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Biopolymer-Lipid Hybrid Composites and their Advances in Bio-imaging and Drug Delivery

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Abstract

Understanding the molecular anatomy, rationalizing the selection criteria, functionalization strategies of interrelating biopolymers with lipids are key to establish a hybrid combinatorial system owing to distinct properties and functions serving a special purpose. In recent years, many studies have been reported on developing these hybrid systems that can offer great advantages such as enhanced solubility, adhesion, and mechanical properties, site-specific delivery, better stability, and bioavailability of payload with minimal side effects. The comprehensive spotlights the importance and types of functionalization techniques explored for these conjunctional systems for obtaining synergistic properties for bio-imaging and drug delivery applications. Along with recent trends, the scrutiny even addresses the future perspective of these hybrid systems impacting biomedical innovations in radiology and medical imaging.

Keywords: Biopolymers; Lipid; Functionalization; Drug Delivery; Bioimaging Applications.

Introduction

Biopolymers have earmarked their importance in the biomedical and pharmaceutical applications. Researchers are still working for the facilitation of better therapeutic effects and medical benefits. In this context, several strategies are on a play like functionalization of biopolymers with physicochemical modification, functionalization of biopolymers with lipids, functionalization of lipids with biopolymers, development of composites or hybrid systems for bringing together the benefits of individual moieties/systems (e.g., a combination of polymers or combination of systems) and technical advancements. Biopolymer-lipid systems provide a plethora of applications in the biomedical- bio imaging and pharmaceutical fields. Materials meant for biomedical/pharmaceutical applications like tissue engineering, wound healing, drug delivery, and gene delivery should possess certain properties like biocompatibility, biodegradation, low toxicity, low antigenicity, high bio-activity, processability, and appropriate mechanical strength. Based on a specific application the materials are supposed to have a specific property. For example, during tissue regeneration, the material should support cell growth and proliferation [1-5].

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Controlled drug delivery in cancer therapy

Lipid-polymer hybrid nanoparticles are efficiently used for delivering a single drug as well as a combination of drugs for a better therapy in diseases like cancer. As the entrapment efficiency and drug release patterns are more promising with the lipid-polymer hybrid nanoparticles, it has been a successfully reported carrier system with interesting in vitro (Cell Lines) and in vivo (animal model) studies. Hydrophilic drugs are incorporated in the aqueous polymeric core and hydrophobic drugs are loaded into the lipid or lipid-PEG shell. Either physical entrapment or chemical covalent bonding is followed to modulate the encapsulation efficiency and drug release profile [6-9]. Chan et al. reported the effective prevention of arterial restenosis by using lipid-polymer hybrid nanoparticles loaded with paclitaxel for targeted drug delivery. This single drug delivery system was developed by the nanoprecipitation method using polylactic acid, tocopherol derivative, lecithin, and peptide as components. Shi et al have also reported the application of lipid-polymer hybrid nanoparticles of doxorubicin prepared by emulsification solvent evaporation method and shown positive results in the management of cervical cancer [10-11].

Kong et al. have developed these hybrid nanoparticles by nanoprecipitation method for combinatorial therapy comprising of camptothecin and iron oxide for the treatment of breast cancer. The materials include polylactide co- glycolide, lecithin, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–polyethylene glycol. These nanoparticles are activated by a magnetic field for stimuli-responsive drug release. There is a synergistic effect with the sequential release of the two loaded agents. Using the same polymer lipid materials, Aryal et al. also has reported the positive results of combinatorial therapy with such hybrid nanoparticles loaded with Gemcitabine HCl and Paclitaxel following the nanoprecipitation method for the treatment of pancreatic cancer. [12-16]. Several reports are published by scientists proving the advantageous involvement of lipid-based polymeric nanoparticles in different types of cancer therapy showing prolonged drug delivery [17-21]. By altering the ratios of lipid to polymer, optimized carriers were developed by several researchers that meet the desired goals of controlled drug delivery with minimum off-site effects. Cheow and Hadinoto worked on the factors influencing the size of the carrier and could develop hybrid nanoparticles of required nanometric size using high lipid to polymer ratio with standard production yield following the nanoprecipitation method [22-24]. On the another end, Liu et al. developed the multilamellar liposomal nanoparticles following the emulsification solvent evaporation method with excess lipids in the system having high lipid to polymer ratio. They used PLGA and 1,2-dilauroylphosphatidylocholine in the experiments. They also revealed the influence of lipid to polymer ration on percent entrapment efficiency. They developed hybrid nanoparticles of lipid-polymer with monolayer lipid shell showing the controlled release of paclitaxel [25-28]. Incorporation of two anticancer drugs into a single lipid-polymer hybrid nanoparticle system has been achieved successfully by covalent grafting of the drugs – doxorubicin and camptothecin with the polymer by Aryal et al. They synthesized the doxorubicin-poly lactic acid and camptothecin-poly lactic acid conjugates at optimum molar ratio and encapsulated within a shell of egg-phosphotidylcholine-1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol following nanoprecipitation method [29]. These hybrid nanoparticles of lipid-polymer construction are well suited for the conjugation of both hydrophobic and hydrophilic drugs (paclitaxel and cisplatin) for synergistic anticancer therapy. [30-35].

