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Review

Redox-stimuli-responsive drug delivery systems with supramolecular ferrocenyl-containing polymers for controlled release

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ABSTRACT

The chemically and electrochemically reversible ferrocene/ferricinium redox couple has attracted considerable attention, and a major application is dynamic redox switching of drug delivery systems (DDSs) constructed with ferrocenyl (Fc)-containing polymers. Owing to the accompanying hydrophobic/hydrophilic, neutral/cationic and complexation/dissociation transitions, the "on-demand" release of loaded drugs has been achieved in response to external redox stimuli. Thus, Fc-containing polymers provide a flexible and robust platform for the design and development of functional and smart DDSs. This review summarizes the most recent progress in the fabrication of DDSs with Fc-containing polymers based on the host–guest interactions of Fc/β-cyclodextrin (β-CD) and pillar[6]arene (PA). Fabrication techniques

Abbreviations: A549, A549 lung cancer cells; AAO, anodized alumina substrates; Ad, adamantane; ALMA, allyl methacrylate; ATRP, atom transfer radical polymerization; AuNPs, gold nanoparticles; CAC, critical aggregation concentration; CB[7], cucurbituril; β-CD, β-cyclodextrin; $β-CD_2$, β-CD dimer; β-CD-hydrazone-DOX, β-CD coupled with doxorubicin using a hydrazone bond; CD-PCL, β-cyclodextrin-poly(ε-caprolactone); βCDPSH, thiolated β-CD polymer; CLSM, confocal laser scanning microscopy; CPT, camptothecin; CSP, cationic supramolecular polymer; DDA, dimethyldodecylamine; DDS, drug delivery system; Dextran-Alexa 488, a fluorescence dye labeled dextran, Alexa Fluor®488; Dextran-TRITC, tetramethylrhodamine isothiocyanate-labeled dextran; DMPA, 2,2-dimethoxy-2-phenylacetophenone; DOX, doxorubicin; DOX·HCl, doxorubicin hydrochloride; DPDS, diphenyl disulfide; DS, dextran sulfate; DSPC, 1,2-distearoyl-snglycero-3-phosphocholine; DSPE, 1,2-dimyristoyl-snglycero-3-phosphoethanolamine; DSPG, 1,2-distearoyl-snglycero-3-phosphoglycerol; DTT, dithiothreitol; EDTA, disodium ethylene diamine tetraacetate dehydrate; E-QCM, electrochemical quartz crystal microbalance; Fc, C-centered radical ferrocenyl $Fe(II)C_{10}H_9–$; Fc_2, Fc dimer; FCAP, pillar[5]arene capped with Fcium units; FACP5, Fcium carboxylic acid capped pillar[5]arene; FCAPa, Fc-capped hydrophobic pillar[5]arene; Fc-β-CD, mono-ferrocenyl functionalized β-cyclodextrin; Fc-CHO, ferrocenecarboxaldehyde; Fc-CPT, camptothecin modified ferrocene derivative; Fc-DSP, ferrocenyl-modified phospholipid; Fc-HEUR, ferrocenyl-functionalized hydrophobically modified ethoxylated urethane; Fcium, C-centered radical of ferricenium $[Fe(III)C_{10}H_9-]^+$, the oxidized form of ferrocenyl); FcPEG, poly (ethylene oxide) end-decorated by ferrocenyl; Fc-PCL, ferrocenyl-ended poly(ε-caprolactone); Fc-POEGMA, poly(oligo(ethylene glycol)monomethyl ether methacrylate) with ferrocene terminus; Fc-SS-β-CD, β-CD and ferrocenyl termini connected by a central disulfide link; Fc-PS-PTMSPMA, ferrocenyl-poly(styrene)-b-poly[3-(trimethoxysilyl)-propylmethacrylate]; 5-FU, 5-Fluorouracil; GEM, gemcitabine; GSH, glutathione; GUVs, giant unilamellar vesicles; MTZ, mitoxantrone; MMP-9, metal matrix proteinase 9; HCPT, 10-hydroxycamptothecine; HepG2, liver cancer cells; HMSs, hollow mesoporous silica nanoparticles; HP-β-CD, 2-hydroxypropyl-β-cyclodextrin; IC50, half maximal inhibitory concentration; ITO, indium tin oxide; LbL, layer-by-layer; LCMs, large compound micelles; LCVs, large compound vesicles; LCST, low critical solution temperature; LUVs, large unilamellar vesicles; MAEFc, 2-(methacryloyloxy)ethyl ferrocene-carboxylate; MCF-7, human breast cancer cell line Michigan Cancer Foundation-7; MCs, microcapsules; M-DDSs, multidrug delivery system; MEA, microelectrode array; MG, malachite green; MNPs, magnetic nanoparticles; mPEG-Ada, adamantane-terminated poly(ethylene glycol)methyl ether; mPEG-β-CD, methoxy polyethylene glycol modified by β-cyclodextrin; mPEG-Fc, ferrocene-ended methoxy polyethylene glycol; MRP1 siRNA, multidrug-resistant protein siRNA; MSNPs, mechanized silica nanoparticles; MSNs, mesoporous silica nanoparticles; MSE, miniemulsion-solvent evaporation; NCs, nanocapsules; NPs, nanoparticles; NR, Nile red; PA, pillar[6]arene; PAA^-, poly(acrylic acid); PAH or PAH^+, poly(allylamine hydrochloride); PAH-Fc, ferrrocene-modified poly(allylamine hydrochloride); PACMO-*b*-PAEFC, poly(N-acryloylmorpholine)-*block*-poly(2-acryloyloxyethyl ferrocenecarboxylate); PAEFC-*b*-PDMAEMA, poly(2-acryloyloxyethyl ferrocenecarboxylate)-block-poly(2-(dimethylamino)ethyl methacrylate); PC, porous polycarbonate membranes; PDMAEMA-*b*-PBzMA-*b*-PVFC, poly[2-(dimethylamino)ethyl methacrylate]-block-poly(benzyl methacrylate)-block-poly(4-vinylbenzyl ferrocenecarboxylate); pDNA, plasmid DNA; PEG-*b*-PMAEFc, poly(ethylene glycol)-*b*-poly(2-(methacryloyloxy)ethyl ferrocene-carboxylate); PEG-diFc, diferrocene-ended polyethylene glycol; PEG-Fc, PEG terminated by ferrocene group; PEI-2-CD, PEI-conjugating β-cyclodextrin through 2-hydroxyl; PEI-6-CD, PEI-conjugating β-cyclodextrin through 6-hydroxyl; PEI-Fc, ferrrocene-modified poly(ethyleneimine); PEO-Fc, poly(ethylene oxide) end-capped by ferrocene group; PFcMA, poly-2-(methacryloyloxy)ethyl ferrocenecarboxylate; PFS, poly(ferrocenylsilane); PFS^+, positively charged poly(ferrocenylsilane); PFS^-, negatively charged poly(ferrocenylsilane); PISA, polymerization-induced self-assembly; PMDETA, N,N,N′,N′,N″-pentamethyldiethylenetriamine; PNIPAM-β-CD, poly(N-isopropylacrylamide) with β-cyclodextrin terminal; P(NIPAM-co-AMA)-*b*-PMMA, poly(N-isopropylacrylamide-*co*-aminoethyl methacrylate)-*b*-polymethyl methacrylate; PNIPAM-P[6], pillar[6]arene-terminal-modified poly(N-isopropylacrylamide); PS-CD NPs, β-CD-modified polystyrene nanoparticles; PS-β-CD, poly(styrene) withβ-cyclodextrin end; PSS^-, poly(styrene sulfonate); PTX, paclitaxel; PVFc-*b*-PEG, poly(vinylferrocene)-block-poly(ethylene glycol); PVFc-*b*-PMMA, poly(vinylferrocene)-block-poly(methyl methacrylate); PVFc-*b*-PMMA-*b*-PDMAEMA, poly(vinylferrocene)-*b*-poly(methyl methacrylate)-*b*-poly(N,N-dimethylaminoethyl methacrylate); PVFc-*b*-P2VP, polyvinylferrocene-*b*-poly(2-vinylpyridine); PVFcium, poly(vinylferricenium); Py, pyrene; RAFT, reversible addition-fragmentation chain transfer polymerization; RhB, Rhodamine B; R6G, rhodamine 6G; RITC-dextran, rhodamine isothiocyanate labeled dextran; ROS, reactive oxygen species; SDS, sodium dodecyl sulfonate; SKOV-3, human ovarian cancer SKOV-3 cell; SMMC-7, human hepatoma cell line SMMC-7721; TCEP, tris(2-carboxyethyl)-phosphine; TEG, triethylene glycol; 6-Ts-β-CD, mono-6-(*p*-tolylsulfonyl)-β-cyclodextrin; TTC, trithiocarbonate; WP6, water-soluble pillar[6]arene.

