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Polymeric protective agents for nanoparticles in drug delivery and targeting

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ABSTRACT

Surface modification/functionalization of nanoparticles (NPs) using polymeric protective agents is an issue of great importance and actuality for drug delivery and targeting. Improving the blood circulation half-life of surface-protected nanocarriers is closely related to the elimination of main biological barriers and limiting factors (protein absorption and opsonization), due to the phagocytic activity of reticuloendothelial system. For passive or active targeted delivery, in biomedical area, surface-functionalized NPs with tissue-recognition ligands were designed and optimized as a result of modern research techniques. Also, multi-functionalized nanostructures are characterized by enhanced bioavailability, efficacy, targeted localization, active cellular uptake, and low side effects. Surface-protected NPs are obtained from biocompatible, biodegradable and less toxic natural polymers (dextran, β-cyclodextrin, chitosan, hyaluronic acid, heparin, gelatin) or synthetic polymers, such as poly(lactic acid), poly(lactic-*co*-glycolic) acid, poly(ε-caprolactone) and poly(alkyl cyanoacrylates). PEGylation is one of the most important functionalization methods providing steric stabilization, long circulating and 'stealth' properties for both polymeric and inorganic-based nanosystems. In addition, for their antimicrobial, antiviral and antitumor effects, cutting-edge researches in the field of pharmaceutical nanobiotechnology highlighted the importance of noble metal (platinum, gold, silver) NPs decorated with biopolymers.

Abbreviations: AD, Alzheimer's disease; ANEP, anti-neuroexcitation peptide; APTS, aminopropyltriethoxysilane; atRA, All-*trans*-retinoic acid; BBB, blood-brain barrier; BMP, bone morphogenetic protein; BSA, bovine serum albumin; CA, cyanoacetate; CCM, Czech Collection of Microorganisms; CPT, camptothecin; CUR, curcumin; DNA, deoxyribonucleic acid; DOX, doxorubicin; DTX, docetaxel; EGFR, epidermal growth factor receptor; ER, estrogen receptor; 5-FU, 5-fluorouracil; GFAP, glial fibrillary acidic protein; HA, hyaluronic acid; HDCA, hexadecyl cyanoacetate; HeLa, human cervix epithelial; IBCA, isobutyl cyanoacrylate; IL-13, interleukin-13; LCMV, lymphocytic choriomeningitis virus; LMWH, low molecular weight heparin; MOMP, recombinant major outer-membrane peptide; mPEG, methoxy poly(ethylene glycol); MRI, magnetic resonance imaging; MSNPs, mesoporous silica nanoparticles; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NPs, nanoparticles; PBCA, poly(butyl cyanoacrylate); PBS, phosphate-buffered saline; PCL, poly(ε-caprolactone); PEG, poly(ethylene glycol); pEGFP, enhanced green fluorescent protein plasmid; PEI, polyethylenimine; PEO, poly(ethylene oxide); PHDCA, polyhexadecyl cyanoacrylate; PIBCA, poly(isobutyl cyanoacrylate); PIHCA, poly(isohexyl cyanoacrylate); PLA, poly (lactic acid); PLGA, poly(lactic-*co*-glycolic) acid; PMMA, poly(methyl methacrylate); PSMA, prostate-specific membrane antigen; PTX, paclitaxel; PVP, polyvinylpyrrolidone; RBEC, rat brain endothelial cells; RCA, rhodamine B cyanoacetate; RES, reticuloendothelial system; RGDS, fibronectin-derived arginine–glycine–aspartic acid–serine sequence; rhG-CSF, recombinant human granulocyte colony-stimulating factor; RNA, ribonucleic acid; siRNA, small interfering RNA; SNPs, silica nanoparticles; SPIONPs, superparamagnetic iron oxide nanoparticles; TEOS, tetraethoxysilane; TNBC, triple-negative breast cancer; TNF-BP, tumor necrosis factor alpha blocking peptide; TRIS, tris (hydroxymethyl)aminomethane; UFH, unfractionated heparin.