Hybrid applications in targeted bio-imaging and drug delivery

Lipid-polymer hybrid nanoparticles are also useful for active targeted drug delivery. This is achieved by the functionalization of the nanoparticles with different active targeting moieties like small folate molecules or transferrin or antibodies or aptamers or single-chain variable fragments or peptides or arginyl glycyl aspartic acid (RGD). Such targeted drug delivery reduces off-site toxicities and enhances the therapeutic efficiency of the drug at a lower dose. Certain receptors overexpressed at specific cancer cells can also be treated as ligands for targeted drug delivery [36-41]. Targeted drug delivery has a big advantage in reducing the toxicity towards healthy cells particularly in the case of cancer chemotherapy. Also, targeted drug delivery allows enhanced exposure of diseased cells to the administered drug by which the dosing can be modulated to reduce unnecessary administration of excess doses [42-44]. For example, folic acid overexpression in a cancerous cell can be considered as a targeted drug delivery principle. Zheng et al. developed a targeted drug delivery system of lipid-polymer hybrid nanoparticles for breast cancer treatment using an aromatase inhibitor following the nanoprecipitation method using poly lactide-co-glycolide; phosphatidylcholine; 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; D-a-tocopherol PEG 1000 succinate and transferrin ligands [45-48]. Liu et al. reported the docetaxel targeting for breast and ovarian cancer cell lines. Here folic acid was used as a ligand for the targeted delivery. They followed the emulsification-solvent evaporation method for the preparation of hybrid nanoparticles using poly lactide-co-glycolide; 1,2-dilauroyl-sn-glycero-3-phosphocholine and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–polyethylene glycol. They have shown prolonged therapy with targeted drug delivery (Figure1).

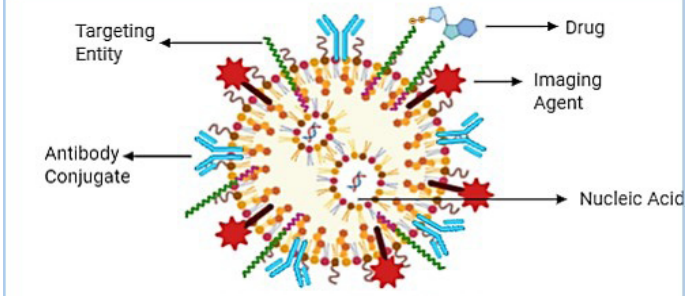

Figure 1: Biopolymer Lipid- Hybrid Conjugate exhibiting multiple sites for multidisciplinary applications.

Wu et al. developed reduction sensitive hybrid nanoparticles using folate as a ligand to deliver the anti-cancer drug, doxorubicin using the materials – poly lactide-co-glycolide, soybean lecithin, monomethoxy-poly(ethylene glycol)-S-S-hexadecyl (mPEG-S-S-C16) monolayer, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–polyethylene glycol-folate. These doxorubicin-loaded hybrid nanoparticles have shown enhanced uptake by the cancer cell lines and shown cytotoxicity in folate overexpressing human oral cavity squamous cancer cells, KB cells xenografted in mice. Folate targeted hybrid nanoparticles of paclitaxel were developed using thin-film hydration and ultrasound dispersion technique and evaluated using mammary carcinoma cells which have shown greater therapeutic efficacy than non-targeted nanoparticles [50-52]. Doxorubicin loaded

hybrid nanoparticles further liganded with folate for active targeted drug delivery has shown higher uptake of doxorubicin and increased cytotoxicity in MCF-7 cells compared to non-targeted nanoparticles. These are fabricated by the emulsification solvent evaporation technique. Mitomycin C loaded soybean phosphatidyl choline-polylactic acid-DPPE/DSPE-PEG/DSPE-PEG-folate hybrid nanoparticles have shown improved pharmacokinetic profile with better in vitro and in vivo therapeutic efficiency. Dave et al. have prepared, statistically optimized, and evaluated norfloxacin loaded hybrid nanoparticles for targeted drug delivery using polylactic acid and soya lecithin. They followed the emulsification-solvent evaporation method [53-58].

