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BICELLES AS THERANOSTIC NANO DELIVERY SYSTEM IN COMBATING DISEASES

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ABSTRACT The issues of insolubility, resistance, non-specificity and toxicity of drug, and several biological barriers have directed the requirement of a suitable delivery system against diseases to overcome these obstacles. The emergence of nano-delivery system such as lipid-based bicelles has attracted attention owing to their suitable small size and morphological versatility, and stability. Conventional bicelles composed of a mix of phospholipids such as 1,2-dihexanoyl-sn-glycero-3-phosphocholine (DHPC) and 1,2-dimirystoyl-sn-glycero-3 phosphocholine (DMPC) possessing various hydrophobic chains-lengths have made their bilayer domains to facilitate entrapment of different hydrophobic chemotherapeutics for delivery to the specified zone/s of interest against various diseases. Owing to the leakage of entrapped cargos for destabilization of bicelles after interactions with plasma proteins, organic-inorganic hybrid bicelles through hydration of the admixture of long-chain organo-alkoxysilane lipid and short-chain phospholipid DHPC (molar ratio, 7:2) have offered higher thermal stability and remarkable structural integrity such as easy coupling of ligands through silane-coupler chemistry in the field of disease theranostics for the targeted therapy. This review demonstrates chiefly the synthesis/preparation, surface functionalization, characterization, and biomedical applications of bicelles as theranostic nano delivery system against diseases.

KEYWORDS : Diseases; Bicelles, Theranostic nano delivery system; Biomedical applications

INTRODUCTION

The exposures of pathogenic micro-organisms such as parasites, bacteria and viruses, and toxic agents such as chemicals, environmental pollutants and ultraviolet rays usually generate toxic free radicals in the body system leading to global broad-spectrum disorders / diseases such as inflammation, infection, erythema/edema, neurodegeneration, and cancer with significant morbidity and mortality throughout the year.[1,2] Before the development of disorders / diseases in the host body, body defense mechanisms such as innate and acquired, and antioxidant defenses become activated to counter and eradicate micro-organisms and also to scavenge free radicals for prevention of the body.[1,3] However, the defense system may be overwhelmed by the excessive exposures of micro-organisms and toxic pathogens resulting in aggravated systemic disorders / diseases.[4] To vanquish the insolubility, toxicity, non-specificity and biological hurdles of drugs, and also the development of drug resistance for inappropriate treatment, nano-delivery systems such as bicelles as nanomedicine have attracted attention for their biomedical applications on targeted theranostic delivery.[5]

Bicelles are composed of lipid nanodisc by short and long alkyl chain phospholipids dispersed in aqueous solution to form a bilayer organization.[6-9] The alternate formulations of bicelles are consisted with the admix of phospholipids and hydrophilic co-surfactants such as poly-oxyethylene sorbitan mono-oleate (Tween 80), cholesterol sulfate, and dodecyl trimethyl-ammonium chloride (DTAC), while non-ionic surfactants such as Tween 80s are favorable for their defiance to dilution and for effective bicelle-formulation owing to lower judgmental micelle concentrations compared to short-chain phospholipids or other ionic co-surfactants.[10-13] Additionally, the combinations of non-ionic surfactants and phospholipids provide denser stuffing of hydrophobic chains owing to moderate repulsions between head groups to enhance stability of the bicelles. The size of bicelles may be regulated by changing the components of lipid mixtures.[14] Various applications of bicelles have been reported as nano-material synthesis, coating materials and drug delivery-vehicles.[15-19] The nanohybrid platforms composed of inorganic and organic counterparts such as liposomes like partially silica-coated bi-layered nano-hybrids namely bicelles have attracted considerable interest in several biomedical applications such as diagnosis, drug delivery, and treatment of various diseases owing to their low toxicity, regulated size and shape, suitable biocompatibility, and good stability in the physiological conditions.[6,20,21] In addition, the compact siloxane network on the surface of silica-coated nano-hybrids makes them capable for rendering multi-functional abilities such as loading of various therapeutic contents, imaging moieties, and surface functionalization with targeted ligands in a facile and convenient way.[22] This review explores mainly the recent progress of biomedical applications of bicelles as theranostic nano delivery system against diseases.

Synthesis/Preparation of bicelles and their functionalization

Bicelles with drug are prepared by mixing DPPC, DHPC and drug with their appropriate amounts in chloroform solution to get a molar ratio of DPPC:DHPC to 3:5.[23] After mixing, the chloroform is removed by a rotary evaporator, followed by their hydration with water for reaching 5% (w/v) of total lipid concentration and 1 µg /mL of drug. Then the resulting sample is sonicated to several cycles and freezed until the sample becomes transparent, and stored as bicelles for further usages. Bicelles without drug are prepared following the same method without any inclusion of drug.