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Drug delivery
Stimuli-responsiveness
Controlled release
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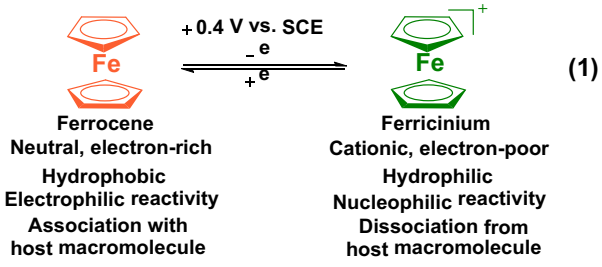
include solution self-assembly, mini-emulsion, layer-by-layer and template techniques. These Fc-containing polymers involve main-chain, side-chain and dendritic topologies in which the polymers behave in various supramolecular fashions. The discussed DDSs contain micelles, vesicles, nanoparticles, nanotubes, multilayer films and bulk hydrogels, and the corresponding stimuli involves electrochemistry, redox reagents, pH and temperature. Focus also is on the mechanisms of stimuli-responsiveness, fabrication methods, controlled release behaviors and potential applications of these DDSs including synergy with medicinal properties of ferrocene derivatives. The prospects of Fc-containing polymer-based DDSs are in nanomedicine whereby it will be possible to selectively deliver specific drugs to sick organs. Many studies detailed here concern chemical studies that still need to be adapted to *in vitro*, then *in vivo* studies in animals. From that point an ultimate and formidable challenge will consist in adapting such DDSs to man diagnosis and therapy.

Contents

1. Introduction

Since Arimoto and Haven's seminal report in 1955 [1], ferrocenyl (Fc)-containing macromolecules [2–7] have attracted considerable attention of chemists and material scientists. The reasons for this constant interest for ferrocene-containing materials are the remarkable properties of ferrocene. Ferrocene is an orange d^6 Fe(II) 18-electron neutral sandwich complex that is oxidized at a rather mild potential of around +0.4 V vs. saturated calomel electrode (SCE) to a green d^5 Fe(III) 17-electron cationic form, ferricinium (Fcium) that is then converted back into its original neutral form using a reductant (Eq. 1) [7].



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