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Review

Recent advances in polymeric micelles for anti-cancer drug delivery

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ABSTRACT

Block co-polymeric micelles receive increased attention due to their ability to load therapeutics, deliver the cargo to the site of action, improve the pharmacokinetic of the loaded drug and reduce off-target cytotoxicity. While polymeric micelles can be developed with improved drug loading capabilities by modulating hydrophobicity and hydrophilicity of the micelle forming block co-polymers, they can also be successfully cancer targeted by surface modifying with tumor-homing ligands. However, maintenance of the integrity of the self-assembled system in the circulation and disassembly for drug release at the site of drug action remain a challenge. Therefore, stimuli-responsive polymeric micelles for on demand drug delivery with minimal off-target effect has been developed and extensively investigated to assess their sensitivity. This review focuses on discussing various polymeric micelles currently utilized for the delivery of chemotherapeutic drugs. Designs of various stimuli-sensitive micelles that are able to control drug release in response to specific stimuli, either endogenous or exogenous have been delineated.

Contents

Abbreviations: ANAs, antinuclear antibodies; APRPG, Ala-Pro-Arg-Pro-Gly; CAP, capecitabine; CMC, critical micelles concentration; DOPE, dioleoyl(phosphatidylethanolamine); DOTMA, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride; DOX, doxorubicin; DSPE, distearoyl(phosphatidylethanolamine); EPR, Enhanced Permeability and Retention; FN, fibronectin; HUVECs, human umbilical vein endothelial cells; LL, Lipofectin® lipids; LCST, lower critical solution temperature; MTX, methotrexate; PAA, poly(amino acids); pAsp, poly(L-aspartic acid); PCL, poly-ε-caprolactone; PDT, photodynamic therapy; PEG, poly(ethylene glycol); PEI, polyethylenimine; PEO, poly(ethylene oxide); pHis, poly(L-histidine); PLA, poly(L-lactide); PLGA, poly(lactide-co-glycolic acid); pNIPAAm, poly(N-isopropylacrylamide); PPO, poly(propylene oxide); PVP, poly(N-vinyl pyrrolidone); PEO–PS–PMMAZO, poly(ethylene oxide)-b-polystyrene-b-poly[6-(4-methoxy-4-oxy-azobenzene)hexyl methacrylate; ROS, reactive oxygen species; RSV, resveratrol; SPION, superparamagnetic iron oxide nanoparticles; TAPC, 5,10,15,20-tetrakis (4-aminophenyl)-21H,23H-chlorin; TPGS, D-α-tocopheryl polyethylene glycol succinate; TPP, meso-tetraphenylporphine.

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1. Introduction

Amphiphilic block co-polymers that form self-assembled micellar structure spontaneously have gained much attention in recent years for their application in drug delivery. Polymeric micelles composed of amphiphilic block-co-polymers are nano-sized, spherical, supramolecular colloidal particles with a hydrophobic core and a hydrophilic corona (Aliabadi and Lavasanifar, 2006; Torchilin, 2007). The amphiphilic block co-polymers, the structural units of polymeric micelles are macromolecules with distinct hydrophobic and hydrophilic block domains. On aqueous exposure, the block co-polymers aggregate to form entropically favored, supra-molecular assembly at or above certain polymer concentration, referred to as critical micelle concentration (CMC). CMC depends on the hydrophilic/hydrophobic balance of the block co-polymers, chemical characteristics, and molecular weight of the blocks.

While hydrophobic segment of the polymer forms the core of the micelles that solubilize the hydrophobic drug molecules, hydrophilic segment forms the corona that provides compatibility of the micelles in the aqueous environment. The hydrophobic core accommodates variety of hydrophobic molecules, such as therapeutics and imaging agents, thus, improving the solubility and stability in the biological system. The hydrophilic corona shields the core, and protects the loaded drugs from interactions with the blood components. The biocompatible polymeric corona causes reduced recognition of the micelles by reticulo-endothelial systems, thus providing long circulation of the loaded component in the blood stream. The nano-ranged size (between 10 and 100 nm) along with the long circulatory property allows polymeric micelles to eventually accumulate in any compromised tissue-vasculature sites, e.g. tumor via a passive targeting phenomenon commonly referred to as Enhanced Permeability and Retention (EPR) effect. Unlike small molecules which go in and out from the interstitial space by diffusion, macromolecules, nanocarriers, including micelles once extravasated cannot diffuse out from the interstitial space (Fig. 1). Maeda and co-worker were the first to establish the concept of EPR and coined the term in 1986 (Matsumura and Maeda, 1986). The concept of EPR is the characteristics of tumor which has recently been exploited for anti-tumor drug delivery (Maeda et al., 2000). The aberrant fenestration on the blood vessels surrounding tumor tissues causes enhanced permeability of macromolecules of certain size to the tumor microenvironment, and poor lymphatic drainage in the tumor area allows retention of the extravasated nanocarriers (Maeda et al., 2000, 2006; Torchilin, 2011; Fang et al., 2011; Iyer et al., 2006).

