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Review

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Core–shell-type lipid–polymer hybrid nanoparticles as a drug delivery platform

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Abstract

The focus of nanoparticle design over the years has evolved toward more complex nanoscopic core–shell architecture using a single delivery system to combine multiple functionalities within nanoparticles. Core–shell-type lipid–polymer hybrid nanoparticles (CSLPHNs), which combine the mechanical advantages of biodegradable polymeric nanoparticles and biomimetic advantages of liposomes, have emerged as a robust and promising delivery platform. In CSLPHNs, a biodegradable polymeric core is surrounded by a shell composed of layer(s) of phospholipids. The hybrid architecture can provide advantages such as controllable particle size, surface functionality, high drug loading, entrapment of multiple therapeutic agents, tunable drug release profile, and good serum stability. This review focuses on current research trends on CSLPHNs including classification, advantages, methods of preparation, physicochemical characteristics, surface modifications, and immunocompatibility. Additionally, the review deals with applications for cancer chemotherapy, vaccines, and gene therapeutics.

Key words: Lipid-polymer hybrid nanoparticles; Core–shell; Drug delivery; Lipoparticles; Cancer

Nanoparticles (NPs) have attracted much attention because of their ability to deliver drugs to the therapeutic targets at relevant times and doses. Of all the common nanoparticulate systems, liposomes and biodegradable polymeric NPs (PNPs) have emerged as the two dominant classes of drug nanocarriers, as evidenced by increasing numbers of clinical trials, research reports, and approved drug products.[1–3] Both classes have advantages and limitations in terms of their physicochemical and biological properties. Historically, lipids have been used for several decades in various drug delivery systems including liposomes,[1] solid lipid NPs,[4] nanostructured lipid carriers,[5] and lipid–drug conjugates.[6] Most liposomes are biocompatible, biodegradable, nontoxic or mildly toxic, flexible, and nonimmunogenic for systemic and nonsystemic administration if their component lipids are from natural sources.[7] However, liposomal drug products have several limitations from the viewpoint of physical and chemical stability, batch-to-batch reproducibility, sterilization, drug entrapment, and manufacturing scale-up.[3,7–9] Generally, PNPs are advantageous in terms of smaller particle size, tissue penetrating ability, a greater variety of preparation methods, availability of various polymers, improved stability in biological fluids, versatile drug loading, and release profiles.[2,10] The limitations of PNPs include use of toxic organic solvents in the production process,[11] poor drug encapsulation for hydrophilic drugs, drug leakage before reaching target tissues, polymer cytotoxicity, polymer degradation, and scale-up issues.[10]

Novel, integrated systems known as lipid–polymer hybrid nanoparticles (LPHNs) have been introduced in an effort to mitigate some limitations associated with liposomes and PNPs.[12] Briefly, the biomimetic characteristics of lipids and architectural advantage of polymer core are combined to yield a theoretically superior delivery system. LPHNs are solid, submicron particles composed of at least two components: the polymer and the lipid. Various bioactive molecules such as drugs, genes, proteins, and targeting ligands can be entrapped, adsorbed, or covalently attached in the hybrid system. The common choices of biodegradable polymers include polylactic-*co*-glycolic acid (PLGA), polycaprolactone (PCL), dextran, or albumin because

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Table 1
Various classes of lipid–polymer hybrid nanoparticles (LPHNs).

Type	Description	Synonyms	Reference
Polymer core–lipid shell	Colloidal supramolecular assemblies consisting of polymer particles coated with lipid layer (s)	Lipoparticles Lipid–polymer particle assemblies Lipid-coated NPs Nanocell Polymer-supported lipid shells	Troutier et al,[20] Hetzer et al[62] Troutier et al,[19] Thevenot et al,[17,18] Bathfield et al[63] Messerschmidt et al[59] Sengupta et al[55] Bershteyn et al[78]
Core–shell-type hollow lipid–polymer–lipid NPs	Hollow inner core surrounded by concentric lipid layer, followed by polymeric layer, again followed by lipid layer along with lipid–PEG.		Shi et al[68]
Erythrocyte membrane-camouflaged polymeric NPs	Sub-100-nm polymeric particles are coated with RBC membrane derived vesicles to mimic complex surface chemistry of erythrocyte membrane	Biomimetic NPs	Hu et al[76]
Monolithic LPHNs	Lipid molecules are dispersed in a polymeric matrix	Mixed lipid–polymer particles	Gao et al[14]
Polymer-caged liposomes	These systems are composed of polymers, anchored or grafted at the surfaces of the liposomes to provide stability		Lee et al[8,9]

