeya HY, Ghozlan SH, Ewas BM, Khattab SN. Surface-modified lipid-based nanocarriers as a pivotal delivery approach for cancer therapy: application and recent advances in targeted cancer treatment. Beni-Suef University Journal of Basic and Applied Sciences. 2024;13(1):106.

28. Allen TM, Cullis PR. Liposomal drug delivery systems: From concept to clinical applications. Advanced Drug Delivery Reviews. 2013;65(1):36-48.

29. Barenholz Y. Liposome application: problems and prospects. Current Opinion in Colloid & Interface Science. 2001;6(1):66-77.

30. Liu Q, Li J, Pu G, Zhang F, Liu H, Zhang Y. Co-delivery of baicalein and doxorubicin by hyaluronic acid decorated nanostructured lipid carriers for breast cancer therapy. Drug Delivery. 2016;23(4):1364-8.

31. Rizwanullah M, Ahmad MZ, Garg A, Ahmad J. Advancement in design of nanostructured lipid carriers for cancer targeting and theranostic application. Biochimica et Biophysica Acta (BBA) - General Subjects. 2021;1865(9):129936.

32. Sánchez-López E, Guerra M, Dias-Ferreira J, Lopez-Machado A, Ettcheto M, Cano A, et al. Current Applications of Nanoemulsions in Cancer Therapeutics. Nanomaterials (Basel). 2019;9(6).

33. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: structure, composition, types, and clinical applications. Heliyon. 2022;8(5):e09394.

34. Wissing SA, Kayser O, Müller RH. Solid lipid nanoparticles for parenteral drug delivery. Advanced Drug Delivery Reviews. 2004;56(9):1257-72.

35. Khan S, Sharma A, Jain V. An Overview of Nanostructured Lipid Carriers and its Application in Drug Delivery through Different Routes. Adv Pharm Bull. 2023;13(3):446-60.

36. Gajbhiye KR, Salve R, Narwade M, Sheikh A, Kesharwani P, Gajbhiye V. Lipid polymer hybrid nanoparticles: a custom-tailored next-generation approach for cancer therapeutics. Molecular Cancer. 2023;22(1):160.

37. Kumar A, Singh AK, Chaudhary RP, Sharma A, Yadav JP, Pathak P, et al. Unraveling the multifaceted role of nanoemulsions as drug delivery system for the management of cancer. Journal of Drug Delivery Science and Technology. 2024;100:106056.

38. Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, Chourasia MK. Nanoemulsion: Concepts, development and applications in drug delivery. Journal of Controlled Release. 2017;252:28-49.

39. Feng T, Wei Y, Lee RJ, Zhao L. Liposomal curcumin and its application in cancer. Int J Nanomedicine. 2017;12:6027-44.

40. Tahir N, Madni A, Correia A, Rehman M, Balasubramanian V, Khan MM, Santos HA. Lipid-polymer hybrid nanoparticles for controlled delivery of hydrophilic and lipophilic doxorubicin for breast cancer therapy. International Journal of Nanomedicine. 2019;14(null):4961-74.

41. Sivadasan D, Ramakrishnan K, Mahendran J, Ranganathan H, Karuppaiah A, Rahman H. Solid Lipid Nanoparticles: Applications and Prospects in Cancer Treatment. International Journal of Molecular Sciences. 2023;24(7):6199.

42. Rajana N, Mounika A, Chary PS, Bhavana V, Urati A, Khatri D, et al. Multifunctional hybrid nanoparticles in diagnosis and therapy of breast cancer. Journal of Controlled Release. 2022;352:1024-47.

43. Mohanty A, Uthaman S, Park I-K. Utilization of Polymer-Lipid Hybrid Nanoparticles for Targeted Anti-Cancer Therapy. Molecules. 2020;25(19):4377.

44. Truong TH, Alcantara KP, Bulatao BPI, Sorasitthiyanukarn FN, Muangnoi C, Nalinratana N, et al. Chitosan-coated nanostructured lipid carriers for transdermal delivery of tetrahydrocurcumin for breast cancer therapy. Carbohydrate Polymers. 2022;288:119401.

45. Naseem N, Kushwaha P, Haider F. Leveraging nanostructured lipid carriers to enhance targeted delivery and efficacy in breast cancer therapy: a comprehensive review. Naunyn-Schmiedeberg's Archives of Pharmacology. 2025;398(1):449-68.