Bicelles are also fabricated by the admix of phospholipids such as long-chain DMPC and short-chain DHPC to assemble as a flat bilayer, and to stabilize the rim, respectively.[5] Owing to the leakage of entrapped drugs for the destabilization of conventional bicelles after interactions with plasma proteins, inorganic-organic hybrid bicelles composed of DHPC and long-chain CFL with poly-organo-siloxane surfaces have been prepared to get higher stability and to facilitate conjugation of ligands as targeted therapeutics.[5] The hybrid bicelles are formed with a potent cross-linked siloxane network, and achieving the sol-gel process succeeded by the poly-condensation by simply hydration of the admix of long-chain organo-alkoxysilane lipid and short-chain phospholipid DHPC in the molar ratio of 7:2.

Bicelles are also prepared based on lecithin-non-ionic surfactant mixtures.[24] In brief, hydrogenated soybean lecithin (SL) and poly(oxyethylene)cholesteryl ethers ($ChEO_{10}$) are dissolved in di-propylene glycol (DPG) with the weight ratio of (SL+$ChEO_{10}$)/DPG to 1/10, succeeded by the adjoining of water until the concentration of water reaches to 78 (wt %). Then ultrasonication at 50W and 20kHz for 5 min is performed to prepare bicelle-sample, and the sample is retained in a water bath at 25℃.

To get higher cellular uptake and theranostic efficacy, bicelles may be functionalized with several ligands such as peptides, proteins, antibodies, aptamers, cell growth factors, and other small molecules and cargos through utilizing direct driving forces such as van der Waal's force, electrostatic interaction, and hydrogen bonding (Figure 1).[25-27] The hybrid bicelles may be synthesized with edge and plan - shape ligand (cell-penetrating peptides) modifications of octa-arginine sequences from short alkyl chain DHPC and long alkyl chain CFL phospholipids, respectively, while edge-based compared to plan-based bicelles may increase bio-interactions through their surface curvatures and larger contact angles at the contact site/s.[28] The surface functionalization of bicelles with PEGs may enhance their half-life

kinetics by steric stabilization with reduced RES uptake to target the specific site/s of interest.[29-31]

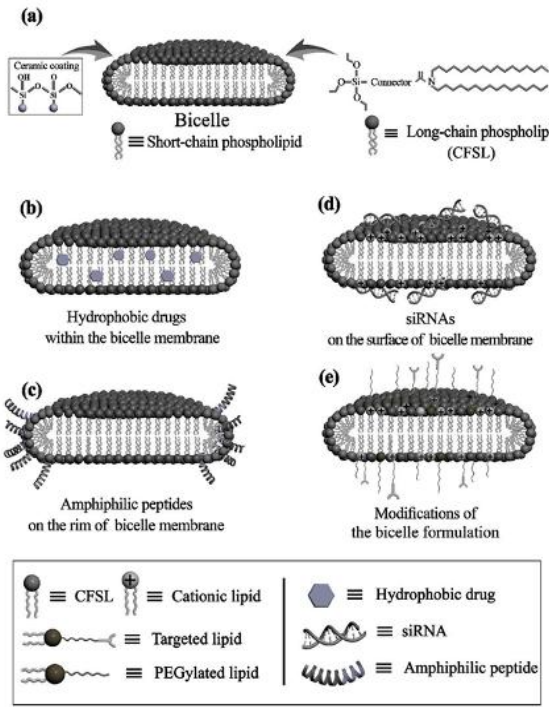

Figure 1. A schematic representation of general molecular structure and design strategies of bicelles for therapeutic delivery (a-e). Hydrophobic molecules may be ingrained in bilayer membranes (b). Amphiphilic peptides may be anchored on the curved rim-zone of bicelle (c). siRNAs may be laden on the surface of cationic lipid-assimilated bicelle (d). Bicelles may be surface functionalized to provide stealth effect by incorporating PEGylated lipids, and to aid active endocytosis by acquainting targeting lipids, as well as to modify the surface charge by drugging cationic lipids (e).

Characterization of bicelles

The morphology of bicelles is determined through the microscopic observations utilizing transmission electron microscopy (TEM) / cryo-TEM techniques. The size distribution of the bicelles is measured through the dynamic light scattering (DLS) technique. The information regarding the precise inner structures of bicelles is determined through SANS measurement. The significant peak of asymmetric stretching vibration of the siloxane network on the surface of hybrid bicelles is identified via the Fourier transform infrared (FT-IR) spectrum analysis.

Biocompatibility of hybrid bicelles

The investigations regarding inherent characteristics such as biocompatibility of hybrid bicelles in both immune and cancer cells have been performed.[32] The *in vitro* cytotoxicity assays of hybrid bicelles in immune cells (BMDCs and T-cells) and HUVECs have shown their insignificant toxicity relating to good biocompatibility, and may be utilized for various theranostic applications both *in vitro* and *in vivo*.

