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Review article

Smart chemistry-based nanosized drug delivery systems for systemic applications: A comprehensive review

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ABSTRACT

This review focuses on the smart chemistry that has been utilized in developing polymer-based drug delivery systems over the past 10 years. We provide a comprehensive overview of the different functional moieties and reducible linkages exploited in these systems, and outline their design, synthesis, and application from a therapeutic efficacy viewpoint. Furthermore, we highlight the next generation nanomedicine strategies based on this novel chemistry.

1. Introduction

The design of drug nanocarriers for controlling disease pathologies, either by enrichment of therapeutics at the diseased site or by controlling pathogens using novel therapeutic agents, is of considerable importance [1–3]. These nanocarriers are prepared from a range of inorganic and organic compounds including polymers, lipids, dendrimers, carbon nanotubes, quantum dots, and mesoporous materials. Assemblies using such materials result in the formation of various nanoscale architectures, such as microspheres, polymeric nanoparticles, micelles, conjugates, vesicles, liposomes, and polyplexes [4–8] with which active therapeutic molecules have been physically encapsulated, complexed, or chemically conjugated. These nanocarriers possess unique functional characteristics to effect the delivery of therapeutic cargo, including internalization beyond biological barriers such as the blood brain barrier or interaction with receptors on cellular surfaces

Abbreviations: AAP, arylazopyrazoles; BIC, block ionomeric complex; BSA-*c*-PheoA, bovine serum albumin-*cis*-aconityl pheophorbide-A; CA, *cis*-aconitic anhydride; CPP, cell-penetrating peptides; CPT, camptothecin; CSO-SS-SA, chitosan-SS-stearic acid; CS-SS-PCL, chitosan-S-S-poly(ε-caprolactone); CuAAC, copper (I) catalyzed azide–alkyne cycloaddition reaction; CUR, curcumin; Dendrimer–GFLG–DOX, mPEGylated peptide dendrimer–GFLG–doxorubicin; Dex-SS-CPT, dextran-SS-camptothecin; DMMAn, dimethylmaleic anhydride; DOX, doxorubicin; DTX, docetaxel; EPR, enhanced permeation and retention; FA, folic acid; Gd, gadolinium; GSH, glutathione (GSH); HA, hyaluronic acids; HECS-*ss*-OA, *O*,*N*-hydroxyethyl chitosan-octylamine; His, histidine; hPAMAM, hyperbranched poly (amidoamine); HPMA, *N*-(2-hydroxypropyl) methacrylamide; HYA-*b*-PLA, hyaluronic acid (HYA)-*b*-poly(lactic acid) (PLA); IRI, irinotecan; LCST, lower critical solution temperature; Mel, melittin; MMP, metalloproteinase; mPEG2K-(GPVGLIGK)GK8-α-TOS, α-Tocopherol succinate (α-TOS)- oligopeptide GPVGLIGK-NH2 (GK8)-methoxy-polyethylene glycol; mPEG-*b*-P(DPA-DE)LG, Methyloxy-poly(ethylene glycol)-*block*-poly[dopamine-2-(dibutylamino) ethylamine-L-glutamate]; mPEG-*b*-P(TTMA-*co*-DPA), PETD, methoxy poly(ethyleneglycol)-*b*-poly((2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl) ethane methacrylate)-*co*-2-(diisopropylamino)ethyl methacrylate); mPEG-*b*-PCL-*b*-PPEMA, methoxy poly(ethylene glycol)-*b*-poly(ε-caprolactone)-*b*-poly(2-(2-*oxo*-1,3,2-dioxaphospholoyloxy)ethyl methacrylate); mPEG-*b*-PLA-*b*-DNP-Phis, poly (ethylene glycol)-poly(D,L-lactide)-poly(2,4 dinitrophenol-L-histidine); mPEG-PCL, methoxy poly(ethylene glycol)-poly(ε-caprolactone); mPEG-SeSe-St, mPEG-diselenide-starch; mPEG-S-S-C16, monomethoxy-poly(ethylene glycol)-SS-hexadecyl; mPEG-SS-Pleu, poly(ethylene glycol) monomethyl ether-SS-poly(D-leucine-L-leucine); MRI, magnetic resonance imaging; MSN, mesoporous silica nanoparticles; MTX, mitoxantrone; NIR, near infrared light; NP, nanoparticles; P123, pluronic P123; P123-Hyd-DTX, pluronic P123-Hydrazine-doxorubicin; PAA-*g*-PEG, polyamide amine-*g*-polyethylene glycol; PBC, poly(benzyl carbamate); PBLG, poly(γ-benzyl-L-glutamate); PBYP-*g*-PEG-*g*-DOX, PEGylated polyphosphoester-doxorubicin prodrug; PCL, polycaprolactone; PDT, photodynamic therapy; PEG, polyethylene glycol; PEG-P (TMBPEC-*co*-MPMC), poly(ethylene glycol)-poly(2,4,6, trimethoxybenzylidene-pentaerythritol carbonate-*co*-5-methyl-5-propargyl-1,3-dioxan-2-one); PEG-SS-PBLG, poly(ethylene glycol)-SS-poly(γ-benzyl L-glutamate); PEG-SS-PCL, poly(ethylene glycol)-SS-poly(ε-caprolactone); PEI, polyethylenimine; PEO, polyethylene oxide; PEO-Fc, poly(ethylene oxide)-ferrocene; PGA, poly-γ-glutamic acid; Phe-OCA, phenyl *O*-carboxyanhydride; PIA–PEG–FA–PHIS, poly (itaconic acid)–poly(ethylene glycol)–folate–poly(L-histidine); PLA, poly(lactic acid); PLGA, poly(lactic and glycolic) acid; PLH–PLGA–TPGS, poly(L-histidine)–poly(lactide-*co*-glycolide)–tocopheryl polyethylene glycol succinate; PLL, poly-L-Lysine; PMAC-*g*-(ADPC-*co*-Mal-DOX), poly(5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one)-*graft*-12-acryloyloxy dodecyl phosphorylcholine-*co*-6-maleimidocaproyl doxorubicin; PNIPAM, poly (*N*-isoacrylamide); PNVCL, poly (*N*-vinyl caprolactam).; PPEMA, poly(2-(2-*oxo*-1,3,2-dioxaphospholoyloxy)ethyl methacrylate); PS-β-CD, poly(styrene)-β-cyclodextrin; PTX, paclitaxel; Ptxl – PLA, paclitaxel-polylactide conjugates; PVA, polyvinyl alcohol; PVA-*cis*-aconityl-DOX, polyvinyl alcohol-*cis*-aconityl-doxorubicin; RAFT, peversible addition–fragmentation chain transfer (RAFT); ROP, ping-opening polymerization; SA, stearic acid; Se, selenium; SWCNT, single-walled carbon nanotubes; SWCNTs-HA, hyaluronic acid (HA)-modified single-walled carbon nanotubes; UCST, upper critical solution temperature; β-CD, β-Cyclodextrin

