



A Review on Lipid-Polymer Hybrid Nanoparticles for Combinatorial Drug Delivery

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ABSTRACT

The lipid polymer hybrid nanoparticles have revolutionized the field of nanomedicine through its advantageous features of both the polymeric nanoparticles and liposomes. They exhibit high stability, biocompatibility, selective targeting, prolonged circulation time, greater drug encapsulation efficiency, and significant biological response. These unique properties enable them to be potentially applied in the field of drug and gene delivery.

Keywords: Nanoparticles, nanomedicine, biocompatibility, gene delivery.

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INTRODUCTION

The development of nanotechnology in the field of drug delivery has improved the pharmacokinetics of a number of poorly soluble and poorly permeable drugs. During the past few decades, numerous nanoparticulate drug delivery systems have been approved for clinical use. The various nanocarriers for drug delivery include polymeric nanoparticles, liposomes, micelles, solid lipid nanoparticles, nano-structured lipid carriers, dendrimers, carbon nanotubes, etc.¹

Among them, polymeric nanoparticles and liposomes are the most dominant nanocarriers for drug delivery. Polymeric nanoparticles are the colloidal systems ranging in the nanometric size. They can be composed of either biodegradable or non-biodegradable polymers. The implementation of amphiphilic polymers led to the formation of nanoparticles with hydrophobic core and hydrophilic shell. The polymeric nanoparticles permit higher drug loading and also provides controlled drug release kinetics. They could also be tailored to furnish a variety of surface decorated nanoparticles for enhancing their physicochemical properties. Polymeric nanoparticles can be synthesized by a number of techniques on the basis of the types of drugs to be encapsulated and their application. Several polymeric nanoparticles have been approved for clinical use such as Genexol-PM, a nanoparticulate formulation comprising of paclitaxel and poly (d,l-lactide)-b-polyethylene glycol-methoxy,

approved for metastatic breast cancer therapy. On the other hand, liposomes are spherical vesicles composed of lipid bilayer made up of either natural or synthetic amphiphilic lipid molecules. They are extensively employed for drug delivery owing to their ease of fabrication methods, favorable safety profile, amenable to surface modification, and long systemic circulation half-life. Numerous drug loaded liposomal formulations have been approved for clinical use including AmBisome (amphotericin B liposomes), DepoCyt (cytarabine liposomes), DepoDur (morphine liposomes), and DaunoXome (daunorubicin liposomes)¹.

DESIGNING OF NANOPARTICLES

Factors that affect the clearance and biodistribution of nanoparticles, such as particle physicochemical properties and targeting ligand functionalization, should be carefully considered for the optimal design of therapeutic nanoparticles.

Size

Size is an important parameter on the basis of physiological parameters such as hepatic filtration, tissue extravasation/diffusion, and kidney excretion. Nanoparticles smaller than 10 nm can be rapidly cleared by the kidneys or through extravasation, while larger nanoparticles may have higher tendency to be cleared by cells of the mononuclear phagocyte system (also referred as reticuloendothelial system, RES) To capitalize on the enhanced permeability and retention effect and to efficiently escape from the physiological barriers, many studies show that the optimal nanoparticle size range of approximately 10–250 nm.²

Surface Charge

It has been established that the surface charge of nanoparticles also can affect their uptake by the mononuclear phagocyte system (MPS) cells. Neutrally



charged particles have demonstrated much lower opsonization rates than charged particles. It was found that positively charged nanoparticles generate a higher immune response compared to that of neutral or negatively charged nanoparticle formulations. Davis *et al.* in a study has proposed that the optimal range of nanoparticle surface charge should be between -10 and $+10$ mV for reduced phagocytosis and minimized nonspecific interactions of nanoparticles.²

PE Gylation

Surface modification of nanoparticles with PEG, with favorable intrinsic physicochemical properties, was found to reduce nanoparticle accumulation in off-target organs such as liver and spleen. A PEG shell on the nanoparticle surface shields hydrophobic or charged particles from being attached to blood proteins, leading to prolonged circulation half-life. Based on the PEG density there is two type of configurations 'mushroom' and 'brush'. It has been stated in studies that the brush configuration would create more effective blocking or repulsion of opsonins than the mushroom one.²

Ligand Functionalization

The conjugation of targeting ligands to the surface of PE Gylated nanoparticles has shown to affect the biodistribution. Although targeting ligands could improve the cell or tissue-specific delivery of nanoparticles, they may compromise particle's surface properties by masking the PEG layer and adversely affecting the nanoparticles' anti-biofouling properties in vivo. The successful development of targeted nanoparticle technology for efficient drug delivery depends on striking a balance between cellular targeting and immune evasion.²

Targeting Ligands

An essential aspect for the successful development of targeted nanoparticles depends on the choice of targeting ligands. Several variables that could be considered include ligand biocompatibility, cell specificity, binding affinity, and purity of the ligand. Other important factors that have to be considered are the size and charge of the ligand molecule and their ease of modification and conjugation to the nanoparticles. The five different classes of targeting ligands, includes antibodies and antibody fragments, aptamers, peptides, sugars, and small molecules.²

PHYSICOCHEMICAL CHARACTERISTICS

Interaction and mechanism of hybrid particle formation

Different mechanisms of lipid-polymer hybrid particle formation can be distinguished based on the method of preparation. In the single step method, polymer particle formation involves the precipitation of the polymer from an organic solution and the diffusion of the organic solvent in an aqueous medium. Then, the lipid molecules self-assemble spontaneously by hydrophobic interaction on the polymeric particle surface to form a monolayer.