Biomedical applications of bicelles

Bicelles have emerged as a versatile theranostic system for numerous biomedical usages such as gene/drug delivery, disease diagnosis, bioimaging to treat biological disorders/diseases.[33-35] The progress in the usages of hybrid bicelles for disease-theranostics has provided a suitable framework with the incorporation of two or more therapeutic components for giving multifunctional capabilities and additional targeting of multiple contents to diseased cells. Hybrid bicelles with their biomembrane mimetic features have increased their therapeutic index of cargos against diseases through alteration of diseased site/s-accumulations, pharmacokinetics, and biodistribution in an *in vivo* system.[36] In addition, cargos are retained within the stable hybrid bicelles under physiological conditions, and are liberated upon exposures to various stimuli such as treatment with the reducing agents, temperature variations, pH change and light irradiation.[37,34] A few reports have been exhibited regarding the usages of hybrid bicelles to treat cancer.[32,38,34] A few researchers have fabricated hydrophobic DOX-loaded hybrid bicelles as versatile and effective cargo delivery platform for chemotherapeutic treatment against cancer showing their excellent stability, good biocompatibility, prolong storage and pH-sensitive liberation *in vivo*.[32] A few investigators have utilized PEG-modified DOX-loaded hybrid bicelles to treat tumor for suppression with higher cellular uptake, adhesion, and local drug accumulation both *in vitro* and *in vivo*.[34] A few scientists have utilized antioxidant-loaded self-assembled bicelles to form new nano structures through their penetration into the skin with stratum corneum inside the skin tissue, and to reinforce the barrier function and free radical scavenging activity against UV-radiation-exposed oxidative damage of lipids, proteins and cellular DNA in the biological sites.[39-43] To encounter the various drawbacks of chemotherapy such as low efficacies, tumor metastasis, drug resistance and several adverse reactions,[44] photothermal and photodynamic therapy utilizing hybrid bicelles have gained considerable attention to deliver therapeutic cargo and photothermal component simultaneously to malignant cells to get higher therapeutic efficacy.[45] A few other investigators have utilized multifunctional hybrid bicelles (DOX/ICG@HBs) loaded with DOX and ICG for NIRF imaging guided chemo/photothermal therapy against cancer cells to get higher combined therapeutic efficacies such as deep tumor targeting penetrating capability, selective cargo release and fluorescence imaging guided photothermal therapy without producing any significant off-target toxicity.[38]

Elimination of bicelles

Bicelles, consisted of short and long -chain phospholipids, are decomposed to constituent lipids, and ultimately to free fatty acids and glycerol, and recycled into the systemic metabolic process. Cholesterol, converted by enzymes to bile acids, salts, or neutralized/oxy sterols, may be reabsorbed, excreted into bile, or removed through peripheral tissue by reverse cholesterol transport. In general, endocytosed/phagocytosed bicelles are processed and cracked within the phago-lysosomal compartment by phospholipases or other enzymes, and a few metabolized components are excreted via hepato-pancreatic biliary system and the small intestine as fecal clearance. Hybrid bicelles may be primarily removed through the hepato-pancreatic biliary system and the small intestine as fecal elimination by mononuclear phagocyte system, followed by the metabolism and recycling of their broken organic lipid components to fundamental contents by the natural enzymes in the biological system, while their stable inorganic poly-organo-siloxane network undergoes a natural long-term bio-degradation process in the body. The breakdown processed byproducts of bicelles including hybrid (>6 nm) may be sequestered in the liver and spleen for several months, or excreted via the glomerular bed (<5 nm).[2]

CONCLUSIONS AND FUTURE PERSPECTIVES

Bicelles and silica-coated nanohybrid bicelles have been utilized as theranostic agents against diseases owing to their several suitable physico-chemical characteristics such as tunable nano size and shape, good biocompatibility, higher physiological stability, and topologically inorganic-organic domains for easily functionalization to target selectively to diseased site/s and release toxic-dosage of therapeutic moieties in a sustained manner over time against internal or external stimuli to overcome several shortcomings such as recurrence, drug-resistance, tumor hypoxia, metastasis and other biological barriers and to get maximal therapeutic benefit. However, further investigations are required regarding the entire clinical safety assessment, toxicity evaluation, optimization of synthesized formulation and functionalization with theranostic agents, similarity from batch to batch scaled up manufacturing production, detailed cellular uptake mechanisms and biological interactions, biodistribution, pharmacokinetics and elimination/degradation parameters, and route/s of administration before going to clinical translation for considering bicelles as theranostic nano delivery systemic medicine against diseases.

Conflict of interest: None declared.

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