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[9]. The key advantages of nanocarrier-mediated drug delivery systems include greater accumulation of drugs at the diseased or pathological sites, enhanced cellular uptake, prolonged circulation time, high systemic stability, and reduction of toxic effects of the encapsulated compounds on healthy tissues [10–16].

A specialized class of carriers, known as "stimuli-responsive nanocarriers," has recently emerged as a notable delivery vehicle [17]. These smart nanocarriers change their structures, compositions, or conformations in response to an external or internal physical or biochemical stimulus, culminating in the release of the encapsulated active species. Immediate release of the physically entrapped active therapeutics may be effected following structural changes in the nanocarrier (such as degradation or decomposition) whereas degradation of the linker in the polymer-therapeutic conjugate leads to cargo release with the rate of release depending largely on the linker degradation rate [18–20]. Such specificity allows the temporal or spatial control of cargo release in the diseased tissues.

This review provides a comprehensive outline of the chemistries involved in fabricating such stimuli-responsive nanocarriers. We focus on the chemistries involved in fabricating polymers with various functional moieties and preparing stimuli-responsive nanocarriers and their end applications.

2. Concepts of stimuli-responsive nanocarriers

2.1. Chemical and biochemical stimuli

The various chemical and biochemical stimuli are based on the redox microenvironment, ionic levels, and intracellular pH difference of specific tissues, enzyme overexpression, and antigen-antibody interactions (Fig. 1) [21]. A well-known example is the difference in pH between the intra- and extracellular environments. pH also acts as a prominent attribute to distinguish between diseased and normal tissues in the body. The pH of solid tumors can itself be differentiated into two sub-categories: the slightly acidic extracellular pH and the highly acidic intracellular pH. For cancer cells, the differential environmental conditions within and outside the cell are due to the limited drainage and anaerobic conditions of cancerous tissues [22]. Despite the difference in pH being subtle, it qualifies as a potent design strategy for targeted delivery of drugs to the affected tissues. Thus, the distinct biochemical attributes of tumors may be utilized to effectively deliver drugs and genes [23]. Here, the relevant intracellular pH intervals (pH 7.4 to pH 4.5) correspond to variations in cytosol (pH 7.40–6.80), endosomes (pH 6.0–4.4), lysosomes (pH 5.0–4.5), and extracellular matrix (pH 7.45–7.35) [24–26]. The difference in the endsomal pH gradient and the subsequent endosome-lysosome fusion can also be utilized to deliver therapeutic agents intracellularly [27,28].