Composite applications in gene delivery

For several genetic disorders, cancers, chronic diseases, gene delivery is a promising treatment strategy. However, the delivery of genes is a challenging task due to their unique characteristics. The use of biodegradable nanoparticles and cationic liposomes are attractive strategies for the effective delivery of genetic materials. Lipid-based polymeric non-viral carriers have several advantages like the absence of viral risk factors, less immunogenicity, less harm, low processing cost, and better success rate. Hybrid nanoparticles have also addressed the problems like less stability, cytotoxicity, the larger particle size of cationic liposomes and polymeric nanoparticles. Because these lipid-polymer hybrid nanoparticles provide stability, longer circulation times, and biodegradability [59-61]. The genetic level of cancer therapy has made revolutionized with the concept of siRNA delivery. This siRNA has sequence-specific interference causing post-transcriptional gene silencing in RNA. The administration of siRNA to cancer cells has been proved to prevent the expression of proteins involved in tumor generation and progression. Out of several vectors tried for its effectiveness in vivo delivery, the recently established lipid-based hybrid nanoparticles have gained importance for the delivery of siRNA [62].

ONPATTRO (RNAi lipid-based therapeutic) introduced by Alnylam Pharmaceuticals Inc. has got US FDA approval for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. Yang et al. reported that the cationic lipid-polymer hybrid nanoparticles fabricated following one step nanoprecipitation technique have been found as effective delivery carriers for siRNA which can effectively deliver siP1k1 (active targeting against P1k1 oncogene) to BT474 cell lines and BT474 xenograft murine model. The experiments have shown increased tumor inhibition than compared to non-targeted nanoparticles. The researchers have developed differentially charged hollow core/shell hybrid nanoparticles for effective delivery of siRNA and tested for reduced luciferase activity in luciferase-expressing xenograft tumors (Dual-Luc HeLa cells) using GL3 siRNA [63]. Shi et al. developed hybrid nanoparticles following a modified double emulsion solvent evaporation technique encapsulating siRNA along with DSPE-PEG, lecithin, poly lactide-co-glycolide, and a cationic lipid-like a molecule, G0-C_{14}. Effective tumor inhibition through silencing of prohibitin 1 gene with the effective delivery of siPHB1 was reported in the A549 xenograft BALB/C nude mice model [64]. Gao et al. developed cationic liposomal nanoparticles encapsulated with anionic cholesterol grafted siRNA for effective delivery of siEGFR which shown the highest inhibition of tumor growth making use of transferrin receptor-mediated active targeted delivery [65].

Hybrid applications in inflammation therapy

Lipid-polymer hybrid nanoparticles are used for the delivery of anti-TNFα siRNA and capsaicin for topical treatment of skin inflammation. Desai et al. have developed this combinatorial carrier system for the simultaneous release of siRNA against TNFα and capsaicin as an anti-inflammatory drug. Hybrid nanoparticles permitted deeper delivery of capsaicin into dermal tissue and a synergistic effect is shown by siRNA gene material on skin inflammation [66].

Biopolymer composite applications in diagnostic and imaging agent delivery

Lipid-polymer hybrid nanoparticles are also useful in magnetic resonance imaging and computed tomography. These carriers are useful in the delivery of bioimaging agents like iron oxide, quantum dots, fluorescent dyes, and inorganic nanocrystals. Valencia et al. have studied the formation of lipid-quantum dot hybrid nanoparticles following a quick mixing method within the microfluid system. These quantum dots showed high stability by retaining their fluorescent properties in aqueous media. Gold nanocrystals and quantum dots were loaded into the hybrid nanoparticles through nanoprecipitation and studies their efficiency in mouse macrophage cells. The results showed promising CT imaging and visual imaging with the effective availability of gold nanocrystals and quantum dots respectively [67-69].

Applications in combinatorial therapies

Chemotherapy with radiotherapy:

Wang et al have also achieved a concurrent therapy of chemotherapy and radiotherapy through small lipid-polymer hybrid nanoparticles loaded with docetaxel in the polymer core and radiotherapy agent, indium 111 or yttrium 90 in the lipid shell. The results showed enhanced cytotoxic effects in prostate cancer cells rather than their counterpart treatment [70]. In addition to the combination of chemotherapy with radiation, Werner et al. added the ligand-based targeted delivery for promising results. They used folate as an active targeting ligand for the hybrid nanoparticles synthesized following the nanoprecipitation method to load paclitaxel (an anticancer drug) and yttrium-90 (radiating agent). The system comprises of poly lactide-co-glycolide core and a lipid outer shell made of soybean lecithin; 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-diethylene-triamine-penta acetate (DMPE–DTPA); 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–polyethylene glycol (DSPE–PEG) and DSPE–PEG-folate. From their reports, it was evident that the folate targeted hybrid nanoparticles with dual chemotherapeutic and radiotherapeutic agents have shown better efficiency in the ovarian peritoneal metastasis model than compared with nontargeted and single drug therapies [71].