46. Nordin N, Yeap SK, Rahman HS, Zamberi NR, Mohamad NE, Abu N, et al. Antitumor and Anti-Metastatic Effects of Citral-Loaded Nanostructured Lipid Carrier in 4T1-Induced Breast Cancer Mouse Model. Molecules. 2020;25(11):2670.

47. Dumontel B, Rosso G, Cauda V. Natural and Artificial Phospholipid Bilayer Coatings on Solid-State Nanoparticles, Current and Future Perspectives. Nanomedicine. 2024;19(8):653-5.

48. Mehta M, Bui TA, Yang X, Aksoy Y, Goldys EM, Deng W. Lipid-Based Nanoparticles for Drug/Gene Delivery: An Overview of the Production Techniques and Difficulties Encountered in Their Industrial Development. ACS Materials Au. 2023;3(6):600-19.

49. Lombardo D, Kiselev MA. Methods of Liposomes Preparation: Formation and Control Factors of Versatile Nanocarriers for Biomedical and Nanomedicine Application. Pharmaceutics. 2022;14(3).

50. Naseri N, Valizadeh H, Zakeri-Milani P. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application. Adv Pharm Bull. 2015;5(3):305-13.

51. Luchini A, Vitiello G. Understanding the Nano-bio Interfaces: Lipid-Coatings for Inorganic Nanoparticles as Promising Strategy for Biomedical Applications. Front Chem. 2019;7:343.

52. Liu L, Pan D, Chen S, Martikainen M-V, Kårlund A, Ke J, et al. Systematic design of cell membrane coating to improve tumor targeting of nanoparticles. Nature Communications. 2022;13(1):6181.

53. Li J, Wei Y, Zhang C, Bi R, Qiu Y, Li Y, Hu B. Cell-Membrane-Coated Nanoparticles for Targeted Drug Delivery to the Brain for the Treatment of Neurological Diseases. Pharmaceutics [Internet]. 2023; 15(2).

54. Oh KS, Lee KE, Han SS, Cho SH, Kim D, Yuk SH. Formation of Core/Shell Nanoparticles with a Lipid Core and Their Application as a Drug Delivery System. Biomacromolecules. 2005;6(2):1062-7.

55. Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. Journal of Nanobiotechnology. 2022;20(1):262.

56. Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P, et al. A brief review on solid lipid nanoparticles: part and parcel of contemporary drug delivery systems. RSC Advances. 2020;10(45):26777-91.

57. Zielińska A, Carreiró F, Oliveira AM, Neves A, Pires B, Venkatesh DN, et al. Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology. Molecules. 2020;25(16).

58. Kumari A, Singla R, Guliani A, Yadav SK. Nanoencapsulation for drug delivery. Excli j. 2014;13:265-86.

59. Gardouh AR, Gad S, Ghonaim HM, Ghorab MM. Design and Characterization of Glyceryl Monostearate Solid Lipid Nanoparticles Prepared by High Shear Homogenization. Journal of Pharmaceutical Research International. 2013;3(3):326-46.

60. Simonazzi A, Cid AG, Villegas M, Romero AI, Palma SD, Bermúdez JM. Chapter 3 - Nanotechnology applications in drug controlled release. In: Grumezescu AM, editor. Drug Targeting and Stimuli Sensitive Drug Delivery Systems: William Andrew Publishing; 2018. p. 81-116.

61. Schubert MA, Müller-Goymann CC. Solvent injection as a new approach for manufacturing lipid nanoparticles--evaluation of the method and process parameters. Eur J Pharm Biopharm. 2003;55(1):125-31.

62. Naguib YW, Rodriguez BL, Li X, Hursting SD, Williams RO, 3rd, Cui Z. Solid lipid nanoparticle

formulations of docetaxel prepared with high melting point triglycerides: in vitro and in vivo evaluation. Mol Pharm. 2014;11(4):1239-49.

63. Akbari Z, Amanlou M, Karimi-Sabet J, Golestani A, Niassar M. Application of Supercritical Fluid Technology for Preparation of Drug Loaded Solid Lipid Nanoparticles. International Journal of Nanotechnology and Nanoscience. 2020;16:13-33.

64. Charcosset C, El-Harati A, Fessi H. Preparation of solid lipid nanoparticles using a membrane contactor. J Control Release. 2005;108(1):112-20.