Polymer-based nanocarrier systems that contain a unique pH-sensitive modality undergo destabilization or decomposition at the target site, thereby releasing the encapsulated therapeutics. In many cases, biochemical signatures specific to a disease can also be utilized as triggering factors. For example, enzyme-responsive carrier destabilization represents a well-known process in biomedical science. An enzyme-facilitated dendrimer-based fluorogenic substrate is used to detect tumor-associated matrix metalloproteinase (MMP) 7 [29,30]. Similarly, other enzymes, such as proteases, glucuronidases, or carboxylesterases, whose expression differs in intracellular and extracellular environments can be used as biochemical triggers. Cathepsin B, an intracellular protease, has been widely studied for its ability to degrade protein- or polypeptide-based nanocarriers. Such specificity allows precise cargo delivery at the diseased site in response to certain pathological stimulus present in the local area [31].

With respect to tumors, as the poorly vascularized membranes formed by cancer cells lead to hypoxic conditions with low pH and nutrient levels in the local tissues, such tumor microenvironments may be used to facilitate nanocarrier cargo release [32-34]. This reducing environment arises by virtue of cytosolic and subcellular levels (~2–10 mM) of glutathione tripeptide (γ-glutamyl-cysteinyl-glycine, GSH) that are nearly 100–1000 fold higher as compared to the extracellular levels (~2–20 μM). Reports further indicate that the GSH levels in tumors are 4-fold higher than that in the cytosol of normal cells, a difference that has been capitalized on profoundly in the redox-sensitive delivery of tumor-targeted therapeutic agents. In the endosome, the redox potential is regulated by gamma interferon-inducible lysosomal thiol reductase (GILT), a specific reducing enzyme, in the co-presence of reducing agents including cysteine rather than GSH. Alternatively, the reductive environment in lysosomes is regulated by high levels of cysteine, such as thiols, which maintain low-mass iron in the reduced state in the acidic internal compartment. Typically, materials responsive to redox and thiol activity include disulfide bonds that are stable in the oxidizing environment of the extracellular compartments but experience rapid degradation or thiol-disulfide exchange in the reducing environment of the intracellular compartments [34–36].

2.2. Physical stimuli

Various physical stimulus, including light, temperature, and electric or magnetic field, can induce cargo release at a desired location in the body (Fig. 1) [37]. Temperature-sensitive nanocarriers change their physical state upon systemic circulation and release the encapsulated compound at specific areas in the body with elevated temperatures. Similarly, light or a magnetic field can be employed as an external source to induce encapsulated cargo diffusion. In particular, tissue-compatible radiation at UV, near-IR, or IR frequencies is often used that is harmless to the patient but strong enough to cause conformational change in the nanocarrier architecture [38–40]. For either biological or physical stimuli, the drug is released from the nanocarrier through various mechanisms and enters the desired site of action in the diseased tissue. For example, in scenarios where the drug is chemically conjugated on the nanoparticles, the chemical linkage between drug and carrier needs to be destabilized or broken for the drug to be released, whereas physically entrapped drug may release slowly on its own or

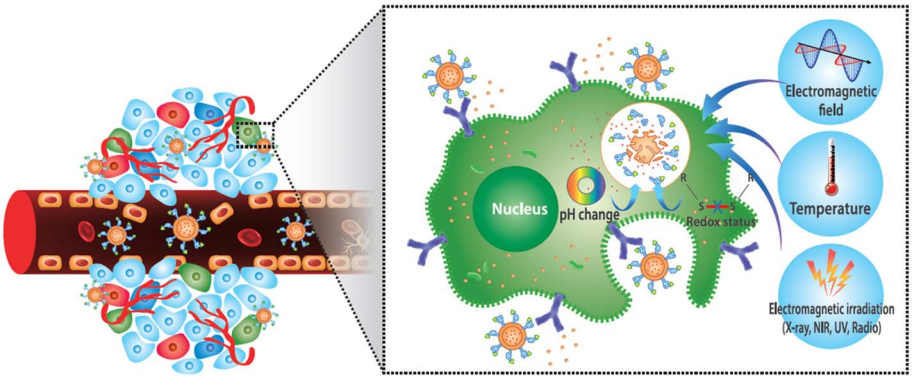

Fig. 1. Schematic illustration of proposed mechanisms of stimuli-responsive nanocarriers upon systemic administration.