The mechanism of hybrid particle formation in the two-step method the process occurs in two steps. First, after forming a bilayer of phospholipid in aqueous solution it attaches to the polystyrene particle surface by adsorption to form homo dispersed and stable phospholipid vesicle-covered particles. Second, after bilayer attachment, hydrophobic attractions between the polystyrene surface and hydrocarbon chain of the phospholipid bilayer results in the collapse of the bilayer structure and leave a monolayer covering the polymer particle. In the process, the lipid and polymer contact is favored by forces like electrostatic interactions, hydrophobic attractions, or van der Waals forces. The input of external energy such as heating, sonication, or agitation aids to rearrange lipids onto the polymer particles. Surface charges play a major role in forming the lipid layer onto polymer particles. Stable particles are formed by electrostatic interactions between a negatively charged polymer and a cationic lipid. Moreover, the affinity of the phospholipid for polymer particle depends on the hydrophilicity of the polystyrene surface. Surface hydration of the polystyrene particles can shield the attractive forces and decrease affinity for the lipid monolayer coverage.²

Structure

Polymeric particle's morphology, two-dimensional fluidity, lipid shell permeability, and distribution of lipids have been assessed using confocal laser scanning microscopy and cryo-transmission electron microscopy (Cryo-TEM). Lipid composition and its concentration play a significant role in the formation of various structures of hybrid nanoparticles. Thus, the presence of excess lipid during the preparation leads to the formation of multilamellar lipid coatings on the particle or may form free liposomal vesicles.²

Stability

The phospholipids that constitute the shell of the hybrid nanoparticles may act as surfactants to stabilize the hybrid nanoparticle. Four major factors that affect the colloidal stability of lipoparticles have been so far identified, pH and ionic strength of the aqueous medium, temperature, curvature of radius of lipoparticles, and vesicle-to-particle ratio.

Lipoparticles usually tends to become unstable with an increase in ionic strength of the continuous phase. The adsorption of lipid onto polymer particle is affected by its incubation temperature. When incubation occurs at a temperature (T) below glass transition temperature (T_g), the entire vesicle adheres onto particles without rupturing. However, when T is greater than T_g , lipid reorganization onto the polymeric particle is accelerated. Small vesicles having a higher curvature radius tend to coat the smaller polymer particles. One approach to improving the colloidal stability is by creating steric repulsions between particles after incorporating a lipid-PEG conjugate into the formulation. Another approach to improve the colloidal



stability is to incorporate suitable amounts of additional surfactants along with the phospholipids.²

Drug loading and entrapment efficiency

A reason for poor drug loading (DL) and entrapment efficiency (EE) in hybrid nanoparticles is the presence of excess lipids that can form vesicles by entrapment or adsorption of the drug either by hydrophobic interactions and/or by hydrogen bonding. Moreover, during purification, these vesicles are washed away, leading to drug loss.

Various techniques exist for loading the drug into hybrid nanoparticles (HNs). The drug can be loaded into both the polymeric core and the lipid shell, thereby increasing the total drug payload, or two different drugs can be loaded into the core and the shell. The most commonly used strategy is to incorporate the drug into core production or lipid film formation. Another option is by adsorbing or absorbing the drug in the cores and lipid vesicles separately before combining to form HNs. However, the DL is generally expected to be better in the incorporation approach than the adsorption approach. The macromolecules or proteins show highest loading efficiency near their isoelectric point when they have minimum solubility and maximum adsorption. For smaller molecules, using ionic interactions between the drug and polymer can be an effective way to increase drug loading.²

The plausible advantages of nano-carriers:³

- Improvement to a drug's overall pharmacokinetic and Pharmacodynamic properties without an Alteration of its molecular structure;
- Enhanced effective tissue targeting,
- Cellular targeting, and molecular targeting;
- The ability to circumvent many inherent biological impediments; targeted and nontargeted drug delivery to their respective site of action (cytosol, nucleus, etc).
- Enhanced therapeutic index of the drug;
- Delivery of multiple drugs with differing chemical properties.

CONCLUSIONS

The lipid polymer hybrid nanoparticles have revolutionized the field of nanomedicine through its advantageous features of both the polymeric nanoparticles and liposomes. They exhibit high stability, biocompatibility, selective targeting, prolonged circulation time, greater drug encapsulation efficiency, and significant biological response. These unique properties enable them to be potentially applied in the field of drug and gene delivery. However, most of the current researches on LPHNPs have been restricted to its in vitro efficacy. Their translation into effective therapeutics is still in its infancy and several challenges in this field are yet to be resolved. The key areas which need to be focused include their stability, safety, toxicity, pharmacokinetic profiles, optimization of the targeting ligands, and in vivo fate. The future warrants the implementation of drug delivery vehicles which mimic the lipid enveloped biological structures to promote the development of combinational therapy.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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