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1. Introduction

Surface modification is an essential requirement for the masking/camouflaging of nanoparticles (NPs) against the reticuloendothelial system (RES) activity. It is already known that the RES does not recognize surface-protected polymeric NPs (*e.g.*, peptides and proteins nanocarriers), thus improving the blood circulation half-life of those nanosystems (Gref et al., 1994; Kumari et al., 2010). For the purpose of biodistribution and management of the biological effects due to internalization (cellular uptake), the surface of NPs may be associated with various functional groups, process known as functionalization. Protein absorption and opsonization, the main biological barriers and limiting factors for long-circulating nanocarriers and controlled drug delivery, can be removed by applying appropriate methods for surface functionalization (Owens and Peppas, 2006). Surface-functionalized NPs with tissue-recognition ligands were designed and optimized for passive or active targeted delivery in antitumor therapy, tissue engineering, biomolecular applications (separation and detection, artificial cell membranes), diagnostic imaging (Jiang et al., 2013; Mout et al., 2012; Weingart et al., 2013). Multifunctional NPs demonstrate enhanced efficacy, targeted localization at the tumoral level, active cellular uptake and low side effects (Kumari et al., 2010; Subbiah et al., 2010).

Polymeric protective agents/surfactants increase systemic circulation time mainly for intravenously administered multifunctional NPs. By modifying the surface of NPs for drug delivery and targeting, the nanocarriers can move a long time in the bloodstream and they are not recognized by mononuclear phagocytic system and macrophages. Such biocompatible, biodegradable and less toxic NPs are prepared starting from natural polymers, such as dextran, β-cyclodextrin, chitosan, hyaluronic acid (HA), heparin, gelatin, modified cationic gelatin with spermine, or synthetic polymers, mainly poly(lactic acid) (PLA), poly(lactic-*co*-glycolic) acid (PLGA), poly(ε-caprolactone) (PCL) and poly(alkyl cyanoacrylates). In this regard, these especially designed nanocarriers are distinguished by improved physicochemical and pharmacokinetic properties in terms of encapsulation efficiency, bioavailability and controlled release (Kumari et al., 2010; Parraga et al., 2014).

PEGylation represents the adsorption/grafting of poly(ethylene glycol) (PEG) to the surface of NPs. Applied for natural/synthetic polymers or inorganic nanostructures in drug delivery and targeting, PEGylation is one of the most preferred functionalization methods with the lowest occurrence of harmful effects *in vivo*, reducing non-specific uptake and increasing the selective cellular uptake by binding/internalization through receptor-mediated endocytosis. As a hydrophilic protective layer on the surface of NPs, PEG and PEG-containing copolymers provide steric stabilization, improve the biocompatibility and blood circulation half-life, in some cases by several orders of magnitude, and significantly reduce the protein adsorption and opsonization. In these conditions, protected from the immune system, long circulating ("Kupffer cell-evading") 'stealth' NPs are used for vascular drug delivery and site-specific targeting release at the level of tissues, cell surface antigens and ligands, such as small molecules, peptides, aptamers, antibodies, antibody fragments (Alexis et al., 2008; Moghimi et al., 2001; Owens and Peppas, 2006).