65. Sridhar R, Ramakrishna S. Electrosprayed nanoparticles for drug delivery and pharmaceutical applications. Biomatter. 2013;3(3).

66. Abdel-Salam FS, Elkheshen SA, Mahmoud AA, Ammar HO. Diflucortolone valerate loaded solid lipid nanoparticles as a semisolid topical delivery system. Bulletin of Faculty of Pharmacy, Cairo University. 2016;54(1):1-7.

67. Desgouilles S, Vauthier C, Bazile D, Vacus J, Grossiord J-L, Veillard M, Couvreur P. The Design of Nanoparticles Obtained by Solvent Evaporation: A Comprehensive Study. Langmuir. 2003;19(22):9504-10.

68. Gökçe EH, Yapar EA, Tanrıverdi ST, Özer Ö. Chapter 14 - Nanocarriers in cosmetology. In: Grumezescu AM, editor. Nanobiomaterials in Galenic Formulations and Cosmetics: William Andrew Publishing; 2016. p. 363-93.

69. Zhuang J, Fang RH, Zhang L. Preparation of particulate polymeric therapeutics for medical applications. Small Methods. 2017;1(9).

70. Lammari N, Tarhini M, Miladi K, Louaer O, Meniai AH, Sfar S, et al. Chapter 14 - Encapsulation methods of active molecules for drug delivery. In: Chappel E, editor. Drug Delivery Devices and Therapeutic Systems: Academic Press; 2021. p. 289-306.

71. Gurevich EV, Gurevich VV. Beyond traditional pharmacology: new tools and approaches. British Journal of Pharmacology. 2015;172(13):3229-41.

72. Beck H, Härter M, Haß B, Schmeck C, Baerfacker L. Small molecules and their impact in drug discovery: A perspective on the occasion of the 125th anniversary of the Bayer Chemical Research Laboratory. Drug Discovery Today. 2022;27(6):1560-74.

73. Tong S, Hou S, Ren B, Zheng Z, Bao G. Self-assembly of phospholipid-PEG coating on nanoparticles through dual solvent exchange. Nano Lett. 2011;11(9):3720-6.

74. Liz-Marzán LM, Lado-Touriño I. Reduction and Stabilization of Silver Nanoparticles in Ethanol by Nonionic Surfactants. Langmuir. 1996;12(15):3585-9.

75. López-Estevez AM, Gref R, Alonso MJ. A journey through the history of PEGylated drug delivery nanocarriers. Drug Delivery and Translational Research. 2024;14(8):2026-31.

76. Robertson JD, Rizzello L, Avila-Olias M, Gaitzsch J, Contini C, Magoń MS, et al. Purification of Nanoparticles by Size and Shape. Scientific Reports. 2016;6(1):27494.

77. Tehrani SF, Bharadwaj P, Leblond Chain J, Roullin VG. Purification processes of polymeric nanoparticles: How to improve their clinical translation? J Control Release. 2023;360:591-612.

78. Yokoyama T, Masuda H, Suzuki M, Ehara K, Nogi K, Fuji M, et al. CHAPTER 1 - BASIC PROPERTIES AND MEASURING METHODS OF NANOPARTICLES. In: Hosokawa M, Nogi K, Naito M, Yokoyama T, editors. Nanoparticle Technology Handbook. Amsterdam: Elsevier; 2008. p. 3-48.

79. Yildiz SN, Entezari M, Paskeh MDA, Mirzaei S, Kalbasi A, Zabolian A, et al. Nanoliposomes as nonviral vectors in cancer gene therapy. MedComm. 2024;5(7).

80. Zhang N, Song J, Han Y. Research Progress of Phospholipid Vesicles in Biological Field. Biomolecules. 2024;14(12).

81. Jia N, Zhang X, Li W, Chen D, Hu H. Phospholipid-Coated Guanosine Diphosphate Auxiliary CaP Active Nanoparticles Can Systematically Improve the Efficiency of Gene Therapy for Cancer Disease. ACS Biomaterials Science and Engineering. 2020;6(4):2107-16.

82. Álvarez-Benedicto E, Farbiak L, Márquez Ramírez M, Wang X, Johnson LT, Mian O, et al. Optimization of phospholipid chemistry for improved lipid nanoparticle (LNP) delivery of messenger RNA (mRNA). Biomaterials Science. 2022;10(2):549-59

.

