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REVIEW

Lipid Nanoparticles as Theranostic Vesicle

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Abstract

Lipid nanoparticles (LNP) are the most well-studied first approved nanomedicine for drug delivery of therapeutic and vaccine formulation products. However, their nature is under constant investigation especially their liquid crystal state which leads to their complex biological behavior. LNPs are generally regarded as safe (GRAS) and suitable for ameliorating the toxicity and/or improving the pharmacokinetics of newly approved biomaterials with promising functionality and effects. During the past decade, many promising theranostic applications for LNPs have emerged resulting in huge potential for them in this field. Although there is progress in theranostic application, the gap between the bench and clinical application is undeniable, and that must be addressed to exploit the benefits of these nanomedicines for society.

Keywords: Theranostic, Vesicle, Lipid nanoparticle, Diagnosis, Therapy

1. Introduction

Diagnosis and treatment of diseases gain great advances in recent decades. To improve the safety and efficacy of the treatment, new delivery systems and therapeutic molecules are constantly discovered. For early detection of pathological states, novel diagnostic tools are being extensively investigated. However, the combination of the two fields can be applied synergistically in complex diseases for maximum efficacy [1].

Theranostic is a combination of diagnosis and therapy, which utilize the imaging technique for supervising targeted therapies for complex diseases in terms of efficacy and safety such as cancer. It also allows personalized therapy in vivo by real-time visualization and monitoring, to ensure the right dose at the right time, and to provide maximum safety with minimal risks [2].

The application of nanotechnology in theranostic is termed nano theranostic, it includes the concomitant delivery of a drug with an imaging agent. Some of the diagnostic tools include single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), ultrasound (US), and computed tomography (CT), while the therapeutic strategy is directed toward chemotherapy, ultrasound (US), photothermal therapy (PTT), sono-dynamic therapy (ST), photodynamic therapy (PDT). Nonotheranostic is considered a precise and personalized tool, that provides rational and effective management of complex diseases [3,4].

Biomaterials are naturally occurring, semi-synthetic, or chemically synthesized materials to be applied in biological organisms as medicinal and pharmaceutical products. A biomaterial either alone or in a complex system such as lipid-based, polymer-based, inorganic, or viral nanoparticles, can direct the therapeutic and diagnostic effect by interaction with a living system. Nanotheranostic can be applied to a wide range of complex diseases such as neurological disorders, cardiovascular diseases, pulmonary diseases, cancer, etc. [5].

This review is aimed at summarizing and presenting the latest technologies of lipid-based nanoparticle integration for concurrent diagnosis and disease treatment.

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Table 1. Functionalized phospholipids commonly utilized.

Molecule	Application
PEG-5000	Stealth nanoparticle
PEG-2000-MAL	Thiol-reactive lipid for conjucation
hexanoylamine	Mitochondrial targeting
DNP ((2,4-dinitrophenyl)	Anti-genic nanoparticlecle
CF (carboxyfluorescein)	Fluorescent nanoparticles

1.1. Lipid nanoparticles and mixed nanosystems

LNP represents one of the major categories for the delivery of therapeutic and diagnostic molecules, due to its safety, biodegradability, biocompatibility, mimic natural and physiological components, and ability to incorporate both lipophilic and hydrophilic molecules. LNP represents liposome, nanoemulsion, noisome, transferosome, nanostructured lipid carrier, solid lipid nano-particle, lipid-based micelles, and the hybrid system of this class of nanoparticle [6].

LNP is composed of lipids (fats and oil) and surfactants, with the components, are usually self-assembled into a liquid crystalline phase, that represents a metastable and complex phase that is essential to the system function, as shown in table (1). The most advanced one is that of cationic ionizable lipids with a pka below 6.5 and so they are charged during development and non-charged at physiological pH. This class has been used recently during the development of COVID-19 by forming a complex when genetic materials (mRNA or siRNA) are mixed with them. The mRNA vaccine uses a cation ionizable lipid for genetic material complexation as well as a pegylated lipid for providing stealth stability [7].

The advanced nanosystem also has functionalities to respond to different external or physiological stimuli such as magnetic field, alterations, and heat that after stimulus transduction leads to changes in membrane integrity and size, so releasing the encapsulated contents [9].

As a theranostic tool, LPN will enhance the safety, efficacy, and pharmacokinetics of therapeutic and imaging agents, making them suitable for concurrent diagnosis, while circumventing the biological difficulties by functionalization a targeting moiety to achieve specific cell and tissue targeting. Their advantages include the absence of toxicity, versatility, high degree of encapsulation of both lipophilic and hydrophilic moieties, simple and easily scale-up production process, generally regarded as safe (GRAS) due to the presence of their component in food products as well as in the human body, and enhance bioavailability [10].