Chemotherapy with photothermal therapy

Zheng et al. successfully combined chemotherapy and photothermal therapy by synthesizing polylactide co-glycolide-lecithin-PEG hybrid nanoparticles following step sonication method for the controlled delivery of doxorubicin and indocyanine green to the cancer cells environment. This therapeutic strategy has resulted in apoptotic cell death of doxorubicin sensitive as well as resistant MCF-7 or MCF-7/ADR tumor cells. This combination therapy has also inhibited the recurrence of cancer under systemic settings. To overcome the individual limitations existing with chemotherapy of cisplatin and photothermal therapy of indocyanine green, Gu et al. have fabricated a combination therapy merged with active targeting with the use of folate as the ligand. Such a hybrid system has shown promising results

in folate receptor overexpressing MCF-7 cells. These carriers are developed by following a step sonication method using poly lactide-co-glycolide, lecithin, DSPE–PEG_{2000}, and DSPE–PEG_{2000}-FA [72].

Chemotherapy with immunotherapy

Park et al. have reported the combination delivery of TGF-β inhibitor and IL-2 using lipid-polymer hybrid nanoparticulate gels that showed enhanced cancer immunotherapy. This has combated the immunoinhibitory nature of the cancer environment. This therapy has enhanced the natural killer cell activity and CD8+ T-cell infiltration. The lipid shell used for this development purpose is comprised of phosphatidylcholine-Cholesterol-1,2-distearoyl-sn-glycero-3-phosphoethanolamine–polyethylene glycol along with the polymer poly lactide-co-glycolide [73].

Chemotherapy with genetic therapy

Chemotherapy alone sometimes suffers from resistance to the anticancer drug. Hence, a combinatorial therapy concept has emerged. In that line, cisplatin-resistant tumors are dealt with simultaneous delivery of siRNAs targeting the specific REV1, REV3L genes responsible for the transformation susceptible translesion DNA synthesis pathway. Such combination therapy has given promising results with remarkable suppression of the said genes which synergistically inhibited the tumor growth in the prostate xenograft mouse model with human metastatic lymph node carcinoma comparing with cisplatin therapy alone. [74] In a similar line, Deng et al. have showcased their research with promising results. They developed layer-by-layer hybrid nanoparticles for systemic simultaneous delivery of doxorubicin and siRNA for the treatment of potential triple-negative breast cancer in a xenograft model. Jiang et al. have developed nanodepot gel liposome-based simultaneous delivery of doxorubicin (encapsulated in the aqueous interior of liposome) and anticancer membrane-associated TNF-related apoptosis-inducing protein-ligand (entrapped in the outer shell made of cross-linked hyaluronic acid). This system has shown promising substantial inhibition of tumor growth in MDA-MB-231 murine xenograft model. Several reports are published for the effective targeting of chemotherapeutic agent loaded hybrid nanoparticles which are functionalized for active targeting with the ligand, arginylglycylaspartic acid (RGD). RGD modified lipid-polymer nanoparticles of camptothecin, curcumin, isoliquiritigenin, and docetaxel have shown increased tumor inhibition and management in several types of cancers. In the management of carcinoembryonic antigen-presenting pancreatic cancer cells, hybrid nanoparticles are embedded with half-antibody (displaying anti-carcinoembryonic activity) were fabricated and evaluated using CEA-positive BxPC-3 pancreatic cancer cells. The results have shown increased cellular uptake and higher cytotoxicity effect compared with non-targeted nanoparticles. Other notable applications of lipid-polymer hybrid nanoparticles include the photoresponsive controlled release of doxorubicin, delivery of mRNA to lung tissues, delivery of insulin and MRI directed targeted delivery of doxorubicin [75-80].

Conclusion

In summary, multi-valent, multi-function polymer-based conjugates are great promise for both targeting the drug delivery and as potential bioimaging agents. The regular approach for the synthesis of lipid or polymer bioconjugates includes many different stages and can result into multiplex mixture and a big array of byproducts. The existence of most chemical and biological techniques used to assess the sample are many. As such, steps toward establishing the impact of these biopolymer bullets on the activity of the conjugate are limited. Recent job in controlled alterations in the distribution of ligand or ligand-based conjugates includes shaping of specific multivalent structures has enabled better assessment of multi-valent nature in bioimaging.

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