83. Sun B, Mullapudi SS, Zhang Y, Neoh KG. Glycosylated phospholipid-coated upconversion nanoparticles for bioimaging of non-muscle invasive bladder cancers. Microchimica Acta. 2022;189(9).

84. Ma Y, Tong S, Bao G, Gao C, Dai Z. Indocyanine green loaded SPIO nanoparticles with phospholipid-PEG coating for dual-modal imaging and photothermal therapy. Biomaterials. 2013;34(31):7706-14.

85. Shen C, Wang X, Zheng Z, Gao C, Chen X, Zhao S, Dai Z. Doxorubicin and indocyanine green loaded superparamagnetic iron oxide nanoparticles with PEGylated phospholipid coating for magnetic resonance with fluorescence imaging and chemotherapy of glioma. Int J Nanomedicine. 2019;14:101-17.

86. Wang J, Yan R, Guo F, Yu M, Tan F, Li N. Targeted lipid-polyaniline hybrid nanoparticles for photoacoustic imaging guided photothermal therapy of cancer. Nanotechnology. 2016;27(28).

87. Du J, Zhang Y, Jin Z, Wu H, Cang J, Shen Y, et al. Targeted NIRF/MR dual-mode imaging of breast cancer brain metastasis using BRBP1-functionalized ultra-small iron oxide nanoparticles. Materials Science and Engineering C. 2020;116.

88. Mirzaeinia S. Liposomes and Lipid Nanoparticles as Peritoneal Drug Delivery Systems. Exploring Drug Delivery to the Peritoneum2024. p. 51-77.

89. Paun RA, Jurchuk S, Tabrizian M. A landscape of recent advances in lipid nanoparticles and their translational potential for the treatment of solid tumors. Bioengineering and Translational Medicine. 2024;9(2).

90. Notabi MK, Arnspang EC, Andersen MØ. Antibody conjugated lipid nanoparticles as a targeted drug delivery system for hydrophobic pharmaceuticals. European Journal of Pharmaceutical Sciences. 2021;161.

91. Waheed I, Ali A, Tabassum H, Khatoon N, Lai WF, Zhou X. Lipid-based nanoparticles as drug delivery carriers for cancer therapy. Frontiers in Oncology. 2024;14.

92. Shaw I, Boafo GF, Ali YS, Liu Y, Mlambo R, Tan S, Chen C. Advancements and prospects of lipid-based nanoparticles: dual frontiers in cancer treatment and vaccine development. Journal of Microencapsulation. 2024;41(3):226-54.

93. Sawant RR, Torchilin VP. Multifunctionality of lipid-core micelles for drug delivery and tumour targeting. Molecular Membrane Biology. 2010;27(7):232-46.

94. Kazemi EK, Abedi-Gaballu F, Hosseini TFM, Mohammadi A, Mansoori B, Dehghan G, et al. Glimpse into the Cellular Internalization and Intracellular Trafficking of Lipid-Based Nanoparticles in Cancer Cells. Anti-Cancer Agents in Medicinal Chemistry. 2022;22(10):1897-912.

95. Irvine DJ. Drug delivery: One nanoparticle, one kill. Nature Materials. 2011;10(5):342-3.

96. Oliveira MS, Mendes LP, Torchilin VP. Targeted delivery of anticancer drugs: New trends in lipid nanocarriers. Nanostructures for Cancer Therapy2017. p. 455-84.

97. Krishnamurthy S, Vaiyapuri R, Zhang L, Chan JM. Lipid-coated polymeric nanoparticles for cancer drug delivery. Biomaterials Science. 2015;3(7):923-36.

98. Sen A, Kumar K, Khan S, Pathak P, Singh A. Current Therapy in Cancer: Advances, Challenges, and Future Directions. Asian Journal of Nursing Education and Research. 2024.

99. Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares LG. Current Challenges in Cancer Treatment. Clinical therapeutics. 2016;38 7:1551-66.

100. Elzoghby AO, Mostafa SK, Helmy MW, ElDemellawy MA, Sheweita SA. Multi-Reservoir Phospholipid Shell Encapsulating Protamine Nanocapsules for Co-Delivery of Letrozole and Celecoxib in Breast Cancer Therapy. Pharm Res. 2017;34(9):1956-69.