of their biocompatibility, biodegradability, nontoxicity, and previous use in approved products.[13,14] Lipids used are often zwitterionic, cationic, anionic, and neutral phospholipids such as lecithin, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-dipalmitoyl-3-trimethylammonium-propane (DPTAP), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), or 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE).[15–21] Various classes of LPHNs are summarized in Table 1 and are classified by the arrangement of lipid and polymer in the hybrid system.

Because of their perceived advantages over other existing hybrid systems, significant effort has been directed toward understanding CSLPHNs.[22–31] The primary objective of this review article is to discuss CSLPHNs, which are composed of polymeric core and lipid shell. Discussion of other types of LPHNs is limited as it is not within the scope of this communication.

Core–shell-type LPHNs

CSLPHNs continue to gain recognition in drug, gene, protein, and vaccine delivery.[32–35] Based on the CSLPHN concept, a new nanoparticulate drug delivery system, known as "Supra molecular bio-vector™" (SMBV™), was introduced in the early 1990s by Biovector Therapeutics.[36] SMBV is an artificial analog of virus composed of a modified polysaccharide hydrogel core covered with phospholipids acting as a shell. Because of its size (~60 nm) and architecture mimicking the structure of viruses,[37] SMBV has been investigated for various purposes such as delivery of anticancer agents,[38] nasal vaccines,[37] and antisense oligonucleotides.[39] Originally, core–shell-type hybrid microparticles and NPs were synthesized with a lipid shell and a core that was made from inorganic materials such as silica,[40] magnetic iron oxide,[41] or organic materials such as polysaccharides,[42] polystyrene,[43] polyelectrolyte capsule,[44] or polymer microgels.[45] Comprehensive reviews by Troutier and Ladaviere[46] and Richter et al[47] are available on lipid membrane systems supported by various organic and inorganic colloidal solid cores and are not highlighted in this review. Instead, our main focus is on polymeric cores (preferably biodegradable) that can be used in drug delivery systems.

CSLPHNs systems can be described as a polymeric core coated with single or multiple layers of lipids that constitute the shell. Based on the concept of core–shell architecture, lipoparticles or lipid/polymer particle assemblies were first synthesized for various biotechnological and biomedical applications such as immunological kits and biosensors for amplifying biomolecular recognition.[17,19] The special features of lipoparticles are imparted by their method of preparation and use of the types of lipid materials. They are generally prepared by mixing liposomes and PNPs to form lipid–polymer complexes in which a lipid bilayer or lipid multilayers cover the surface of the polymeric core. The space between polymeric core and lipid layer is usually occupied by water or aqueous buffer (Figure 1, *A*). Cationic or zwitterionic phospholipids have been used to construct the shell of the lipoparticles to promote electrostatic interactions with oppositely charged polymers.

In a recent report, Zhang et al[12] designed a novel CSLPHN system composed of three functional building blocks, each having distinct attributes that influence the whole hybrid delivery system (Figure 1, *B*). The first building block is a polymeric core composed of a biodegradable hydrophobic polymer (e.g., PLGA) and acts as the carrier for poorly water-soluble drugs. This core imparts controlled drug release from the system. The second component is the shell or the outer corona of the hybrid particles composed of hydrophilic substrates, most commonly lipid–PEG conjugates. This layer allows the particles to evade uptake by the immune system and imparts long-circulating characteristics. The shell can also be manipulated to facilitate the attachment of targeting ligands. Finally, the third component is composed of a lipid monolayer at the interface of core and shell.