Liposomes represent the prominent type of LNP, which consists primarily of phospholipids. The amphiphilic nature of liposomal lipids enables the encapsulation of both lipophilic and hydrophilic molecules, at the same time surface functionalization is easily achieved by physical or chemical modification of their lipids during the self-assembly process [11].

Since their approval by FDA in 1995 as the first nano-drug delivery system, liposomes offer several advantages including biocompatibility, tunable drug release, high biological stability, and high encapsulation efficiency for therapeutic and diagnostic moieties making them attractive tools for theranostic purposes [12,13].

1.2. Theranostic applications of lipid-nano particles

The most recent examples of LNP as s trends in nano-theranostics include the following.

1. Quantum Dots

QDs are nano semiconductor particles with a size between 1 and 10 nm that have different electronic and optical properties from bulk materials because of their quantum mechanics. The QDs have many applications in luminescence, electronics, and disease diagnosis with several advantages like narrow emission spectrum, and broad absorption spectrum making them suitable for diagnosis. However, their toxicity and lack of biocompatibility can limit their human uses, which can be solved by using lipid nanoparticles for diagnostic or theranostic purposes [14].

Seleci et al., developed a liposome with core-incorporated topotecan and surface modified with CdSe/ZnS QDs. These nanoparticles were effective as delivery tools for therapeutic and diagnostic molecules, as evident by flow cytometry and fluorescence microscopy [15].

2. Inorganic nanoparticles

The combination of LNP technology with the inorganic nanoparticles results in a hybrid technology that allows diagnosis and treatment. The hybrid technology has been developed to overcome certain limitations of the inorganic nanoparticles such as solubility and toxicity and combine the advantages of both classes. The hybrid technology offers a solution for the delivery of the inorganic nanoparticles that can be incorporated in the aqueous pore, inside the membrane, or attached to the surface, depending on

the effect and desired function required. Some candidates for this technology include palladium, silver, gold, and superparamagnetic iron oxide [16].

Wereszczynska and Zalewski use a liposomal formulation consisting of fatty acid combined with gadolinium and zinc phthalocyanine for concurrent cancer diagnosis and treatment. Gd acts as an MRI contrast agent and ZnPc as a photosensitizer that can alter dynamic and liposomal membrane structure [17].

3. Photodynamic (PDT) and photothermal therapy (PTT)

PDT uses a photosensitizer agent for tumor elimination, that becomes excited after light irritation to produce free radicals, reactive oxygen species, singlet or triplet oxygen, and so oxidizing cell components, vascular damage, inflammatory and immune response, and cell ablation. The main clinical limitations associated with this type of therapy include lack of specificity and targeting, short half-life, lipophilicity, and tolerance to and resistance of some tumors to the effect of ROS by upregulation of glutathione. These limitations can be addressed by using LNP technology by stabilizing and solubilizing PS, targeted delivery, and co-delivery with other diagnostic and therapeutic molecules [18].

PTT uses a photothermal agent as the non-invasive type of therapy such as small organic dyes, inorganic nanomaterials, and metal nanoparticles that generate hyperthermia under near IR irradiation causing cancer cell death. However, it may cause serious injuries and pain to patients that may be addressed by using NSAIDs or incorporation of these agents using an NLP that offers a better solution [19].

Panikar et al., by using Na YF4:Yb, Er nanoparticle to complex photosensitizer agent methylene blue and encapsulation the complex inside a liposome. Resulting in active targeting and enhanced ROS generation and so better photophysical properties [20].

4. Cell membrane

The cell membrane can be utilized as an effective delivery tool for bioactive agents and it represents the next step in terms of biological stability and biocompatibility. Cell membrane-based nanoparticles are nanohybrids combining the advantages of bio-functionality and biomimicry, and can interact with complex biological microenvironments. In this technology the proteolipid vesicle act as a "Trojan horse" by carrying drug or imaging molecules. CB-based nanoparticles represent a new class of DDS