In addition to demonstrating EPR effect for eventual passive targeting of polymeric micelles to the tumor sites, polymeric micelles could actively be targeted to tumor by their easy surface functionalization (Jhaveri and Torchilin, 2014). Amphiphilic block co-polymers having ligand/antibodies at the distal end of the hydrophilic block possessing strong affinity for cancer homing receptors/antigens could be inserted into the micellar assembly without disrupting micellar thermodynamic stability. The newly developed surface modified polymeric micelles are actively targeted nanocarrier system that would deliver loaded cargo more efficiently to the tumor compared to passive targeted micellar system relying only on EPR effect or passive targeting for accumulation in tumor area (Yang et al., 2013; Sawant et al., 2014; Chung et al., 2014; Liao et al., 2011). Therefore, advantages of polymeric micelles as drug delivery carriers in cancer therapy include their potential to solubilize the pharmaceutical components of poor aqueous solubility into the hydrophobic core, improve the pharmacokinetic properties and biodistribution, and specifically target their payload to the tumor tissues by tuning their size for passive targeting via EPR effect, or by anchoring tumor targeted ligands on the micellar surface by using various amenable surface functionalization techniques. Moreover, polymeric micelles offer tunable payload release when constituted by using stimuli-sensitive block co-polymers, which disassemble under certain physiologic condition triggering disassembly of the system leading to drug release (Na et al., 2006; Torchilin, 2009).

Various amphiphilic co-polymers, including di-block (A–B), triblock (A–B–A), and graft co-polymers have been utilized to form micelles. The most common hydrophilic block in the co-polymeric structure is poly(ethylene oxide) (PEO), also referred to as poly(ethylene glycol) (PEG). PEG is hydrophilic, electrically neutral, non-toxic, and flexible polymer that has commonly been used to coat nanoparticles. PEG-coating decreases the interaction of the nanocarrier-surface with serum components, thus prolonging their circulation. Other hydrophilic block forming polymers include chitosan, poly(N-vinyl pyrrolidone) (PVP), and poly(N-isopropylacrylamide) (pNIPAAm). There are various polymer blocks utilized to form micellar core, including the class of polyethers such as poly(propylene oxide) (PPO), various polyesters such as poly(L-lactide) (PLA), poly-ε-caprolactone (PCL), poly(lactide-co-glycolic acid) (PLGA), poly(β-aminoesters), polyamino acids such as poly(L-histidine) (pHis), poly(L-aspartic acid) (pAsp) and lipids such as dioleoyl(phosphatidylethanolamine) (DOPE), distearoyl(phosphatidylethanolamine) (DSPE). The assembly of block co-polymers, in which PPO attached to PEG as A–B–A triblock co-polymers (PEO–PPO–PEO) is known as Pluronics. The block co-polymers included in the poly(ester) class are prone to hydrolysis in the biological system and gets degraded to non-toxic monomers (Anseth et al., 2002; Wu and Wang, 2001). Unlike polyethers and esters, aliphatic chains in the lipid core do not disintegrate easily to form monomers. Unlike other classes of core-forming polymers, block co-polymers of poly(aminoacids) could carry drugs by chemical modifications due to the presence of functionalizable groups in the co-polymer. Micelles containing poly(ethers) and poly(ester)-core encapsulate poorly-water soluble pharmaceutical agents by physical encapsulation. An important class of micellar system could also be constituted comprising of polymers with stimuli-sensitive behavior (Jhaveri and Torchilin, 2014; Yang et al., 2013; Na et al., 2006; Torchilin, 2009). In this paper, structural features as well as current trend in using various polymeric micelles comprised of extensively studied micelles-forming block-co-polymers, including Pluronics, PEGylated PLA, PCL, lipid, PLGA, poly(amino acids) for the delivery of chemotherapeutic drugs in cancer has been discussed. Structural features of few currently utilized stimuli-sensitive polymeric micelles and their use in anticancer drug delivery have been represented.

2. Polymeric micelles of therapeutic application in cancer treatment

2.1. Pluronics®

Pluronics®, also known as poloxamers are amphiphilic, nonionic block copolymer of A–B–A structure, which is composed of hydrophobic propylene oxide (PO) fragments, and hydrophilic ethylene oxide (EO) branches. Poloxamers consist of a central poly(propylene oxide) (PPO) block forming hydrophobic core that is flanked on both sides by two hydrophilic chains of poly(ethylene oxides) (PEO) forming hydrophilic corona, yielding a structure of (PEO)a–(PPO)b–(PEO)a type as shown in