A modern research area highlighted the pharmacological importance of noble metal (platinum, gold, silver) NPs decorated/conjugated with biopolymers for their antimicrobial, antiviral and cytostatic properties (Rai et al., 2015; Thanh and Green, 2010). Due to their unique (surface) physico-chemical and biopharmaceutical properties, inorganic NPs functionalized with various biocompatible, biodegradable and non-toxic natural/synthetic polymers, such as chitosan, heparin, HA, xanthan gum, PEG, polystyrene sulfonate, polyethyleneimine (PEI), have revealed their importance mainly for antitumor drug delivery and targeting: functionalized gold NPs as drug/nucleic acid delivery system for cancer therapy (Alex and Tiwari, 2015; Han et al., 2007; Muddineti et al., 2015); surface multi-functionalized stimuli-responsive magnetic NPs as versatile platforms designed and optimized for chemo- or gene therapy and magnetic resonance imaging (MRI) with applications in the detection, diagnosis and treatment of oncological, cardiovascular and neurological disorders, such as superparamagnetic iron oxide nanoparticles (SPIONPs) (Cinteza et al., 2006; Hao et al., 2010; Medeiros et al., 2011; Nguyen and Kim, 2014; Sun et al., 2008; Wahajuddin and Arora, 2012; Wu et al., 2008); porous hollow iron oxide NPs for targeted delivery and controlled release of cisplatin against breast cancer SK-BR-3 cells (Cheng et al., 2009); monoclonal antibody (anti-HER2/neu)-PEG-functionalized mesoporous silica NPs for selective targeting breast cancer cells (Liberman et al., 2014; Tsai et al., 2009); ultrastable, redispersible, small, and highly PEG-trimethylchlorosilane-modified mesoporous silica nanotherapeutics for doxorubicin (DOX) delivery against human cervix epithelial (HeLa) cancer cells (Lin et al., 2011).

2. Natural polymers

2.1. Dextran

Dextran is a natural biocompatible and biodegradable polymer widely used in drug industry and nanobiotechnology. Various dextran-coated NPs were prepared and optimized for drug delivery and targeting, such as: fluoresceinated dextran using novel polyvinylpyrrolidone (PVP) hydrogel NPs less than 100 nm diameter, applied for the encapsulation of water-soluble antitumor agents, evading reticuloendothelial system (RES), with longer residence in blood and negligible (<1%) uptake by the liver and spleen macrophages (Gaur et al., 2000); long-circulating (48–72 h) 'stealth' NPs bearing heparin or dextran covalently bound to poly (methyl methacrylate) (PMMA), recognized to a small extent by the macrophages (Passirani et al., 1998); poly(methyl vinyl ether-*co*-maleic anhydride) (Gantrez® AN) NPs highly bioadhesive to the digestive mucosa, obtained by solvent displacement method and coated with hydroxyl-functionalized dextran and amino-derivative dextran (Porfire et al., 2009, 2010); amphotericin B–chitosan–dextran sulfate NPs (mean size 600–800 nm) synthesized by polyelectrolyte complexation method, with reduced nephrotoxicity (Tiyaboonchai and Limpeanchob, 2007); insulin containing polyethylenimine (PEI)–dextran sulfate spherical NPs (250 nm mean diameter), with zinc sulfate as a stabilizer and prolonged hypoglycemic effect (Tiyaboonchai et al., 2003); biocompatible and biodegradable NPs (130–230 nm diameter) with dextran/chitosan shell and bovine serum albumin (BSA)/chitosan core–doxorubicin (DOX) loading and delivery (Qi et al., 2010) and DOX-loaded BSA NPs with folic acid modified dextran surface (Hao et al., 2013), both nanoformulations exhibiting antitumor effects in experimental model of murine ascites hepatoma H22 tumor-bearing mice; dextran–protamine–solid lipid NPs as a non-viral vectors for gene therapy, optimized for transfection *in vitro* (in cell lines – clathrin/caveolae-mediated endocytosis) and *in vivo* after intravenous administration to BALB/c mice (Delgado et al., 2012); dextran–protamine coated nanostructured lipid carriers as mucus-penetrating nanoparticles for lipophilic drugs (saquinavir), assessed on Caco-2 cell monolayers (enterocyte-like model) and Caco-2/HT29-MTX cell monolayers (mucus model) (Beloqui et al., 2014); dextran- and albumin-derivatized iron oxide (Fe_3O_4) NPs with an improved stability, biocompatibility and blood circulation time (Berry et al., 2003).