101. Wu C, Xu J, Hao Y, Zhao Y, Qiu Y, Jiang J, et al. Application of a lipid-coated hollow calcium phosphate nanoparticle in synergistic co-delivery of doxorubicin and paclitaxel for the treatment of human lung cancer A549 cells. International journal of nanomedicine. 2017:7979-92.

102. Allam AA, Potter SJ, Bud'ko SL, Shi D, Mohamed DF, Habib FS, Pauletti GM. Lipid-coated superparamagnetic nanoparticles for thermoresponsive cancer treatment. Int J Pharm. 2018;548(1):297-304.

103. Zhang J, Xu L, Hu H, Chen E. The combination of MnO(2)@Lipo-coated gefitinib and bevacizumab inhibits the development of non-small cell lung cancer. Drug Deliv. 2022;29(1):466-77.

104. Gelperina S, Kisich K, Iseman MD, Heifets L. The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis. Am J Respir Crit Care Med. 2005;172(12):1487-90.

105. Cheng Z, Fobian S-F, Gurrieri E, Amin M, D'Agostino VG, Falahati M, et al. Lipid-based nanosystems: the next generation of cancer immune therapy. Journal of Hematology & Oncology. 2024;17(1):53.

106. Yaghmur A, Østergaard J, Mu H. Lipid nanoparticles for targeted delivery of anticancer therapeutics: Recent advances in development of siRNA and lipoprotein-mimicking nanocarriers. Advanced Drug Delivery Reviews. 2023;203:115136.

107. Yingchoncharoen P, Kalinowski DS, Richardson DR. Lipid-Based Drug Delivery Systems in Cancer Therapy: What Is Available and What Is Yet to Come. Pharmacol Rev. 2016;68(3):701-87.

108. Ashfaq R, Rasul A, Asghar S, Kovács A, Berkó S, Budai-Szűcs M. Lipid Nanoparticles: An Effective Tool to Improve the Bioavailability of Nutraceuticals. Int J Mol Sci. 2023;24(21).

109. Battaglia L, Gallarate M. Lipid nanoparticles: state of the art, new preparation methods and challenges in drug delivery. Expert Opin Drug Deliv. 2012;9(5):497-508.

110. Omidian H, Gill EJ, Cubeddu LX. Lipid Nanoparticles in Lung Cancer Therapy. Pharmaceutics. 2024;16(5).

111. Sharma S, Chakraborty M, Yadav D, Dhullap A, Singh R, Verma RK, et al. Strategic Developments in Polymer-Functionalized Liposomes for Targeted Colon Cancer Therapy: An Updated Review of Clinical Trial Data and Future Horizons. Biomacromolecules. 2024;25(9):5650-69.

112. Furtado e Faria GN, Bhavsar D, Munshi A, Ramesh R. Lipid nanoparticles loaded with anticancer bioactives: state of the art. Cancer Therapy: Potential Applications of Nanotechnology2024. p. 423-79.

113. Takechi-Haraya Y, Goda Y, Sakai-Kato K. Control of Liposomal Penetration into Three-Dimensional Multicellular Tumor Spheroids by Modulating Liposomal Membrane Rigidity. Molecular Pharmaceutics. 2017;14(6):2158-65.

114. Cai X, Drummond CJ, Zhai J, Tran N. Lipid Nanoparticles: Versatile Drug Delivery Vehicles for Traversing the Blood Brain Barrier to Treat Brain Cancer. Advanced Functional Materials. 2024;34(41).

115. Yaghmur A, Østergaard J, Mu H. Lipid nanoparticles for targeted delivery of anticancer therapeutics: Recent advances in development of siRNA and lipoprotein-mimicking nanocarriers. Advanced Drug Delivery Reviews. 2023;203.

116. Manzari-Tavakoli A, Babajani A, Tavakoli MM, Safaeinejad F, Jafari A. Integrating natural compounds and nanoparticle-based drug delivery systems: A novel strategy for enhanced efficacy and selectivity in cancer therapy. Cancer Medicine. 2024;13(5).

117. El Moukhtari SH, Garbayo E, Amundarain A, Pascual-Gil S, Carrasco-León A, Prosper F, et al. Lipid nanoparticles for siRNA delivery in cancer treatment. Journal of Controlled Release. 2023;361:130-46.

118. Utreja P, Jain SK, Tiwary AK. Novel drug delivery systems for sustained and targeted delivery of anti- cancer drugs: current status and future prospects. Current drug delivery. 2010;7 2:152-61.