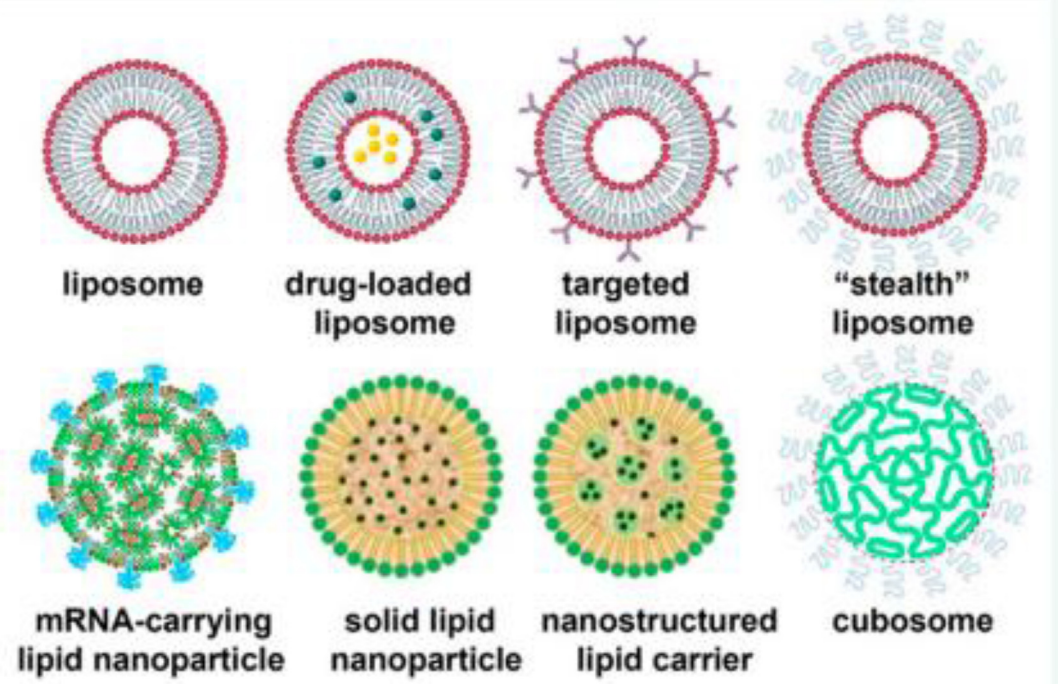

Figure 1. Different types of lipid nanoparticles (LNP) [8].

with unique functional and biomimetic properties of cell membranes and the versatility of synthetic nanomaterials [21].

Depending on the target and applications, the cell membrane may originate from red or white blood cells, cancer cells, mesenchymal stem cells, platelets, and neutrophils each having its advantages. For instance coating with cancer cells will enhance tumor affinity, and circulation time and facilitate theranostics applications. The most important advantage of this class of DDS is the ability to escape the immune system, enhanced circulation time, EPR, and tumor targeting [22].

Li et al., developed and designed a bioreactor for concurrent PDT and tumor cell starvation, to improve the anticancer treatment by deprivation of metabolic and nutrient supply pathways of tumor cells. These effects can be achieved by incorporation inside the porphyrin MOF porous network with glucose oxidase and catalase molecules that can be engulfed by cancer cells. After internalization inside cancer cells decomposition of intracellular glucose and increase cytotoxic singlet oxygen effect under light irradiation. Resulting in enhanced long-term synergistic cancer starvation [23].

Chem and co-workers developed PLGA nanoparticles that can be incorporated inside a polymeric network and be coated by cancer cells for better tumor targeting, imaging, and photothermal properties, that can facilitate targeting, tumor endocytosis, and accumulation [24].

1.3. Theranostic application of lipid nanoparticles

Despite the FDA approval of liposomes, there is no theranostic approval despite the extensive research on lipid nanoparticles yet has been approved. Lipids as biocompatible, GRAS with minimal toxicity have been used to alleviate toxicity associated with certain chemotherapeutic molecules for the preservation of the safety and efficacy of these agents, requiring LNP to have sufficient encapsulation of them with minimal biological interaction. During the development of nanosystems, the extreme concern is focused on particle clearance and metabolism, immunologic reaction, potential toxicity biodistribution, and protein binding. New tools are required to evaluate the biological and self-assembly properties of LNP, since their chaotic nature, with their fundamental properties, is under controllable and no-controllable factor. A limited translation of the LNP product to the market is related to the lacking of specific guidelines and the gap between regulation and science [25,26].

2. Conclusion

The development of LNP application and technology provides a multifunctional and complex nanosystem that attracts great attention for using them as a vector to develop the COVID-19 vaccine as industries are now having much more experience in the evaluation and production of them. However, till now the limited approval of nano theranostic for human use is related to the limited regulatory guidance on the efficacy and safety standards. Regarding this point, many studies can be utilized to improve and alter therapeutic and disease outcomes to pave a new way for the development of personalized remedies. LNP is a biocompatible and versatile class of nanoparticles, they are a safe choice for nano theranostic development (see Fig. 1).

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