119. Sun B, Mullapudi SS, Zhang Y, Neoh KG. Glycosylated phospholipid-coated upconversion nanoparticles for bioimaging of non-muscle invasive bladder cancers. Microchimica Acta. 2022;189(9):349.

120. Boudou T, Kharkar P, Jing J, Guillot R, Pignot-Paintrand I, Auzely-Velty R, Picart C. Polyelectrolyte multilayer nanoshells with hydrophobic nanodomains for delivery of Paclitaxel. Journal of controlled release. 2012;159(3):403-12.

121. Yingchoncharoen P, Kalinowski DS, Richardson DR, Barker EL. Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. Pharmacological reviews. 2016;68(3):701-87.

122. Luchini A, Vitiello G. Understanding the nano-bio interfaces: Lipid-coatings for inorganic nanoparticles as

promising strategy for biomedical applications. Frontiers in chemistry. 2019;7:343.

123. Esim O, Hascicek C. Lipid-Coated Nanosized Drug Delivery Systems For An Effective Cancer Therapy. Current drug delivery. 2020.

124. Liu H, Li Y, Mozhi A, Zhang L, Liu Y, Xu X, et al. SiRNA-phospholipid conjugates for gene and drug delivery in cancer treatment. Biomaterials. 2014;35(24):6519-33.

125. Chen J, Gao P, Yuan S, Li R, Ni A, Chu L, et al. Oncolytic Adenovirus Complexes Coated with Lipids and Calcium Phosphate for Cancer Gene Therapy. ACS nano. 2016;10 12:11548-60.

126. Cheng J, Kenaan A, Zhao D, Qi D, Song J. Photo-polymerizable ferrous sulfate liposomes as vehicles for iron fortification of food. Nanomedicine: Nanotechnology, Biology and Medicine. 2020;30:102286.

127. Aksan A, Farrag K, Aksan S, Schroeder O, Stein J. Flipside of the coin: iron deficiency and colorectal cancer. Frontiers in immunology. 2021;12:635899.

128. Naoum FA. Iron deficiency in cancer patients. Revista Brasileira de Hematologia e Hemoterapia. 2016;38:325 - 30.

129. Phipps O, Brookes MJ, Al-Hassi HO. Iron deficiency, immunology, and colorectal cancer. Nutrition Reviews. 2020;79(1):88-97.

130. Percivalle NM, Carofiglio M, Conte M, Rosso G, Bentivogli A, Mesiano G, et al. Artificial and Naturally Derived Phospholipidic Bilayers as Smart Coatings of Solid-State Nanoparticles: Current Works and Perspectives in Cancer Therapy. International Journal of Molecular Sciences. 2022;23(24):15815.

131. Gandhi S, Shastri DH. Lipid-based Nanoparticulate Drug Delivery. Pharmaceutical nanotechnology. 2024.

132. Zhu J, Lee H, Huang R, Zhou J, Zhang J, Yang X, et al. Harnessing nanotechnology for cancer treatment. Frontiers in Bioengineering and Biotechnology. 2024;12.

133. Ghazal H, Waqar A, Yaseen F, Shahid M, Sultana M, Tariq M, et al. Role of nanoparticles in enhancing chemotherapy efficacy for cancer treatment. Next Materials. 2024;2.

134. Bhattacharya S, Beninger P. The Emerging Role of Cell Membrane-coated Nanomaterials in Cancer Therapy. Current Pharmaceutical Design. 2024;30(10):727-41.

135. Namiki Y, Fuchigami T, Tada N, Kawamura R, Matsunuma S, Kitamoto Y, Nakagawa M. Nanomedicine for cancer: Lipid-based nanostructures for drug delivery and monitoring. Accounts of Chemical Research. 2011;44(10):1080-93.

136. Kang JH, Ko YT. Lipid-coated gold nanocomposites for enhanced cancer therapy. International Journal of Nanomedicine. 2015;10:33-45.

137. Esim O, Hascicek C. Lipid-coated nanosized drug delivery systems for an effective cancer therapy. Current Drug Delivery. 2021;18(2):147-61.

138. Li Y, Zhang C, Min T, Ping Y, Li K. Lipid-Based Tumor-targeted Systems. New Nanomaterials and Techniques for Tumor-targeted Systems2020. p. 293-336.